BIOMARKERS OF CARDIOVASCULAR HEALTH IN CHILDHOOD SURVIVORS OF A BRAIN TUMOUR AND THE FEASIBILITY OF EXERCISE TRAINING

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TITLE: Biomarkers of Cardiovascular Health in Childhood Survivors of a Brain Tumour and the Feasibility of Exercise Training

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ABSTRACT

The pediatric population is highly impacted by brain tumours, as they are the most common type of solid tumour affecting children. Medical advances have improved the survival rate of children with brain tumours, but many survivors still experience late effects. In adulthood, 18% of pediatric brain tumour (PBT) survivors have reported cardiovascular issues such as strokes, blood clots, and angina, but little is known about the cardiovascular health of these survivors during childhood. The primary objective of this thesis was to measure the proportion of PBT survivors with values of body mass index (BMI), waist circumference (WC), and aerobic fitness meeting the cut-offs associated with unfavourable cardiovascular health (BMI≥+2 SDs, WC≥90th percentile, and % peak oxygen uptake (VO_{2peak}) predicted<85%). The secondary objective was to observe the effects of 12 weeks of exercise training on the BMI, WC, blood pressure (BP), and aerobic fitness of PBT survivors and describe the feasibility of an exercise training program for this population. In this thesis, 32 PBT survivors who had all received cranial radiation were included (age=12.3±3.4 years, age at diagnosis=7.0±2.5 years, time since treatment completion=4.5±2.8 years, 21/32 male). While WC was measured for 13/32 participants, BMI and aerobic fitness were measured for all. Of the participants, 5/32 children completed a 12-week pilot exercise program consisting of two group and two in-home exercise sessions per week. A control group (n=2, age=14.8±3.6 years, 1/2 male) and an intervention group (n=5, age=15.0±2.3, 3/5 male) had BMI, WC, BP, and aerobic

fitness measurements taken pre- and post-training. Of the participants, 15.6% (5/32) had a BMI≥+2 SDs, 30.7% had a WC≥90th percentile, and 86.7% had a %VO_{2peak} predicted<85%. In total, 81% (26/32) of the participants had at least one identified biomarker reflecting unfavourable cardiovascular health. A training effect was only observed in BP (change of +9%). The exercise program was feasible with an adherence rate of 88% (21/24) to the group and in-home sessions. All (5/5) participants completed the program without injuries or adverse events during the training program. Findings from this thesis indicate that 81% brain tumour survivors have at least one biomarker indicating unfavourable cardiovascular health in childhood. This thesis also provides novel information to be considered before implementing exercise as a therapy for improving the cardiovascular health of survivors. Future additional research is required to determine the appropriate duration, frequency, and intensity of aerobic exercise to stimulate a training effect on these cardiovascular biomarkers.

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LIST OF ABBREVIATIONS

AHA	American Heart Association
BMI	Body mass index
BP	Blood pressure
CDC	United States Centers for Disease Control and Prevention
CHEMP	Child Health & Exercise Medicine Program
CHMS	Canadian Health Measures Survey
DBP	Diastolic blood pressure
IOTF	International Obesity Task Force
MAP	Mean arterial pressure
MCH	McMaster Children's Hospital
NHANES	National Health and Nutrition Examination Survey
NHANES III	Third National Health and Nutrition Examination Survey
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
PBT	Pediatric brain tumour
SBP	Systolic blood pressure
SD	Standard deviation
SK	The Hospital for Sick Children (Sick Kids)
VO_{2peak}	Peak oxygen uptake
WC	Waist circumference
WHO	World Health Organization
W_{peak}	Peak aerobic power

CHAPTER 1: LITERATURE REVIEW

1.1 INTRODUCTION

1.1.1 Pediatric Brain Tumours (PBTs)

The pediatric population is highly impacted by brain tumours, as they are the most common type of solid tumour affecting children, accounting for 25% of all pediatric cancer-related deaths (Pruitt, Ayyangar, Craig, White, & Neufeld, 2011). Fortunately, advances in medicine have dramatically improved the brain tumour survival rate of children from 50% to 70% over the past 25 years (Bleyer, 1999; Ness et al., 2010). In the most recent statistical report released by the Central Brain Tumor Registry of the United States, there were a total of 9,690 PBT survivors living in the United States between 1995 and 2010 (Ostrom et al., 2013). Though there is no evidence to suggest that these survivors burden the healthcare system with their frequent health problems, it is important to understand these issues and intervene early nonetheless.

Brain tumours can be classified by the cell type of origin and the location of development. A brain tumour is classified as a primary tumour if it originates from brain cells, whereas a secondary tumour originates from cells elsewhere in the body and spreads to the brain (Graham et al., 2012). Based on the cell type of origin, most primary brain tumours can be classified into two groups: glial and nonglial tumours. Glial tumours, also known as gliomas, are formed from glial cells, which are supportive and protective cells in the brain. Common gliomas

include astrocytomas and ependymomas. Nonglial tumours develop from nonglial cells and include tumours arising from primitive neuroectodermal cells, such as medulloblastomas. With respect to the location of brain tumour development, the brain can be divided into three sections: posterior fossa, hemispheric, and midline. Within these sections, the frequency of brain tumours varies, with 49% of brain tumours developing in the posterior fossa, 37% in hemispheric regions, and 14% in midline sections (Graham et al., 2012). For a more detailed breakdown of each type of tumour and its frequency of occurrence, refer to Table 1 below.

Table 1. Brain region and frequency of occurrence of common PBTs.
(Graham et al., 2012)

Brain Region	Frequency of Occurrence
Posterior Fossa	**49%**
Medulloblastoma	15%
Cerebellar astrocytoma	15%
Brainstem glioma	15%
Ependymoma	4%
Hemispheric	**37%**
Low-grade astrocytoma	23%
High-grade astrocytoma	11%
Other	3%
Midline	**14%**
Craniopharyngioma	8%
Chiasmal glioma	4%
Pineal region tumor	2%

The age of a child appears to be a factor that influences the type of brain tumour and the location in which it develops. For instance, children up to the age

of three, adolescents, and adults most often develop tumours in the supratentorial region of the brain, whereas children between four and ten years of age tend to develop tumours in the infratentorial or posterior fossa region (Epelman, 2013). Overall, posterior fossa brain tumours are most common in the pediatric population and include medulloblastoma, cerebral astrocytoma, ependymoma, and brainstem glioma (Piscione, Bouffet, Mabbott, Shams, & Kulkarni, 2014).

The methods for treating PBTs include surgery, chemotherapy, and radiation therapy. Depending on the location and grade of the tumour, one or more of these treatments may be used (Pruitt et al., 2011). Cranial radiation is one method of treatment that has improved brain tumour survival rates, but it can be very damaging to the brain. For example, cranial radiation is not used in children under the age of three since it can be highly disruptive to the developing central nervous system, inhibiting axonal, dendritic, and myelin growth (Gottardo & Gajjar, 2006). Overall, the use of radiation is limited, but when necessary, conformal techniques are used to treat the tumour.

Although the above treatments have increased the PBT survival rates, survivors often experience adverse acute and late effects. Acute effects may appear mere months after the removal of the tumour while late effects appear years after treatment. Notable early effects in pediatric survivors include damage to the blood brain barrier, edema, and temporary demyelination (Gurney et al., 2003; Ness et al., 2010; Ullrich & Pomeroy, 2003). Late effects include brain

damage, neurocognitive impairments, reduced physical performance, and endocrine issues (Gurney et al., 2003; Ness et al., 2010; Ullrich & Pomeroy, 2003). These late effects affect up to two-thirds of survivors and may cause disabling or life-threatening conditions (Gottardo & Gajjar, 2006).

The development of biomarkers for cardiovascular disease has also been reported as a late effect in PBT survivors in adulthood (Kelly, 2011; Wolfe et al., 2012). However, there is a gap in the current literature, as little is known about these cardiovascular biomarkers in survivors during childhood. It is important to understand the proportion of survivors who have biomarkers present in childhood so that therapies can be developed to alleviate these factors. For instance, at present, research has been conducted to develop therapies for improving late effects such as neurocognition issues, endocrinopathies, motor defects, and fatigue (Lim, Lange, & King, 2010). However, there is very little research that is focused on therapies to prevent the development of biomarkers for cardiovascular disease in this population.

1.1.2 Cardiovascular Disease

Cardiovascular disease is an umbrella term used to describe a variety of diseases associated with the heart and blood vessels (Elisaf, 2001). Cardiovascular disease is quite common; in Canada alone, approximately 1.6 million people live with the disease and an average of 70,000 people die yearly because of it (Health Canada, 2010).

The term *cardiovascular risk factor* has been used to describe any factors that may promote or influence the development of cardiovascular disease (deGoma, Knowles, Angeli, Budoff, & Rader, 2012). This term was first coined in 1961 publications by the Framingham Study as the relationship between hypertension, cholesterol, left ventricle hypertrophy, and coronary heart disease (deGoma et al., 2012). Traditional risk factors often include family history, age, dyslipidemia, hypertension, diabetes mellitus, and cigarette smoking (Mozaffarian, Wilson, & Kannel, 2008). However, as new research emerges, non-traditional risk factors and biomarkers have been identified. These biomarkers are used as indicators of cardiovascular health, but cannot be validated as predictors of future cardiovascular disease due to insufficient literature.

The difference between cardiovascular risk factors and biomarkers was addressed in a statement released by the American Heart Association (AHA) (Balagopal et al., 2011). According to this framework presented by the AHA, a cardiovascular disease risk factor is a quantifiable biological characteristic that precedes a distinct outcome of cardiovascular disease, predicts that outcome, and is in the biological causal path (Balagopal et al., 2011). Cardiovascular biomarkers, however, are non-causal biological indicators of processes that are involved in the development of cardiovascular disease (Balagopal et al., 2011). An important difference between the two is that risk factors help to identify individuals with a greater risk for developing cardiovascular disease in the future, or future health status. Biomarkers, however, are not predictive and are a

measure of current health status. Overall, many of these novel biomarkers can be used as indicators of current cardiovascular health status but they have not been approved as predictors or causal to cardiovascular disease. For the purpose of this thesis, the aforementioned AHA framework has been adapted to identify biomarkers associated with unfavourable cardiovascular health in children. Based on this framework, there is an underlying assumption that the biomarkers measured in this thesis are valid indicators of current health status in children. It should be noted that these biomarkers could potentially be important for future health status, but research to support their use as predictors or causal for cardiovascular disease is lacking (Balagopal et al., 2011).

Although adults are primarily affected by cardiovascular disease, biomarkers for poor cardiovascular health often start developing during childhood and adolescence. Left untreated, these biomarkers can worsen into adulthood and contribute to adverse cardiovascular conditions later in life (Raitakari et al., 2003). Given that a possible late consequence of PBT treatment is the deterioration of cardiovascular health, it is important to monitor survivors' cardiovascular biomarkers early in life. It is also important to determine the proportion of survivors with these biomarkers in childhood, as it draws attention to the prevalence and severity of these issues. Early detection may provide health care professionals with better opportunities to properly intervene with treatments to reduce these biomarkers that are linked to poor cardiovascular health.

1.2 MEASURING BIOMARKERS OF CARDIOVASCULAR HEALTH

Cardiovascular biomarkers can be measured both serologically and non-serologically. Blood lipids and inflammatory markers such as C-reactive protein, interleukin-6, and intracellular adhesion molecule have been identified as strong predictors of poor cardiovascular health that can be measured from serological samples (Wijnstok et al., 2010). However, given that it is not always feasible to take the blood samples necessary to test for these serological biomarkers, other markers can be measured without the use of blood. For the purpose of this thesis, blood samples will not be taken, so non-serological biomarkers including body mass index (BMI), waist circumference (WC), blood pressure (BP) and aerobic fitness will be measured instead. These four markers will be equally considered as biomarkers for cardiovascular health and rationales to explain their relationship with cardiovascular disease are included in the following paragraphs. For each marker, the specific cut-off values used to determine if an individual's measurements classify them as having unfavourable cardiovascular health will also be discussed (refer to Table 3).

1.2.1 BMI

BMI is a measure of overall body size that is calculated by comparing an individual's body mass relative to height squared. Although BMI is not a direct measure of adiposity, it is a feasible and efficient method to classify children's body size as normal, overweight, or obese. For this reason, BMI is the most

common anthropometric measurement used in Canadian pediatric studies (Patton & McPherson, 2013). A BMI that is high enough to classify a child as being obese is considered a biomarker for poor cardiovascular health. Obese children have been found to have hypertension and higher concentrations of these biomarkers including triglycerides, low-density lipoproteins, and C-reactive protein than children of normal weight (Maximova, Kuhle, Davidson, Fung, & Veugelers, 2013). These children also have a higher risk of cardiovascular disease-related morbidity and mortality (Friedemann et al., 2012; Giussani et al., 2013). For these reasons, BMI is considered a valid biomarker for measuring cardiovascular health in youth.

