TRI-PONDERAL MASS INDEX AS A MEASURE OF ADIPOSITY IN SURVIVORS OF CHILDHOOD BRAIN TUMORS

TRI-PONDERAL MASS INDEX AS A MEASURE OF ADIPOSITY IN SURVIVORS OF CHILDHOOD BRAIN TUMORS

By E. DANIELLE SIMS, H.B.Sc.

A Thesis Submitted to the School of Graduate Studies in Partial Fulfilment of the Requirements for the Degree Master of Science

Descriptive Note

MASTER OF SCIENCE (2019)

(Medical Sciences)

Department of Pediatrics

McMaster University, Hamilton, Ontario

TITLE: Tri-ponderal mass index as a measure of adiposity in survivors of childhood brain tumors

AUTHOR: E. Danielle Sims, H.B.Sc. (University of Toronto)

SUPERVISOR: Dr. M. Constantine Samaan

NUMBER OF PAGES: xi, 59

LAY ABSTRACT

Over the last thirty years, childhood cancer survival rates have greatly improved. However, these rates decrease over the lifespan of survivors. Certain groups within the survivors of childhood cancer population, including survivors of childhood brain tumors (SCBT), are at a higher risk of obesity, heart disease and type 2 diabetes. Excess body fat is a major contributor to the development of these adverse health outcomes in the general population and may represent an entry point to prevent and treat these conditions in SCBT. However, measuring fat mass in the clinical setting requires specialized equipment that can be expensive, time-consuming and not readily available in all settings. Therefore, this thesis aims to explore measures of fat mass that are both feasible and reliable in a clinical setting in SCBT compared to the general pediatric population. We have identified the tri-ponderal mass index (TMI), defined as weight divided by height cubed (kg/m^3) as a valid measure of the fat mass in both SCBT and healthy children. We conclude that TMI may serve as a reliable and feasible measure of adiposity in both SCBT and healthy children in clinical settings and assist in the early identification of survivors at risk of obesity and cardiometabolic outcomes to prioritize early interventions to improve outcomes.

ABSTRACT

Introduction: Survivors of childhood brain tumors (SCBT) are an emerging group of cancer survivors that has an increased risk of cardiovascular disease, stroke, and type 2 diabetes. SCBT have equivalent obesity rates but excess fat mass (adiposity) when compared to the general population. As adiposity is an important and potentially modifiable risk factor for cardiometabolic outcomes in the general population, its measurement may allow for early stratification of adverse health outcomes in SCBT so that they can be targeted with prevention and treatment strategies designed to improve outcomes.

However, measuring adiposity often requires specialized equipment that is not always readily available, and a clinical measure is needed to facilitate these measurements in a feasible fashion. Tri-ponderal Mass Index (TMI; kg/m^3) is a superior measure of adiposity compared to Body Mass Index (BMI) z-score in healthy children. However, it has not been assessed in SCBT. The aim of this thesis was to validate TMI as an adiposity measure in SCBT compared to non-cancer controls.

Methods: A cross-sectional analysis was completed from a cohort study sample including 44 SCBT (n=20 female) and 137 (n=64 female) healthy controls between 5-17 years of age. Total adiposity was determined by fat mass percentage (%FM) using bioelectrical impedance analysis and central adiposity was assessed by waist-to-hip (WHR) and waist-to-height (WHtR) ratios.

Results: TMI demonstrated equally strong correlations with total adiposity and stronger association with WHtR compared to BMI z-score in SCBT and healthy control children. **Conclusions:** TMI may serve as a reliable and feasible clinical measure of adiposity in both SCBT and healthy children. The availability of TMI may allow for early stratification of survivors at risk of excess adiposity to allow early targeting with interventions to improve health outcomes.

ACKNOWLEDGEMENTS

I would like to thank the children and their families who participated in this study and made this research possible. I would also like to thank my supervisor, Dr. M. Constantine Samaan, and committee members, Drs. Adam Fleming, Carol Portwine and Lehana Thabane for all of their support and input. Furthermore, I thank Kuan-Wen Wang for her mentorship and training and the collaborators of this study who have assisted with participant recruitment, including Drs. Sarah Burrow, Donna Johnston and Shayna Zelcer. I would also like to thank JoAnn Duckworth, Andrea Woodard and the rest of the clinical staff for their continuous support and assistance with recruitment. In addition, I would like to thank all of the undergraduate students who helped with study logistics.

Lastly, I would like to thank the Canadian Institutes of Health Research (CIHR) Canadian Graduate Scholarship-Masters for the financial support for the second year of my Masters.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

ALL – acute lymphoblastic leukemia

BIA – bioelectrical impedance analysis

BMI – body mass index

CanDECIDE – Canadian Study of Determinants of Endometabolic Health in ChIlDrEn

CNS – central nervous system

DXA – dual-energy X-ray absorptiometry

HDL – high-density lipoprotein

SCBT – survivors of childhood brain tumors

SCC – survivors of childhood cancer

SDS – standard deviation score

TMI – tri-ponderal mass index

WHR – waist-to-hip ratio

WHtR – waist-to-height ratio

DECLARATION OF ACADEMIC ACHIEVEMENT

The contributions of authors for the scholarly publication are described in the Chapter 3. E. Danielle Sims is the first author of the published paper and defined the research questions, design, collected data, performed analyses and interpreted the results with the support of the supervisor, committee members, and co-authors of the manuscript emanating from this thesis work.

CHAPTER 1: INTRODUCTION

Incidence of Childhood Cancer

While cancer is less common in children compared to adults, childhood cancer can greatly impact long term health outcomes, including both physical and mental health[1], in this population. The worldwide age-standardized incidence rates of cancer (using the world standard population) in adult males and females are 218.6 and 182.6 per 100,000 person-years, respectively[2], compared to only 163.2 and 143.6 per million person-years in boys and girls, respectively, 0-19 years of age[3].

However, the incidence of cancer in children and adolescents has increased on average by 0.6% per year since 1975[4,5]. During this time period, the overall incidence of cancer in children and adolescents 0-19 years of age has increased by approximately 33.7%[5]. Furthermore, the highest incidences of childhood cancer are seen in children 0-4 years of age at 197.1 per million person-years and 15-19 years of age at 185.3 per million person-years, with a higher incidence in males (163.2 per million person-years) compared to females (143.6 per million person-years)[3].

The two most common cancers in children 0-14 years of age are Acute Lymphoblastic Leukemia (ALL) accounting for 26% and brain and central nervous system (CNS) tumors accounting for 21% of childhood cancer diagnoses, [6]. This growing population will require special consideration throughout treatment as well as post-therapy

in order to mitigate the long term health effects evident in survivors of childhood cancer (SCC).

Survival in Childhood Cancer

While the incidence of childhood cancer has progressively increased over the last four decades, mortality rates have declined at a faster rate[5]. The mortality rate of children diagnosed with cancer has decreased by 2.7% on average annually between 1975-1998 and 2.4% between 2002-2010[5], with an overall reduction in mortality rates of 66% between 1970-2014[4].

Short-term survival rates

Similarly, short-term survival rates in SCC have seen a significant improvement in recent years as cancer management techniques have evolved, with the 5-year survival rate of all childhood cancers rising from only 58% to 83% over the last 30 years[5]. However, these rates vary within certain groups of the SCC population. In the survivors of childhood brain tumors (SCBT) group, the 5-year survival rate has only increased to 75% from 57% in the mid 1970s[5].

As the 5-year survival rate rises, SCC represent an emerging population that requires close surveillance to manage the development of late effects and improve longevity in this population.

Long-term survival rates

While long-term (15-year) survival rates have also greatly improved from 54% to 74% over the last three decades[5], these survival rates remain lower than that of the short-term 5-year survival rate in SCC. Specifically, in brain and CNS tumors, the 15-year survival rate drops to 66%[6].

With the decline in survival rates throughout the lifespan of SCC, identifying the underlying causes of death in this population are crucial to prevent early mortality.

Comorbidities in SCC

SCC are at a higher risk of developing future adverse effects that may compromise long-term survival rates in this population[7]. Particularly, SCC face an increased risk of developing obesity[8,9] and cardiometabolic disorders including hypertension[10], fasting hyperinsulinemia[8], dyslipidemia with low high-density lipoprotein (HDL) cholesterol[8,10], diabetes mellitus[10,11], stroke[12] and cardiovascular disease[13].

Geenen et al. reported approximately 75% of SCC develop one or more adverse events and nearly 25% have five or more events[7]. Of the SCC who experienced at least one event, 48.6% have psychosocial/cognitive problems, 40.6% orthopedic disorders, 24.8% neurologic disorders, 23.8% endocrine disorders, 17.2% cardiovascular events and 9.9% metabolic events[7].

In addition, nearly 37% of SCC develop at least one severe or disabling or life-threatening disorder; with 24% experiencing a severe event and almost 13% undergoing a disabling or life threatening event[7]. Adverse events were graded in accordance with the Common Terminology Criteria for Adverse Events version 3.0 (CTCAEv3.0) developed through the US National Cancer Institute[7,14,15]. Examples of life-threatening or disabling events include BMI >40kg/m^2, acute myocardial infarction, stroke, hypothyroidism resulting in thyroid storm and hypertension resulting in hypertensive crisis[7,14,15].

Furthermore, approximately 3.2% of SCC will pass as a result of an adverse event within a median follow-up of 17 years[7]. Of these, the common adverse events that were severe, life-threatening or disabling or caused death included 14.2% orthopedic disorders, 11.9% second tumors, 9.4% obesity and 5.3% resulting from endocrine disorders[7].

Furthermore, a similar study that also included a sibling control group for comparison[16] demonstrated that only 62% of SCC reported having one or more chronic health conditions, slightly lower than the 75% reported by Geenen et al.[7], in comparison to only 37% in the sibling control group[16].

Within the SCC group, SCBT have a higher risk of hypothyroidism[17], growth hormone deficiency[17], cardiovascular conditions[17,18] and stroke[12] compared to controls. For instance, SCBT have a 29-fold higher relative risk for stroke[12] and 14.3 for hypothyroidism, 277.8 for growth hormone deficiency and 24.7 for osteoporosis[19] compared to non-cancer controls.

The development of comorbidities, such as endocrine, nutritional, respiratory and circulatory diseases, in the SCC population contributes to early mortality[7,20]. Mortality in SCC is attributed to 58% from recurrence or progression of primary cancer, 34.7% from nonexternal causes and 7.3%% from external causes[20]. Nonexternal causes included, but are not limited to, 18.5% due to subsequent neoplasm, 6.9% due to diseases of the circulatory system (including ischemic heart disease, cardiomyopathy, heart failure, cerebrovascular diseases and other cardiac diseases), 2.6% due to diseases of the respiratory system, 1.1% due to diseases of the digestive system, and 0.6% due to endocrine, nutritional, metabolic diseases and immune disorders[20].

However, these proportions change throughout the lifespan of SCC, with nonexternal causes of death surpassing recurrence or progression of primary disease as the major cause of death by 15-19 years after diagnosis[20]. Relatively early post diagnosis (5-9 years), the mortality rate (deaths/1,000 person-years) due to recurrence is 9.9 compared to only 2.0 in due to nonexternal causes, whereas 15-19 years after diagnosis the mortality rate due to recurrence drops to only 1.5 and rises to 2.5 for nonexternal causes[20]. By 30-34 years after diagnosis, the mortality rate due to recurrence further drops to 0.5 and for nonexternal causes rises to 10.1; including 4.6 from second neoplasms, 1.4 from cardiac diseases, 0.9 due to pulmonary and 3.2 due to other nonexternal causes[20].

As SCC advance past the 5-year survival mark and enter into long term survival, nonexternal causes of death exceed that of recurrence and are becoming an increasingly

important topic in cancer survivorship research. SCBT are one such group that is vulnerable to many of these future health conditions and will require close monitoring during and post-therapy. Therefore, developing strategies to prevent the onset of future adverse effects in SCBT may assist in reducing early mortality rates and improving long term survival. It is therefore critical to identify and target potentially modifiable risk factors for the development of these comorbidities to minimize the impact on health-related quality of life in SCBT.

Risk factors for Comorbidities

Risk factors include characteristics, conditions or exposures that increase an individual's risk of developing a disease or outcome and include both non-modifiable and modifiable risk factors. While non-modifiable risk factors such as age, sex, race/ethnicity or family history assist in identifying and targeting individuals who are at an increased risk of developing a particular health condition, these factors cannot be altered.

Important non-modifiable risk factors for cardiometabolic outcomes in the general population include the above factors. For example, advancing age is associated with cardiovascular disease[21] and stroke[22,23]. Furthermore, family history is an important risk factor for metabolic syndrome[24], diabetes[25], cardiovascular disease[26] and stroke[27,28]. Non-modifiable risk factors may be a potential screening tool for early stratification of patients at risk, however these factors cannot be changed to reduce future risks of these outcomes.

In contrast, modifiable risk factors provide an entry point to initiate prevention strategies and alleviate future adverse health outcomes. One potentially modifiable risk factor for the development of cardiometabolic disorders in the general population is obesity, and specifically excess adiposity[29-37].

Overweight is defined as having a body mass index (BMI) ≥25.0 and <30.0 kg/m^2 in adults[38] and a BMI percentile ≥85th percentile and <95th percentile[39,40] in children, and obesity as a BMI ≥30.0 kg/m^2 in adults[38] and ≥95th percentile in children[39,40]. In the general population, non-modifiable factors that may increase the risk for obesity include racial and ethnic differences[41], parental obesity[42-45], an early adiposity rebound during childhood[42,46] and a higher birth weight[47,48]. Potentially modifiable risk factors for obesity include physical inactivity[49], increased screen time[50,51], dietary patterns[52,53] and reduced sleep[54].

Behavioural risk factors such as diet and physical activity play a critical role in the development of obesity and cardiometabolic disorders. For example, fast-food consumption is positively associated with both weight gain and insulin resistance [55], whereas increased intake of fruit and vegetables can decrease the risk of cardiovascular disease[56]. Furthermore, reduced physical activity is a risk factor for obesity[49], coronary heart disease[57], diabetes[58] and stroke[59]. Similarly, improvements in physical activity is associated with a reduction in the risk of type 2 diabetes[60,61] and cardiovascular events[62].

Obesity is associated with additional health complications including dyslipidemia[30] and hypertension[31,32]. Furthermore, obesity, characterized by excess adiposity, is an important risk factor for metabolic syndrome[33], diabetes[34,35], cardiovascular disease[36] and stroke[36,37] in the general population. Reductions in BMI standard deviation score (SDS) have been shown to reduce cardiometabolic risk, with greater reductions resulting in better improvements[63]. Since SCC, and particularly SCBT, are vulnerable to both obesity[8,9] and its associated cardiometabolic outcomes[8,10-13], preventing and managing excess adiposity in SCBT may improve longevity and future health-related quality of life in this population.

Excess adiposity is a potentially modifiable risk factor for the development of cardiometabolic disorders in the general population and may be an important risk factor in the SCBT population. Targeting excess adiposity, as well as behavioural risk factors including diet and physical activity, may allow for early prevention strategies to be deployed in SCBT and reduce the risk of future adverse health effects in this population.

Obesity and Adiposity in SCC

Since excess adiposity is an important cardiometabolic risk factor in the general population, it may be able to be used in a similar fashion in SCC to identify patients at risk. Certain groups within the SCC population are vulnerable to becoming obese post

diagnosis and treatment. Managing and preventing obesity in these groups may assist in mitigating future adverse health effects.

However, SCBT have similar BMI compared to non-cancer controls, yet reportedly higher adiposity[64-68]. These results suggest excess adiposity may play a critical role in the development of the cardiometabolic disorders that are evident in SCBT, and that monitoring adiposity, rather than BMI, may be of greater value in this population. In the general population, it has been found that measures of adiposity may be superior compared to BMI to assess risk for cardiometabolic outcomes[69], and this is likely to also be the case in SCBT.

Specifically, the treatment that SCBT undergo may contribute to the development of adiposity and impact long term health outcomes. Hypothalamic damage is thought to be the main cause for obesity in SCBT, and may result from treatments including surgery and radiation, or the tumor itself[70]. Damage to the hypothalamus can result in hyperphagia, hyperinsulinemia and weight gain[70-72]. Furthermore, SCBT treated with a combination of surgery, radiation and chemotherapy have a relative risk of 3.0 for stroke and 3.6 for thrombi compared to those treated with only surgery and radiation, and those treated with surgery alone have the lowest risk (0.6 for stroke and 0.7 for thrombi compared to those treated with surgery and radiation)[19].

Furthermore, physical performance and ability may be impacted in SCC following diagnosis and treatment and may contribute to the development of excess adiposity. SCC have lower physical activity and strength compared to sibling controls[73,74]. In addition, SCC are more likely to face performance limitations and restricted participation in routine activities, with SCBT facing the highest risk[75]. Furthermore, CRT is associated with inactivity in SCC[74]. SCBT in particular have reportedly lower grip strength, knee extension strength and peak oxygen uptake compared to healthy controls[76]. Since physical inactivity is an important risk factor for obesity and cardiometabolic outcomes, the reduced physical activity in SCC may be one contributor to their increased risk of future adverse events.

