THE BUILT ENVIRONMENT & BODY MASS IN SURVIVORS OF CHILDHOOD BRAIN TUMORS VERSUS CONTROLS

THE ASSOCIATION OF THE BUILT ENVIRONMENT WITH BODY MASS MEASURES IN SURVIVORS OF CHILDHOOD BRAIN TUMORS AND NON-CANCER CONTROLS

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TITLE: The Association of the Built Environment with Body Mass Measures in Survivors of Childhood Brain Tumors and Non-Cancer Controls

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Lay Abstract

Childhood obesity is a global epidemic. Survivors of childhood brain tumors (SCBT) are a subpopulation of childhood cancer survivors who exhibit numerous comorbidities including obesity. SCBT have increased amounts of adipose tissue compared to non-cancer controls at similar body mass. While tumor and treatment related drivers of obesity exist in this population, the impact of environmental factors on obesity and the fat mass are not well understood.

In this cross-sectional study, we aimed to determine the association between the built environment and body mass in SCBT and non-cancer controls. There was no association between the built environment and body mass measures in survivors. This study suggests the disproportionate importance of the biological mechanisms including the original tumors and their treatments on body mass in SCBT. Interventions to mitigate obesity and cardiometabolic risk in survivors need to focus on addressing tumor and treatment impacts.

Abstract

Background: While the obesity epidemic is impacting children, survivors of childhood brain tumors (SCBT) are particularly vulnerable to obesity-driven cardiometabolic comorbidities. SCBT have excess body fat (adiposity) with similar body mass measures when compared to matched non-cancer controls. The effect of the built environment on the risk of obesity has received relatively limited attention in survivors.

Aim & Methods: The aim of this project was to determine the impact of the built environment on body mass index (BMI) percentile, body fat percentage (BF%), waist-to-hip ratio (WHR), and waist-to-height-ratio (WHtR) in SCBT and non-cancer controls. The data for this secondary analysis were derived from participants in the Canadian Study of Determinants of Endometabolic Health in Children (CanDECIDE), a prospective cohort study based at McMaster Children's Hospital, a tertiary pediatric academic center in Hamilton, Ontario, Canada. The Neighborhood Environment Walkability Scale (NEWS) was used to assess the built environment. Multivariable regression analyses were used to define the predictors of the association.

Results: The built environment was not associated with BMI percentile in SCBT and non-cancer controls including residential density (B 0.276, p value 0.436), land use mix diversity (B -0.286, p value 0.301), land use mix access (B 0.004, p value 0.993), street connectivity (B 0.297, p value 0.431), walking/cycling facilities (B 0.185, p value 0.540), neighborhood aesthetics (B 0.270, p value 0.513), safety from traffic (B -0.368, p value 0.418), and safety from crime (B -0.074, p value 0.907). The built environment was also not associated with adiposity measures (BF%: residential density B 0.031, p value 0.851, land use mix diversity B -0.082, p value 0.513, land use mix access B -0.036, p value 0.861, street connectivity B 0.309, p value 0.055, walking/cycling facilities B 0.109, p 0.439, neighborhood aesthetics B 0.127, p value 0.503,

safety from traffic B -0.047, p value 0.825, and safety from crime B -0.154, p value 0.601; WHR: residential density B -0.042, p value 0.362, land use mix diversity B 0.043, p value 0.131, land use mix access B -0.028, p value 0.558, street connectivity B -0.044, p value 0.252, walking/cycling facilities B 0.026, p value 0.476, neighborhood aesthetics B 0.062, p value 0.137, safety from traffic B -0.048, p value 0.336, and safety from crime B -0.083, p value 0.239; WHtR: residential density B 0.011, p value 0.865, land use mix diversity B 0.033, p value 0.462, land use mix access B -0.032, p value 0.662, street connectivity B 0.021, p value 0.720, walking/cycling facilities B 0.042, p value 0.493, neighborhood aesthetics B 0.018, p value 0.790, safety from traffic B -0.020, p value 0.789, and safety from crime B -0.086, p value 0.392).