There are a number of different reference data for BMI cut-off values commonly used for children. For example, the International Obesity Task Force (IOTF) created age- and sex-specific BMI smoothed percentile curves that intersect with the BMI cut-offs for adults of 25 kg/m^2 (overweight) and 30 kg/m^2 (obese) (Voss, Metcalf, Jeffery, & Wilkin, 2006). The IOTF identified these points of intersection as the various cut-offs for children between the ages of 2 and 18. These cut-off values are often used for comparing international data (Shields & Tremblay, 2010). The United States Centers for Disease Control and Prevention (CDC) also developed a set of BMI cut-offs specifically for children and youth aged 2 to 20 in the CDC 2000 Growth Reference. According to the CDC, children are defined as being overweight if their BMI is ≥85th and <95th percentiles, whereas being obese is defined as having a BMI that is ≥95th percentile

(Kuczmarski et al., 2002). The CDC 2000 Growth Reference was developed using data collected from five American surveys taken between 1963 and 1994. For this reason, this growth reference is not ideal, as CDC used data that is representative of how a select group of children grew at a specific time and place (de Onis & Lobstein, 2010). The WHO also created a set of BMI cut-off values in the WHO 2007 Growth Reference. These cut-off values are for children between the ages of 5 and 19 and are based on Z-scores. The Z-score cut-off for being classified as overweight is ≥+1 and <+2 SDs, whereas being obese is >+2 SDs (de Onis & Lobstein, 2010). The WHO data were generated from a sample of children from Brazil, Ghana, India, Norway, Oman, and the United States. The children included were specifically selected based on their exposure to socially and economically favourable conditions that would allow for optimal growth. As a result, the WHO data represents a gold standard of growth achievement and describes how children should grow. In comparison, the IOTF and CDC data represents data of a reference population (de Onis, Garza, Onyango, & Borghi, 2007; Shields & Tremblay, 2010). For these reasons, The Dietitians of Canada, The Canadian Paediatric Society, The College of Family Physicians of Canada, and Community Health Nurses of Canada, suggest that the WHO Growth Reference 2007 data be used to evaluate children and adolescents (Dietitians of Canada, Canadian Paediatric Society, College of Family Physicians of Canada, Community Health Nurses of Canada, & Secker, 2010).

1.2.2 WC

Measuring WC provides information on a child's level of abdominal adipose tissue. Elevated stores of abdominal adipose tissue have been found to be consistent with and strongly associated with elevated concentrations of biomarkers for poor cardiovascular health (Freedman, Serdula, Srinivasan, & Berenson, 1999). Stores of abdominal adipose tissue are released and travel to the liver where they are broken down into free fatty acids, which can contribute to the development of insulin resistance and lipoproteins. Moreover, abdominal adipose tissue has been found to release inflammatory adipokines and angiotensinogen, which can contribute to cardiovascular disease (Klein et al., 2007). As a result, WC has been validated as a predictor of cardiovascular disease and other cardiovascular biomarkers in children (Savva et al., 2000).

Measuring WC is a very feasible method for assessing cardiovascular health in children, as it is a cost-effective and simple procedure (de Koning, Merchant, Pogue, & Anand, 2007). There are multiple ways of measuring WC based on different anatomical locations, but researchers have yet to come to a consensus on the best measurement site (McGuire & Ross, 2008). The National Institutes of Health (NIH) recommends using the top of the iliac crest as the measurement site, while the WHO suggests the measurement be taken at the midpoint between the highest point of the iliac crest and the last floating rib (McGuire & Ross, 2008). Recent research indicates that the WC measurement

site does not affect the relationship with cardiovascular biomarkers in children (Harrington, Staiano, Broyles, Gupta, & Katzmarzyk, 2013). However, the absolute values of WC measured at different anatomical sites differ; therefore, it is suggested that measurements from multiple anatomical sites not be pooled (Harrington et al., 2013). For the purpose of this thesis, WC will be measured according to NIH protocol, as the most used and cited pediatric WC growth reference by the Third National Health and Nutrition Examination Survey (NHANES III) used NIH protocol. This thesis will use NHANES III data for identifying WC as a biomarker of unfavourable cardiovascular health, so it would be prudent to maintain consistency with the protocols.

There are no universally accepted cut-off values for WC. One possible reason for this could be the fact that WC varies depending on the ethnicity, age, and gender of the population (Schwandt, Kelishadi, & Haas, 2008). Growth curve modeling has been used to derive adolescent WC cut-off points from adult cut-off points established by the National Cholesterol Education Program Adult Treatment Panel III and the International Diabetes Federation (Jolliffe & Janssen, 2007). These WC cut-off points have been used to identify abdominal obesity in Canadian adolescents 12 years and older who were surveyed in the CHMS (Janssen, Shields, Craig, & Tremblay, 2011). However, a major problem with these cut-off points is that they are only available for youth over the age of 12 and their use becomes limited when studying a sample with younger children. As a resolution, WC percentiles can be used as cut-off markers for children younger

than 12 years of age. Percentiles have been created for various countries including Canada, Italy, Spain, Germany, and the United States of America. However, for countries other than the United States, percentile cut-offs have yet to be determined. The American percentiles were developed by Fernandez et al. (2004) using NHANES III WC reference data to develop age-specific percentiles for children between 2 and 18 years of age (Fernandez, Redden, Pietrobelli, & Allison, 2004). These percentiles are extensively cited and widely used by other studies, as the 90th percentile of this data has been considered a valid WC cut-off value (Bassali, Waller, Gower, Allison, & Davis, 2010; Burns & Arslanian, 2009a; Messiah, Arheart, Lipshultz, & Miller, 2008; Tran, Clark, & Racette, 2013). Children with a WC≥90th percentile of NHANES III reference data have a higher risk of having other cardiovascular biomarkers such as dyslipidemia, insulin resistance, and hypertension than those at lower percentiles (Bassali et al., 2010; Burns & Arslanian, 2009b; Katzmarzyk, 2004; Messiah et al., 2012). Since there is limited information available in pediatric literature for Canadian cut-off percentiles, a WC≥90th percentile of NHANES III data will be classified as having excess central adiposity and therefore, unfavourable cardiovascular health.

1.2.3 BP

High BP is a cardiovascular biomarker that is frequently measured to determine whether an individual is at risk of having poor cardiovascular health. Children with elevated BP can be classified as either prehypertensive or hypertensive based on percentiles for age, sex, and height. The U.S. Department

of Health and Human Service: National Heart, Lung, and Blood Institute (NHLBI) defines the cut-off point for prehypertension as having average systolic BP (SBP) and diastolic BP (DBP) that are ≥90th and <95th percentile. It follows that the cut-off point for hypertension is having BP that is ≥95th percentile (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents, 2004). Hypertensive children are considered to be at the greatest risk of developing cardiovascular illnesses including increased cardiac mass, atherosclerosis, and left ventricle hypertrophy (Redwine & Falkner, 2012). In fact, research has already discovered early development of atherosclerosis in children with hypertension (Luma & Spiotta, 2006). For these reasons, BP is considered a valid biomarker of cardiovascular health and is one that can be easily measured.

1.2.4 Aerobic Fitness

Assessing an individual's aerobic fitness provides information on the functioning of his or her cardiovascular system. In this system, the heart and blood vessels are vital for transporting oxygen-rich blood to muscles. Individuals with high aerobic fitness have stronger hearts that can pump more blood with each heartbeat compared to those who are less fit. On the other hand, children with poor aerobic fitness tend to develop other unfavourable biomarkers and have an increased risk of suffering with poor cardiovascular health in adulthood (Dencker et al., 2012). There is a growing body of evidence that suggests that the level of aerobic fitness of children and adolescents are inversely related to the

clustering of biomarkers (Anderssen et al., 2007; Garcia-Artero et al., 2007). Moreover, there is strong evidence to suggest that high aerobic fitness during childhood plays a role in development of healthy cardiovascular profiles in adulthood (Ruiz et al., 2009). However, despite this growing amount of research, there are no published cut-off values with which to compare individuals' levels of aerobic fitness in the context of future cardiovascular health.

Aerobic fitness can be assessed in many ways, such as the use of a cycle ergometer or treadmill running test to measure peak aerobic power (W_{peak}) and peak oxygen uptake (VO_{2peak}). W_{peak} is a measure of the highest workload at which an individual reaches exhaustion when peddling. VO_{2peak} is a measure of the highest rate of oxygen consumption at the completion of a test (Day, Rossiter, Coats, Skasick, & Whipp, 2003). While W_{peak} can be easily measured with a cycle ergometer, VO_{2peak} requires additional equipment for gas analysis, making it more complicated and more expensive to measure. Complicating the process further is the required use of a mouthpiece to analyze respired gases, which for some PBT survivors with hypersensitive pharyngeal reflexes, makes it difficult to complete the test with the mouthpiece in place. For this reason, W_{peak} would be a more suitable way to measure aerobic fitness. Fortunately, there is a significant relationship ($r=0.97$) between W_{peak} and VO_{2peak} (Bentley & McNaughton, 2003). As a result, W_{peak} can be measured and converted to VO_{2peak}. However, the testing protocols for measuring W_{peak} and VO_{2peak} tend to be quite taxing, making it difficult for individuals with chronic conditions to complete them. As an

alternative, the six-minute walk test can be used to assess the functional exercise capacity of those with chronic conditions. The test is self-paced and assesses functional exercise capacity by measuring the distance that an individual can walk in six minutes (Bartels, de Groot, & Terwee, 2013).

Currently, there are no standard cut-off values for W_{peak} or distance travelled during the six-minute walking test that could be used to determine if these measurements are indicative of poor cardiovascular health. However, there have been multiple published cut-off values for VO_{2peak} that define a low level of aerobic fitness for children. Despite numerous studies, cut-off values vary depending on the nature of the study, without leading to any established consensus on a universal cut-off value for VO_{2peak} (Ruiz et al., 2007). Not all of these cut-off values are relevant to this Master's thesis as some values are based on different age ranges than the sample included in this thesis. Of the relevant cut-off values, one set of values published by Lobelo et al. (2009) measured aerobic fitness using a treadmill test as opposed to the cycle ergometer used in this thesis (Lobelo, Pate, Dowda, Liese, & Ruiz, 2009). The most suitable values were published by Adegboye et al. (2011), as the age range and testing protocol most closely matched those used in this current thesis (Adegboye et al., 2011).

Table 2 shows the optimal cut-off values found by Adegboye et al. (2011) for males and females aged 8 to 11 and 14 to 17 (Adegboye et al., 2011). These values do not cover a continuous age range, as the cut-off values for children between the ages of 11 and 14 are noticeably missing. One method to

compensate for this limitation is to express the relationship between the cut-off values and average VO_{2peak} values as a percentage, then use the average of these percentages as the percent cut-off for the entire age range. This cut-off (shown in the last column of Table 2) can then be compared to percent-predicted VO_{2peak} data, which expresses the relationship between a measured value of VO_{2peak} and the expected VO_{2peak} for a healthy individual of the same sex and height or age. If the percent-predicted VO_{2peak} falls below the percent cut-off of 85% in this case, the individual will be classified as having a biomarker identifying poor cardiovascular health. It must be noted that this method of identifying aerobic fitness as a biomarker of poor cardiovascular health is not a perfect solution as there is an important assumption built into the logic. This assumption is that expressing the cut-off value as a percentage will compensate for age differences, but since there are no continuous age-specific cut-off values, expressing a cut-off percentage is the most appropriate solution.

Table 2. Absolute and percent cut-offs for low aerobic fitness in children and adolescents.

Sex	Age (years)	Absolute Cut-Off for Low Aerobic Fitness (mL O_2/min/kg)	Measured Aerobic Fitness (mL O_2/min/kg)	Percent Cut-off
Female	8 to 11	37.4	45.4	82%
	14 to 17	33.0	52.4	63%
Male	8 to 11	43.6	50.5	86%
	14 to 17	46.0	42.0	110%
			Average	85%

Source: (Adegboye et al., 2011)

Table 3. Cut-off values for biomarkers associated with unfavourable cardiovascular health.

Measured Outcome	Cut-Off Value	Source
BMI	Z-Score >+2 SD	The WHO Growth Reference 2007
WC	WC ≥90th Percentile	NHANES III
BP	SBP and DBP ≥95th Percentile	NHLBI
Aerobic Fitness	<85% Predicted VO_{2peak}	Adegboye et al. 2011

1.3 PBT SURVIVORS WITH CARDIOVASCULAR BIOMARKERS AND CARDIOVASCULAR DISEASE DURING ADULTHOOD

A coordinated approach was used to identify relevant literature related to biomarkers of cardiovascular health among adults who have survived a PBT. To this end, the following key words were used in PubMed: “Brain Tumor,” “Cardiovascular Disease,” “Cardiovascular,” “Long-Term,” “Childhood Cancer,” and “Adult” in a literature search last completed on June 28, 2014.