Certain groups within the SCC population, including SCBT, are more adipose and physically inactive compared to healthy controls. Both excess adiposity and physical inactivity are potentially modifiable risk factors for cardiometabolic outcomes in the general population. Managing the development of adiposity and improving physical activity in SCC may offer an entry point for prevention strategies to be initiated to reduce the risk of cardiometabolic disorders in this population.

Obesity Prevention and Management Strategies

In the general population, various obesity management strategies have been implemented[77-82]. Several studies have demonstrated improvements in weight and

adiposity outcomes as well as cardiovascular risk factors[77-82], however whether these same improvements are seen with similar interventions in the SCC population is unclear. As previously stated, certain groups within the SCC population face an increased risk of obesity and cardiometabolic outcomes and require special consideration for obesity management strategies due to treatment-related adverse effects. For example, SCBT are susceptible to hypothalamic dysfunction due to radiation therapy[70] that can make managing obesity in this population a challenge. Furthermore, SCBT encounter various physical challenges, including obesity, sensory loss, muscle weakness, poor exercise tolerance and inability to live independently, due to treatment and late effects[75,76] that may pose limitations to the design, type and frequency of an obesity intervention in this population. Therefore, obesity management strategies in SCBT, as well as SCC in general, must be tailored to the patients' needs.

Obesity Interventions in SCBT

In SCBT, Wang et al. conducted a systematic review summarizing the existing lifestyle interventions, pharmacotherapy and bariatric surgery obesity treatment strategies in SCBT[83]. Two lifestyle-based interventions were identified, six pharmacotherapy studies and three studies assessing bariatric surgery in SCBT[83]. Overall, the existing evidence base on obesity management strategies in SCBT was determined to be of low quality with only some studies demonstrating effective results but with the small sample sizes and short follow-up duration, none were recommended [83]. Wang et al. concluded that further

studies with sufficient sample size and long-term follow-up are urgently needed[83]. Future studies are needed to create interventions to treat and prevent cardiometabolic disorders in this population.

Adiposity Measurement Tools

Excess adiposity is an important risk factor for cardiometabolic outcomes, including cardiovascular disease and type 2 diabetes[29,84,85]. However, regular measurements of adiposity in the clinical setting can be both time consuming and require specialized equipment.

While Dual-energy X-ray absorptiometry (DXA) scans are the gold standard for measuring adiposity[86,87], it may not be feasible for routine use in clinical practice as it requires specialized equipment that can be expensive and may not be readily available in all settings[88]. Therefore, BMI, weight over height squared (kg/m^2), is commonly used as an alternate measure of adiposity. BMI uses easily accessible routine clinical measurements; height and weight. However, BMI has limitations within certain populations. Particularly, BMI can misclassify obesity in children[89,90]. Tri-ponderal mass index (TMI), defined as weight over height cubed (kg/m^3), uses the same measurements as BMI, however is a more accurate predictor of adiposity, as measured by DXA, in healthy children compared to BMI and BMI z-score[91]. Therefore, TMI may also serve as

a feasible clinical measure of adiposity in SCBT. However, the validation of TMI as a measure of adiposity in SCBT is required.

Canadian Study of Determinants of Endometabolic Health in ChIlDrEn (CanDECIDE Study)

The Canadian Study of Determinants of Endometabolic Health in ChIlDrEn (CanDECIDE Study) is a prospective cohort study recruiting lean and obese cancer survivors including SCBT and healthy non-cancer controls[92]. The aim of this study is to identify the determinants of endometabolic health, including obesity and cardiometabolic outcomes, in children who survive cancer and compare them to the general pediatric population.

Published data from the CanDECIDE study show that SCBT have increased total and central adiposity, yet similar BMI compared to non-cancer controls[65]. Furthermore, while supratentorial tumors and radiotherapy were both associated with total adiposity in SCBT, lifestyle factors, including diet, physical activity, screen time and sleep duration were not[65].

These initial findings confirm adiposity as an important potential determinant of endometabolic health in SCBT and reveals that BMI may not be an adequate marker of adiposity in this population. A clinical measure of adiposity that is feasible and does not

require specialized equipment is urgently needed in this population to monitor adiposity and stratify patients who may be at an increased risk for cardiometabolic outcomes. The early prevention of these health outcomes may improve premature mortality due to nonexternal causes in SCBT.

Research Questions

This thesis project will address the following research question:

Does the tri-ponderal mass index associate with total and central adiposity in SCBT and non-cancer control children?

This research question will be addressed through the following aims:

Research Aims

1. Determine the correlation of TMI with total and central adiposity in SCBT and non-cancer control children.
2. Determine the determinants of TMI in SCBT and non-cancer control children.

Chapter 2 will outline clinical measures of total adiposity and their respective limitations. This chapter will introduce TMI as a potential clinical measure of adiposity in children. Chapter 3 will focus on the use of TMI as clinically feasible measure of adiposity in the SCBT population to address the research question through a cross-sectional analysis using the data collected in the CanDECIDE Study.

CHAPTER 2: CLINICAL MEASURES OF ADIPOSITY

Background

Survivors of childhood cancer are at an increased risk of excess adiposity[8,9,93,94] and its associated cardiometabolic outcomes[8,10-13]. To monitor adiposity in this population, a reliable and simple tool is required that can easily be used in clinical practice. A clinical measure of adiposity must be cost-effective, reliable, accurate and easy to implement for frequent use in clinical practice.

Dual-energy X-ray Absorptiometry (DXA)

Dual-energy X-ray Absorptiometry (DXA) is a bone densitometry scan that uses ionizing radiation[95]. It is a non-invasive method that can provide measurements of both total and regional body composition[96,97]. DXA can be used to evaluate bone mineral content and density as well as body, bone, muscle and fat mass. It is an accurate and reliable method[87,98] and maintains a low radiation exposure[99]. Furthermore, DXA is widely used for diagnosing osteoporosis and predicting fracture risk[100] and is used to determine adiposity[86,87,101]. Alternate measures of adiposity are often compared against DXA scans to test for validity and accuracy.

However, while DXA is an accurate and reliable measure of adiposity, it may not be practical for routine measures of adiposity in clinical practice. DXA requires specialized equipment that may not be readily available in different settings as well as in low-income

countries[102,103]. Furthermore, routine DXA scans may not be cost-effective with the equipment itself costing upwards of $100,000[104] and individual scans roughly between $80-$100[105]. DXA is not portable and slightly more time-consuming compared to anthropometry[106]. While the radiation exposure from DXA is relatively low, it is unsafe for use in pregnant women[99,107]. These limitations suggest DXA may not be suitable for routine use to monitor adiposity at every patient visit.

Bioelectrical Impedance Analysis (BIA)

Bioelectrical Impedance Analysis (BIA) is an alternate measure of adiposity that has been validated against DXA in both adults[108,109] and children[110,111]. BIA estimates total adiposity through measurement of the percentage of body fat. The main advantages of BIA compared to DXA is its portability, simplicity and low cost[112].

However, BIA is also limited in some respects. While BIA scales are less expensive, it still requires specialized equipment that is not routinely used or readily available in all settings. Furthermore, BIA may underestimate percent body fat in obese individuals and overestimate in lean individuals[109]. Similar to DXA, BIA can not be used in pregnant women[112,113] or in subjects with pacemakers[112,113]. Significant alterations in hydration status may result in a change to the resistance to the electrical current, and BIA may not be accurate in these circumstances[113,114].

Body Mass Index (BMI)

Unlike DXA and BIA, body mass index (BMI) is a measure of body fat that only relies on routine anthropometric measurements including height and weight and is defined as weight over height squared (kg/m^2). BMI is an affordable tool that can be determined using only routine clinical measurements. Furthermore, BMI has been validated[115] and is widely used to classify obesity in adults[38].

However, BMI changes do not always accurately reflect changes in adiposity[116]. Furthermore, BMI is limited in its ability to measure body fat within certain populations. For example, increased muscle mass can result in a higher BMI that may misclassify muscular individuals as overweight or obese[116,117]. Another such population is children and adolescents. While in adults weight scales over height to the power of two, in children it scales with height powers between 2.5-3.5[90,91,118-120]. Throughout puberty, children undergo growth and development changes that can result in higher values of BMI and consequently misclassify overweight and obese status[91,119,121,122].

Body Mass Index Z-score

Since weight and height changes with age throughout childhood[123], BMI z-score, which is adjusted for age and sex, is often used instead in children[124]. BMI z-scores are determined relative to an external reference[124] and can be converted to BMI-for-age percentiles[124].

BMI z-score relies on the same clinical measurements, height and weight, as BMI and also requires age and sex. The BMI-for-age growth charts are available in clinical settings[124].

While BMI z-score offers an age-adjusted measure suitable in the pediatric population, there are a few weaknesses. BMI z-score may be suitable for assessing adiposity in children, however it is not necessarily an optimal measure to determine changes in adiposity[125,126]. Furthermore, despite the relatively easy use of BMI z-score in clinical practice, BMI z-score requires up-to-date growth charts, however some clinical offices continue to use old growth charts[116,127].

Tri-ponderal Mass Index (TMI)

Tri-ponderal mass index (TMI) is an alternate measure of adiposity that uses the same measures as BMI, height and weight. However, TMI is defined as weight over height cubed (kg/m^3) and is a better estimator of adiposity compared to BMI z-score when validated against DXA scans in adolescents[91]. Similar to BMI, TMI only requires routine clinical measurements, is easy to calculate and affordable. However, in contrast, TMI offers sex-specific obesity classification points and is approximately constant throughout adolescence making it an age-independent measure of adiposity[91]. Furthermore, TMI tracks adiposity more reliably with higher fat mass[91].

However, TMI is only suitable for use in children and adolescents where weight scales over height powers between 2.5-3.5[90,91,118-120]. Following puberty, changes in body composition stabilize and weight scales over height to the power two[119,128]. Therefore, BMI correlates stronger with adiposity compared to TMI in adulthood[115].

While it has been shown that TMI is a better predictor of adiposity in comparison to BMI z-score and that weight/height^3 (TMI) has the optimal power to use in healthy adolescents, this has not yet been confirmed in SCC. Therefore, our aim was to determine the association of TMI with adiposity and the determinants of TMI in SCBT compared to non-cancer control children. This will be addressed in Chapter 3.

CHAPTER 3: TRI-PONDERAL MASS INDEX IN SURVIVORS OF CHILDHOOD BRAIN TUMORS: A CROSS SECTIONAL STUDY

Appendix 1 includes the published version of this paper.

Sims, E. Danielle, Kuan-Wen Wang, Adam Fleming, Donna L. Johnston, Shayna M. Zelcer, Shahrad Rod Rassekh, Sarah Burrow, Lehana Thabane, and M. Constantine Samaan. "Tri-ponderal mass index in survivors of childhood brain tumors: A cross-sectional study." *Scientific reports* 8, no. 1 (2018): 16336.

Tri-ponderal mass index in survivors of childhood brain tumors: A cross-sectional study

E. Danielle Sims[1,2], Kuan-Wen Wang[1,2], Adam Fleming[1,3], Donna L. Johnston[4], Shayna M. Zelcer[5], Shahrad Rod Rassekh[6], Sarah Burrow[7], Lehana Thabane[8,9,10,11] and M. Constantine Samaan[1,2,8*]

[1]Department of Pediatrics, McMaster University, Hamilton, Ontario, Canada

[2]Division of Pediatric Endocrinology, McMaster Children's Hospital, Hamilton, Ontario, Canada

[3]Division of Pediatric Hematology/Oncology, McMaster Children's Hospital, Hamilton, Ontario, Canada

[4]Division of Pediatric Hematology/Oncology, Children's Hospital of Eastern Ontario, Ottawa, Ontario, Canada

[5]Pediatric Hematology Oncology, Children's Hospital, London Health Sciences Center, London, Ontario, Canada

[6]Division of Pediatric Hematology/Oncology/BMT, Department of Pediatrics, British Columbia's Children's Hospital, Vancouver, BC, Canada

[7]Division of Orthopedic Surgery, Department of Surgery, McMaster University Medical Centre, Hamilton, Ontario, Canada

[8]Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Ontario, Canada

[9]Department of Anesthesia, McMaster University, Hamilton, Ontario, Canada

[10]Centre for Evaluation of Medicines, St. Joseph's Health Care, Hamilton, Ontario, Canada

[11]Biostatistics Unit, St Joseph's Healthcare-Hamilton, Hamilton, Ontario, Canada

***Corresponding Author:** Dr. M. Constantine Samaan

Department of Pediatrics,

McMaster University,

Division of Pediatric Endocrinology,

McMaster Children's Hospital,

1280 Main Street West, 3A-57,

Hamilton, Ontario L8S 4K1

Tel: 001-905-521-2100, ext. 75926

Fax: 001-905-3087548

E-mail: samaanc@mcmaster.ca

Abstract

Survivors of childhood brain tumors (SCBT) face a higher risk of cardiometabolic disorders and premature mortality compared to the general population. Excess adiposity is a known risk factor for these comorbidities. However, while SCBT have higher adiposity compared to healthy controls, measuring adiposity in clinical practice involves access to specialized equipment and may impact busy clinical services.

Tri-ponderal Mass Index (TMI; kg/m^3) may be a superior measure of adiposity in adolescents when compared to Body Mass Index (BMI; kg/m^2). However, its use in determining adiposity in SCBT has not been assessed. This study aims to validate TMI as a clinical measure of adiposity in SCBT.

This was a cross-sectional study including 44 SCBT (n=20 female) and 137 (n=64 female) non-cancer control children, 5-17 years of age. BMI and TMI were calculated from height and weight measurements. Fat mass percentage was assessed using bioelectrical impedance analysis and waist to hip and waist to height ratios were used to assess central adiposity. Regression analyses were adjusted for age, sex, puberty and treatment. TMI demonstrated strong correlations to measures of total and central adiposity and predicted adiposity in SCBT and non-cancer controls. TMI may serve as a reliable clinical measure of adiposity in both SCBT and healthy children.

Introduction

Obesity has contributed to the rise of cardiovascular diseases and type 2 diabetes, making them some of the most significant and costly healthcare challenges of the 21st century[129-134], accounting for an estimated 5% of deaths and two trillion dollars worldwide caused by obesity-driven cardiometabolic disorders[134]. One group that is especially impacted by these chronic diseases include childhood cancer survivors[10,16,135].Within this population, survivors of childhood brain tumors (SCBT) represent an emerging group that has been recently reported to develop stroke and type 2 diabetes at higher rates than those seen in the general population[11,12,19]. Obesity leads to increased cardiovascular mortality at a relatively young age in SCBT[6,11,136-144]. Excess adiposity, especially visceral adiposity, has been linked to cardiovascular disease and type 2 diabetes in the general population, and SCBT have more adiposity compared to healthy controls[29,64,84,85,145].

While adiposity is a potentially modifiable risk factor for cardiometabolic risk, measuring adiposity in clinical practice can be time consuming in the clinical setting, and requires the specialized equipment including bioelectrical impedance scales or Dual-energy X-ray Absorptiometry (DXA) scans [86-88]. The availability of feasible and reliable clinical measures of adiposity will circumvent these limitations and help prioritize SCBT for closer monitoring and targeting them in interventions in an attempt to improve outcomes.

The tri-ponderal mass index, defined as weight over height to the power of three (TMI, kg/m^3), is an alternate measure of adiposity in children based off of the Ponderal Index and Rohrer Index[91]. TMI is reported as a more accurate predictor of adiposity compared to Body Mass Index (BMI, kg/m^2) and BMI z-score when validated against DXA scans in adolescents[91]. An important advantage of TMI is that it uses the same height and weight measurements used to calculate BMI. Thus, TMI may offer a feasible clinical measure to assess adiposity. However, TMI has not been validated as a measure of adiposity in SCBT. Our aim is to validate TMI as a clinical measure of adiposity in SCBT and compare this group to non-cancer controls.

Methods

Participants:

Participants were consecutively recruited from McMaster Children's Hospital (Hamilton), Ontario, Canada from November 2012 to November 2017 to partake in the Canadian Study of Determinants of Endometabolic Health in Children (CanDECIDE study)[92,146]. Children between 5-17 years of age were included. Parental informed consent was obtained for participants less than 7 years of age, and parental consent and participant assent were obtained for those 7-15 years of age. Participants provided written informed consent if they were 16 years or older. This is a secondary analysis of the CanDECIDE cohort study data and this analysis has been approved by the Hamilton Integrated

Research Ethics Board. Study procedures were performed in accordance with the relevant guidelines and legal regulations.

Anthropometric and clinical measurements:

Standardized questionnaires were used to collect data on age, sex, puberty, and ethnicity[146,147]. Medical records were consulted to verify and collect data regarding tumor type, location, sidedness and treatment modalities for SCBT.

Anthropometric measurements included weight measured to the nearest 0.1 kg using an electronic weighing scale (Seca, USA) and height using a stadiometer measured to the nearest 0.1 cm. BMI (kg/m^2) and TMI (kg/m^3) were determined using height and weight measurements from all participants. BMI percentile was determined from the Children's BMI Tool for Schools[148] . BMI z-scores were determined from the Centers for Disease Control and Prevention (CDC) growth chart[149].

Fat mass percentage (%FM) was used to determine adiposity in the participants that was measured with the Tanita body fat monitor (Tanita Corporation, Illinois, USA)[65]. Furthermore, BMI z-scores were obtained from the Centers for Disease Control and Prevention (CDC) growth chart[149].