Conclusion: The results of this study suggest that the built environment has less of an impact than brain tumors and their treatments on driving body mass and fat mass changes in SCBT. The use of lifestyle interventions may need to be combined with pharmacotherapies in the treatment of obesity in SCBT.

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List of Abbreviations and Symbols

B = unstandardized regression coefficient

BF% = body fat percentage

BMI = body mass index

CanDECIDE = Canadian Study of Determinants of Endometabolic Health in Children

CI = confidence interval

HO = hypothalamic obesity

NEWS = neighborhood environment walkability scale

PCA = principal component analysis

SCBT = survivors of childhood brain tumors

SD = standard deviation

VIF = variance inflation factor

WHR = waist-to-hip ratio

WHtR = waist-to-height ratio

Declaration of Academic Achievement

I declare that I am the sole author of this thesis. My supervisor, Dr. M. Constantine Samaan, and the members of my thesis committee, Dr. Adam Fleming and Dr. Lawrence Mbuagbaw, have provided their expertise and feedback to support the completion of this work. I have designed the research question, performed all statistical analyses, and interpreted the results with the guidance of my supervisor and committee members.

Chapter 1: Introduction

1.1 Childhood Obesity

The global prevalence of childhood obesity has risen in past decades.[1] In 2022, around 37 million of those 5 years and younger were overweight, and >390 million 5–19-year-olds were overweight, of whom 160 million had obesity.[2] While the rates of obesity in children have stabilized in many high-income countries, childhood obesity remains a global epidemic.[3] Obesity is a multifactorial disease and, on a lifestyle level, it is characterized by excessive weight gain with an imbalance between energy intake and expenditure,[4] which can include a high intake of refined carbohydrates or processed foods, in addition to sedentary lifestyles with the use of technology.[1] However, numerous drivers of weight gain include biological, behavioural, genetic, and environmental factors that drive obesity in the pediatric population.[1] Examples of these factors include maternal health-related issues, changes in weight status in infancy, and the expansion of obesogenic environments, which promote children and adolescents' consumption of excess calories coupled with sedentary lifestyles that reduce opportunities to engage in physical activity.[1]

Children and adolescents who develop obesity may continue living with obesity in adulthood.[5] Therefore, these children's risk of type 2 diabetes mellitus, hypertension, liver disease, and cardiovascular disease later in life is increased.[1,5,6] Children living with obesity also experience several psychological comorbidities, including behavioural and emotional disorders such as depression and low self-esteem.[1,6,7]

Certain groups are at risk of obesity. Indigenous children experience higher rates of obesity compared to non-Indigenous children, bearing the high burden of this chronic disease.[8] Additionally, children in low-income settings exhibit higher weight status versus high-income

households.[9] Due to the risk of adverse outcomes in children living with obesity, there is a requirement for strategies to manage obesity and the comorbidities associated with it.

1.2 Survivors of Childhood Brain Tumors (SCBT)

Survivors of childhood brain tumors (SCBT) constitute a special group of pediatric cancer survivors. Due to the breakthroughs in diagnostic neuroimaging modalities and treatment strategies, survival rates among SCBT have increased substantially over the past few decades.[10] The five-year survival rate of SCBT is >75%.[11] Despite the improvement in survival, attention has shifted to the complications associated with the tumors and their treatments in SCBT. This population exhibits vulnerability to the development of obesity[12-14] and cardiometabolic disorders, including diabetes mellitus and cardiovascular disease.[13,15,16] There are several reasons for excess body mass in SCBT which can include hypothalamic-pituitary damage caused by tumor or cranial irradiation,[17-19] reduced exercise tolerance,[20] and the use of obesogenic drugs including steroids, antidepressants, antipsychotics, and antiepileptic medications.[19] Importantly, studies have illustrated that although SCBT exhibit similar body mass index (BMI) z-scores when compared to non-cancer controls, this population have higher levels of adiposity.[21,22] Children who present with normal weight based on BMI criteria can have increased total and central adiposity that may remain undetected, given their normal BMI.[23]

Therefore, it is imperative to increase awareness of excess adiposity for clinicians, and to create interventions that target obesity and adiposity in this population. These interventions may modify the risk of obesity-related comorbidities.