Survivors of PBTs appear to have cardiovascular biomarkers and conditions throughout adulthood (Kelly, 2011; Wolfe et al., 2012). In a recent study, Ness et al. (2010) compared a group of PBT survivors between the ages of 18 and 59 to an age-matched control group (Ness et al., 2010). The group of survivors had a significantly lower level of aerobic fitness compared to the control group. Similarly, other research has detected inferior aerobic fitness levels in

adult survivors of PBTs when compared to their healthy siblings (Miller et al., 2013). Survivors in adulthood have also been found to have higher SBP, waist-to-hip ratios, and low-density lipoprotein cholesterol, as well as lower high-density lipoprotein cholesterol than healthy controls (Heikens et al., 2000). When comparing adult survivors of various childhood cancers, survivors of brain tumours had the highest prevalence of obesity compared to survivors of other cancers (Felicetti et al., 2014). In addition to elevated biomarkers, Gurney et al. (2003) found that 18% of PBT survivors have one or more cardiovascular conditions in adulthood (Gurney et al., 2003). Upon comparing survivors to their siblings, researchers found that survivors had an increased risk of blood clots and two-times increased risk of having angina-like symptoms (Gurney et al., 2003). In addition, survivors of a PBT have a 40-fold incidence of stroke compared to siblings, with the highest risk posed to those who received cranial radiation of doses greater than 30 Gy (Bowers et al., 2006; Gurney et al., 2003). Overall, the existing literature indicates that adult survivors of PBTs or other childhood cancers tend to have unfavourable cardiovascular health. For this reason, it is of interest to further investigate how soon following treatment do these indicators of poor cardiovascular health emerge.

1.4 PBT SURVIVORS AND CARDIOVASCULAR BIOMARKERS DURING CHILDHOOD: STATE OF THE KNOWLEDGE

Given that PBT survivors appear to have cardiovascular biomarkers and cardiovascular conditions in adulthood, the available literature was studied to

obtain a better understanding of cardiovascular biomarkers present in brain tumour survivors during childhood. More specifically, the biomarkers of cardiovascular health researched included serological biomarkers, BMI, WC, BP, and aerobic fitness. A similar PubMed literature search was performed with the following key words: “Pediatric Brain Tumor,” “Cardiovascular Disease,” “Cardiovascular,” “Childhood Cancer,” “Children,” “Cardiovascular Risk Factor,” “BMI,” “Waist Circumference,” and “Aerobic Fitness” in a literature search last completed on June 28, 2014.

1.4.1 Serological Biomarkers in PBT Survivors

Although serological biomarkers will not be assessed in the present Master’s thesis, it is still worthwhile to review the existing literature on these biomarkers in childhood brain tumour survivors. For example, blood lipids are strong predictors of the risk of cardiovascular disease. In a study of 52 PBT survivors with a mean age of 14.4 years, researchers found that 37% of the participants had at least one abnormal lipid value (Pietila et al., 2009). Furthermore, a significant difference was found in the number of survivors with serological biomarkers between those treated with cranial radiation and those who did not receive radiation. Survivors treated with cranial radiation were more likely to suffer with dyslipidemia and metabolic syndrome (Pietila et al., 2009). Other research on brain tumour survivors during childhood has found that survivors have decreased insulin sensitivity and high-density lipoproteins when compared to healthy controls (Siviero-Miachon et al., 2011). Although there is

limited research available, there is evidence to suggest that brain tumour survivors are likely to have abnormal serological biomarker values during childhood that may increase the risk of developing cardiovascular conditions.

1.4.2 BMI in PBT Survivors

Three studies that measured the BMI of PBT survivors were uncovered in the current literature. In one study of 54 survivors between the ages of 8 and 18, Schulte et al. (2010) found that based on their BMI measurements, 18.5% of the participants were obese, and 50% were normal weight for their age (Schulte et al., 2010). In another study of 46 survivors between 3 and 12 years of age, Lek et al. (2010) measured participants' BMIs at baseline and then 4 years later at a follow-up appointment. At baseline, the percentage of survivors who were obese was 6%, which then increased to 43% at the follow-up (Lek et al., 2010). Most recently, Hansen et al. (2014) studied 48 survivors between 12 to 17 years and found that 29% of survivors in their sample were obese (Hansen et al., 2014). When comparing these studies, it is obvious that there is some inconsistency between the findings, as obesity appears to be much more prevalent in the survivors that Lek et al. (2010) studied. More research is required to clarify this discrepancy.

1.4.3 WC in PBT Survivors

As is the case with aerobic fitness research, the literature on WC in PBT survivors is very limited. One study by Siviero-Miachon et al. (2011) measured

the WCs of 16 PBT survivors during adolescence and early adulthood with a mean age of 18 years. Upon comparing the group of survivors to a group of healthy controls, researchers found that the survivors had a higher WC and presented excess central adiposity (survivors = 76.8 cm vs. control = 67.9 cm; p = 0.024) (Siviero-Miachon et al., 2011). Central adiposity is a key element of cardiovascular health and there remains a clear need to study this issue in PBT survivors (Klein et al., 2007; Savva et al., 2000; Siviero-Miachon et al., 2011).

1.4.4 BP in PBT Survivors

The BP of PBT survivors were also studied by Siviero-Miachon et al. (2011) and Pietila et al. (2009). Siviero-Miachon et al. (2011) studied 16 pediatric survivors in adolescence and early adulthood with a mean age of 18 years. In this study, no differences were observed between the BPs of survivors and age-matched healthy controls (Siviero-Miachon et al., 2011). In contrast, Pietila et al. (2009) found that hypertension was common among 52 young survivors with a mean age of 14 years (Pietila et al., 2009). It is likely that these studies had such different findings on BP due to the difference in sample sizes, further research is required to gain a better understanding of this topic.

1.4.5 Aerobic Fitness in PBT Survivors

The literature on the short-term aerobic fitness levels of PBT survivors is limited, as only one study by Wolfe et al. (2012) could be found. In this study, the aerobic fitness of 12 survivors between the ages of 11 and 18 was measured.

Wolfe et al. (2012) found that survivors had a lower level of aerobic fitness than healthy controls (survivors= 31.8 ml/kg/min vs. control= 49.3 ml/kg/min). It is not entirely known why these survivors are less aerobically fit, but it is suggested that low physical activity levels may contribute to these results (Wolfe et al., 2012).

1.5 EXERCISE AND CARDIOVASCULAR BIOMARKERS IN PEDIATRIC CANCER SURVIVORS

After searching through the available literature, exercise intervention studies focused on PBT survivors could not be found. Instead, interventions have focused on pediatric and adult survivors of all cancers or individual cancers other than brain cancer. Furthermore, few of these studies have examined the effects of exercise on the cardiovascular biomarkers of these cancer survivors.

In one pediatric-based study, Takken et al. (2009) conducted a 12-week exercise intervention focused on survivors of acute lymphoblastic leukemia between 6 and 14 years of age. The exercise intervention incorporated aerobic and strength-training exercises with four exercise sessions per week—two at a physiotherapist's practice and two at home. Following the intervention, results showed that the survivors' BMI and aerobic fitness levels remained unchanged. Takken et al. (2009) suggested that the lack of change could have been due to the fact that the intervention program was not customized for each survivor. Ensuring that an exercise program is individualized for a child is essential because it makes the activity more enjoyable and keeps the child motivated to

finish the program. Thus, it follows that the children may not have been motivated to exercise because they did not enjoy the program (Takken et al., 2009).

Another 12-week exercise intervention by Sharkey et al. (1993) studied 12 individuals with a mean age of 19 years who survived cancer during childhood. The intervention program was based on aerobic exercises that were completed both at home and in-hospital. Following the intervention, there was a trend for an 8% increase ($p=0.1$) in aerobic fitness (Sharkey, Carey, Heise, & Barber, 1993). Although both studies by Takken et al. (2009) and Sharkey et al. (1993) had similar intervention types and durations, only Sharkey et al. found changes in aerobic fitness. It could be argued that participants in this study improved their aerobic fitness because they had a high compliance rate, attending greater than 85% of the training sessions (Sharkey et al., 1993). As a result, the participants were able to receive the full benefits of the intervention. Therefore, ensuring that participants are compliant with the intervention appears to be key for observing changes in the measured biomarkers.

San Juan et al. (2007) created a 16-week exercise intervention for children between 4 and 7 years of age who were receiving maintenance therapy for acute lymphoblastic leukemia. The intervention was hospital-based and incorporated both aerobic and resistance exercises. Following the intervention period, the children experienced an increase in their aerobic fitness by 24% (pre-training 24.3 ± 5.9 vs. post-training 30.2 ± 6.2 mL/kg/min) (San Juan et al., 2007). Findings from this study showed that all children had a lower baseline aerobic

fitness than those who were in the previous study by Takken et al. (2009). It is suggested that improvements in aerobic fitness may have only been observed in the study by San Juan et al. (2007) and not in that of Takken et al. (2009) because the lower baseline level gave the children greater room for improvement in aerobic fitness (Takken et al., 2009).

With respect to ongoing research, there is currently an exercise intervention study being conducted by Soares-Miranda et al. (2013) that is focused on children with solid tumours who have received chemotherapy. The primary goal of this study is to observe the effects of a combination of strength and aerobic exercise on aerobic fitness. However, results have yet to be published (Soares-Miranda et al., 2013).

Overall, there appear to be multiple limitations in the literature regarding exercise interventions. For example, although there are other exercise intervention studies focused on cancer survivors, none of them study the effects of exercise on survivors' cardiovascular biomarkers other than aerobic fitness. There has also yet to be an intervention study focused only on PBT survivors up to age 18, as most studies include survivors who are now in early adulthood. As a result, the effect of exercise on the cardiovascular biomarkers of PBT survivors during childhood remains unknown. Another limitation is that the available exercise interventions that were discussed only measured a few biomarkers. The majority of studies only measured aerobic fitness, but there are many other measurements, as previously discussed, that are viable indicators of

cardiovascular risk. Overall, these gaps in current literature create an opportunity to develop an innovative exercise intervention focused on the effects of exercise on cardiovascular biomarkers in brain tumour survivors during childhood.

1.6 CONSIDERATIONS WHEN DEVELOPING A PEDIATRIC EXERCISE INTERVENTION

1.6.1 Exercise Formats

There are various exercise formats that must be considered when creating a pediatric exercise intervention. One format of exercise intervention is a group-based program that allows children in the study to exercise as a group, usually in a facility such as a community center, school, or hospital, as opposed to in the home. Group exercise interventions appear to be the most practical format for children (Gilliam et al., 2012). Exercising as a group allows for interaction among the children and provides an opportunity to meet new friends. As a result, the children motivate each other to exercise, the compliance with the exercise intervention is high, and the children report having more fun (Gilliam et al., 2012).

In-home exercise programs are another format of intervention. This format usually requires children to follow an exercise program and exercise multiple times per week in their own homes. This format tends to be less feasible, as parents complain that it is too difficult to get their children motivated to exercise while at home, partially because there is less interaction with other children (Gilliam et al., 2012). For this reason, it is believed that a social support system

including family, peers, and a personal trainer helps children to enjoy the in-home exercise program and keeps them motivated to complete the program (Gilliam et al., 2012). In-home exercise programs are beneficial because they reduce the potential inconvenience of driving to and from weekly exercise sessions outside the home (Gilliam et al., 2012). They also make it very easy for participants to continue exercising once the study is finished since they have experience doing the exercises in the comfort of their own homes (Gilliam et al., 2012). Ideally, family members and peers would continue to motivate the child to exercise after the study is complete. This continued physical activity is beneficial for the children's health, making in-home exercise programs an important feature to include in an intervention (Gilliam et al., 2012).

1.6.2 Exercise Type

In addition to the format of the exercise intervention, the types of activities and exercises must be considered and tailored to each participant. Work by Takken et al. (2009) showed that children were less likely to stay committed to the intervention because of a lack of interest in the activities. However, Takken et al. (2009) believe that if the exercises are individualized, children will have more fun and will be more committed to the intervention. Another justification for customized programs is that neurological impairments caused by cancer treatments can lead to children being dizzy or unbalanced, making it harder for them to walk on a treadmill, ride a bike, or participate in other exercises. In these cases, exercises must be appropriately selected based on a child's individual

situation. For instance, walking on a track or riding a stationary bike may be more practical for a child who has difficulty with a treadmill or regular bicycle. In general, exercise interventions must be individualized for each child to ensure that he or she can effectively perform the exercise.

1.6.3 Exercise Intensity, Duration, and Frequency

Other factors that must be considered when creating an exercise intervention are the intensity, duration, and frequency of the exercise sessions. Due to a lack of research, it is difficult to determine the optimal intensity, duration, or frequency of exercise for PBT survivors. The American Cancer Society recommends 60 minutes of moderate to vigorous exercise five days a week for pediatric cancer survivors during their childhood and adolescence. This recommendation is very similar to that for healthy children, but as previously noted, these programs must be individualized based on the limitations of the individuals (Hayes & Newman, 2006).