Statistical Analysis:

Statistical analyses were performed using PASW version 18 statistical package [150]. Data are presented as counts with percentages for categorical variables and means with standard deviation for continuous variables. Only participants with complete datasets were included. Box plots and visual inspection were used to identify any outliers for removal from the analysis. Normality of the data distribution was assessed using the Shapiro-Wilk test[151]. In the case that variables had non-normal distributions, data were log-transformed. Sample size was calculated using the method proposed by Norman and Streiner. We calculated that we need eight subjects per variable to detect significant differences between groups[152].

Spearman's correlations were used to assess the relationship between TMI, BMI z-score, %FM, WHR and WHtR. To assess this relationship adjusted for age, sex and puberty, we ran a Partial Correlations test. Multivariable linear regression analyses were performed to determine the association between TMI with BMI z-score and adiposity measures, %FM, WHR and WHtR in SCBT and controls. The dependent variable was set as %FM, WHtR, WHR or BMI z-score and the independent variables included TMI, age, sex, puberty and treatment. Results were reported as standardized β coefficients and associated p-values, with statistical significance set to alpha of 0.05. A model summary, including the adjusted R Square and the Standard Error of the Estimate, were also reported.

In order to validate that age and puberty differences did not affect the results, analyses were also repeated using an age- and sex-matched control group. Control participants were matched in terms of sex distribution to SCBT participants on a one-to-one ratio and age was matched to closest value, within three years of the SCBT participants.

Results

Population characteristics:

The characteristics of participants are reported in Table 1. We included 44 SCBT (n=20 female, 45.50%), and 137 non-cancer controls (n=64 female, 46.70%).

The SCBT and control groups had similar sex (p= 0.88) and ethnic distribution (Caucasian SCBT: n= 34 (77.30%); controls: n= 91 (66.40%), p= 0.18). SCBT were younger than the non-cancer controls (SCBT: 11.16±4.29; controls: 14.03±2.56, p<0.001), and fewer survivors were pubertal compared to controls (SCBT: n=23 (52.30%); controls: n=121 (88.30%), p<0.001). Survivors had lower weight (p< 0.001) and were shorter (p< 0.001) compared to controls.

In relation to body mass measures, we confirmed previous similar trends in both survivors and controls of BMI z-score (SCBT:0.57±0.94; controls: 0.45±1.12, p= 0.51) and BMI percentile (SCBT: 67.60±26.30 %; controls: 62.20±29.30 %, p= 0.33).

Adiposity levels were similar between groups including fat mass percentage (%FM; SCBT: 24.10±9.30 %; controls: 22.20±9.40%, p= 0.16) and waist-to-height ratio (WHtR) (SCBT: 0.46±0.06; controls: 0.45±0.07, p= 0.17). However, waist to hip ratio (WHR) was higher in SCBT when compared to non-cancer controls (SCBT: 0.87±0.07; controls: 0.82±0.07, p< 0.001).

Due to the age and pubertal staging differences noted, we validated the results of the analysis of the full cohort by performing a subgroup analysis that included age- and sex-matched controls. In the latter analysis age, sex, and puberty adjusted analyses revealed identical trends to those reported for the full study cohort. The data for the matched subgroup analyses are reported in Supplementary Tables S1-S3.

Tumor characteristics and treatments:

A summary of tumor characteristics and treatment methods are reported in Table 2.

The most common tumors in survivors were low-grade gliomas (n=29 (65.90%)). Brain tumors were equally localized to supratentorial and infratentorial regions. The most common treatments include surgery (n=29 (65.90%)), radiotherapy (n=13 (29.50%)) and chemotherapy (n=20 (45.50%)). Eight (18.20%) participants were being managed with a wait and see approach at the time of inclusion in the study.

The association of TMI with body mass and adiposity:

To assess if TMI correlates with body mass measures and adiposity, we used Spearman's correlation test. We conducted unadjusted and age, sex, and puberty-adjusted analyses (Table 3).

TMI levels were similar between the groups (SCBT: 14.12±2.54 kg/m^3; controls: 13.46±2.86 kg/m^3, p= 0.10). TMI correlated with BMI z-score in both groups (Unadjusted, SCBT: ρ= 0.87; p<0.001; controls: ρ= 0.95; p<0.001; Adjusted, SCBT: r= 0.86; p<0.001; controls: r= 0.94; p<0.001).

We next assessed whether TMI correlates with measures of adiposity. TMI correlated significantly with total adiposity (%FM) (Unadjusted, SCBT: ρ= 0.73; p<0.001; controls: ρ= 0.85; p<0.001; Adjusted, SCBT: r= 0.73; p<0.001; controls: r= 0.88; p<0.01). In addition, TMI correlated with measures of central adiposity, including WHR correlated with TMI (Unadjusted, SCBT: ρ= 0.56; p<0.001; controls: ρ= 0.38; p<0.001; Adjusted, SCBT: r= 0.44; p<0.01; controls: r=0.46; p<0.001) and WHtR correlated more strongly with TMI when compared to WHR (Unadjusted, SCBT: ρ= 0.69; p<0.001; controls: ρ= 0.83; p<0.001; Adjusted, SCBT: r= 0.82; p<0.001; controls: r= 0.87; p<0.001). There were similar correlations of TMI and BMI z-score with measures of central adiposity (Table 3). Taken together, the above data indicate that TMI is a stronger predictor of total adiposity than BMI z-score and is equivalent to BMI z-score in predicting central

adiposity. The correlation between TMI and BMI z-score tended to be stronger in non-cancer controls compared to SCBT.

To assess whether TMI is a predictor of body mass and adiposity in SCBT, multivariable linear regression analyses were conducted adjusting for age, sex and puberty. As radiotherapy was a significant predictor of %FM ($p = 0.002$) in SCBT, it was also adjusted for in the regression analyses.

We calculated unstandardized (B) and standardized (β) coefficients, and both trended in the same direction. Moving forward, we report on the latter coefficient (Table 4).

TMI was a strong predictor of BMI z-scores in both SCBT and controls, with a stronger trend in the latter (SCBT: $\beta = 0.867$; $p<0.001$; controls: $\beta = 0.935$; $p<0.001$). TMI was an equally strong predictor of total adiposity (%FM) in both SCBT and controls (SCBT: $\beta = 0.604$; $p<0.001$; controls: $\beta= 0.819$; $p<0.001$). While it had lower correlation with WHR, TMI was associated strongly with WHtR, and the strength of this association was higher in controls compared to SCBT (SCBT: $\beta= 0.793$; $p<0.001$; controls: $\beta= 0.880$; $p<0.001$).

The above threads of data indicate that TMI is a strong predictor of total adiposity and WHtR. The association between TMI and adiposity appears to be stronger in controls compared to SCBT for BMI z-score, %FM and WHtR.

Discussion

Survivors of childhood brain tumors are facing multiple comorbidities including cardiovascular disease and type 2 diabetes, which can impact their quality of life and lifespan[64,70,136-138,153-156]. The identification of potential markers of cardiometabolic risk may offer a path to stratify those in need of close observation and early intervention. In this study, we identified TMI as one such measure. TMI was an equally strong predictor as BMI z-score of total adiposity and WHtR, a stronger predictor of cardiometabolic risk compared to WHR[157-159]. As central adiposity is associated with adverse cardiometabolic outcomes[157-160], the latter finding is of great clinical significance, as it allows the stratification of children with higher central adiposity to a care stream with closer cardiometabolic health monitoring and early interventions.

TMI has been validated against DXA scan-measured adiposity in the general pediatric population [91]. Our data adds to the value of TMI in the general pediatric population and in a population with chronic health needs that has not been studied previously. TMI is a promising marker of adiposity that is clinically feasible and informative. The most widely used clinical measure of body mass, BMI, is a useful population-based measure to report the presence of obesity, and is used interchangeably to report adiposity[115]. However, one of the limitations of BMI is that it may not be adequate to diagnose obesity in certain populations, including adolescents[89,90]. In addition, BMI misclassifies muscular individuals as being overweight or obese, which does not necessarily reflect their future

risk of cardiometabolic disorders.[161]. Furthermore, BMI has a weaker association with cardiovascular risk when compared to waist circumference and WHtR[157,162,163].

Children require special consideration in using BMI to classify obesity and adiposity. Ratios of weight over height to various powers of rho, ρ, (weight/height $^{\rho}$) have been explored to account for the effects of children's growth during puberty, and the adjustment for ρ is critical because incorrect values misclassify tall or physically advanced children as overweight[119,128]. A ρ value equal to two as used in BMI is sufficient when height is constant, however during puberty changes in height increase the ρ value[128].

In pre-school children, weight over height squared is adequate for assessing adiposity[119]. Adiposity generally declines between the ages 5-7 years before it begins to rise again, the adiposity rebound phase[46]. An earlier adiposity rebound than expected is associated with an increased risk of obesity and type 2 diabetes in adults[46,164,165].

As children approach the peripubertal phase of growth and development, their body composition changes with increased adiposity, especially in girls[121,122]. The value of ρ gradually rises from two to three; children who have undergone a growth spurt due to puberty tend to be heavier when compared to less mature children at the same height[119]. The increase in weight accompanying growth spurts results in higher BMI values,

therefore greater values of ρ are required to offset the weight gain experienced in physically advanced children.

However, body composition changes in children become more constant as they get older and ρ decreases back to two [119,128]. Therefore, during puberty, TMI may be a more accurate measure of adiposity in children [119]. For this reason, the use of TMI is more relevant to assess body fat mass in children and, when evaluated in adults, TMI is less reliable compared to BMI when correlated with skinfold thickness[115].

Measures of adiposity in children have relied on technologies that may not be readily available in the clinical setting but have demonstrated accuracy in estimating the fat mass. DXA estimates of trunk and abdominal fat have demonstrated a strong association to total abdominal fat[86-88], while Bioelectrical impedance analysis (BIA) has been validated as a measure of adiposity against DXA[111,166,167]. Our results demonstrate that TMI is a strong predictor of adiposity measured using BIA, which is congruent with adiposity assessments using DXA. This is another strength of this study, as it validates TMI against BIA, a common measure of adiposity that is more easily accessible than DXA.

Our results indicate that TMI may be a better estimate of fat mass and a potential tool for predicting adiposity in children compared to BMI z-score. While some studies have found TMI to be an appropriate measure of adiposity in children, others have

suggested BMI may still be an equivalent measure[91,168]. However, these studies often include children as young as two years of age, and weight scales over height squared in this age group that makes validating TMI as a measure of adiposity in this group a future goal of research[119,168].

There are several strengths in our study. The inclusion of non-cancer controls for comparison to the SCBT group offers validation of this measure in the general pediatric population as well as SCBT. The description of the association of TMI with measures of central adiposity is another strength, as central adiposity is not routinely assessed in clinical practice. Furthermore, the inclusion of an age and sex matched subgroup analysis validates our findings, confirming that differences in age and puberty did not affect the results.

A larger sample size of SCBT is required to validate these results further, and to define their associations. In addition, TMI needs to be validated as a predictor of cardiometabolic outcomes which should be part of longitudinal studies.

In conclusion, TMI represents a clinically feasible measure that uses the same variables measuring BMI but demonstrate higher correlation with adiposity.
The availability of TMI as a clinical measure of adiposity will allow the stratification of patients at risk of excess adiposity to be prioritized for targeted interventions. This is

critical, as these survivors are facing cardiometabolic diseases that are important emergent determinants of outcomes.

Data Availability

The data for the current study used for statistical analysis are available from the corresponding author upon reasonable justification.

Competing interests:

The authors have no competing financial or non-financial interests to declare.

Acknowledgements:

We would like to thank the participants as well as their families for participating in the study. We would also like to thank the staff for assisting in the recruitment of participants.

Author Contributions:

M.C.S. is the guarantor of this study. E.D.S, K.W.W., A.F., D.L.J., S.M.Z., S.R.R., S.B., L.T. and M.C.S. were involved in defining the research question and study design. K.W.W. and E.D.S. were responsible for participant recruitment and data collection and were supported by A.F., S.B., D.L.J and S.M.Z. Support in research methods and statistical analyses were provided by M.C.S. and L.T. The interpretation of the data was completed by E.D.S., K.W.W., A.F., D.L.J., S.M.Z., S.R.R., S.B., L.T. and M.C.S. E.D.S. and M.C.S. drafted the manuscript which was reviewed by all authors, who agreed with its content.

Additional Information

Competing interests: The authors have no competing financial or non-financial interests to declare.

Tables

Table 1. Study Population Characteristics

Variables	**SCBT (n = 44)**	**Controls (n = 137)**	**p-value (between groups)**
	Mean±SD	**Mean±SD**	
Age at enrollment (years)	11.16±4.30	14.03±2.60	<0.001
Sex, No. (%)			
Male	24 (54.60)	73 (53.30)	0.88
Female	20 (45.40)	64 (46.70)	
Puberty			
Pre-pubertal	21 (47.70)	16 (11.70)	<0.001
Pubertal	23 (52.30)	121 (88.30)	
Height (cm)	141.80±25.00	162.70±15.00	<0.001
Weight (kg)	43.20±22.40	59.20±20.60	<0.001
BMI z-score	0.57±0.94	0.45±1.10	0.51
BMI percentile (%)	67.60±26.30	62.20±29.30	0.33
TMI (kg/m^3)	14.10±2.50	13.50±2.90	0.099
Fat mass percentage	24.10±9.30	22.20±9.40	0.16
Waist-to-hip ratio	0.87±0.07	0.82±0.07	<0.001
Waist-to-height ratio	0.46±0.06	0.45±0.07	0.17

Abbreviations: SCBT, survivors of childhood brain tumors; SD, standard deviation; BMI, body mass index; TMI, tri-ponderal mass index

Table 2. Brain tumor characteristics (n=44)

Variables	No. (%)
Brain tumor type	
Non-NF-1, low grade glioma	18(40.90)
PNET/Medulloblastoma	8 (18.20)
NF-1, low grade glioma	9 (20.50)
CNS germ cell tumors	3 (6.80)
Subependymal giant cell astrocytoma	2 (4.50)
Ependymoma	2 (4.50)
Meningioma	1 (2.30)
Choroid plexus papilloma	1 (2.30)
Brain tumor location	
Supratentorial	22 (50.00)
Infratentorial	22 (50.00)
Brain tumor treatments	
Surgery	29 (65.90)
Radiotherapy	13 (29.50)
Chemotherapy	20 (45.50)
No treatment	8 (18.20)

Abbreviations: CNS, Central Nervous System; PNET, Primitive Neuroectodermal Tumor; NF-1, Neurofibromatosis Type 1.

Table 3. Spearman's correlation of TMI and BMI z-score with adiposity measures in SCBT and controls

Unadjusted					
Group	**Variable**	**BMI z-score**	**%FM**	**WHR**	**WHtR**
SCBT	TMI	0.87**	0.73**	0.56**	0.69**
	BMI z-score	-	0.66**	0.55**	0.71**
Controls	TMI	0.95**	0.85**	0.38**	0.83**
	BMI z-score	-	0.80**	0.40**	0.81**
Total	TMI	0.93**	0.83**	0.45**	0.83**
	BMI z-score	-	0.78**	0.45**	0.80**
Partial Correlations - Adjusted for age, sex and puberty					
SCBT	TMI	0.86**	0.73**	0.44*	0.82**
	BMI z-score	-	0.68**	0.46*	0.72**
Controls	TMI	0.94**	0.88*	0.46**	0.87**
	BMI z-score	-	0.90**	0.39**	0.80**
Total	TMI	0.92**	0.85**	0.46**	0.86**
	BMI z-score	-	0.85**	0.41**	0.78**

*p<0.05

**p-value <0.001

Abbreviations: SCBT, survivors of childhood brain tumors; BMI, body mass index; TMI, tri-ponderal mass index; %FM, percent fat mass; WHR, waist-to-hip ratio, WHtR, waist-to-height ratio.

Table 4. Linear regression analyses of TMI in SCBT and controls adjusted for age, sex and puberty

Variable	Population	Standardized coefficient β	p-value	Model Summary	
				Adjusted R Square	SE of the Estimate
Dependent Variable: BMI z-score					
TMI	SCBT	0.867	<0.001	0.71	0.50
	Controls	0.935	<0.001	0.88	0.38
Dependent Variable: %FM					
TMI*	SCBT	0.604	<0.001	0.65	0.10
	Controls	0.819	<0.001	0.81	0.09
BMI z-score*	SCBT	0.584	<0.001	0.65	0.10
	Controls	0.836	<0.001	0.83	0.08
Dependent Variable: Waist-to-hip ratio					
TMI	SCBT	0.425	0.004	0.20	0.03
	Controls	0.436	<0.001	0.31	0.03
BMI z-score	SCBT	0.442	0.002	0.23	0.03
	Controls	0.370	<0.001	0.25	0.03
Dependent Variable: Waist-to-height ratio					
TMI	SCBT	0.793	<0.001	0.67	0.03
	Controls	0.880	<0.001	0.77	0.03
BMI z-score*	SCBT	0.657	<0.001	0.58	0.03
	Controls	0.804	<0.001	0.64	0.04

Abbreviations: SCBT, survivors of childhood brain tumors; BMI, body mass index; %FM, fat mass percentage; SE, standard error. Models were adjusted for age, sex and puberty.

*Radiotherapy emerged as a significant predictor of adiposity, therefore we included it in the analysis.