1.3 The Built Environment

There is increasing attention being given to understanding the link between the built environment and pediatric obesity.[24,25] The built environment is defined as the spaces in which people work, play, and live.[26] The built environment consists of environmental characteristics that make up the layout of a community which can include neighborhood design, roads, buildings, food sources, and recreational facilities.[26] The built environment plays a significant part in daily life as the way neighborhoods are built can facilitate walking and physical activity behaviors, create a healthy food environment, and provide spaces for children to play that is dependent on the amount of parks available.[26] Importantly, walkable spaces have the potential to promote physical activity among children by integrating characteristics such as green spaces, parks, and recreational facilities in neighborhood designs.[25] Walkability is the term used to summarize the characteristics of the environment that facilitate walking engagement.[27,28]

Additionally, it is reported that people living in high walkability neighborhoods, including those with non-residential land uses and streets with small sections, exhibit increased physical activity levels compared to people in low walkability areas.[27] Therefore, the built environment can potentially be modified to manage childhood obesity by creating spaces in which children have access to healthy food choices and ensuring that children can actively participate in physical activity are important considerations for promoting healthy weight trajectories.

1.4 Gaps in the Literature

Although childhood obesity and its link to the built environment have been studied, it is unclear how the latter impacts body mass and adiposity in SCBT. Also, the evidence regarding the built environment's effects on weight and body mass among children has been inconsistent.

There have been no studies investigating the impact of the built environment on body mass measures in SCBT. Therefore, this thesis project was designed to assess the association of the built environment with body mass measures in children with and without brain tumors.

Chapter 2: The Association of the Built Environment with Body Mass Measures in Survivors of Childhood Brain Tumors and Non-Cancer Controls

ABSTRACT

Background: Obesity is one comorbidity that survivors of childhood brain tumors (SCBT) deal with that may increase cardiometabolic risk. Exploring the environment and body mass measures associations in SCBT can provide insights on the mechanisms driving obesity and increased adiposity in this population and may help with the development of prevention approaches and treatments to improve cardiometabolic outcomes.

Objectives: The goal of this study was to determine the links between the built environment and body mass measures in SCBT and controls.

Methods: This was a secondary cross-sectional analysis deploying the Canadian Study of Determinants of Endometabolic Health in Children (CanDECIDE) study data. Sixty-four SCBT and 121 non-cancer controls were included. Body mass measures encompassed body mass index (BMI) percentile, body fat percentage (BF%), waist-to-hip ratio (WHR), and waist-to-height ratio (WHtR). The Neighborhood Environment Walkability Scale (NEWS) was used to assess the built environment. Multivariable linear regression analyses were used to define the links between the built environment and body mass measures, adjusted for age, sex, maternal ethnicity, and diagnosis. Additional factors included in the model encompassed annual family income, diet, screen time, and maternal BMI.

Results: There was no association between BMI percentile and NEWS domains including residential density (B 0.276, p value 0.436), land use mix diversity (B -0.286, p value 0.301), land use mix access (B 0.004, p value 0.993), street connectivity (B 0.297, p value 0.431), walking/cycling facilities (B 0.185, p value 0.540), neighborhood aesthetics (B 0.270, p value 0.513), safety from traffic (B -0.368, p value 0.418), and safety from crime (B -0.074, p value 0.907). The same trend emerged with adiposity (BF%: residential density B 0.031, p value 0.851,