1.7 STUDY RATIONALE

1.7.1 The Importance of Further Research

After reviewing the literature, it is apparent that further research is needed on the cardiovascular biomarkers in brain tumour survivors during childhood. Although the current literature has reported biomarker values, it has not determined the proportion of survivors who have biomarker measurements

indicating poor cardiovascular health. Furthermore, little is known on the effects of exercise training on these biomarkers in PBT survivors. At present, the number of studies is limited, there are issues with the existing literature, and there are questions that still need to be investigated.

1.7.2 Objectives

1.7.2.1 Objective 1

The primary objective of this study was to measure the proportion of PBT survivors with values of BMI, WC, and aerobic fitness meeting the cut-offs associated with unfavourable cardiovascular health.

1.7.2.2 Objective 2

The secondary objective of this study was to observe the effects of 12 weeks of group and in-home exercise training on the BMI, WC, BP, and aerobic fitness of PBT survivors and describe the feasibility of an exercise training program for this population.

1.7.3 Hypotheses

1.7.3.1 Hypothesis 1

It was hypothesized that >50% of pediatric-aged brain tumour survivors would have at least one biomarker meeting the cut-off value associated with unfavourable cardiovascular health.

1.7.3.2 Hypothesis 2

It was hypothesized that PBT survivors would experience a reduction in BMI, WC, and BP, and an increase in aerobic fitness after 12 weeks of the exercise intervention.

CHAPTER 2: METHODS

2.1 PARTICIPANTS

In total, 32 PBT survivors between the ages of 6 and 17 participated in this study. To achieve this sample size, data from three different studies were pooled (Table 4). Eight participants came from a multicentre study conducted at McMaster University and The Hospital for Sick Children (SK) entitled, *The neuro-protective effects of exercise in children treated with cranial radiation for brain tumours*, hereafter referred to as Study 1. Dr. Brian Timmons was the principal investigator at the McMaster University site, while Dr. Donald Mabbott was the principal investigator at SK. The remaining 24 participants came from two separate studies by the same investigators. One of these studies was conducted by the Child Health & Exercise Medicine Program (CHEMP) at McMaster University led by Dr. Timmons (Study 2). This study recruited six PBT survivors from the MCH. The other study was conducted in Dr. Mabbott's lab at SK that recruited 18 participants from SK (Study 3).

Upon receiving approval from the Hamilton Integrated Research Ethics Board and SK Research Ethics Board, participant recruitment for all three studies was conducted. Participants were recruited from and enrolled at each respective hospital if they met the study's inclusion criteria. The inclusion criteria required children to be between 6 and 17 years of age and for there to have been at least one year since successful treatment with cranial radiation for a brain tumour.

Participants must have also declared English as their native language or have had at least two years of schooling in English at the time of their first assessment. Inclusion criteria also dictated that there be no more than 10 years between the diagnosis of a participant's brain tumour and the study start date. Children were excluded if they had a pre-morbid history of brain injury, neurological disorder, visual or sensory impairment, cerebral palsy, developmental delay, or learning disability. Children were also excluded if they had severe neurological/motor dysfunction that would prevent safe participation in the exercise intervention for Study 1.

Recruitment for the three studies was conducted at either McMaster Children's Hospital (MCH) or SK. Participants for Studies 1 and 2 were recruited from the 3F Child and Youth: Pediatric Out-Patient Clinic at the MCH. Patients were prescreened for their eligibility based on inclusion criteria and then approached and informed about the study during normal clinic visits. Patients who did not have a scheduled visit during the recruitment period were informed via telephone. Participants at SK for Studies 1 and 3 were recruited from a prescreened list of patients. These patients were approached during regular clinic visits and also contacted via a recruiting mail-out. For all studies, children, and parents or guardians were informed about the study, then asked to sign written assent and consent forms, respectively, if they agreed to participate.

The recruitment process for Studies 1, 2, and 3 included in objective 1 are displayed in Figure 1. For Study 1, 302 patients were assessed for eligibility from

the 3F neuro-oncology outpatient clinic at MCH. Of these patients, 15 met the inclusion criteria, and 5 consented to participate in the study. For Study 2, 27 patients from the 3F neuro-oncology outpatient clinic at MCH were assessed for eligibility. Of these patients, 16 were eligible, and 6 consented to the study. At SK, 150 patients were assessed for eligibility. Of these patients, 85 met the inclusion criteria, 3 consented to Study 1 (SK site), and 18 consented to Study 3.

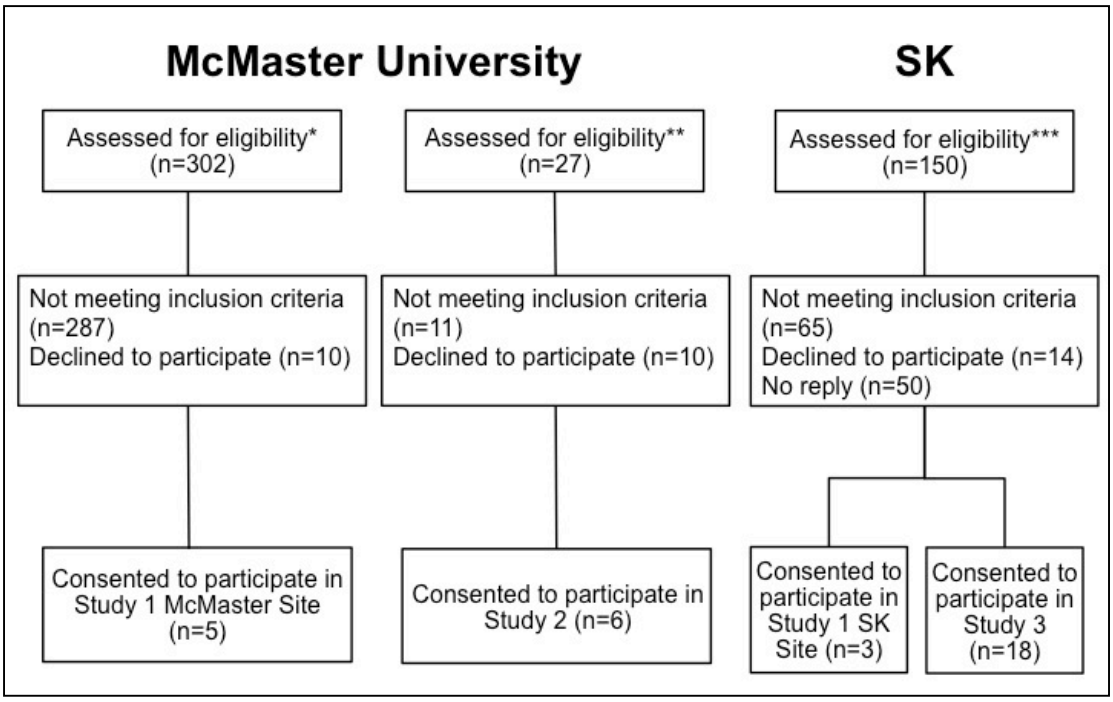

Figure 1. Consort tables for participant recruitment in Studies 1, 2, and 3.

*Assessed for eligibility defined as all neuro-oncology outpatients within the past 10 years at the 3F clinic.

**Assessed for eligibility defined as neuro-oncology outpatients approached during 3F clinic visits between December 2010 and June 2011.

***Assessed for eligibility defined as SK neuro-oncology outpatients between 7 and 17 years at the time of recruitment.

The recruitment process for objective 2 is displayed in Figure 2. Out of 302 patients assessed for eligibility from the 3F neuro-oncology outpatient clinic at MCH, 15 were eligible and 5 consented to participate in the study.

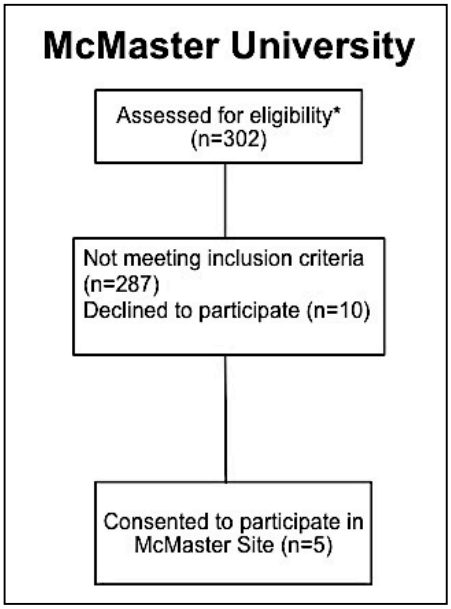

Figure 2. Consort table for the participant recruitment in Study 1 at the McMaster University site.

*Assessed for eligibility defined as all neuro-oncology outpatients within past 10 years at the 3F clinic.

Table 4. The number of participants pooled from each study.

	Total # of Participants	# of Participants in Objective 1	# of Participants in Objective 2
Study 1	8	8	5
Study 2	6	6	0
Study 3	18	18	0

2.2 STUDY DESIGNS

2.2.1 Study 1

For Study 1, a crossover design was used to ensure that all participants had an opportunity to complete the exercise intervention. Upon enrollment, participants at both study sites were assigned to either the wait-list control group or the immediate group. The wait-list control group waited 12 weeks before starting the exercise intervention, while the immediate group started the intervention immediately after enrollment.

Regardless of the group, all participants had BMI, WC, BP, and aerobic fitness measurements taken three times during this study—at the initial, middle, and final visits. At the McMaster University site, the initial or baseline visit was conducted in July 2013 for two participants who were enrolled in the wait-list control group. After 12 weeks of normal activity without the intervention, the participants returned for their middle visit in September 2013. At the same point in time, three other participants were enrolled in the immediate group and had their initial or baseline visit in September 2013 as well. Both groups then started the 12-week exercise intervention, which ended in December 2013. At this point, the wait-list control group had its final visit while the immediate group had its middle visit. The immediate group then completed its final visit in March 2014 after 12 weeks without exercise intervention. Unfortunately, due to unforeseen circumstances, SK started its exercise program later than expected. As a result,

this thesis was only able to capture the measurements from the participants' initial visit. For this reason, it is not possible to capture the effects of exercise on the cardiovascular biomarkers of the participants enrolled at that study site.

As previously mentioned, Study 1 included a 12-week exercise intervention consisting of two group exercise sessions and two in-home exercise sessions per week. These exercise sessions were designed by a certified personal trainer. The in-home sessions focused on muscle strengthening through individual structured exercises, while the group sessions focused on aerobic fitness and muscle strengthening through games and circuit exercises. Please refer to Appendices A, B, and C for a sample of the exercises performed during group sessions, in-home sessions, and circuits, respectively.

The exercise intervention at the McMaster University site took place from September to December 2013. Group sessions were held every Monday and Wednesday evening for approximately one hour. The sessions were initially held at the Churchill Lawn Bowling Club in Hamilton, Ontario, but were relocated to the David Braley Athletic Centre at McMaster University in Hamilton, Ontario due to unforeseen circumstances. A team of recruited volunteers attended each group session, participating in activities with the children and training them one-on-one. This interaction was vital for motivating the participants and ensuring that they completed the exercises safely and with proper technique. During the sessions, participants wore heart rate monitors (FT1, Polar Electro, Kempele,

Finland) and were monitored every ten minutes to ensure that they maintained a heart rate of at least 70% of their measured maximum rate.

Each child completed the in-home sessions at his or her house, usually with the help of a family member. Participants did not have their heart rate monitored or recorded during the in-home sessions. Instead, they were required to complete an exercise logbook, recording how many sets and repetitions of each exercise they completed (Appendix D).

2.2.2 Study 2

Study 2 was designed to be a single visit in which the participant would be measured and tested. After written assent and consent was obtained from children and parents or guardians, respectively, all participants visited the CHEMP laboratory at McMaster University. During this visit, BMI was measured for all participants and aerobic fitness was measured for all but one participant who could not perform the required test.

2.2.3 Study 3

Likewise, Study 3 was designed as a single visit that was completed after written assent and consent was obtained from children and parents or guardians, respectively. All participants made a single visit to the Cardiopulmonary Exercise Laboratory at SK to have their BMI and WC measured. Aerobic fitness was

measured for all participants, except one child who could not perform the required test.

2.3 ASSESSMENT MEASUREMENTS

All of the measurements below were recorded during the three visits for Study 1. As previously mentioned, only BMI and aerobic fitness were recorded during the single visit for Study 2 and only BMI, WC, and aerobic fitness were measured during the single visit for Study 3. Table 5 summarizes the biomarker measurements that were recorded for each study.

Table 5. A summary of the cardiovascular biomarkers measured in Studies 1, 2, and 3.