Supplementary Tables

Supplementary Table S1. Study Population Characteristics of Age and Sex Matched Controls

Variables	**Age and sex matched Controls (n = 44)**	**p-value (between age and sex matched groups)**
	Mean±SD	
Age at enrollment (years)	12.30±3.40	0.090
Sex, No. (%)		
Male	24 (54.60)	1.00
Female	20 (45.40)	
Puberty, No. (%)		
Pre-pubertal	14 (31.80)	0.13
Pubertal	30 (68.20)	
Height (cm)	153.55±19.30	0.01
Weight (kg)	49.89±19.60	0.046
BMI z-score	0.36±1.30	0.37
BMI percentile (%)	57.00±34.40	0.07
TMI (kg/m^3)	13.40±3.00	0.13
Fat mass percentage (%FM)	21.60±9.10	0.15
Waist-to-hip ratio	0.84±0.07	0.026
Waist-to-height ratio	0.45±0.08	0.27

Abbreviations: SD, standard deviation; BMI, body mass index; %FM, percent fat mass; TMI, tri-ponderal mass index

Supplementary Table S2. Spearman's correlations between body mass and adiposity measurements for age and sex matched controls

Unadjusted					
Group	**Variable**	**BMI z-score**	**%FM**	**WHR**	**WHtR**
Age and sex matched Controls	TMI	0.95**	0.90**	0.56**	0.86**
	BMI z-score	-	0.87**	0.49**	0.80**
Total (age and sex matched groups)	TMI	0.94**	0.83**	0.58**	0.83**
	BMI z-score	-	0.79**	0.54**	0.80**
Partial Correlations - Adjusted for age, sex and puberty					
Age and sex matched Controls	TMI	0.95**	0.91**	0.56**	0.88**
	BMI z-score	-	0.92**	0.44*	0.79**
Total (age and sex matched groups)	TMI	0.91**	0.84**	0.51**	0.86**
	BMI z-score	-	0.82**	0.45**	0.77**

*$p<0.05$

**$p<0.001$

Abbreviations: BMI, body mass index; TMI, tri-ponderal mass index; %FM, percent fat mass; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio

Supplementary Table S3. Regression analysis of age and sex matched controls adjusted for age, sex and puberty

Variable	Standardized coefficient β	p-value	**Model Summary**	
			Adjusted R Square	**SE of the Estimate**
Dependent Variable: BMI z-score				
TMI	0.950	<0.001	0.89	0.43
Dependent Variable: %FM				
TMI	0.888	<0.001	0.84	0.08
BMI z-score	0.890	<0.001	0.85	0.08
Dependent Variable: Waist-to-hip ratio				
TMI	0.551	<0.001	0.33	0.03
BMI z-score	0.433	0.004	0.21	0.03
Dependent Variable: Waist-to-height ratio				
TMI	0.895	<0.001	0.77	0.03
BMI z-score	0.796	<0.001	0.61	0.05

Abbreviations: BMI, body mass index; %FM, fat mass percentage; SE, standard error. Models were adjusted for age, sex and puberty.

CHAPTER 4: DISCUSSION

SCBT are more adipose compared to non-cancer controls[64-68], however adiposity is not routinely measured in clinical practice. Furthermore, SCBT are at a higher risk of cardiovascular conditions[17,18] and stroke[12] compared to the general population. With excess adiposity being a major risk factor for cardiometabolic outcomes in the general population[33-37], managing and preventing excess adiposity, and consequently reducing cardiometabolic risk[63], is crucial in the SCBT population. Since current management strategies in this population are limited and show variable success[83], early detection and prevention may be the most effective tool to mitigate long term health complications in SCBT.

The approach of early prevention rather than late management of excess adiposity and associated health complications may offer greater long term health benefits in SCBT. Excess adiposity is difficult to successfully lose once developed[169]. Furthermore, in the general population, sustaining weight loss over a prolonged period of time is often unsuccessful, with approximately only 20% of individuals able to maintain weight loss over an extended five year period[170]. This suggests that treating obesity may only provide short term success rather than lasting long term health benefits that improve the overall health-related quality of life.

While obesity treatment techniques, such as pharmacotherapy and bariatric surgery, demonstrate initial effective weight loss in the general population[171], these methods can be associated with additional health complications[169]. For example, some of

the short-term complications from bariatric surgery can include hemorrhage, anastomotic leaks, infection and arrhythmias, and long term complications can include neuropathies as a result of nutritional deficiencies as well as emotional disorders[172,173]. Furthermore, adverse effects associated with pharmacotherapy treatment for obesity can include increased blood pressure, incidence of psychiatry disorders and gastrointestinal adverse events[174]. Therefore, available obesity management techniques often pose an additional risk for further health complications, while only 20% of individuals are able to maintain this weight loss[170].

Furthermore, once obesity develops, the risk for developing additional health conditions increases considerably. In the general population, obesity is associated with dyslipidemia[30] and hypertension[31,32], and is an important risk factor for metabolic syndrome[33], diabetes[34,35], cardiovascular disease[36] and stroke[36,37]. The development of further health complications introduces additional challenges to managing obesity in patients. For example, the health condition itself may limit the extent of the management strategy that can be used. Those who develop cardiovascular conditions or type 2 diabetes for example will require special consideration when developing safe practice to implement exercise programs[175]. Instead of only targeting the prevention of excess adiposity, additional health complications may need to be considered and managed simultaneously. Early prevention of excess adiposity may allow for additional health outcomes to be circumvented and therefore may provide increased long term health benefits compared to late management techniques. However, to successfully initiate early

prevention strategies, stratifying those at risk needs to be easily determined with minimal disruption to clinical practice or cost.

While DXA and BIA are reliable measures of adiposity in both children and adults, specialized equipment that is not readily available or feasible in all settings is required. An effective tool must be affordable, easy-to-use and reliable. TMI is cost-effective, readily available and easy-to-use in clinical practice, making it a clinically feasible measure of adiposity that can easily be implemented into routine practice. Our results identified TMI as a strong predictor of adiposity in both SCBT and non-cancer children. The use of TMI as a measure of adiposity in children may allow for early screening and stratification of SCBT at risk of future cardiometabolic disorders.

Furthermore, TMI may also be useful in other populations. For example, TMI may be able to be used in a similar manner in other groups within the SCC population. For example, survivors of childhood ALL are another group of SCC who face an increased risk of obesity[176-178], dyslipidemia[176], insulin resistance[176,178,179], hypertension[176-178], cardiovascular disease[176,179,180], stroke[12] and metabolic syndrome[178]. Therefore, TMI may also provide insight into the development of excess adiposity and may serve as a predictor of associated cardiometabolic outcomes in this population.

Not only is this tool important to the SCC population, but it may also be instrumental in other high risk disease groups as well as the general population.

Childhood obesity is a growing epidemic[181] and since children who are obese are more likely to become obese in adulthood[182], the close monitoring of adiposity trajectories in all children is crucial for early prevention.

Strengths

This research provides the first analysis of TMI as a measure of adiposity in SCBT. Previously, TMI has only been explored as a measure of adiposity in healthy children. Our results confirm that TMI demonstrates a strong association with total adiposity and central adiposity measure, WHtR, in the SCBT population.

Our analyses also included a non-cancer control group for comparison. Our results for the non-cancer controls were similar to that seen in previous research which provides confidence in our results. Furthermore, our inclusion of an age and sex matched control subgroup provides further confidence that the differences in age and puberty did not affect the interpretation of results.

Limitations

As the CanDECIDE Study is a prospective cohort study spanning over 25 years[92], new participants are continuously being recruited and new data collected. At the time of this analysis, the relatively small sample size of SCBT did not allow for further subgroup

analyses based on age groups, sex or brain tumor characteristics. However, with additional data being collected, future subgroup analyses will be possible and can provide further insight into the development of excess adiposity in this population.

Unfortunately, DXA scans were not readily available for this analysis and could not be used to verify TMI in SCBT. However, BIA, which was used as an alternate measure of total adiposity in our analyses, has previously been validated against DXA scans[108-111] and our results can still be interpreted with confidence. This in itself highlights the immediate need for an easy-to-use and cost-effective tool to measure adiposity.

Future directions

One of the important strengths to TMI is that it only requires the routine clinical measurements, height and weight, in order to be calculated. Height and weight measurements are not only currently being continuously taken in clinical practice but have been part of routine measurements in the clinical setting for several years in the past. This significant point means that TMI can not only be easily implemented into clinical practice moving forward, but can also be applied retrospectively to track trends in adiposity in cases where DXA scans may not have been available. Therefore, TMI can be used to develop adiposity trajectories through retrospective analysis in not only the SCBT

population, but in any group of children where height and weight measurements are available.

The development of these trajectories may provide insight into early determinants and cut-off points for SCBT who will become at risk of developing future cardiometabolic disorders. Identifying these crucial points may allow for early stratification and risk management.

Future research is needed to validate TMI in additional SCC groups as well as other disease groups, ideally against available adiposity data from DXA scans. Furthermore, whether TMI is a predictor of cardiometabolic outcomes in the SCC population will need to be determined. Our results show TMI is strongly correlated to WHtR, a stronger predictor of cardiometabolic risk compared to BMI[69,158,183], in SCBT. Therefore, TMI may be able to be used in a similar manner to predict cardiometabolic risk in SCBT. In emerging studies in non-cancer children, TMI demonstrates good prediction accuracy for homeostasis model assessment insulin resistance[184] and has a moderate discriminatory power in detecting metabolic syndrome[185]. However, further studies to confirm whether TMI can be used as a screening tool for cardiometabolic risk is required.

Trends in the adiposity trajectories of SCC developed through mapping TMI across time will need to be analysed longitudinally to identify the early determinants of future excess adiposity and cardiometabolic outcomes. Once identified, early prevention

strategies will need to be deployed in the SCC population to determine if future adverse events can be effectively reduced through early prevention.

CHAPTER 5: CONCLUSIONS

Survivors of childhood cancer are an emerging group that is at an increased risk of future comorbidities, including obesity[8,9], hypertension[10], dyslipidemia[10], diabetes mellitus[10,11], stroke[12] and cardiovascular disease[13]. Particularly, SCBT have a higher risk of hypothyroidism[17], growth hormone deficiency[17], cardiovascular conditions[17,18] and stroke[12] compared to controls.

Identifying early determinants of these health outcomes is crucial for early stratification and prevention of those at risk. One such factor is excess adiposity which is an important risk factor for many of these cardiometabolic outcomes in the general population[33,34,37,186,187], and represents a potentially modifiable risk factor in SCC to improve long term health outcomes.

However, results from a systematic review conducted by Wang et al. on obesity interventions in SCBT found that there is currently limited high quality evidence on the effectiveness of lifestyle-based interventions, pharmacotherapy and bariatric surgery to treat obesity in this population[188]. Therefore, these findings highlight an urgent need for clinically feasible methods to monitor and identify excess adiposity in this population at an early stage.

Since it has been shown that SCBT are more adipose compared to the general population[64-68,93,94,189,190], and there is currently limited high quality evidence on the effectiveness of obesity management strategies in SCBT[188], early stratification of those at

risk is critical in order to prevent excess adiposity and its associated comorbidities in this population. Therefore, a measure of adiposity that is both clinically feasible and reliable is required to identify and target SCBT at risk.

While DXA is considered the gold standard for measuring adiposity, it requires specialized equipment and may not be feasible for routine use in a clinical setting[86,87]. TMI (weight/height^3 (kg/m^3)), uses routine clinical measurements and is a more accurate predictor of adiposity compared to BMI z-score in children when validated against DXA[91]. Furthermore, TMI offers a measure of adiposity that is sex-specific, age-independent and tracks adiposity more reliably with higher fat mass in adolescents[91].Therefore, this thesis assessed TMI as a potential clinical measure of adiposity in SCBT. Our results validate TMI as a reliable clinical measure of adiposity in SCBT and healthy children[191]. TMI demonstrates strong correlations and associations to total and central adiposity in both SCBT and healthy control children[191].

The use of TMI as a clinical measure of adiposity will allow for the early stratification of SCBT at risk of excess adiposity and may assist in the prevention of future cardiometabolic outcomes in this population. This is crucial as nonexternal causes of death, such as cardiometabolic disorders, exceed that of mortality rates due to recurrence or progression of primary disease as SCC advance past the five-year survival period[20]. The simplicity and affordability of TMI will allow for it to be easily implemented into routine clinical practice without disruption to busy clinical services.

REFERENCES

1 Hudson, M. M. *et al.* Health status of adult long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Jama* **290**, 1583-1592 (2003).

2 Bray, F. *et al.* Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a cancer journal for clinicians* **68**, 394-424 (2018).

3 Steliarova-Foucher, E. *et al.* International incidence of childhood cancer, 2001–10: a population-based registry study. *The Lancet Oncology* **18**, 719-731 (2017).

4 Siegel, R. L., Miller, K. D. & Jemal, A. Cancer statistics, 2017. *CA: a cancer journal for clinicians* **67**, 7-30 (2017).

5 Howlader, N. *et al.* SEER Cancer Statistics Review, 1975-2010.[Based on the November 2012 SEER data submission, posted to the SEER web site, April 2013.]. *Bethesda, MD: National Cancer Institute* **9** (2013).

6 Ward, E., DeSantis, C., Robbins, A., Kohler, B. & Jemal, A. Childhood and adolescent cancer statistics, 2014. *CA: a cancer journal for clinicians* **64**, 83-103 (2014).

7 Geenen, M. M. *et al.* Medical assessment of adverse health outcomes in long-term survivors of childhood cancer. *Jama* **297**, 2705-2715 (2007).

8 Talvensaari, K. K., Lanning, M., Tapanainen, P. & Knip, M. Long-term survivors of childhood cancer have an increased risk of manifesting the metabolic

syndrome. *The Journal of Clinical Endocrinology & Metabolism* **81**, 3051-3055 (1996).

9 Oeffinger, K. C. *et al.* Obesity in adult survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. *Journal of Clinical Oncology* **21**, 1359-1365 (2003).

10 Meacham, L. R. *et al.* Cardiovascular risk factors in adult survivors of pediatric cancer—a report from the childhood cancer survivor study. *Cancer Epidemiology and Prevention Biomarkers* **19**, 170-181 (2010).

11 Meacham, L. R. *et al.* Diabetes mellitus in long-term survivors of childhood cancer: increased risk associated with radiation therapy: a report for the childhood cancer survivor study. *Archives of internal medicine* **169**, 1381-1388 (2009).

12 Bowers, D. C. *et al.* Late-occurring stroke among long-term survivors of childhood leukemia and brain tumors: a report from the Childhood Cancer Survivor Study. *Journal of Clinical Oncology* **24**, 5277-5282 (2006).

13 Mulrooney, D. A. *et al.* Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort. *Bmj* **339**, b4606 (2009).

14 Trotti, A. *et al.* 3 edn 176-181 (Elsevier).

15 Cancer Therapy Evaluation, P. (National Cancer Institute Bethesda, MD, 2006).

16 Oeffinger, K. C. *et al.* Chronic health conditions in adult survivors of childhood cancer. *New England Journal of Medicine* **355**, 1572-1582 (2006).

17 Gurney, J. G. *et al.* Endocrine and cardiovascular late effects among adult survivors of childhood brain tumors: Childhood Cancer Survivor Study. *Cancer* **97**, 663-673, doi:10.1002/cncr.11095 (2003).

18 Heikens, J. *et al.* Long term survivors of childhood brain cancer have an increased risk for cardiovascular disease. *Cancer* **88**, 2116-2121, doi:10.1002/(sici)1097-0142(20000501)88:9<2116::aid-cncr18>3.0.co;2-u (2000).

19 Gurney, J. G. *et al.* Endocrine and cardiovascular late effects among adult survivors of childhood brain tumors. *Cancer* **97**, 663-673 (2003).

20 Armstrong, G. T. *et al.* Late mortality among 5-year survivors of childhood cancer: a summary from the Childhood Cancer Survivor Study. *Journal of Clinical Oncology* **27**, 2328 (2009).

21 Chobanian, A. V. *et al.* The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. *Jama* **289**, 2560-2571 (2003).

22 Kissela, B. M. *et al.* Age at stroke: temporal trends in stroke incidence in a large, biracial population. *Neurology* **79**, 1781-1787 (2012).

23 Robins, M. & Baum, H. M. The National Survey of Stroke. Incidence. *Stroke* **12**, I45-57 (1981).

24 Lee, W.-Y., Jung, C.-H., Park, J.-S., Rhee, E.-J. & Kim, S.-W. Effects of smoking, alcohol, exercise, education, and family history on the metabolic syndrome as defined by the ATP III. *Diabetes research and clinical practice* **67**, 70-77 (2005).

25 Hariri, S. *et al.* Family history of type 2 diabetes: a population-based screening tool for prevention? *Genetics in Medicine* **8**, 102 (2006).

26 Lloyd-Jones, D. M. *et al.* Parental cardiovascular disease as a risk factor for cardiovascular disease in middle-aged adults: a prospective study of parents and offspring. *Jama* **291**, 2204-2211 (2004).

27 Kubota, M. *et al.* Is family history an independent risk factor for stroke? *Journal of Neurology, Neurosurgery & Psychiatry* **62**, 66-70 (1997).