land use mix diversity B -0.082, p value 0.513, land use mix access B -0.036, p value 0.861, street connectivity B 0.309, p value 0.055, walking/cycling facilities B 0.109, p 0.439, neighborhood aesthetics B 0.127, p value 0.503, safety from traffic B -0.047, p value 0.825, and safety from crime B -0.154, p value 0.601; WHR: residential density B -0.042, p value 0.362, land use mix diversity B 0.043, p value 0.131, land use mix access B -0.028, p value 0.558, street connectivity B -0.044, p value 0.252, walking/cycling facilities B 0.026, p value 0.476, neighborhood aesthetics B 0.062, p value 0.137, safety from traffic B -0.048, p value 0.336, and safety from crime B -0.083, p value 0.239; WHtR: residential density B 0.011, p value 0.865, land use mix diversity B 0.033, p value 0.462, land use mix access B -0.032, p value 0.662, street connectivity B 0.021, p value 0.720, walking/cycling facilities B 0.042, p value 0.493, neighborhood aesthetics B 0.018, p value 0.790, safety from traffic B -0.020, p value 0.789, and safety from crime B -0.086, p value 0.392).

Conclusion: The body mass and adiposity measures in this study did not seem influenced by domains of the built environment. These findings may argue that the tumors and their treatments are one driver of body mass in SCBT and that the built environment may not be a main driver of body mass. However, this finding also brings the question of what the best obesity intervention is. It is likely the combination of lifestyle modification and pharmacotherapies are needed to treat obesity in survivors.

Keywords: pediatric, obesity, adiposity, pediatric brain tumors, survivorship

INTRODUCTION

The most common solid tumors in children are brain tumors that also have become the main cause of cancer-related deaths in children.[29] Advances in management have improved survival in these patients,[10] leading to the emergence of a new population of survivors of childhood brain tumors (SCBT). The current survival rates exceeding 75% at five years post management.[11] However, improved survival has been associated with vulnerability to metabolic morbidities including obesity,[12-14] that can drive cardiometabolic diseases.[13,15,16] SCBT have adverse cardiovascular risk profiles when compared to non-cancer controls and exhibit early biomarkers of cardiovascular disease including elevated low-density lipoprotein cholesterol, increased insulin resistance, and excess total body fat mass.[30]

There are multiple reasons for the susceptibility to gain weight in SCBT such as hypothalamic-pituitary damage caused by radiation therapy[17-19] and reduced exercise tolerance.[20]

In addition, other factors that contribute to weight gain in SCBT can include obesogenic drugs such as steroids, antidepressants, antipsychotics, and antiepileptic medications.[19] Furthermore, SCBT have higher total and central levels of adiposity versus controls, which can be associated with increased cardiometabolic risk.[21,22] Adiposity measures including body fat percentage (BF%), waist-to-hip ratio (WHR), and waist-to-height ratio (WHtR) are more robust when compared to body mass index (BMI) in predicting cardiometabolic health,[31] with WHtR in pediatric population being a predictor of central adiposity and metabolic and cardiovascular health.[32-34]

Childhood obesity is driven by biological, behavioral, genetic, and the environment.[1]

Importantly, the built environment has been highlighted as a potential contributor to weight gain in children.[26] The built environment refers to major physical spaces such as buildings, streets,

homes, playgrounds, and other infrastructure in which individuals live, work, and play.[26] A built environment that can promote healthy weight trajectories among children consists of features such as walkable neighborhood designs, access to safe spaces, and the availability of local stores that offer healthy food choices.[26] Residents living in high walkability neighborhoods have been linked to lower body mass measures.[27,35,36] In addition, built environment features such as buildings, transportation infrastructure, and land use impact the physical activity levels of residents.[26] Green spaces, parks, and recreational facilities may have an influence on child weight status,[25] suggesting that altering the built environment can be a part of the multiprong approach to manage obesity. As survivors of childhood cancers are generally inactive,[37] there is a growing need in understanding the impact of the built environment on obesity risk in this population. Currently, there are no studies on the association between the environmental contributors of weight gain in SCBT.