	Study 1	Study 2	Study 3
BMI	✔	✔	✔
WC	✔		✔
BP	✔		
Aerobic Fitness	✔	✔	✔

2.3.1 BMI

Participants had their standing height and body mass measured using standard protocols while wearing lightweight clothing. Height was measured to the nearest 0.1 cm using a Harpenden Stadiometer. Body mass was measured to the nearest 0.1 kg using an Ancaster digital scale. Both measurements were taken twice and the average of the two was recorded. BMI was calculated according to body mass ÷ height^2, then converted into BMI Z-scores using sex-

and age-based data from the WHO Reference 2007 (World Health Organization, 2014).

2.3.2 WC

Participants had their WC measured according to the NIH protocol, which recommends using the top of the iliac crest as the measurement site. Measurements were recorded in triplicate and averaged. WC measurements were classified based on sex- and age-based percentiles derived by Fernandez et al. (2004) from NHANES III reference data (Fernandez et al., 2004).

2.3.3 BP

Participants' seated SBP and DBP were recorded after five minutes of seated rest with feet flat against the floor. BP was recorded in triplicate and averaged using a digital BP monitor (Ultraview SL2200, Spacelabs Healthcare, Snoqualmie, WA). Mean Arterial Pressure (MAP) was calculated based on the equation, $\left(\frac{1}{3}\times SBP\right)+\left(\frac{2}{3}\times DBP\right)$ (Razminia et al., 2004).

2.3.4 Aerobic Fitness

Aerobic fitness was assessed using the *McMaster All-Out Progressive Continuous Cycling Test* protocol for all three studies. The test was performed on a cycle ergometer (Corival, Lode, Groningen, Netherlands). The test began at a predetermined initial workload (i.e. resistance), which was increased every two

minutes throughout the test. Both the initial workload and the incremental workload increases were based on the participant's height. Participants were asked to cycle between 60 to 70 revolutions per minute until they could no longer cycle at this cadence, even with encouragement. At this point, the test was considered complete.

During the test, the participant's heart rate was recorded every minute using a heart rate monitor (FT1, Polar Electro, Kempele, Finland). VO_{2peak} was not directly measured because hypersensitive pharyngeal reflexes prevented some participants from keeping a mouthpiece in their mouth. As an alternative, absolute W_{peak} was measured for each participant then converted to absolute VO_{2peak}. The data that were used for this conversion is plotted in Appendix E, Figure A. VO_{2peak} and W_{peak} were positively correlated for both healthy children and children with chronic diseases (Healthy children: R^2_{male}=0.82, R^2_{female}=0.78; Children with chronic diseases: R^2_{male}=0.80, R^2_{female}=0.68). Given that the correlations for both groups were similar, converting W_{peak} to VO_{2peak} was deemed to be appropriate for survivors. Absolute W_{peak} was measured as the maximal power output of the participant at the moment the test finished. Absolute VO_{2peak} was compared to predicted absolute VO_{2peak} specific to each participant's height and sex using the following equation: Measured VO_{2peak} ÷ Predicted VO_{2peak}. Predicted values were derived from a population of healthy children. Using the actual and predicted data, % predicted VO_{2peak} was calculated. For

example, 100% indicated that the participant reached the predicted VO_{2peak} and anything less indicated that they had a lower VO_{2peak} than expected.

2.4 CUT-OFF THRESHOLDS FOR DETERMINING BIOMARKERS OF UNFAVOURABLE CARDIOVASCULAR HEALTH

2.4.1 BMI

Based on WHO Reference 2007 data, a Z-score >+2 SD is considered obese (World Health Organization, 2014). Therefore, any participant with a BMI Z-score>+2 SD was classified as obese.

2.4.2 WC

The cut-off threshold used to classify WC was the 90^{th} percentile of the NHANES III reference data (Fernandez et al., 2004). Any participant with a WC≥90^{th} percentile was considered to have excess central adiposity.

2.4.3 Aerobic Fitness

Based on the data provided by Adegboye et al. (2011), any participant that had a %predicted VO_{2Peak}<85% was considered to have low aerobic fitness (Adegboye et al., 2011). Because the original data of Adegboye et al. (2011) included age- and sex-specific values, an additional comparison using only these groups was conducted. Six participants were excluded from the age- and sex-specific classification because their ages were not captured in the age ranges provided by Adegboye et al. (2011).

2.5 ANALYSES

2.5.1 Objective 1

For objective 1, BMI, WC, and aerobic fitness data that were recorded for each participant at Study 1 initial visits were pooled with data from Studies 2 and 3. Based on the specific cut-off values for each biomarker measurement (BMI>+2 SD, WC≥90th percentile, and aerobic fitness<85% predicted), participants were grouped accordingly. For each biomarker, the number of participants meeting the cut-off was divided by the total number of participants to calculate the proportions.

Using a non-parametric binomial test with test proportion of 0.117 (SPSS Inc., Version 20.0, Chicago, IL), the proportion of survivors with a BMI>+2 SDs was compared to the Canadian pediatric population who fit the same BMI classification. The data on the Canadian pediatric population were collected by the Canadian Health Measures Survey (CHMS) between 2009 and 2011 for youth between 5 and 17 years of age (Roberts, Shields, de Groh, Aziz, & Gilbert, 2012). Similarly, a non-parametric binomial test with test proportion of 0.176 (SPSS Inc., Version 20.0, Chicago, IL) was used to compare the proportion of PBT survivors with a WC≥90th percentile to the proportion of American children with the same WC classification. The American data were published by Li et al. (2006) and are based on data from the National Health and Nutrition Examination Survey (NHANES) conducted between 1999 and 2004 (Li, Ford, Mokdad, &

Cook, 2006). Unfortunately, the proportion of survivors with an aerobic fitness<85% predicted could not be compared to any other populations, as these data do not currently exist. For both tests, significance was set at $p<0.05$. All values are expressed as a proportion with 95% confidence intervals.

Medical information for all 32 participants was collected from their medical charts at the respective hospitals, then tabularized. Medication history was not available for all participants. The parent-reported medication history was only available for the five participants in Study 1 at the McMaster University site.

2.5.2 Objective 2

To analyze the effects of the exercise intervention, participants were organized into an intervention (n=5) and a control (n=2) group. All participants who received the exercise intervention were included in the intervention group (n=5). These findings were compared to the control group (n=2), which was composed of the participants who were wait-list controlled before starting the intervention. Inferential statistical tests were not completed to determine whether a significant change occurred from pre- to post-exercise for the control or intervention groups. The reasoning behind this decision is that the control group had too few participants to perform a inferential statistics. Instead, the Cohen's d effect size was calculated for the pre- to post-exercise change in BMI, WC, BP, and aerobic fitness (Cohen, 1988). However, the literature shows that Cohen's d tends to be positively biased when calculating effect sizes for small samples

(Durlak, 2009). To adjust for this bias, Cohen's d was calculated using the formula $d = \frac{Mean_{Post-Exercise} - Mean_{Pre-Exercise}}{SD_{Pooled}}$ and was bias corrected by multiplying d by $\left(\frac{N-3}{N-2.25}\right) \times \sqrt{\frac{N-2}{N}}$ where N is equal to the total sample size (Durlak, 2009; McGrath & Meyer, 2006). The effect size was then interpreted as small (d=0.2), medium (d=0.5), or large (d=0.8) (Cohen, 1988).

The training effect was calculated as the difference between the control effect size and intervention effect size. The rationale for this calculation is that the effect size measures the size of change observed in the control group, which could have been due to non-training factors such as learning or growth. On the other hand, effect sizes for the intervention group could have been due to both non-training factors and training factors. Therefore, the difference in effect sizes provides an indication of the training effect. All values are expressed as mean±SD.

The medical history for these participants was retrieved from their hospital medical charts and tabularized. As previously mentioned, information on medication history was only available through parent report for the five participants from McMaster University.

Given the novel nature of the exercise intervention, additional information pertaining to feasibility and implementation of the program are provided. To

assess feasibility, the following information was studied: recruitment, compliance, retention, exercise session structure, and child and parent perceptions.

2.5.3 Sample Size and Power

For objective 1, a sample of convenience was used to generate the sample size based on participants from Studies 1, 2, and 3. For objective 2 however, a sample size was determined based on a calculation performed by Dr. Timmons and Dr. Mabbott using *G*Power: Statistical Power Analysis*. Due to a lack of available research on PBT survivors, pilot testing was conducted by Dr. Timmons to identify the number of participants necessary to detect changes in aerobic fitness due to exercise. Based on the pilot findings, PBT survivors averaged an aerobic fitness of only 75% predicted. To observe a 20% increase in aerobic fitness, the Dawson-Saunders & Trapp equation estimated that a total of 40 participants would be required to compare the control (n=20) and intervention (n=20) groups with a power of 0.80. The sample size calculation based on aerobic fitness was used as a reference to observe a change in the measured cardiovascular biomarkers, since there were no data on the effects of exercise training on BMI, WC, or BP in PBT survivors.

CHAPTER 3: RESULTS

3.1 OBJECTIVE 1

Objective 1: To measure the proportion of PBT survivors with values of BMI, WC, and aerobic fitness meeting the cut-offs associated with unfavourable cardiovascular health.

Note: Data for the first objective were collected from Studies 1, 2 and 3. These data were pooled for a total of 32 participants.

3.1.1 Participants' Characteristics

The medical histories for each participant from Studies 1, 2, and 3 are listed in Table 6. Table 7 displays the characteristics for the group of participants in Studies 1, 2, and 3.

Table 6. Participants' medical history.

Patient	Hospital	Age	Gender	Age at diagnosis (years)	Age at treatment completion (years)	Time since treatment completion (years)	Tumour type	Treatment		
								Surgery	Chemotherapy	Radiation
1	MCH	12.2	F	7.1	7.3	4.9	Medulloblastoma	✔	✔	✔
2	MCH	15.6	F	7.0	10.6	5.0	Non-Germ cell tumour		✔	✔
3	MCH	17.9	F	12.1	11.2	6.7	Germ cell tumour		✔	✔
4	MCH	6.5	M	3.6	4.3	2.2	Medulloblastoma	✔	✔	✔
5	MCH	11.9	M	5.3	10.8	1.1	Medulloblastoma	✔	✔	✔
6	MCH	12.9	M	9.2	10.4	2.5	Medulloblastoma		✔	✔
7	MCH	14.7	M	8.9	11.7	3.0	Medulloblastoma	✔	✔	
8	MCH	16.7	M	5.0	10.4	6.3	Low grade glioma	✔	✔	
9	MCH	16.9	M	8.5	12.9	4.0	Germ cell tumour	✔	✔	✔
10	MCH	17.3	M	8.2	8.4	8.9	Sarcoma	✔	✔	✔
11	MCH	17.8	M	11.7	16.3	1.5	Germ cell tumour		✔	✔
12	SK	7.4	F	N/A	3.7	3.7	Pineoblastoma	✔	✔	✔
13	SK	7.7	F	3.0	4.9	2.8	Medulloblastoma	✔	✔	✔
14	SK	8.0	F	5.8	6.1	1.9	Ependymoma		✔	✔
15	SK	8.4	F	6.2	6.3	2.1	Ependymoma	✔	✔	✔
16	SK	9.7	F	N/A	7.8	1.9	Medulloblastoma	✔	✔	✔
17	SK	10.8	F	7.0	7.1	3.7	Medulloblastoma	✔	✔	✔
18	SK	11.8	F	10.7	10.8	1.0	Medulloblastoma	✔	✔	✔
19	SK	16.8	F	6.4	6.6	10.2	Medulloblastoma	✔	✔	✔

Patient	Hospital	Age	Gender	Age at diagnosis (years)	Age at treatment completion (years)	Time since treatment completion (years)	Tumour type	Treatment		
								Surgery	Chemotherapy	Radiation
20	SK	9.0	M	4.6	5.3	3.7	Medulloblastoma	✔	✔	✔
21	SK	9.7	M	8.1	8.3	1.4	Medulloblastoma	✔	✔	✔
22	SK	10.2	M	5.8	5.8	4.4	Medulloblastoma	✔	✔	✔
23	SK	10.2	M	7.8	8.5	1.7	Medulloblastoma	✔	✔	✔
24	SK	10.3	M	3.3	3.7	6.6	Ependymoma	✔	✔	✔
25	SK	10.4	M	N/A	9.4	1.0	Medulloblastoma	✔	✔	✔
26	SK	10.8	M	4.8	5.0	6.0	Medulloblastoma	✔	✔	✔
27	SK	11.2	M	N/A	2.8	8.4	Ependymoma	✔	✔	✔
28	SK	11.3	M	N/A	5.5	5.8	Medulloblastoma	✔	✔	✔
29	SK	12.3	M	N/A	4.1	8.2	Medulloblastoma	✔	✔	✔
30	SK	15.6	M	N/A	5.5	10.1	Medulloblastoma	✔	✔	✔
31	SK	15.9	M	7.4	8.3	7.6	Medulloblastoma	✔	✔	✔
32	SK	16.3	M	N/A	9.8	6.5	High grade glioma	✔	✔	✔

Table 7. Participants' characteristics for each study.