28 Kim, H. *et al.* Family history as a risk factor for stroke in young women. *American journal of preventive medicine* **27**, 391-396 (2004).

29 Juonala, M. *et al.* Childhood adiposity, adult adiposity, and cardiovascular risk factors. *New England Journal of Medicine* **365**, 1876-1885 (2011).

30 Freedman, D. S., Dietz, W. H., Srinivasan, S. R. & Berenson, G. S. The relation of overweight to cardiovascular risk factors among children and adolescents: the Bogalusa Heart Study. *Pediatrics* **103**, 1175-1182 (1999).

31 Must, A. *et al.* The disease burden associated with overweight and obesity. *Jama* **282**, 1523-1529 (1999).

32 Timpson, N. J. *et al.* Does greater adiposity increase blood pressure and hypertension risk? Mendelian randomization using the FTO/MC4R genotype. *Hypertension* **54**, 84-90 (2009).

33 Demerath, E. W. *et al.* Visceral adiposity and its anatomical distribution as predictors of the metabolic syndrome and cardiometabolic risk factor levels. *The American journal of clinical nutrition* **88**, 1263-1271 (2008).

34 Chan, J. M., Rimm, E. B., Colditz, G. A., Stampfer, M. J. & Willett, W. C. Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. *Diabetes care* **17**, 961-969 (1994).

35 Mokdad, A. H. *et al.* Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. *Jama* **289**, 76-79 (2003).

36 Larsson, B. *et al.* Abdominal adipose tissue distribution, obesity, and risk of cardiovascular disease and death: 13 year follow up of participants in the study of men born in 1913. *Br Med J (Clin Res Ed)* **288**, 1401-1404 (1984).

37 Hu, G. *et al.* Body mass index, waist circumference, and waist-hip ratio on the risk of total and type-specific stroke. *Archives of internal medicine* **167**, 1420-1427 (2007).

38 World Health, O. *Obesity: preventing and managing the global epidemic*. (World Health Organization, 2000).

39 Himes, J. H. & Dietz, W. H. Guidelines for overweight in adolescent preventive services: recommendations from an expert committee. *The American journal of clinical nutrition* **59**, 307-316 (1994).

40 Barlow, S. E. & Dietz, W. H. Obesity evaluation and treatment: expert committee recommendations. *Pediatrics* **102**, e29-e29 (1998).

41 Wang, Y. & Beydoun, M. A. The obesity epidemic in the United States—gender, age, socioeconomic, racial/ethnic, and geographic characteristics: a systematic review and meta-regression analysis. *Epidemiologic reviews* **29**, 6-28 (2007).

42 Reilly, J. J. *et al.* Early life risk factors for obesity in childhood: cohort study. *Bmj* **330**, 1357 (2005).

43 Parsons, T. J., Power, C., Logan, S. & Summerbelt, C. D. Childhood predictors of adult obesity: a systematic review. *International journal of obesity* **23** (1999).

44 Whitaker, R. C., Wright, J. A., Pepe, M. S., Seidel, K. D. & Dietz, W. H. Predicting obesity in young adulthood from childhood and parental obesity. *New England Journal of Medicine* **337**, 869-873 (1997).

45 Thibault, H., Contrand, B., Saubusse, E., Baine, M. & Maurice-Tison, S. Risk factors for overweight and obesity in French adolescents: physical activity, sedentary behavior and parental characteristics. *Nutrition* **26**, 192-200 (2010).

46 Whitaker, R. C., Pepe, M. S., Wright, J. A., Seidel, K. D. & Dietz, W. H. Early adiposity rebound and the risk of adult obesity. *Pediatrics* **101**, e5-e5 (1998).

47 Johnsson, I. W., Haglund, B., Ahlsson, F. & Gustafsson, J. A high birth weight is associated with increased risk of type 2 diabetes and obesity. *Pediatric obesity* **10**, 77-83 (2015).

48 Gillman, M. W., Rifas-Shiman, S., Berkey, C. S., Field, A. E. & Colditz, G. A. Maternal gestational diabetes, birth weight, and adolescent obesity. *Pediatrics* **111**, e221-e226 (2003).

49 Patrick, K. *et al.* Diet, physical activity, and sedentary behaviors as risk factors for overweight in adolescence. *Archives of pediatrics & adolescent medicine* **158**, 385-390 (2004).

50 Boone, J. E., Gordon-Larsen, P., Adair, L. S. & Popkin, B. M. Screen time and physical activity during adolescence: longitudinal effects on obesity in young adulthood. *International Journal of Behavioral Nutrition and Physical Activity* **4**, 26 (2007).

51 Eisenmann, J. C., Bartee, R. T. & Wang, M. Q. Physical activity, TV viewing, and weight in US youth: 1999 Youth Risk Behavior Survey. *Obesity research* **10**, 379-385 (2002).

52 Maskarinec, G., Novotny, R. & Tasaki, K. Dietary patterns are associated with body mass index in multiethnic women. *The Journal of nutrition* **130**, 3068-3072 (2000).

53 Berg, C. *et al.* Eating patterns and portion size associated with obesity in a Swedish population. *Appetite* **52**, 21-26 (2009).

54 Patel, S. R. Reduced sleep as an obesity risk factor. *Obesity Reviews* **10**, 61-68 (2009).

55 Pereira, M. A. *et al.* Fast-food habits, weight gain, and insulin resistance (the CARDIA study): 15-year prospective analysis. *The lancet* **365**, 36-42 (2005).

56 Liu, S. *et al.* Fruit and vegetable intake and risk of cardiovascular disease: the Women's Health Study. *The American journal of clinical nutrition* **72**, 922-928 (2000).

57 Williams, P. T. Physical fitness and activity as separate heart disease risk factors: a meta-analysis. *Medicine and science in sports and exercise* **33**, 754 (2001).

58 Hu, F. B. *et al.* Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. *New England journal of medicine* **345**, 790-797 (2001).

59 Lee, C. D., Folsom, A. R. & Blair, S. N. Physical activity and stroke risk: a meta-analysis. *Stroke* **34**, 2475-2481 (2003).

60 Hu, F. B. *et al.* Walking compared with vigorous physical activity and risk of type 2 diabetes in women: a prospective study. *Jama* **282**, 1433-1439 (1999).

61 Hu, F. B. *et al.* Physical activity and television watching in relation to risk for type 2 diabetes mellitus in men. *Archives of internal medicine* **161**, 1542-1548 (2001).

62 Hu, F. B. *et al.* Physical activity and risk for cardiovascular events in diabetic women. *Annals of internal medicine* **134**, 96-105 (2001).

63 Ford, A. L., Hunt, L. P., Cooper, A. & Shield, J. P. H. What reduction in BMI SDS is required in obese adolescents to improve body composition and cardiometabolic health? *Archives of disease in childhood* **95**, 256-261 (2010).

64 Wang, K. W. *et al.* Overweight, obesity and adiposity in survivors of childhood brain tumours: a systematic review and meta-analysis. *Clinical Obesity* (2017).

65 Wang, K. W. *et al.* Adiposity in childhood brain tumors: A report from the Canadian Study of Determinants of Endometabolic Health in Children (CanDECIDE Study). *Scientific reports* **7**, 45078, doi:10.1038/srep45078 (2017).

66 Siviero-Miachon, A. A., Spinola-Castro, A. M. & Guerra-Junior, G. Adiposity in childhood cancer survivors: insights into obesity physiopathology. *Arquivos Brasileiros de Endocrinologia & Metabologia* **53**, 190-200 (2009).

67 Steinberger, J. *et al.* Cardiovascular risk and insulin resistance in childhood cancer survivors. *The Journal of pediatrics* **160**, 494-499 (2012).

68 Meacham, L. R. *et al.* Body mass index in long-term adult survivors of childhood cancer: A report of the Childhood Cancer Survivor Study. *Cancer: Interdisciplinary International Journal of the American Cancer Society* **103**, 1730-1739 (2005).

69 Ashwell, M., Gunn, P. & Gibson, S. Waist-to-height ratio is a better screening tool than waist circumference and BMI for adult cardiometabolic risk factors: systematic review and meta-analysis. *Obesity reviews* **13**, 275-286 (2012).

70 Lustig, R. H. *et al.* Risk factors for the development of obesity in children surviving brain tumors. *The Journal of Clinical Endocrinology & Metabolism* **88**, 611-616 (2003).

71 Sorva, R. Children with craniopharyngioma: early growth failure and rapid postoperative weight gain. *Acta Pædiatrica* **77**, 587-592 (1988).

72 Pinto, G. *et al.* Hormonal factors influencing weight and growth pattern in craniopharyngioma. *Hormone Research in Paediatrics* **53**, 163-169 (2000).

73 Hoffman, M. C. *et al.* Deficits in physical function among young childhood cancer survivors. *Journal of clinical oncology* **31**, 2799 (2013).

74 Ness, K. K. *et al.* Predictors of inactive lifestyle among adult survivors of childhood cancer. *Cancer* **115**, 1984-1994 (2009).

75 Ness, K. K. *et al.* Limitations on physical performance and daily activities among long-term survivors of childhood cancer. *Annals of internal medicine* **143**, 639-647 (2005).

76 Ness, K. K. *et al.* Physical performance limitations among adult survivors of childhood brain tumors. *Cancer* **116**, 3034-3044 (2010).

77 Reinehr, T., de Sousa, G., Toschke, A. M. & Andler, W. Long-term follow-up of cardiovascular disease risk factors in children after an obesity intervention. *The American journal of clinical nutrition* **84**, 490-496 (2006).

78 Davison, K. K., Jurkowski, J. M., Li, K., Kranz, S. & Lawson, H. A. A childhood obesity intervention developed by families for families: results from a pilot study. *International Journal of Behavioral Nutrition and Physical Activity* **10**, 3 (2013).

79 Sacher, P. M. *et al.* Randomized controlled trial of the MEND program: a family-based community intervention for childhood obesity. *Obesity* **18**, S62-S68 (2010).

80 Brown, T. *et al.* Systematic review of long-term lifestyle interventions to prevent weight gain and morbidity in adults. *Obesity reviews* **10**, 627-638 (2009).

81 Norris, S. L. *et al.* Efficacy of pharmacotherapy for weight loss in adults with type 2 diabetes mellitus: a meta-analysis. *Archives of Internal Medicine* **164**, 1395-1404 (2004).

82 Buchwald, H. *et al.* Bariatric surgery: a systematic review and meta-analysis. *Jama* **292**, 1724-1737 (2004).

83 Wang, K. W. *et al.* The effectiveness of interventions to treat hypothalamic obesity in survivors of childhood brain tumours: a systematic review. *Obesity Reviews* (2017).

84 Poirier, P. *et al.* Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss. *Circulation* **113**, 898-918 (2006).

85 Haffner, S. M. Abdominal adiposity and cardiometabolic risk: do we have all the answers? *The American journal of medicine* **120**, S10-S16 (2007).

86 Clasey, J. L. *et al.* The use of anthropometric and dual-energy X-ray absorptiometry (DXA) measures to estimate total abdominal and abdominal visceral fat in men and women. *Obesity* **7**, 256-264 (1999).

87 Glickman, S. G., Marn, C. S., Supiano, M. A. & Dengel, D. R. Validity and reliability of dual-energy X-ray absorptiometry for the assessment of abdominal adiposity. *Journal of Applied Physiology* **97**, 509-514 (2004).

88 Huang, T. T. K., Watkins, M. P. & Goran, M. I. Predicting total body fat from anthropometry in Latino children. *Obesity* **11**, 1192-1199 (2003).

89 Quételet, A. *Sur l'homme et le developpement de ses faculties*. (1835).

90 Quetelet, A. *Physique sociale, ou essai sur le développement des facultés de l'homme*. Vol. 2 (C. Muquardt, 1869).

91 Peterson, C. M. *et al.* Tri-Ponderal Mass Index vs Body Mass Index in Estimating Body Fat During Adolescence. *JAMA pediatrics* (2017).

92 Samaan, M. C., Thabane, L., Burrow, S., Dillenburg, R. F. & Scheinemann, K. Canadian Study of Determinants of Endometabolic Health in ChIlDrEn

(CanDECIDE study): a cohort study protocol examining the mechanisms of obesity in survivors of childhood brain tumours. *BMJ open* **3**, e002869 (2013).

93 Janiszewski, P. M. *et al.* Abdominal obesity, liver fat, and muscle composition in survivors of childhood acute lymphoblastic leukemia. *The Journal of Clinical Endocrinology & Metabolism* **92**, 3816-3821 (2007).

94 Wang, K. W. *et al.* Overweight, obesity and adiposity in survivors of childhood brain tumours: a systematic review and meta-analysis. *Clinical obesity* **8**, 55-67 (2018).

95 Damilakis, J., Adams, J. E., Guglielmi, G. & Link, T. M. Radiation exposure in X-ray-based imaging techniques used in osteoporosis. *European radiology* **20**, 2707-2714 (2010).

96 Visser, M. *et al.* Validity of fan-beam dual-energy X-ray absorptiometry for measuring fat-free mass and leg muscle mass. *Journal of applied physiology* **87**, 1513-1520 (1999).

97 Haarbo, J., Gotfredsen, A., Hassager, C. & Christiansen, C. Validation of body composition by dual energy X-ray absorptiometry (DEXA). *Clinical Physiology* **11**, 331-341 (1991).

98 Going, S. B. *et al.* Detection of small changes in body composition by dual-energy x-ray absorptiometry. *The American journal of clinical nutrition* **57**, 845-850 (1993).

99 Njeh, C. F., Samat, S. B., Nightingale, A., McNeil, E. A. & Boivin, C. M. Radiation dose and in vitro precision in paediatric bone mineral density

measurement using dual X-ray absorptiometry. *The British journal of radiology* **70**, 719-727 (1997).

100 Lochmüller, E. M., Müller, R., Kuhn, V., Lill, C. A. & Eckstein, F. Can novel clinical densitometric techniques replace or improve DXA in predicting bone strength in osteoporosis at the hip and other skeletal sites? *Journal of bone and mineral research* **18**, 906-912 (2003).

101 Kaul, S. *et al.* Dual-energy X-ray absorptiometry for quantification of visceral fat. *Obesity* **20**, 1313-1318 (2012).

102 Shetty, S. *et al.* Osteoporosis in healthy South Indian males and the influence of life style factors and vitamin D status on bone mineral density. *Journal of osteoporosis* **2014** (2014).

103 Handa, R., Kalla, A. A. & Maalouf, G. Osteoporosis in developing countries. *Best Practice & Research Clinical Rheumatology* **22**, 693-708 (2008).

104 Lewiecki, E. M., Richmond, B. & Miller, P. D. Uses and misuses of quantitative ultrasonography in managing osteoporosis. *Cleveland Clinic journal of medicine* **73**, 742 (2006).

105 Cadarette, S. M. *et al.* Development and validation of the Osteoporosis Risk Assessment Instrument to facilitate selection of women for bone densitometry. *Canadian Medical Association Journal* **162**, 1289-1294 (2000).

106 Kamel, E. G., McNeill, G. & Van Wijk, M. C. W. Usefulness of anthropometry and DXA in predicting intra-abdominal fat in obese men and women. *Obesity research* **8**, 36-42 (2000).

107 Prado, C. M. M. & Heymsfield, S. B. Lean tissue imaging: a new era for nutritional assessment and intervention. *Journal of Parenteral and Enteral Nutrition* **38**, 940-953 (2014).

108 Thomson, R., Brinkworth, G. D., Buckley, J. D., Noakes, M. & Clifton, P. M. Good agreement between bioelectrical impedance and dual-energy X-ray absorptiometry for estimating changes in body composition during weight loss in overweight young women. *Clinical Nutrition* **26**, 771-777 (2007).

109 Sun, G. *et al.* Comparison of multifrequency bioelectrical impedance analysis with dual-energy X-ray absorptiometry for assessment of percentage body fat in a large, healthy population–. *The American journal of clinical nutrition* **81**, 74-78 (2005).

110 Okasora, K. *et al.* Comparison of bioelectrical impedance analysis and dual energy X-ray absorptiometry for assessment of body composition in children. *Pediatrics international* **41**, 121-125 (1999).

111 Tyrrell, V. J. *et al.* Foot-to-foot bioelectrical impedance analysis: a valuable tool for the measurement of body composition in children. *International Journal of Obesity & Related Metabolic Disorders* **25** (2001).

112 Kyle, U. G. *et al.* Bioelectrical impedance analysis—part II: utilization in clinical practice. *Clinical nutrition* **23**, 1430-1453 (2004).

113 Mialich, M. S., Sicchieri, J. M. F. & Junior, A. A. J. Analysis of body composition: a critical review of the use of bioelectrical impedance analysis. *Int J Clin Nutr* **2**, 1-10 (2014).

114 Kyle, U. G. *et al.* Bioelectrical impedance analysis—part I: review of principles and methods. *Clinical nutrition* **23**, 1226-1243 (2004).

115 Keys, A., Fidanza, F., Karvonen, M. J., Kimura, N. & Taylor, H. L. Indices of relative weight and obesity. *Journal of chronic diseases* **25**, 329-343 (1972).

116 Daniels, S. R. The use of BMI in the clinical setting. *Pediatrics* **124**, S35-S41 (2009).

117 Prentice, A. M. & Jebb, S. A. Beyond body mass index. *Obesity reviews* **2**, 141-147 (2001).

118 Cole, T. J. Weight-stature indices to measure underweight, overweight, and obesity. *Anthropometric assessment of nutritional status. New York: Wiley-Liss* **83** (1991).

119 Cole, T. J. Weight/height p compared to weight/height2 for assessing adiposity in childhood: influence of age and bone age on p during puberty. *Annals of human biology* **13**, 433-451 (1986).

120 Heymsfield, S. B. *et al.* Scaling of adult body weight to height across sex and race/ethnic groups: relevance to BMI. *The American journal of clinical nutrition* **100**, 1455-1461 (2014).

121 Kaplowitz, P. B. Link between body fat and the timing of puberty. *Pediatrics* **121**, S208-S217 (2008).

122 Kaplowitz, P. B., Slora, E. J., Wasserman, R. C., Pedlow, S. E. & Herman-Giddens, M. E. Earlier onset of puberty in girls: relation to increased body mass index and race. *Pediatrics* **108**, 347-353 (2001).

123 Ellis, K. J. Human body composition: in vivo methods. *Physiological reviews* **80**, 649-680 (2000).

124 Must, A. & Anderson, S. E. Body mass index in children and adolescents: considerations for population-based applications. *International journal of obesity* **30**, 590 (2006).

125 Cole, T. J., Faith, M. S., Pietrobelli, A. & Heo, M. What is the best measure of adiposity change in growing children: BMI, BMI%, BMI z-score or BMI centile? *European journal of clinical nutrition* **59**, 419 (2005).

126 Berkey, C. S. & Colditz, G. A. Adiposity in adolescents: change in actual BMI works better than change in BMI z score for longitudinal studies. *Annals of epidemiology* **17**, 44-50 (2007).

127 Barlow, S. E., Bobra, S. R., Elliott, M. B., Brownson, R. C. & Haire-Joshu, D. Recognition of childhood overweight during health supervision visits: does BMI help pediatricians? *Obesity* **15**, 225-225 (2007).

128 Franklin, M. F. Comparison of weight and height relations in boys from 4 countries. *The American journal of clinical nutrition* **70**, 157S-162S (1999).

129 Zimmet, P., Alberti, K. & Shaw, J. Global and societal implications of the diabetes epidemic. *Nature* **414**, 782-787 (2001).

130 Zimmet, P. Z., Magliano, D. J., Herman, W. H. & Shaw, J. E. Diabetes: a 21st century challenge. *The lancet Diabetes & endocrinology* **2**, 56-64 (2014).

131 Murray, C. J. L. & Lopez, A. D. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. *The lancet* **349**, 1436-1442 (1997).

132 Danaei, G. *et al.* National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2· 7 million participants. *The Lancet* **378**, 31-40 (2011).

133 Murray, C. J. L. & Lopez, A. D. Mortality by cause for eight regions of the world: Global Burden of Disease Study. *The lancet* **349**, 1269-1276 (1997).

134 Dobbs, R. *et al.* Overcoming obesity: An initial economic analysis. 2014. *McKinsey & Company: www. mckinsey. com/mgi*, 1-106 (2014).

135 Sasaki, K., Srikanthan, A., Baxter, N. & Lega, I. Diabetes Mellitus in Childhood Cancer Survivors: A Systematic Review. *Canadian Journal of Diabetes* **41**, S27 (2017).

136 Mertens, A. C. *et al.* Late mortality experience in five-year survivors of childhood and adolescent cancer: the Childhood Cancer Survivor Study. *Journal of Clinical Oncology* **19**, 3163-3172 (2001).

137 Prasad, P. K., Signorello, L. B., Friedman, D. L., Boice, J. D. & Pukkala, E. Long-term non-cancer mortality in pediatric and young adult cancer survivors in Finland. *Pediatric blood & cancer* **58**, 421-427 (2012).

138 Samaan, M. C. & Akhtar-Danesh, N. The impact of age and race on longevity in pediatric astrocytic tumors: A population-based study. *Pediatric blood & cancer*, doi:10.1002/pbc.25522 (2015).

139 Poirier, P. *et al.* Obesity and cardiovascular disease. *Arteriosclerosis, thrombosis, and vascular biology* **26**, 968-976 (2006).

140 Nayga Jr, R. M. Obesity and heart disease awareness: a note on the impact of consumer characteristics using qualitative choice analysis. *Applied Economics Letters* **4**, 229-231 (1997).

141 Wheelock, V. Healthy eating: the food issue of the 1990s. *British food journal* **94**, 3-8 (1992).

142 Romero-Corral, A. *et al.* Normal weight obesity: a risk factor for cardiometabolic dysregulation and cardiovascular mortality. *European heart journal* **31**, 737-746 (2009).

143 Vatten, L. J., Nilsen, T. I. L., Romundstad, P. R., Drøyvold, W. B. & Holmen, J. Adiposity and physical activity as predictors of cardiovascular mortality. *European Journal of Cardiovascular Prevention & Rehabilitation* **13**, 909-915 (2006).

144 Wajchenberg, B. L. Subcutaneous and visceral adipose tissue: their relation to the metabolic syndrome. *Endocrine reviews* **21**, 697-738 (2000).

145 Wang, K. W. *et al.* PS1-176 Where Have All the Fat Cells Gone? A Comparative Analysis of Adiposity Patterns in Childhood Brain Tumor Survivors and Non-Cancer Controls. *Canadian Journal of Neurological Sciences* **43**, S11-S11 (2016).

146 Samaan, M. C. *et al.* Recruitment feasibility to a cohort study of endocrine and metabolic health among survivors of childhood brain tumours: a report from the Canadian study of Determinants of Endometabolic Health in ChIlDrEn (CanDECIDE). *BMJ Open* **4**, e005295, doi:10.1136/bmjopen-2014-005295 (2014).

147 Samaan, M. C., Thabane, L., Burrow, S., Dillenburg, R. F. & Scheinemann, K. Canadian Study of Determinants of Endometabolic Health in ChIlDrEn (CanDECIDE study): a cohort study protocol examining the mechanisms of obesity in survivors of childhood brain tumours. *BMJ Open* **3**, doi:10.1136/bmjopen-2013-002869 (2013).

148 Nihiser, A. J. *et al.* Body mass index measurement in schools. *J Sch Health* **77**, 651-671; quiz 722-654, doi:10.1111/j.1746-1561.2007.00249.x (2007).

149 Kuczmarski, R. J. *et al.* 2000 CDC Growth Charts for the United States: methods and development. *Vital Health Stat 11*, 1-190 (2002).

150 SPSS Inc. PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc. (2009).

151 Ghasemi, A. & Zahediasl, S. Normality tests for statistical analysis: a guide for non-statisticians. *International journal of endocrinology and metabolism* **10**, 486 (2012).

152 Norman, G. R. & Streiner, D. L. PDQ Statistics. **3rd Edition** (2003).

153 Chambless, L. B., Parker, S. L., Hassam-Malani, L., McGirt, M. J. & Thompson, R. C. Type 2 diabetes mellitus and obesity are independent risk factors for poor

outcome in patients with high-grade glioma. *Journal of neuro-oncology* **106**, 383-389 (2012).

154 Nader, P. R. *et al.* Identifying risk for obesity in early childhood. *Pediatrics* **118**, e594-e601 (2006).

155 Pui, C. H. *et al.* Treatment outcomes in black and white children with cancer: results from the SEER database and St Jude Children's Research Hospital, 1992 through 2007. *J Clin Oncol* **30**, 2005-2012, doi:10.1200/JCO.2011.40.8617 (2012).

156 Wang, K.-W. *et al.* Adiposity in childhood brain tumors: a report from the Canadian Study of Determinants of Endometabolic Health in Children (CanDECIDE Study). *Scientific reports* **7**, 45078 (2017).

157 Savva, S. C. *et al.* Waist circumference and waist-to-height ratio are better predictors of cardiovascular disease risk factors in children than body mass index. *International journal of obesity* **24**, 1453 (2000).

158 Savva, S. C., Lamnisos, D. & Kafatos, A. G. Predicting cardiometabolic risk: waist-to-height ratio or BMI. A meta-analysis. *Diabetes, metabolic syndrome and obesity: targets and therapy* **6**, 403 (2013).

159 Sayeed, M. A. *et al.* Waist-to-height ratio is a better obesity index than body mass index and waist-to-hip ratio for predicting diabetes, hypertension and lipidemia. *Bangladesh Medical Research Council Bulletin* **29**, 1-10 (2003).

160 Ali, O. *et al.* Obesity, central adiposity and cardiometabolic risk factors in children and adolescents: a family-based study. *Pediatric obesity* **9** (2014).

161 Witt, K. A. & Bush, E. A. College athletes with an elevated body mass index often have a high upper arm muscle area, but not elevated triceps and subscapular skinfolds. *Journal of the American Dietetic Association* **105**, 599-602 (2005).

162 Yusuf, S. *et al.* Obesity and the risk of myocardial infarction in 27 000 participants from 52 countries: a case-control study. *The Lancet* **366**, 1640-1649 (2005).

163 Wells, J. C. K. Commentary: the paradox of body mass index in obesity assessment: not a good index of adiposity, but not a bad index of cardio-metabolic risk. *International journal of epidemiology* **43**, 672 (2014).

164 Rolland-Cachera, M.-F. *et al.* Adiposity rebound in children: a simple indicator for predicting obesity. *The American journal of clinical nutrition* **39**, 129-135 (1984).

165 Eriksson, J. G., Forsen, T., Tuomilehto, J., Osmond, C. & Barker, D. J. P. Early adiposity rebound in childhood and risk of Type 2 diabetes in adult life. *Diabetologia* **46**, 190-194 (2003).

166 Kabiri, L. S., Hernandez, D. C. & Mitchell, K. Reliability, validity, and diagnostic value of a pediatric bioelectrical impedance analysis scale. *Childhood Obesity* **11**, 650-655 (2015).

167 Beeson, W. L. *et al.* Comparison of body composition by bioelectrical impedance analysis and dual-energy X-ray absorptiometry in Hispanic diabetics. *International journal of body composition research* **8**, 45 (2010).

168 Mei, Z. *et al.* Validity of body mass index compared with other body-composition screening indexes for the assessment of body fatness in children and adolescents. *The American journal of clinical nutrition* **75**, 978-985 (2002).

169 Pandita, A. *et al.* Childhood obesity: prevention is better than cure. *Diabetes, metabolic syndrome and obesity: targets and therapy* **9**, 83 (2016).

170 Wing, R. R. & Phelan, S. Long-term weight loss maintenance–. *The American journal of clinical nutrition* **82**, 222S-225S (2005).

171 Douketis, J. D., Macie, C., Thabane, L. & Williamson, D. F. Systematic review of long-term weight loss studies in obese adults: clinical significance and applicability to clinical practice. *International journal of obesity* **29**, 1153 (2005).

172 Pories, W. J. Bariatric surgery: risks and rewards. *The Journal of Clinical Endocrinology & Metabolism* **93**, s89-s96 (2008).

173 Birkmeyer, J. D. *et al.* Surgical skill and complication rates after bariatric surgery. *New England Journal of Medicine* **369**, 1434-1442 (2013).

174 Rucker, D., Padwal, R., Li, S. K., Curioni, C. & Lau, D. C. W. Long term pharmacotherapy for obesity and overweight: updated meta-analysis. *Bmj* **335**, 1194-1199 (2007).

175 Hordern, M. D. *et al.* Exercise prescription for patients with type 2 diabetes and pre-diabetes: a position statement from Exercise and Sport Science Australia. *Journal of Science and Medicine in Sport* **15**, 25-31 (2012).

176 Oeffinger, K. C. *et al.* Cardiovascular risk factors in young adult survivors of childhood acute lymphoblastic leukemia. *Journal of pediatric hematology/oncology* **23**, 424-430 (2001).

177 Chow, E. J., Pihoker, C., Hunt, K., Wilkinson, K. & Friedman, D. L. Obesity and hypertension among children after treatment for acute lymphoblastic leukemia. *Cancer* **110**, 2313-2320 (2007).

178 Nottage, K. A. *et al.* Metabolic syndrome and cardiovascular risk among long-term survivors of acute lymphoblastic leukaemia-From the St. Jude Lifetime Cohort. *British journal of haematology* **165**, 364-374 (2014).

179 Oeffinger, K. C. *et al.* Insulin resistance and risk factors for cardiovascular disease in young adult survivors of childhood acute lymphoblastic leukemia. *Journal of clinical oncology* **27**, 3698-3704 (2009).

180 Mody, R. *et al.* Twenty-five–year follow-up among survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. *Blood* **111**, 5515-5523 (2008).

181 Ebbeling, C. B., Pawlak, D. B. & Ludwig, D. S. Childhood obesity: public-health crisis, common sense cure. *The lancet* **360**, 473-482 (2002).

182 Serdula, M. K. *et al.* Do obese children become obese adults? A review of the literature. *Preventive medicine* **22**, 167-177 (1993).

183 Li, W.-C. *et al.* Waist-to-height ratio, waist circumference, and body mass index as indices of cardiometabolic risk among 36,642 Taiwanese adults. *European journal of nutrition* **52**, 57-65 (2013).

184 Ashley-Martin, J., Ensenauer, R., Maguire, B. & Kuhle, S. Predicting cardiometabolic markers in children using tri-ponderal mass index: a cross-sectional study. *Archives of disease in childhood*, archdischild-2018 (2019).

185 Ramírez-Vélez, R. *et al.* Tri-Ponderal Mass Index vs. Fat Mass/Height3 as a Screening Tool for Metabolic Syndrome Prediction in Colombian Children and Young People. *Nutrients* **10**, 412 (2018).

186 Hubert, H. B., Feinleib, M., McNamara, P. M. & Castelli, W. P. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. *Circulation* **67**, 968-977 (1983).

187 Garrison, R. J., Kannel, W. B., Stokes, J. & Castelli, W. P. Incidence and precursors of hypertension in young adults: the Framingham Offspring Study. *Preventive medicine* **16**, 235-251 (1987).

188 Wang, K. W. *et al.* The effectiveness of interventions to treat hypothalamic obesity in survivors of childhood brain tumours: a systematic review. *Obesity Reviews* **18**, 899-914, doi:http://dx.doi.org/10.1111/obr.12534 (2017).

189 Karakurt, H., Sarper, N., Kılıç, S. Ç., Gelen, S. A. & Zengin, E. Screening survivors of childhood acute lymphoblastic leukemia for obesity, metabolic syndrome, and insulin resistance. *Pediatric hematology and oncology* **29**, 551-561 (2012).

190 Mayer, E. I. E., Reuter, M., Dopfer, R. E. & Ranke, M. B. Energy expenditure, energy intake and prevalence of obesity after therapy for acute lymphoblastic

leukemia during childhood. *Hormone Research in Paediatrics* **53**, 193-199 (2000).

191 Sims, E. D. *et al.* Tri-ponderal mass index in survivors of childhood brain tumors: A cross-sectional study. *Scientific Reports* **8**, 16336 (2018).

APPENDIX 1

Published Copy: Tri-ponderal mass index in survivors of childhood brain tumors: A cross-sectional study

SCIENTIFIC REPORTS

OPEN

Tri-ponderal mass index in survivors of childhood brain tumors: A cross-sectional study

Received: 24 May 2018
Accepted: 22 October 2018
Published online: 05 November 2018

E. Danielle Sims[1,2], Kuan-Wen Wang[1,2], Adam Fleming[1,3], Donna L. Johnston[4], Shayna M. Zelcer[5], Shahrad Rod Rassekh[6], Sarah Burrow[7], Lehana Thabane[8,9,10,11] & M. Constantine Samaan[1,2,8]

Survivors of childhood brain tumors (SCBT) face a higher risk of cardiometabolic disorders and premature mortality compared to the general population. Excess adiposity is a known risk factor for these comorbidities. However, while SCBT have higher adiposity compared to healthy controls, measuring adiposity in clinical practice involves access to specialized equipment and may impact busy clinical services. Tri-ponderal Mass Index (TMI; kg/m^3) may be a superior measure of adiposity when compared to Body Mass Index (BMI; kg/m^2). However, its use in determining adiposity in SCBT has not been assessed. This study aims to validate TMI as a clinical measure of adiposity in SCBT. This was a cross-sectional study including 44 SCBT (n = 20 female) and 137 (n = 64 female) non-cancer control children, 5–17 years of age. BMI and TMI were calculated from height and weight measurements. Fat mass percentage was assessed using bioelectrical impedance analysis and waist to hip and waist to height ratios were used to assess central adiposity. Regression analyses were adjusted for age, sex, puberty and treatment. TMI demonstrated strong correlations to measures of total and central adiposity and predicted adiposity in SCBT and non-cancer controls, with stronger trends in the latter group. TMI may serve as a reliable clinical measure of adiposity in both SCBT and healthy children.

Obesity has contributed to the rise of cardiovascular diseases and type 2 diabetes, making them some of the most significant and costly healthcare challenges of the 21st century[1–6]. One group that is especially impacted by these chronic diseases include childhood cancer survivors[7–9]. Within this population, survivors of childhood brain tumors (SCBT) represent an emerging group that has been recently reported to develop stroke and type 2 diabetes at higher rates than those seen in non-cancer control populations[10–12]. Obesity leads to increased cardiovascular mortality at a relatively young age in SCBT[12–22].