	Study 1	Study 2	Study 3	Total
Sample	8	6	18	32
Gender				
Male	5	5	11	21
Female	3	1	7	11
Age (years)	12.7±3.6	14.3±4.4	11.5±2.9	12.3±3.4
Height (cm)	141.3±16.9	150.7±24.1	142.0±15.2	144.7±5.2
Body mass (kg)	54.1±36.4	50.1±16.8	39.4±13.4	47.9±7.6
Age at diagnosis (years)	6.4±2.4	7.8±3.7	7.0±1.6	7.0±2.5
Age at treatment completion (years)	7.9±3.2	10.8±3.8	6.7±2.2	7.8±3.1
Time since treatment completion (years)	4.8±2.1	3.5±2.4	4.8±3.2	4.5±2.8
Tumour type				
Ependymoma	1	0	3	3
Germ cell tumour	1	2	0	2
High grade glioma	0	0	1	1
Low grade glioma	0	1	0	2
Medulloblastoma	4	3	13	18
Non germ cell tumour	1	0	0	1
Pineoblastoma	0	0	1	1
Sarcoma	1	0	0	1

3.1.2 The Proportion of PBT Survivors with Biomarkers of Unfavourable Cardiovascular Health

Based on a sample of 32 participants from this study, 19% had biomarker values meeting the respective cut-off indicating favourable cardiovascular health, while 81% had at least one biomarker value meeting the respective cut-off indicating unfavourable cardiovascular health.

The proportions of PBT survivors who have a BMI>+2 SD, WC≥90th percentile, and aerobic fitness <85% predicted are displayed in Tables 8, 9, and 10 respectively. Table 8 reports the comparison between the proportion of survivors and Canadian youth with a BMI>+2 SD and Table 9 compares the proportion of survivors and American youth with a WC≥90th percentile. The additional analysis of age- and sex-specific fitness cut-offs is reported in Table 14, Appendix F. Of the 24 participants who were analyzed, 100% were below the respective age- and sex-specific cut-offs identifying low aerobic fitness.

The proportion of survivors with BMI>+2 SD is not different from the proportion of Canadian youth (p=0.159) (Table 8). There was no difference in the proportion of survivors and the proportion of American youth between 2 and 19 years of age who fell into a WC percentile beyond this cut-off (p=0.092).

Table 8. The proportion of PBT survivors aged 6 to 17 years and the Canadian youth aged 5 to 17 years with BMI>+2 SD according to WHO 2007.

	PBT Survivors (n=32)	Canadian Pediatric Population (n=2,213)	P value
BMI>+2 SD	15.6%	11.7%	0.159
95% Confidence Interval	6.2% to 31.4%	9.9% to 13.7%	

Source: (World Health Organization, 2014)

Table 9. The proportion of PBT survivors aged 6 to 17 and American youth aged 2 to 19 who have a WC≥90th percentile.

	PBT Survivors (n=13)	American Pediatric Population (n=68,817)	P value
WC≥90th Percentile	30.7%	17.6%	0.092
95% Confidence Interval	12.4% to 58.0%	17.3% to 17.9%	

Source: (Fernandez et al., 2004)

Table 10. The proportion of PBT survivors aged 6 to 17 who have an aerobic fitness <85% predicted.

	PBT Survivors (n=30)
Aerobic Fitness <85% Predicted	86.7%
95% Confidence Interval	69.7% to 95.3%

3.2 OBJECTIVE 2

Objective 2: To observe the effects of 12 weeks of group and in-home exercise training on the BMI, WC, BP, and aerobic fitness of PBT survivors and describe the feasibility of an exercise training program for this population.

Note: Data for the second objective were collected at the McMaster site of Study 1 and includes five participants.

3.2.1 Participants' Characteristics

The participants' medical histories and a list of parent reported medications are included in Table 11. These medications were all started prior to enrollment into the study. All parents reported that their child was consistent with his/her medication and did not change the dose throughout the duration of the study. The control and intervention groups are characterized in Table 12.

Table 11. Participants' medical history.

Participant	Control	Intervention	Age (years)	Gender	Age at diagnosis (years)	Age at treatment (years)	Time since treatment (years)	Tumour Type	Parent Reported Medication
1	✔	✔	12.2	F	7.1	7.3	4.8	Medulloblastoma	Fluoxetine Concerta Saizen
2		✔	12.9	M	9.2	10.4	2.5	Medulloblastoma	None
3		✔	15.6	F	7.0	10.6	5.0	Non-Germ cell tumour	Humatrope Desmopressin Cortef Bromocriptine Aviane Synthroid
4		✔	16.9	M	8.5	12.9	4.0	Germ cell tumour	None
5	✔	✔	17.3	M	8.2	8.4	8.9	Sarcoma	Vitamin D

Table 12. Participants' characteristics for the control and intervention groups at baseline.

	Control (n=2)	Intervention (n=5)
Age (years)	14.8±3.6	15.0±2.3
Gender		
Male	1	3
Female	1	2
Height (cm)	145.3±6.1	150.7±13.8
Body mass (kg)	45.1±4.3	69.3±39.0
Age at diagnosis (years)	7.7±0.8	8.0±0.9
Age at treatment completion (years)	7.9±0.8	9.9±2.2
Time since treatment completion (years)	6.9±2.9	5.0±2.4
Tumor type		
Germ cell tumour	0	1
Medulloblastoma	1	2
Non germ cell tumour	0	1
Sarcoma	1	1

3.2.2 Exercise and BMI, WC, BP, and Aerobic Fitness

Pre- and post-exercise values for BMI, WC, BP, and aerobic fitness are listed in Table 13 with the respective percent change, effect size, and treatment effect.

3.2.3 Feasibility

The feasibility of the exercise program was assessed through quantifiable variables including the number of participants recruited, compliance, and retention. As previously stated, 5% of patients assessed for eligibility (15/302) met the inclusion criteria for the study. Of these eligible patients, 33% (5/15) were

enrolled in the study. In terms of participants' compliance with the exercise program, a mean of 88% (21/24) of group and in-home sessions were completed. Retention was maintained as all participants completed the study and none were lost to follow-up.

Table 13. The changes in BMI, WC, BP and aerobic fitness following a 12-week exercise program.

	Control Group (n=2)				Intervention Group (n=5)				Training Effect
	Pre-Exercise	Post-Exercise	% Change	Effect Size	Pre-Exercise	Post-Exercise	% Change	Effect Size	
BMI (kg/m^2)	22±4	23±4	+5%	0.12	30±13	28±11	-7%	0.09	-0.03
WC (cm)	74.4±4.4	78.2±3.0	+5%	0.41	92.3±24.9	91.2±23.2	-1.2%	0.04	-0.37
MAP (mmHg)	76±1	77±1	+1%	0.46	78±2	86±5	+10%	1.56	+1.10
Relative VO_{2peak} (mL O_2/kg/min)	25.5±1.3	27.3±3.7	+7.1%	0.26	21.1±6.7	22.0±5.9	+4.3%	0.11	-0.15

CHAPTER 4: DISCUSSION

With the latest medical advancements, the number of children surviving brain tumours has increased. As a result, there has been greater interest in the sequela that may develop in these survivors after they have been treated. However, little research has been devoted to the cardiovascular health of these brain tumour survivors during childhood. Instead, most literature has focused on children who survived other cancers or PBTs assessed as adults. The goal of this thesis was to reduce this void in the literature by providing insight on the biomarkers of cardiovascular health of PBT survivors while they are still in childhood. It is important to study cardiovascular health during this time as poor health has been found to persist into adulthood. To address this gap, the primary objective of this thesis was to study a sample of brain tumour survivors during childhood and determine the proportion of these survivors with unfavourable cardiovascular health based on biomarkers including BMI, WC, and aerobic fitness. The second objective was to determine the effects and feasibility of a 12-week exercise program on the BMI, WC, BP, and aerobic fitness of these children. The following discussion is formatted to address each objective separately.

4.1 OBJECTIVE 1

This thesis is the first to examine the proportion of PBT survivors between 6 and 17 years of age who have a BMI, WC, or aerobic fitness measurement

associated with poor cardiovascular health. Based on the findings, the conclusion is that the majority of survivors have at least one cardiovascular biomarker associated with poor cardiovascular health.

4.1.1 BMI

According to BMI measurements taken in this thesis, the proportion of participants who were obese (BMI>+2 SDs) (WHO Reference, 2007) was 15.6%. Previous work by Hansen et al. (2014), Schulte et al. (2010), and Lek et al. (2010) examined the BMI of childhood brain tumour survivors. Lek et al. (2010) reported the highest proportion of obese survivors at 43% (n=46), followed by Hansen et al. (2014) at 29% (n=48), and Schulte et al. (2010) at 18.5% (n=54). Evidently, the findings of this thesis are in line with those of Schulte et al. (2010), but considerably lower than those of both Lek et al. (2010) and Hansen et al. (2014).

It is possible that the differences in proportion are a result of the varying tumour types captured in the samples of each study. For instance, Hansen et al. (2014) (n=48; age at diagnosis=8.3 years; years since treatment=5.6) and Lek et al. (2010) (n=46; age at diagnosis=7.5 years; years since treatment=3.9) included survivors of all brain tumour types, whereas Schulte et al. (2010) (n=54; age at diagnosis=7.4 years; years since treatment=6.4) excluded survivors of craniopharyngiomas. For the purpose of this thesis, craniopharyngioma survivors were included, but none of the participants had been diagnosed with this type of

tumour. This type of brain tumour is distinctive because of its proximity to the hypothalamic-pituitary axis. Tumours in this region, and the surgery or radiation used to treat them, can damage the axis, resulting in endocrine issues, such as growth hormone deficiency, hypothyroidism, and reduced levels of leptin and ghrelin (Harz, Muller, Waldeck, Pudel, & Roth, 2003). In fact, the majority of pediatric survivors with a tumour located in this area develop these issues, all of which contribute to the development and progression of obesity (Elowe-Gruau et al., 2013; Hansen et al., 2014; Harz et al., 2003). For this reason, obesity is more likely to develop in survivors of craniopharyngiomas than in survivors of any other type of brain tumour. However, although the development of endocrine issues and onset of obesity is most common in survivors of craniopharyngiomas, survivors of other tumour types may also experience similar issues if the axis is damaged by the tumour or during treatment (Lustig et al., 2003).

The age at diagnosis and number of years since treatment can also have an effect on the proportion of children who are obese. Survivors who are diagnosed with a tumour at younger ages tend to have higher BMIs than those diagnosed at older ages (Lustig et al., 2003). The length of time since treatment is also positively correlated to BMI. The age at diagnosis and number of years since treatment are relatively similar among the three studies and this thesis (age at diagnosis=7.0 years; years since treatment=4.5). For this reason, these two factors are unlikely to explain the difference in the proportion of obese survivors between the studies by Hansen et al. (2014), Lek et al. (2010), and this thesis.

Based on the findings from this thesis, there was no significant difference between the proportion of obese survivors (15.6%) and obese Canadian youth (11.7%) (p=0.159) (Roberts et al., 2012). One reason for this may be the absence of craniopharyngioma survivors in the sample of this thesis, as one would expect the proportion to be higher if there were participants with this diagnosis. Lastly, a significant difference between the groups was likely not detected due to the small sample size of the survivors.

4.1.2 WC

This thesis is the first to measure and report the proportion of PBT survivors with a WC≥90th percentile according to NHANES III data (Fernandez et al., 2004). For this reason, there are limited data with which to compare the findings of this thesis. Only one study was discovered in which the WC was measured for Korean children who survived childhood cancer (n=98, age at diagnosis=5.9 years; years since treatment=3.9; 32.7% brain tumour) (Sohn et al., 2011). Of these children, 13.3% had a WC≥90th percentile, which is lower than the 30.7% of brain tumour survivors in the current thesis. The higher proportion in this thesis is likely a reflection of the small sample size (n=13) used to calculate the proportion.

Unlike BMI, WC measurements for the brain tumour survivors could not be compared to those of Canadian youth because the WC measurements from the CHMS were analyzed by Roberts et al. (2012) using a different protocol than that

used for this thesis. Roberts et al. (2012) identified youth as abdominally obese using absolute cut-off values that only included children between 12 and 17 years of age (Roberts et al., 2012). For this thesis, a cut-off based on WC≥90th percentile was used, as this cut-off included children between 2 and 19 years of age, which covered the entire age range of participants in this thesis (Fernandez et al., 2004). The lack of a universally accepted WC cut-off makes it difficult to compare data between studies that have not used the same measurement protocols. Although the WC findings could not be compared to the Canadian population, WC measurements of American youth were available that used the same protocol as this thesis (Li et al., 2006). Li et al. (2006) used WC measurements recorded in the NHANES (1999-2004) for 68,814 youth to calculate the proportion of youth with a WC≥90th percentile (Li et al., 2006). After comparing the proportions of PBT survivors to the American youth who had a WC≥90th percentile, a significant difference was not detected between the two. This may be due to the limited sample of survivors who had WC measured. As a result, this is likely a poor reflection of the actual population of PBT survivors.