Excess adiposity, especially visceral adiposity, has been linked to cardiovascular disease and type 2 diabetes in the general population, and SCBT have more adiposity compared to healthy controls[23–27].

While adiposity is a potentially modifiable risk factor for cardiometabolic risk, measuring adiposity in clinical practice can be time consuming in the clinical setting, and requires specialized equipment including bioelectrical impedance scales or Dual-energy X-ray Absorptiometry (DXA) scans[28–30]. The availability of feasible and reliable clinical measures of adiposity will circumvent these limitations and help prioritize SCBT for closer monitoring and targeting them in interventions in an attempt to improve outcomes.

The tri-ponderal mass index, defined as weight divided by height cubed (TMI, kg/m^3), is an alternate measure of adiposity in children[31]. TMI is reported as a more accurate predictor of adiposity compared to Body Mass

[1]Department of Pediatrics, McMaster University, Hamilton, Ontario, Canada. [2]Division of Pediatric Endocrinology, McMaster Children's Hospital, Hamilton, Ontario, Canada. [3]Division of Pediatric Hematology/Oncology, McMaster Children's Hospital, Hamilton, Ontario, Canada. [4]Division of Pediatric Hematology/Oncology, Children's Hospital of Eastern Ontario, Ottawa, Ontario, Canada. [5]Pediatric Hematology Oncology, Children's Hospital, London Health Sciences Center, London, Ontario, Canada. [6]Division of Pediatric Hematology/Oncology/BMT, Department of Pediatrics, British Columbia's Children's Hospital, Vancouver, BC, Canada. [7]Division of Orthopedic Surgery, Department of Surgery, McMaster University Medical Centre, Hamilton, Ontario, Canada. [8]Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Ontario, Canada. [9]Department of Anesthesia, McMaster University, Hamilton, Ontario, Canada. [10]Centre for Evaluation of Medicines, St. Joseph's Health Care, Hamilton, Ontario, Canada. [11]Biostatistics Unit, St Joseph's Healthcare-Hamilton, Hamilton, Ontario, Canada. Correspondence and requests for materials should be addressed to M.C.S. (email: samaanc@mcmaster.ca)

Variables	SCBT (n = 44) Mean ± SD	Controls (n = 137) Mean ± SD	p-value (between groups)
Age at enrollment (years)	11.16 ± 4.30	14.03 ± 2.60	<0.001
Sex, No. (%)			
Male	24 (54.60)	73 (53.30)	0.88
Female	20 (45.40)	64 (46.70)	
Puberty			
Pre-pubertal	21 (47.70)	16 (11.70)	<0.001
Pubertal	23 (52.30)	121 (88.30)	
Height (cm)	141.80 ± 25.00	162.70 ± 15.00	<0.001
Weight (kg)	43.20 ± 22.40	59.20 ± 20.60	<0.001
BMI z-score	0.57 ± 0.94	0.45 ± 1.10	0.51
BMI percentile (%)	67.60 ± 26.30	62.20 ± 29.30	0.33
TMI (kg/m^3)	14.10 ± 2.50	13.50 ± 2.90	0.099
Fat mass percentage	24.10 ± 9.30	22.20 ± 9.40	0.16
Waist-to-hip ratio	0.87 ± 0.07	0.82 ± 0.07	<0.001
Waist-to-height ratio	0.46 ± 0.06	0.45 ± 0.07	0.17

Table 1. Study Population Characteristics. Abbreviations: SCBT, survivors of childhood brain tumors; SD, standard deviation; BMI, body mass index; TMI, tri-ponderal mass index.

Index (BMI, kg/m^2) and BMI z-score when validated against DXA scans in adolescents[31]. An important advantage of TMI is that it uses the same height and weight measurements used to calculate BMI. Thus, TMI may offer a feasible clinical measure to assess adiposity. However, TMI has not been validated as a measure of adiposity in SCBT. Our aim is to validate TMI as a clinical measure of adiposity in SCBT and compare this group to non-cancer controls.

Results

Population characteristics. The characteristics of participants are reported in Table 1. We included 44 SCBT (n = 20 female, 45.50%), and 137 non-cancer controls (n = 64 female, 46.70%).

The SCBT and control groups had similar sex (p = 0.88) and ethnic distribution (Caucasian SCBT: n = 34 (77.30%); controls: n = 91 (66.40%), p = 0.18). SCBT were younger than the non-cancer controls (SCBT: 11.16 ± 4.29; controls: 14.03 ± 2.56, p < 0.001), and fewer survivors were pubertal compared to controls (SCBT: n = 23 (52.30%); controls: n = 121 (88.30%), p < 0.001). Survivors had lower weight (p < 0.001) and were shorter (p < 0.001) compared to controls.

In relation to body mass measures, we confirmed previous similar trends in both survivors and controls of BMI z-score (SCBT:0.57 ± 0.94; controls: 0.45 ± 1.12, p = 0.51) and BMI percentile (SCBT: 67.60 ± 26.30%; controls: 62.20 ± 29.30%, p = 0.33).

Adiposity levels were similar between groups including fat mass percentage (%FM; SCBT: 24.10 ± 9.30%; controls: 22.20 ± 9.40%, p = 0.16) and waist-to-height ratio (WHtR) (SCBT: 0.46 ± 0.06; controls: 0.45 ± 0.07, p = 0.17). However, waist to hip ratio (WHR) was higher in SCBT when compared to non-cancer controls (SCBT: 0.87 ± 0.07; controls: 0.82 ± 0.07, p < 0.001).

Due to the age and pubertal staging differences noted, we validated the results of the analysis of the full cohort by performing a subgroup analysis that included age- and sex-matched controls. In the latter analysis age, sex, and puberty adjusted analyses revealed identical trends to those reported for the full study cohort. The data for the matched subgroup analyses are reported in Supplementary Tables S1–S3.

Tumor characteristics and treatments. The details of tumor characteristics and treatment methods are reported in Table 2.

The most common tumors in survivors were low-grade gliomas (n = 29 (65.90%)). Brain tumors were equally localized to supratentorial and infratentorial regions. The treatments included surgery (n = 29 (65.90%)), radiotherapy (n = 13 (29.50%)) and chemotherapy (n = 20 (45.50%)). Eight (18.20%) participants were being managed with a wait and see approach at the time of inclusion in the study.

The association of TMI with body mass and adiposity. To assess if TMI correlates with body mass measures and adiposity, we used Spearman's correlation test. We conducted unadjusted and age, sex, and puberty-adjusted analyses (Table 3).

TMI levels were similar between the groups (SCBT: 14.12 ± 2.54 kg/m^3; controls: 13.46 ± 2.86 kg/m^3, p = 0.10). TMI correlated with BMI z-score in both groups (Unadjusted, SCBT: ρ = 0.87; p < 0.001; controls: ρ = 0.95; p < 0.001; Adjusted, SCBT: r = 0.86; p < 0.001; controls: r = 0.94; p < 0.001).

We next assessed whether TMI correlates with measures of adiposity. TMI correlated significantly with measures of total adiposity including fat mass percentage (%FM) (Unadjusted, SCBT: ρ = 0.73; p < 0.001; controls: ρ = 0.85; p < 0.001; Adjusted, SCBT: r = 0.73; p < 0.001; controls: r = 0.88; p < 0.01). In addition, TMI correlated with measures of central adiposity, including WHR (Unadjusted, SCBT: ρ = 0.56; p < 0.001; controls: ρ = 0.38; p < 0.001; Adjusted, SCBT: r = 0.44; p < 0.01; controls: r = 0.46; p < 0.001), and WHtR correlated more strongly

Variables	No. (%)
Brain tumor type	
Non-NF-1, low grade glioma	18(40.90)
PNET/Medulloblastoma	8 (18.20)
NF-1, low grade glioma	9 (20.50)
CNS germ cell tumors	3 (6.80)
Subependymal giant cell astrocytoma	2 (4.50)
Ependymoma	2 (4.50)
Meningioma	1 (2.30)
Choroid plexus papilloma	1 (2.30)
Brain tumor location	
Supratentorial	22 (50.00)
Infratentorial	22 (50.00)
Brain tumor treatments	
Surgery	29 (65.90)
Radiotherapy	13 (29.50)
Chemotherapy	20 (45.50)
No treatment	8 (18.20)

Table 2. Brain tumor characteristics (n = 44). Abbreviations: CNS, Central Nervous System; PNET, Primitive Neuroectodermal Tumor; NF-1, Neurofibromatosis Type 1.

Group	Variable	BMI z-score	%FM	WHR	WHtR
Unadjusted					
SCBT	TMI	0.87**	0.73**	0.56**	0.69**
	BMI z-score	—	0.66**	0.55**	0.71**
Controls	TMI	0.95**	0.85**	0.38**	0.83**
	BMI z-score	—	0.80**	0.40**	0.81**
Total	TMI	0.93**	0.83**	0.45**	0.83**
	BMI z-score	—	0.78**	0.45**	0.80**
Partial Correlations - Adjusted for age, sex and puberty					
SCBT	TMI	0.86**	0.73**	0.44*	0.82**
	BMI z-score	—	0.68**	0.46*	0.72**
Controls	TMI	0.94**	0.88*	0.46**	0.87**
	BMI z-score	—	0.90**	0.39**	0.80**
Total	TMI	0.92**	0.85**	0.46**	0.86**
	BMI z-score	—	0.85**	0.41**	0.78**

Table 3. Spearman's correlation of TMI and BMI z-score with adiposity measures in SCBT and controls. *p-value < 0.05, **p-value < 0.001. Abbreviations: SCBT, survivors of childhood brain tumors; BMI, body mass index; TMI, tri-ponderal mass index; %FM, percent fat mass; WHR, waist-to-hip ratio, WHtR, waist-to-height ratio.

with TMI when compared to WHR (Unadjusted, SCBT: $\rho = 0.69$; $p < 0.001$; controls: $\rho = 0.83$; $p < 0.001$; Adjusted, SCBT: $r = 0.82$; $p < 0.001$; controls: $r = 0.87$; $p < 0.001$). There were similar trends of correlations of TMI and BMI z-score with measures of central adiposity (Table 3). Taken together, the above data indicate that TMI is a stronger predictor of total adiposity than BMI z-score and is equivalent to BMI z-score in predicting central adiposity. The correlation between TMI and BMI z-score tended to be stronger in non-cancer controls compared to SCBT.

To assess whether TMI is a predictor of body mass and adiposity in SCBT, multivariable linear regression analyses were conducted adjusting for age, sex and puberty. As radiotherapy was a significant predictor of %FM ($p = 0.002$) in SCBT, it was also adjusted for in the regression analyses.

We calculated unstandardized (B) and standardized (β) coefficients, and both trended in the same direction. Moving forward, we report on the latter coefficient (Table 4).

TMI was a strong predictor of BMI z-scores in both SCBT and controls, with a stronger trend in the latter (SCBT: $\beta = 0.867$; $p < 0.001$; controls: $\beta = 0.935$; $p < 0.001$). TMI was a strong predictor of total adiposity (%FM) in both SCBT and controls (SCBT: $\beta = 0.604$; $p < 0.001$; controls: $\beta = 0.819$; $p < 0.001$). While it had lower correlation with WHR, TMI was associated strongly with WHtR, and the strength of this association was higher in controls compared to SCBT (SCBT: $\beta = 0.793$; $p < 0.001$; controls: $\beta = 0.880$; $p < 0.001$).

Variable	Population	Standardized coefficient β	p-value	Model Summary	
				Adjusted R Square	SE of the Estimate
Dependent Variable: BMI z-score					
TMI	SCBT	0.867	<0.001	0.71	0.50
	Controls	0.935	<0.001	0.88	0.38
Dependent Variable: %FM					
TMI*	SCBT	0.604	<0.001	0.65	0.10
	Controls	0.819	<0.001	0.81	0.09
BMI z-score*	SCBT	0.584	<0.001	0.65	0.10
	Controls	0.836	<0.001	0.83	0.08
Dependent Variable: Waist-to-hip ratio					
TMI	SCBT	0.425	0.004	0.20	0.03
	Controls	0.436	<0.001	0.31	0.03
BMI z-score	SCBT	0.442	0.002	0.23	0.03
	Controls	0.370	<0.001	0.25	0.03
Dependent Variable: Waist-to-height ratio					
TMI	SCBT	0.793	<0.001	0.67	0.03
	Controls	0.880	<0.001	0.77	0.03
BMI z-score*	SCBT	0.657	<0.001	0.58	0.03
	Controls	0.804	<0.001	0.64	0.04

Table 4. Linear regression analyses of TMI in SCBT and controls adjusted for age, sex and puberty Abbreviations: SCBT, survivors of childhood brain tumors; BMI, body mass index; %FM, fat mass percentage; SE, standard error. Models were adjusted for age, sex and puberty. *Radiotherapy emerged as a significant predictor of adiposity, therefore we included it in the analysis.

The above threads of data indicate that TMI is a strong predictor of total adiposity and WHtR. The association between TMI and adiposity appears to be stronger in controls compared to SCBT for BMI z-score, %FM and WHtR.

Discussion

Survivors of childhood brain tumors are facing multiple comorbidities including cardiovascular disease and type 2 diabetes, which can impact their quality of life and lifespan[13–15,27,32–36]. The identification of predictors and markers of cardiometabolic risk may offer a path to stratify those in need of close observation and early intervention. In this study, we identified TMI as one such measure. TMI was an equally strong predictor as BMI z-score, total adiposity and WHtR, the latter being a stronger predictor of cardiometabolic risk compared to WHR[37–39]. As central adiposity is associated with adverse cardiometabolic outcomes[37–40], this is of great clinical significance, as it allows the stratification of children with higher central adiposity to a care stream with closer cardiometabolic health monitoring and early more aggressive interventions.

TMI has been validated against DXA scan-measured adiposity in the general pediatric population[31]. Our data adds to the value of TMI in the general pediatric population and in a population with chronic health needs that has not been studied previously. TMI is a promising marker of adiposity that is clinically feasible and informative. The most widely used clinical measure of body mass, BMI, is a useful population-based measure to report the presence of obesity, and is used interchangeably to report adiposity[41]. However, one of the limitations of BMI is that it may not be adequate to diagnose obesity in certain populations, including adolescents[42,43], hence the use of BMI z-score and percentile data to assess overweight and obesity in children. In addition, BMI misclassifies muscular individuals as being overweight or obese, which does not necessarily reflect their future risk of cardiometabolic disorders[44]. Furthermore, BMI has a weaker association with cardiovascular risk when compared to measures of adiposity including waist circumference and WHtR[37,45,46].

Children require special consideration in using BMI to classify obesity and adiposity. Ratios of weight over height to various powers of rho, ρ, (weight/height$^{\rho}$) have been explored to account for the effects of children's growth during puberty, and the adjustment for ρ is critical because incorrect values misclassify tall or physically advanced children as overweight[47,48]. A ρ value equal to two as used in BMI is sufficient when height is constant, however during puberty changes in height increase the ρ value[48].

In pre-school children, weight over height squared is adequate for assessing adiposity[47]. Adiposity generally declines between the ages 5–7 years before it begins to rise again, the adiposity rebound phase[49]. An earlier adiposity rebound than expected is associated with an increased risk of obesity and type 2 diabetes in adults[49–51].

As children approach the peripubertal phase of growth and development, their body composition changes with increased adiposity, especially in girls[52,53]. The value of ρ gradually rises from two to three; children who have undergone a growth spurt due to puberty tend to be heavier when compared to less mature children at the same height[47]. The increase in weight accompanying growth spurts results in higher BMI values, therefore greater values of ρ are required to offset the weight gain experienced in physically advanced children.

However, body composition changes in children become more constant as they get older and ρ decreases back to two[47,48]. Therefore, during puberty, TMI may be a more accurate measure of adiposity in children[47]. For this reason, the use of TMI is more relevant to assess body fat mass in children and, when evaluated in adults, TMI is less reliable compared to BMI when correlated with skinfold thickness[41].

Measures of adiposity in children have relied on technologies that may not be readily available in the clinical setting but have demonstrated accuracy in estimating the fat mass. DXA estimates of trunk and abdominal fat have demonstrated a strong association to total abdominal fat[28–30], while Bioelectrical impedance analysis (BIA) has been validated as a measure of adiposity against DXA[54–56]. Our results demonstrate that TMI is a strong predictor of adiposity measured using BIA, which is congruent with adiposity assessments using DXA. This is another strength of this study, as it validates TMI against BIA, a common measure of adiposity that is more easily accessible than DXA.

Our results indicate that TMI may offer a better estimate of fat mass and is a potential tool for predicting adiposity in children compared to BMI z-score. While some studies have found TMI to be an appropriate measure of adiposity in children, others have suggested BMI may still be an equivalent measure[31,57]. However, these studies often include children as young as two years of age, and weight scales over height squared in this age group that makes validating TMI as a measure of adiposity in this group a future goal of research[47,57].

There are several strengths of our study. The inclusion of non-cancer controls for comparison to the SCBT group offers validation of this measure in the general pediatric population as well as SCBT. The description of the association of TMI with measures of central adiposity is another strength, as central adiposity is not routinely assessed in clinical practice. Furthermore, the inclusion of an age and sex matched subgroup analysis validates our findings.

A larger sample size of SCBT is required to validate these results further, and to define their associations. In addition, TMI needs to be validated as a predictor of cardiometabolic outcomes which should be part of longitudinal studies.

In conclusion, TMI represents a clinically feasible measure that uses the same variables measuring BMI but demonstrate higher correlation with adiposity.

The availability of TMI as a clinical measure of adiposity will allow the stratification of patients at risk of excess adiposity to be prioritized for targeted interventions. This is critical, as these survivors are facing cardiometabolic diseases that are important emergent determinants of outcomes.

Methods

Participants. Participants were consecutively recruited from McMaster Children's Hospital (Hamilton), Ontario, Canada from November 2012 to November 2017 to partake in the Canadian Study of Determinants of Endometabolic Health in Children (CanDECIDE study)[58,59].

Children between 5–17 years of age were included. Parental informed consent was obtained for participants less than 7 years of age, and parental consent and participant assent were obtained for those 7–15 years of age. Participants provided written informed consent if they were 16 years or older. This is a secondary analysis of the CanDECIDE cohort study data and this analysis has been approved by the Hamilton Integrated Research Ethics Board. Study procedures were performed in accordance with the relevant guidelines and legal regulations.

Anthropometric and clinical measurements. Standardized questionnaires were used to collect data on age, sex, puberty, and ethnicity[58,59]. Medical records were consulted to verify and collect data regarding tumor type, location, sidedness and treatment modalities for SCBT.

Anthropometric measurements included weight measured to the nearest 0.1 kg using an electronic weighing scale (Seca, USA) and height using a stadiometer measured to the nearest 0.1 cm. BMI (kg/m^2) and TMI (kg/m^3) were determined using height and weight measurements from all participants. BMI percentile was determined from the Children's BMI Tool for Schools[60]. BMI z-scores were determined from the Centers for Disease Control and Prevention (CDC) growth chart[61].

Fat mass percentage (%FM) was used to determine adiposity in the participants that was measured with the Tanita body fat monitor (Tanita Corporation, Illinois, USA)[62].

Statistical Analysis. Statistical analyses were performed using PASW version 18 statistical package[63]. Data are presented as counts with percentages for categorical variables and means with standard deviation for continuous variables. Only participants with complete datasets were included. Box plots and visual inspection were used to identify any outliers for removal from the analysis. Normality of the data distribution was assessed using the Shapiro-Wilk test[64]. In the case that variables had non-normal distributions, data were log-transformed. Sample size was calculated using the method proposed by Norman and Streiner. We calculated that we need eight subjects per variable to detect significant differences between groups[65].

Spearman's correlations were used to assess the relationship between TMI, BMI z-score, %FM, WHR and WHtR. To assess this relationship adjusted for age, sex and puberty, we ran a Partial Correlations test. Multivariable linear regression analyses were performed to determine the association between TMI with BMI z-score and adiposity measures (%FM, WHR and WHtR), in SCBT and controls. The dependent variable was set as %FM, WHtR, WHR or BMI z-score and the independent variables included TMI, age, sex, puberty and treatment. Results were reported as standardized β coefficients and associated p-values, with statistical significance set to alpha of 0.05. A model summary, including the adjusted R Square and the Standard Error of the Estimate, were also reported.

In order to validate that age and puberty differences did not affect the results, analyses were also repeated using an age- and sex-matched control group. Control participants were matched in terms of sex distribution to SCBT participants on a one-to-one ratio and age was matched to closest value, within three years of the SCBT participants.

Data Availability

The data for the current study used for statistical analysis are available from the corresponding author upon reasonable justification.

References

1. Zimmet, P., Alberti, K. & Shaw, J. Global and societal implications of the diabetes epidemic. *Nature* **414**, 782–787 (2001).
2. Zimmet, P. Z., Magliano, D. J., Herman, W. H. & Shaw, J. E. Diabetes: a 21st century challenge. *The lancet Diabetes & endocrinology* **2**, 56–64 (2014).
3. Murray, C. J. L. & Lopez, A. D. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. *The lancet* **349**, 1436–1442 (1997).
4. Danaei, G. *et al*. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2· 7 million participants. *The Lancet* **378**, 31–40 (2011).
5. Murray, C. J. L. & Lopez, A. D. Mortality by cause for eight regions of the world: Global Burden of Disease Study. *The lancet* **349**, 1269–1276 (1997).
6. Dobbs, R. *et al*. Overcoming obesity: An initial economic analysis. 2014. *McKinsey & Company: www. mckinsey. com/mgi*, 1–106 (2014).
7. Oeffinger, K. C. *et al*. Chronic health conditions in adult survivors of childhood cancer. *New England Journal of Medicine* **355**, 1572–1582 (2006).
8. Meacham, L. R. *et al*. Cardiovascular risk factors in adult survivors of pediatric cancer—a report from the childhood cancer survivor study. *Cancer Epidemiology and Prevention Biomarkers* **19**, 170–181 (2010).
9. Sasaki, K., Srikanthan, A., Baxter, N. & Lega, I. Diabetes Mellitus in Childhood Cancer Survivors: A Systematic Review. *Canadian Journal of Diabetes* **41**, S27 (2017).
10. Bowers, D. C. *et al*. Late-occurring stroke among long-term survivors of childhood leukemia and brain tumors: a report from the Childhood Cancer Survivor Study. *Journal of Clinical Oncology* **24**, 5277–5282 (2006).
11. Gurney, J. G. *et al*. Endocrine and cardiovascular late effects among adult survivors of childhood brain tumors. *Cancer* **97**, 663–673 (2003).
12. Meacham, L. R. *et al*. Diabetes mellitus in long-term survivors of childhood cancer: increased risk associated with radiation therapy: a report for the childhood cancer survivor study. *Archives of internal medicine* **169**, 1381–1388 (2009).
13. Mertens, A. C. *et al*. Late mortality experience in five-year survivors of childhood and adolescent cancer: the Childhood Cancer Survivor Study. *Journal of Clinical Oncology* **19**, 3163–3172 (2001).
14. Prasad, P. K., Signorello, L. B., Friedman, D. L., Boice, J. D. & Pukkala, E. Long-term non-cancer mortality in pediatric and young adult cancer survivors in Finland. *Pediatric blood & cancer* **58**, 421–427 (2012).
15. Samaan, M. C. & Akhtar-Danesh, N. The impact of age and race on longevity in pediatric astrocytic tumors: A population-based study. *Pediatric blood & cancer*, https://doi.org/10.1002/pbc.25522 (2015).
16. Ward, E., DeSantis, C., Robbins, A., Kohler, B. & Jemal, A. Childhood and adolescent cancer statistics, 2014. *CA: a cancer journal for clinicians* **64**, 83–103 (2014).
17. Poirier, P. *et al*. Obesity and cardiovascular disease. *Arteriosclerosis, thrombosis, and vascular biology* **26**, 968–976 (2006).
18. Nayga, R. M. Jr. Obesity and heart disease awareness: a note on the impact of consumer characteristics using qualitative choice analysis. *Applied Economics Letters* **4**, 229–231 (1997).
19. Wheelock, V. Healthy eating: the food issue of the 1990s. *British food journal* **94**, 3–8 (1992).
20. Romero-Corral, A. *et al*. Normal weight obesity: a risk factor for cardiometabolic dysregulation and cardiovascular mortality. *European heart journal* **31**, 737–746 (2009).
21. Vatten, L. J., Nilsen, T. I. L., Romundstad, P. R., Drøyvold, W. B. & Holmen, J. Adiposity and physical activity as predictors of cardiovascular mortality. *European Journal of Cardiovascular Prevention & Rehabilitation* **13**, 909–915 (2006).
22. Wajchenberg, B. L. Subcutaneous and visceral adipose tissue: their relation to the metabolic syndrome. *Endocrine reviews* **21**, 697–738 (2000).
23. Poirier, P. *et al*. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss. *Circulation* **113**, 898–918 (2006).
24. Juonala, M. *et al*. Childhood adiposity, adult adiposity, and cardiovascular risk factors. *New England Journal of Medicine* **365**, 1876–1885 (2011).
25. Haffner, S. M. Abdominal adiposity and cardiometabolic risk: do we have all the answers? *The American journal of medicine* **120**, S10–S16 (2007).
26. Wang, K. W. *et al*. PS1-176 Where Have All the Fat Cells Gone? A Comparative Analysis of Adiposity Patterns in Childhood Brain Tumor Survivors and Non-Cancer Controls. *Canadian Journal of Neurological Sciences* **43**, S11–S11 (2016).
27. Wang, K. W. *et al*. Overweight, obesity and adiposity in survivors of childhood brain tumours: a systematic review and meta-analysis. *Clinical Obesity* (2017).
28. Clasey, J. L. *et al*. The use of anthropometric and dual-energy X-ray absorptiometry (DXA) measures to estimate total abdominal and abdominal visceral fat in men and women. *Obesity* **7**, 256–264 (1999).
29. Glickman, S. G., Marn, C. S., Supiano, M. A. & Dengel, D. R. Validity and reliability of dual-energy X-ray absorptiometry for the assessment of abdominal adiposity. *Journal of Applied Physiology* **97**, 509–514 (2004).
30. Huang, T. T. K., Watkins, M. P. & Goran, M. I. Predicting total body fat from anthropometry in Latino children. *Obesity* **11**, 1192–1199 (2003).
31. Peterson, C. M. *et al*. Tri-Ponderal Mass Index vs Body Mass Index in Estimating Body Fat During Adolescence. *JAMA pediatrics* (2017).
32. Chambless, L. B., Parker, S. L., Hassam-Malani, L., McGirt, M. J. & Thompson, R. C. Type 2 diabetes mellitus and obesity are independent risk factors for poor outcome in patients with high-grade glioma. *Journal of neuro-oncology* **106**, 383–389 (2012).
33. Nader, P. R. *et al*. Identifying risk for obesity in early childhood. *Pediatrics* **118**, e594–e601 (2006).
34. Lustig, R. H. *et al*. Risk factors for the development of obesity in children surviving brain tumors. *The Journal of Clinical Endocrinology & Metabolism* **88**, 611–616 (2003).
35. Pui, C. H. *et al*. Treatment outcomes in black and white children with cancer: results from the SEER database and St Jude Children's Research Hospital, 1992 through 2007. *J Clin Oncol* **30**, 2005–2012, https://doi.org/10.1200/JCO.2011.40.8617 (2012).
36. Wang, K.-W. *et al*. Adiposity in childhood brain tumors: a report from the Canadian Study of Determinants of Endometabolic Health in Children (CanDECIDE Study). *Scientific reports* **7**, 45078 (2017).
37. Savva, S. C. *et al*. Waist circumference and waist-to-height ratio are better predictors of cardiovascular disease risk factors in children than body mass index. *International journal of obesity* **24**, 1453 (2000).
38. Savva, S. C., Lamnisos, D. & Kafatos, A. G. Predicting cardiometabolic risk: waist-to-height ratio or BMI. A meta-analysis. *Diabetes, metabolic syndrome and obesity: targets and therapy* **6**, 403 (2013).
39. Sayeed, M. A. *et al*. Waist-to-height ratio is a better obesity index than body mass index and waist-to-hip ratio for predicting diabetes, hypertension and lipidemia. *Bangladesh Medical Research Council Bulletin* **29**, 1–10 (2003).
40. Ali, O. *et al*. Obesity, central adiposity and cardiometabolic risk factors in children and adolescents: a family-based study. *Pediatric obesity* **9** (2014).
41. Keys, A., Fidanza, F., Karvonen, M. J., Kimura, N. & Taylor, H. L. Indices of relative weight and obesity. *Journal of chronic diseases* **25**, 329–343 (1972).

42. Maynard, L. M. *et al*. Childhood Body Composition in Relation to Body Mass Index. *Pediatrics* **107**, 344–350 (2001).
43. Quetelet, A. *Physique sociale, ou essai sur le développement des facultés de l'homme*. Vol. 2 (C. Muquardt, 1869).
44. Witt, K. A. & Bush, E. A. College athletes with an elevated body mass index often have a high upper arm muscle area, but not elevated triceps and subscapular skinfolds. *Journal of the American Dietetic Association* **105**, 599–602 (2005).
45. Yusuf, S. *et al*. Obesity and the risk of myocardial infarction in 27 000 participants from 52 countries: a case-control study. *The Lancet* **366**, 1640–1649 (2005).
46. Wells, J. C. K. Commentary: the paradox of body mass index in obesity assessment: not a good index of adiposity, but not a bad index of cardio-metabolic risk. *International journal of epidemiology* **43**, 672 (2014).
47. Cole, T. J. Weight/height^p compared to weight/height^2 for assessing adiposity in childhood: influence of age and bone age on p during puberty. *Annals of human biology* **13**, 433–451 (1986).
48. Franklin, M. F. Comparison of weight and height relations in boys from 4 countries. *The American journal of clinical nutrition* **70**, 157S–162S (1999).
49. Whitaker, R. C., Pepe, M. S., Wright, J. A., Seidel, K. D. & Dietz, W. H. Early adiposity rebound and the risk of adult obesity. *Pediatric0s* **101**, e5–e5 (1998).
50. Rolland-Cachera, M.-F. *et al*. Adiposity rebound in children: a simple indicator for predicting obesity. *The American journal of clinical nutrition* **39**, 129–135 (1984).
51. Eriksson, J. G., Forsen, T., Tuomilehto, J., Osmond, C. & Barker, D. J. P. Early adiposity rebound in childhood and risk of Type 2 diabetes in adult life. *Diabetologia* **46**, 190–194 (2003).
52. Kaplowitz, P. B. Link between body fat and the timing of puberty. *Pediatrics* **121**, S208–S217 (2008).
53. Kaplowitz, P. B., Slora, E. J., Wasserman, R. C., Pedlow, S. E. & Herman-Giddens, M. E. Earlier onset of puberty in girls: relation to increased body mass index and race. *Pediatrics* **108**, 347–353 (2001).
54. Kabiri, L. S., Hernandez, D. C. & Mitchell, K. Reliability, validity, and diagnostic value of a pediatric bioelectrical impedance analysis scale. *Childhood Obesity* **11**, 650–655 (2015).
55. Tyrrell, V. J. *et al*. Foot-to-foot bioelectrical impedance analysis: a valuable tool for the measurement of body composition in children. *International Journal of Obesity & Related Metabolic Disorders* **25** (2001).
56. Beeson, W. L. *et al*. Comparison of body composition by bioelectrical impedance analysis and dual-energy X-ray absorptiometry in Hispanic diabetics. *International journal of body composition research* **8**, 45 (2010).
57. Mei, Z. *et al*. Validity of body mass index compared with other body-composition screening indexes for the assessment of body fatness in children and adolescents. *The American journal of clinical nutrition* **75**, 978–985 (2002).
58. Samaan, M. C., Thabane, L., Burrow, S., Dillenburg, R. F. & Scheinemann, K. Canadian Study of Determinants of Endometabolic Health in ChIldrEn (CanDECIDE study): a cohort study protocol examining the mechanisms of obesity in survivors of childhood brain tumours. *BMJ open* **3**, e002869, https://doi.org/10.1136/bmjopen-2013-002869 (2013).
59. Samaan, M. C. *et al*. Recruitment feasibility to a cohort study of endocrine and metabolic health among survivors of childhood brain tumours: a report from the Canadian study of Determinants of Endometabolic Health in ChIldrEn (CanDECIDE). *BMJ Open* **4**, e005295, https://doi.org/10.1136/bmjopen-2014-005295 (2014).
60. Nihiser, A. J. *et al*. Body mass index measurement in schools. *J Sch Health* **77**, 651–671; quiz 722-654, https://doi.org/10.1111/j.1746-1561.2007.00249.x (2007).
61. Kuczmarski, R. J. *et al*. 2000 CDC Growth Charts for the UnitedStates: methods and development. *Vital Health Stat* **11**, 1–190 (2002).
62. Wang, K. W. *et al*. Adiposity in childhood brain tumors: A report from the Canadian Study of Determinants of Endometabolic Health inChildren (CanDECIDE Study). *Scientific reports* **7**, 45078, https://doi.org/10.1038/srep45078 (2017).
63. SPSS Inc. PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc. (2009).
64. Ghasemi, A. & Zahediasl, S. Normality tests for statistical analysis: a guide for non-statisticians. *International journal of endocrinology and metabolism* **10**, 486 (2012).
65. Norman, G. R. & Streiner, D. L. PDQ Statistics. 3rd Edition (2003).

Acknowledgements

We would like to thank the participants as well as their families for participating in the study. We would also like to thank the staff for assisting in the recruitment of participants.

Author Contributions

M.C.S. is the guarantor of this study. E.D.S., K.W.W., A.F., D.L.J., S.M.Z., S.R.R., S.B., L.T. and M.C.S. were involved in defining the research question and study design. K.W.W. and E.D.S. were responsible for participant recruitment and data collection and were supported by A.F., S.B., D.L.J. and S.M.Z. Support in research methods and statistical analyses were provided by M.C.S. and L.T. The interpretation of the data was completed by E.D.S., K.W.W., A.F., D.L.J., S.M.Z., S.R.R., S.B., L.T. and M.C.S. E.D.S. and M.C.S. drafted the manuscript which was reviewed by all authors, who agreed with its contents.

Additional Information

Supplementary information accompanies this paper at https://doi.org/10.1038/s41598-018-34602-5.

Competing Interests: The authors declare no competing interests.

Publisher's note: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.