4.1.3 Aerobic Fitness

The findings from this thesis show that 86.7% (26/30) of PBT survivors have an aerobic fitness that is less than 85% predicted VO_{2peak} cut-off value was derived from findings by Adegboye et al. (2011). When only the age- and sex-specific absolute cut-off values were considered, 100% (24/24) of those participants fell below the cut-offs (Appendix E). Evidently, a higher proportion of

participants were classified as having low aerobic fitness based on the absolute cut-off. Although these proportions differ, the difference does not fundamentally change the findings in this thesis, as the majority (defined as >50% of participants) still has at least one identified cardiovascular biomarker indicating unfavourable health regardless of whether relative or absolute cut-offs are used. For comparison purposes, aerobic fitness, measured as % predicted VO_{2peak}, was analyzed for various pediatric chronic disease populations studied in the CHEMP laboratory (CHEMP, 2014). These chronic diseases included Crohn's disease, cystic fibrosis, juvenile idiopathic arthritis, and type 1 diabetes. Using the 85% predicted VO_{2peak} cut-off, the proportion of children in each disease group with aerobic fitness below this level was calculated. Among these groups, the proportions of children who had % predicted VO_{2peak} below 85% ranged from 24% to 67% (CHEMP, 2014). In comparison, a greater proportion of PBT survivors were below this cut-off.

It is unclear why this difference in aerobic fitness exists between children with chronic diseases and survivors of PBTs. As a result of cranial radiation, survivors of posterior fossa tumours often suffer with late neurological effects such as balance problems and cranial nerve palsies (Wolfe et al., 2012). Although all of the participants in this thesis were able to complete the cycle ergometer exercise test, these neurological late effects may hinder their participation in daily exercise, leading to decreased physical activity levels and lower aerobic fitness. Compared to healthy peers, PBT survivors tend to be less

physically active. It is suggested that these survivors are sedentary during treatment due to increased fatigue, pain, and malaise. This sedentary behaviour often progresses post-treatment, manifesting itself in low exercise rates and poor aerobic fitness (Wolfe et al., 2012). Furthermore, survivors often report a lack of energy, feeling lethargic, difficulty with falling sleep, a lack of concentration, and shortness of breath post-treatment (Macartney, Harrison, VanDenKerkhof, Stacey, & McCarthy, 2014). However, though it is likely due to sequela from the tumour and treatment, the reason behind such reduced aerobic fitness among PBT survivors still requires further research.

4.2 OBJECTIVE 2

Prior to this thesis, the literature primarily focused on the effects of exercise on pediatric cancer survivors as a whole, or specific types of cancer, excluding brain tumours. This thesis addresses a gap in the literature, as this is the first study to investigate the effects of exercise training on biomarkers of cardiovascular health in survivors of a childhood brain tumour.

After completing the exercise training program, the intervention group did not experience significant changes in BMI, WC, or relative VO_{2peak} from pre- to post-training. In addition, very low effect sizes were observed for these three outcomes. Negative values for the training effects for these outcomes indicate that greater effect sizes were observed for the control group than for the intervention group. From this, it can be implied that the exercise intervention did

not provide sufficient stimulus to promote a positive training effect. In the fourth outcome, BP, a large effect size and a positive training effect value were calculated. The following subsections will discuss these findings in detail.

4.2.1 Exercise and BMI

Although the BMI results from this thesis are not in alignment with the hypothesis, these findings are similar to those found in previous works by Takken et al. (2009) and Collett et al. (2007). Both studies found no significant changes in BMI following a 12-week exercise program for pediatric acute lymphoblastic leukemia survivors and pediatric cancer survivors, respectively. The exercise intervention conducted by Takken et al. (2009) was similar to the one used in this thesis. Each week, participants completed two 45-minute exercise sessions per week at a local physiotherapist's clinic and two in-home sessions (Takken et al., 2009). Takken et al. (2009) suggested that the lack of change was due to the timing of the intervention during the summer months when children are on vacation and physical activity tends to decrease (Takken et al., 2009). However, this justification does not apply to the results observed in this thesis, as this exercise program was conducted during the autumn months. A more appropriate explanation for these findings is that the sample size was too small to observe a significant change.

4.2.2 Exercise and WC

Similar reasoning can be used to explain the lack of a change in the participants' WC. Given that this thesis was the first to study the effects of an exercise intervention on WC in the pediatric cancer survivor population, there is no previous pediatric cancer literature with which to compare these findings. In this thesis, the assessment of WC may not have been sensitive enough to detect changes in body fat distribution. In the future, other valid methods to assess body fat distribution such as computed X-ray tomography, magnetic resonance imaging, and dual-energy x-ray absorptiometry could be used (Bosch et al., 2014).

4.2.3 Exercise and BP

Based on the data in Table 11, the intervention had an effect on BP. This finding implies that the exercise intervention was able to stimulate a change in BP, though in this case, it was elevated rather than lowered. This contradicts the existing literature on the effects of exercise on BP in healthy children and adolescents. This literature was reviewed in a meta-analysis by Kelley et al. (2003) in which no evidence was found to support an increase in BP following exercise programs lasting eight weeks or longer (Kelley, Kelley, & Tran, 2003). Unfortunately, as was the case with WC, there are no pediatric cancer-related studies with which to compare these findings.

4.2.4 Exercise and Aerobic Fitness

Although there was a very low effect size and no change in the relative VO_{2peak} for the intervention group, these findings are similar to those found by Takken et al. (2009). Takken et al. (2009) did not observe changes in the aerobic fitness of pediatric acute lymphoblastic leukemia survivors following 12 weeks of exercise (Takken et al., 2009). This lack of change may have been due to the participants' poor adherence to the exercise program. Many participants became bored and did not complete the exercise sessions. However, this is not a possible explanation for the lack of change in the current thesis, as participants were quite compliant, attending 88% of exercise sessions.

In contrast to this thesis and the work by Takken et al. (2009), other literature has reported increases in aerobic fitness for children treated with chemotherapy for acute lymphoblastic leukemia and other childhood cancers following exercise (San Juan et al., 2007; Sharkey et al., 1993; Shore & Shepard, 1999). San Juan et al. (2007) reported a significant increase in aerobic fitness following an exercise intervention. Unlike this thesis, San Juan et al. (2007) studied only children who were actively receiving chemotherapy for acute lymphoblastic leukemia during the exercise intervention. Seven children were enrolled with a mean age of 5.1 years and completed a 16-week exercise program consisted of supervised sessions, three times weekly that lasted 90 to 120 minutes (San Juan et al., 2007). Given the longer exercise intervention, this may explain the increase observed in aerobic fitness. Moreover, it has been

suggested that the aerobic fitness increases could be due to natural recovery from the chemotherapy received by the participants (Takken et al., 2009). Overall, there is some inconsistency between findings from this thesis and the other studies (San Juan et al., 2007; Sharkey et al., 1993), but this is likely given the differences in cancer type, sample size, study compliance, and intervention duration.

4.2.5 Feasibility

Although the exercise program had a sample size that was underpowered and the exercise exposure may not have been sufficiently stimulating to observe a training effect, there were many positive attributes to the program. Despite the fact that questionnaires were not used as a method of assessing the feasibility of this exercise intervention, it is believed that the positive attributes of the study support the intervention's feasibility.

4.2.5.1 Participant Recruitment

Prior to conducting this thesis, a sample size calculation was performed using data recorded from pilot testing by Dr. Timmons. It was determined that a total of 40 participants would be required to compare the control (n=20) and intervention (n=20) groups with a power of 0.80. Unfortunately, only 5 participants completed the study, resulting in low statistical power. Therefore, there is clearly a mismatch between the number of participants required and the number of participants available at the McMaster site.

4.2.5.2 Compliance and Retention

Firstly, the participants and their parents or guardians were extremely compliant with the group and in-home exercise training sessions. All participants completed the entire exercise program without any dropouts, and no participants were lost to follow-up. As previously mentioned, participants completed 88% of both sessions, on average. This high compliance rate is likely due to each participant's satisfaction with the program. The creation of a high-energy environment likely helped foster motivation, engagement, and encouragement during the group sessions. This motivation may have carried over to the in-home sessions, resulting in a high compliance with in-home sessions as well. In a previous exercise intervention by Takken et al. (2009), researchers experienced a lack of motivation in the children, as they became bored with the exercises. Fortunately, participants in this study appeared to enjoy the group format, as there was a lot of social interaction with one another, the volunteers, and the personal trainers. This interaction allowed everyone to foster new friendships and develop a sense of camaraderie within the entire team. At each group session, kinesiology students worked with the participants on a one-to-one basis, along with two personal trainers. The kinesiology students encouraged and monitored each participant to ensure that they were performing the exercises safely with proper technique. Safety was a high priority throughout the entire program, and as a result, there were no injuries and no negative side effects for the participants. Overall, the ability to maintain participant compliance and retention

in this pilot work provides support for the feasibility of conducting future exercise programs of this nature with PBT survivors.

4.2.5.3 Exercise Session Structure

Another limitation of the study by Takken et al. (2009) was that participants became less satisfied and engaged with the exercises, resulting in a lower willingness to exercise. Taking this information into consideration, exercise for this thesis was in the format of relays, group activities, and games that required teamwork, instead of using typical health club equipment such as cycle ergometers and resistance training machines. This format seemed to reduce the monotony of exercising for the children so they were more excited to participate. It was especially suitable that the exercise program was delivered during the autumn months as the sessions were spent both outdoors and indoors. Periods of circuit training were also incorporated into each session that allowed the participants to perform individual exercises and learn exercise techniques to target specific muscle groups. Overall, a balance of games, activities, and individual exercises performed both indoors and outside was successfully achieved, while ensuring the participants were having fun and remaining compliant with the program.

Another successful aspect of the intervention was the incorporation of the in-home training sessions. These sessions were included in the study to reduce the commute and time commitment for participants and their families. Although

volunteers and personal trainers did not attend these visits, parents and siblings were often involved with the in-home sessions. Having this family support was motivating for the participants and helped to reinforce their compliance with the program. As a whole, the in-home exercises appeared to be appropriate, as the participants did not have any concerns or complaints upon being questioned about their in-home training logs on a weekly basis.

4.2.5.4 Child and Parental Perceptions

Overall, there were many positive attributes of the exercise intervention that promote confidence in its feasibility. Though questionnaires were not used to measure participant and parent satisfaction at the end of the program, informal dialogue with the children led us to believe that they were highly satisfied. The participants, many of whom had not exercised prior to the program, enjoyed the activities and games that were incorporated into the sessions, even though it was considered exercise. They also expressed their satisfaction with the social aspect of the program, including meeting new friends and working together. Numerous parents stated that their children looked forward to the weekly sessions and expressed their gratitude for the positive changes they witnessed as a result of the exercise intervention. Participants' parents and teachers described the improvements that they witnessed not only in the children's physical abilities, but also in their mental well-being and self-esteem. This feedback provides further confidence in the viability of the exercise program.

4.3 STRENGTHS AND LIMITATIONS

Reflecting on the findings from this thesis work, there are several strengths and limitations that can be identified. Given that there was little to no focus on the cardiovascular health of brain tumour survivors during childhood in the current literature, the primary strength of this work is its novelty. This is the first study to examine the proportion of childhood survivors with biomarkers for unfavourable cardiovascular health other than BMI.

One of the major limitations in this thesis was the participant enrollment and sample size. A limited sample size is likely a poor representation of the population of PBT survivors. This makes it difficult to draw conclusions from the findings with confidence. Moreover, a small sample size creates weakness in the approach used for the comparisons in Table 8 and 9, as it is difficult to compare the small sample of survivors to the large Canadian and American samples. There is an increased risk of committing a type one error if the small sample misrepresents the survivor population, and a difference is detected between survivors and the Canadian or American samples. Based on sample size calculations, increasing the sample size to at least 81 survivors may improve this weakness. Participant recruitment was difficult for Study 1 at MCH because participants were recruited for data collection for both objectives 1 and 2. If the patients were recruited for objective 1 alone, presumably the recruitment would have improved, as participants would only have to complete a single visit. However, given that Study 1 included a pilot exercise program, patients and their

families were less willing to participate. Many families expressed interest in the study, but could not commit due to involvement in extra-curricular activities or the commute and time requirements of the group exercise sessions. The commute was anticipated to be a limitation of the study based on previous literature. For this reason, the frequency of group training sessions was minimized and in-home sessions were incorporated. In the future, the implementation of a strategy to expand recruitment and the sample size would be beneficial.

A second limitation was potential bias in the recruitment. Although a prescreen was conducted for Study 1, some patients may have been overlooked due to non-medical reasons despite meeting the inclusion criteria. A comprehensive prescreen of all the patients in the clinic was not conducted for Study 2; instead, recruitment was done over a certain time period during clinic visits. For this reason, children who did not have scheduled visits in that time period did not have an equal opportunity to be recruited. In addition, the stringency of the inclusion criteria may have been another source of recruitment bias for this thesis. The inclusion criteria was initially determined by the principal investigators of Study 1, Dr. Timmons and Dr. Mabbott, with the overall goal of the study being to understand the effects of exercise training on neurocognition recovery in PBT survivors treated with cranial radiation. As a result, a bias was created in this thesis, as all included survivors must have received cranial radiation. Moreover, a bias was created by including only survivors who were diagnosed with a brain tumour less than 10 years ago. Once again, this criteria

was determined prior to the initiation of this thesis, but there is no evidence to suggest that survivors diagnosed more than 10 years ago not be included. Overall, these recruitment biases can influence the interpretation of the results in this thesis, as the sample likely does not truly represent the population of PBT survivors. For this reason, it becomes more difficult to make conclusions regarding the cardiovascular health status of PBT survivors.

A third limitation to this thesis was the lack of access to participants' medical histories. When studying a clinical population that is characteristically heterogeneous and conducting a training intervention, it is key to have an understanding of the participants' medical background that may influence the biomarkers or act as a confounding variable. For example, radiation dosage, chemotherapy agents, and medications can all have an influence on cardiovascular biomarkers such as BMI and BP in PBT survivor (Lustig et al., 2003). BMI specifically appears to be positively correlated with the dose of radiation received during treatment (Lustig et al., 2003). Similarly, radiation exposure and chemotherapy agents have both been associated with elevated BP in PBT survivors. Cisplatin, a chemotherapy agent often administered to children with brain tumours, decreases the glomerular filtration rate in the kidney thereby causing BP to increase (Pietila et al., 2009). Medications such as corticosteroids and vasopressin analogues can also increase BP and body mass through water retention (Miesbach et al., 2010). Furthermore, survivors with health issues such as endocrine impairments often require pharmaceutical therapies such as growth

hormone or thyroid hormone replacement, both of which can impact the measured biomarkers. Children who are on growth hormone therapy have lower BMI and WC due to growth hormone-stimulated lipolysis, whereas children with growth hormone deficiency tend to have elevated BMI and WC, as low levels of growth hormone have been found to increase the storage of adipose tissue (Shalitin et al., 2011). Likewise, some PBT survivors may develop hypothyroidism, which can often lead to weight gain if left untreated (Manuela et al., 2014). Because all of these factors can have a significant impact on the measured biomarkers, access to participants' medical histories is vital to fully understand how much of their poor cardiovascular health can be attributed to these factors. Due to the lack of medical information available for this thesis, these factors could not be accounted for in the analysis and therefore, results may be misinterpreted. Without accounting for medical differences and the heterogeneity of the sample, general conclusions are made that might not be a reflection of the entire PBT survivor population.

A fourth limitation of this thesis was the informal measures used to assess the feasibility of the training intervention. Originally, this thesis was not designed to assess the feasibility of a training intervention for PBT survivors, but this developed into a secondary objective. The informal measures used act as a limitation as it was difficult to quantifiably assess feasibility and draw conclusions based on this information. In the future, scaled child and parent questionnaires should be included to quantify and understand participant enjoyment, motivation,

and discomfort of training and the difficulty of the training intervention. This information is important to consider when determining if a training program is feasible. Additionally, focus groups can be used to capture more detailed personal opinions from all participants.

4.4 FUTURE DIRECTIONS

This thesis adds knowledge to an area of research that has received little attention in the current literature. However, further research on the subject of cardiovascular health in PBT survivors is warranted, as the examination of the proportion of PBT survivors with biomarkers of cardiovascular health requires a larger sample size than the sample used in this thesis. A larger, less biased sample size will provide a basis on which to make a more definitive conclusion on the cardiovascular health of PBT survivors. Based on sample size calculations, at least 81 PBT survivors should be recruited in the future. This would achieve a power of 80% when comparing PBT survivors to reference populations. As previously calculated, a sample size of 50 participants would be sufficient to achieve a power of 80% for objective 2. One method may include recruiting survivors from other children's hospitals with neuro-oncology outpatient clinics. In addition, having multiple exercise programs may increase the sample size for objective 2. With respect to the exercise intervention, it is important to accommodate the participants and their families by locating the group sessions closer to them. One possibility is to have multiple group exercise sessions located in neighbouring cities close to Hamilton. This method has been

successfully adopted by Dr. Mabbott and his team at SK as they have multiple training sites across the Greater Toronto Area. However, this option is only possible if the necessary financial resources and personnel are available. Presumably, this would help to increase the enrollment rate and sample size. Furthermore, recruitment bias may be reduced by performing a more comprehensive prescreen of eligible patients. Sending a recruitment mail-out to all eligible patients may provide more equal recruitment opportunity. Moreover, it may be interesting to collect serological biomarkers of cardiovascular health such as glucose, insulin, C-reactive protein, lipids, and cytokines, provided blood samples can be obtained from all participants.

4.5 CONCLUSION

The primary aim of this thesis was to develop an understanding of the proportion of pediatric brain tumour survivors treated with craniospinal radiation with biomarkers of poor cardiovascular health. In summary, it was discovered that the majority of survivors in this thesis have at least one identified biomarker. In particular, the majority of survivors had aerobic fitness levels below the identified cut-off value. It was also noted that the proportion of survivors with a BMI≥2 SDs or WC≥90th percentile is no different from that of Canadian and American youth.

The secondary aim of this thesis was to complete pilot work on the effects of exercise on BMI, WC, BP and aerobic fitness. Findings show that a 12-week group and in-home exercise program was unable to stimulate a training effect in

BMI, WC, or aerobic fitness. Regardless of these outcomes, a major strength of this exercise program was its feasibility.

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APPENDIX A: GROUP TRAINING SESSION SAMPLE

Week 5 agility- October 22-24
Equipment needed- newspapers, agility ladders, hurdles hoops

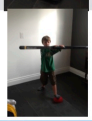
- A) Warmup
- 3 mins-general movements- newspaper race- 2 newspaper sheets per player- each player must race to turning point and back stepping only on newspaper- step on one lay down another repeat
- B) Dynamic ROM
- -2 mins- knees upx10- squats, lungesx8, arm rotationx8, torso twists
- C) Skill development- agility
- Show difference between candence, pace, slow slow quick, quick quick slow. All different planes side to side coronal, frontal and sagitall
- D)Game- 8-10 minutes
- Newspaper race- running with newspaper on front beat your time
- E) CIRCUIT- 15 minutes
- agility ladders, hurdles, hoops
- F) Game-5 minutes
- Clear your yard with newspaper snowballs
- G) Core work- 3-5 mins
- H) cool down and stretches - all major muscle groups!
- I) high fives and goodbyes

APPENDIX B: IN-HOME TRAINING SESSION SAMPLE

WEEK 5-6- Power- exercise
Homework
try to complete 2-3x a week

Exercise	Reps	Sets	Notes
Jump squats	8x	2-3x	Start in a squat position and jump into pencil/ straight then return to squat
Jumping jacks	10x	2-3x	Add some claps!!!
Push-ups	8-10x	2-3x	Hands wider than the mat
Knee drives	8x	2-3x	Stand on left foot and repeat lay lift right knee fast and high for 8 reps then switch sides
Step lunge	10x	2-3x	Place one foot on step and do a lunge watching your knee at 90 degrees!
Wall squats	30 sec-50 sec	4	Hold belly button in- legs like a sitting on a stool-90 degrees

APPENDIX C: CIRCUIT TRAINING SAMPLE

Exercise	Reps	Sets	Notes/ form
Bosu step ups	30 seconds 	1	Increase intensity by jumping up on Bosu *progress 2-change direction - Side squats *progress 2-knees up higher
Stability ball balance	30 seconds	1	Sitting on ball- alternating leg lift *progress 1-varying arm positions to decrease stability progress 2- increase speed
Wobble board with theraband	30 seconds 	1	Balance on board- pull band to sternum * progress 1-start with 1 foot on board one foot on floor for stability * progress 2- to both feet on board
Body blade with lunge	10 each leg forward 	1	Start with right foot balance trainer start blade moving-Hold * progress 1- tadding dynamic movement - performing a lunge *progress 2- moving blade through the different planes

Exercise	Reps	Sets	Notes/form
Plank station	Building up to hold 30 seconds 	1	Should not feel in back. If need to modify go to knees *progress 1-playing elbows on Bosu or wobble board * progress 2- adding dynamic leg raises
Jumping jacks with tubing	10x	1	Trying to reach tubing as high as can with each jump
Rotation row	30 seconds	1	Keep elbow close * progress1-adding isometric/ dynamic squat *progress 2- standing on Bosu or wobble board when performing the rowing action
Cardio station Mountain climbers	15 seconds 	2	May modify by using bench or chair * progress 1-place hands on floor * progress 2-placing hands on Bosu or balance trainers
	Variation- add a move where have to meet in centre after every station		

APPENDIX D: LOG-BOOK SAMPLE

FitKids Week 6: FUNctional Exercise Log Book

Date: Nov. 3rd 2013			Start Time: 4:53 pm			End Time: 5:24 pm	
Exercise	**Set 1**		**Set 2**		**Set 3**	**Set 4**	**Set 5**
Jumping Squats	8 Reps		8 Reps		8 Reps		
Jumping Jacks	10 Reps		10 Reps		10 Reps		
Push-Ups	10 Reps		10 Reps		10 Reps		
Knee Drives	16 Reps		16 Reps		16 Reps		
Step Lunge	10 Reps		10 Reps		10 Reps		
Wall Squats	30 Seconds		30 Seconds		30 Seconds	30 Seconds	

APPENDIX E: VO_{2PEAK} VS. W_{PEAK} FOR HEALTHY AND CHRONIC DISEASE CHILDREN

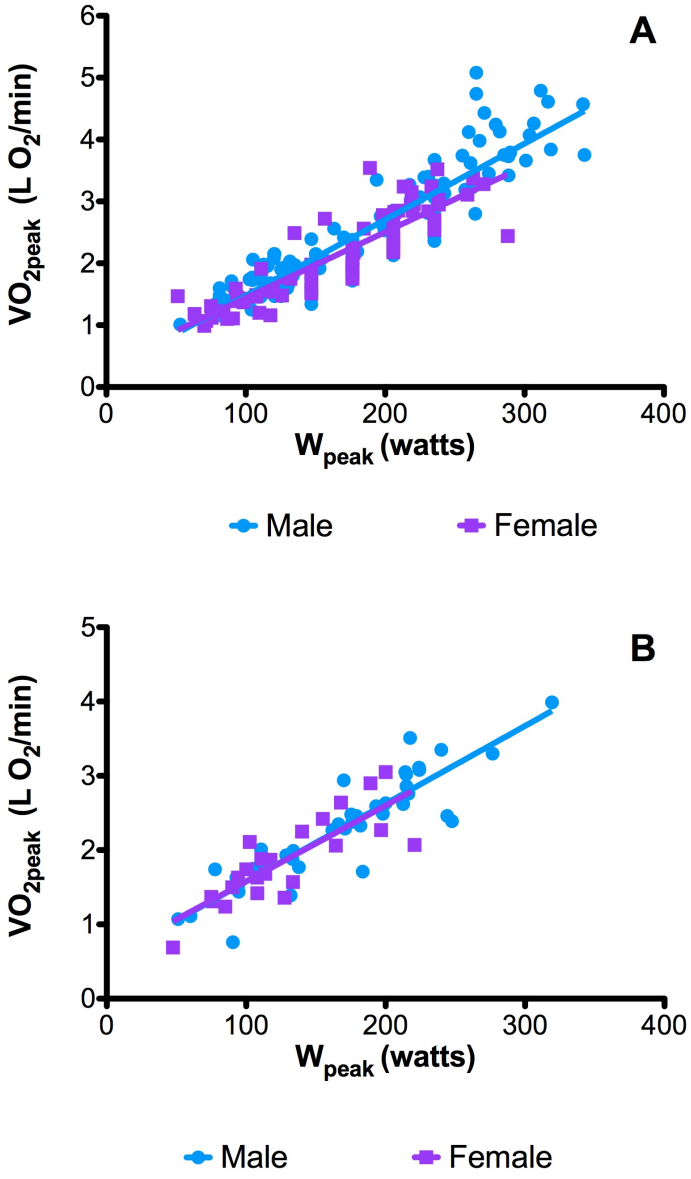


Figure 3. VO_{2peak} vs. W_{peak} for healthy children (A) and children with chronic diseases (B).

APPENDIX F: PBT SURVIVORS WITH LOW AEROBIC FITNESS

Table 14. The proportion of PBT survivors aged 8 to 11 and 14 to 17 who have low aerobic fitness according to age- and sex-specific cut-offs derived by Adegboye et al. (2011).

	PBT Survivors (n=24)
Aerobic Fitness below cut-off	100%
95% Confidence Interval	83.7% to 100.0%