We tested the hypothesis that in SCBT, there is an association between the built environment and BMI-based measures, when compared to non-cancer controls. The secondary hypothesis was that in SCBT, there is an association between the built environment and measures of adiposity when compared to non-cancer controls. The primary objective of this study included the assessment of the impact of the built environment on BMI percentile in SCBT versus controls. The secondary objective was to assess the impact of the built environment on measures of adiposity (BF%, WHR, and WHtR) in SCBT and controls.

MATERIAL AND METHODS

Study design and participants

This was a secondary cross-sectional analysis of data from the Canadian Study of Determinants of Endometabolic Health in Children (CanDECIDE), a prospective cohort study based at an academic tertiary care center in Hamilton, Ontario, Canada-McMaster Children's Hospital. The study protocol and its feasibility has been published.[38,39] The study was granted approval from the Hamilton Integrated Research Ethics Board. As previously reported, inclusion criteria included children 5 years and older who are either lean, overweight, or obese as defined by BMI percentile.[38] The SCBT group was recruited from the Neurooncology clinics in the hospital. The non-cancer controls encompassed children recruited from some clinics within the hospital where they were attending for different reasons and were healthy otherwise and had returned to normal health by the time they were enrolled in the study. For example, we recruited children who were attending the orthopedics clinic who were attending for sprains or fractures that were healed and children had returned to normal function and activity by the time they were assessed for study participation. The other group of healthy children was recruited from the local community.[39] Participants were recruited between November 2012 to November 2016. Participants were excluded due to active infections or a history of infections within two weeks prior to participation, history of autoimmune disease, or usage of immunosuppressive therapy or systemic steroids higher than the maintenance dose of (6-8 mg/m^2/day), or a history of smoking.[38,39] Participants 16 years of age or older provided their own written informed consent, while guardians of 7-15 years of age children provided written informed consent and participants signed assent forms. A parent or guardian provided written informed consent for participants under 7 years of age.[38]

Sociodemographic and clinical data

Sociodemographic data included self-reported age, sex, maternal ethnicity, and annual family income. Anthropometric measures included height measured by 0.1 cm increments using a stadiometer and weight quantified to the nearest 0.1 kg using a weighing scale.

Total adiposity was determined by measuring body fat percentage using the Tanita body fat monitor for children (Tanita Corporation, Illinois, USA). Waist-to-hip and waist-to-height ratios were measured for central adiposity by using a spring-loaded tape measure to 0.1 cm increments followed by ratio calcuations.[38,39] Participant and maternal BMI were calculated, and BMI z-scores and percentiles were computed using the Centers for Disease Control and Prevention charts.[40]

Diet

The Youth and Adolescent Food Frequency Questionnaire was used to assess intake.[38,41]

Screen time

Self-reported screen time watching television or using a computer or playing computer games, and tablet or a cellphone used to measure daily screen time and reported in hours per day.

Built environment

The built environment was evaluated using the Neighborhood Environment Walkability Scale (NEWS), a validated tool that measures factors related to neighborhood design, access, and safety.[27,38] The NEWS tool is based on empirical literature from transportation and urban planning to assess various built environment domains including residential density, land use mix diversity and access, street connectivity, walking/cycling facilities, neighborhood aesthetics, safety from traffic, and safety from crime. Residential density assessed the frequency of types of neighborhood residences such as detached single-family residences to 13-story or higher

apartments/condominiums. Responses range from 1 (none) to 5 (all). Land use mix diversity was determined by walking proximity from a resident's home to various non-residential land uses including schools, stores, and fitness facilities. Responses range from a 1- to 5-minute walk (coded as 5) to a 31+ minute walk (coded as 1). Land use mix access, street connectivity, walking/cycling facilities, neighborhood aesthetics, safety from traffic, and safety from crime included responses from 1 (strongly disagree) to 4 (strongly agree). Excluding residential density, all built environment domain scores are computed by calculating the mean across all subscale items. Residential density items were weighted relative to the average density of single-family detached residences and values were then summed. Higher scores on the NEWS tool reflect higher walkability within neighborhoods by illustrating favorable built environment characteristics that facilitate walking and cycling behaviors.[27]

Statistical Analysis

Sample size calculation was performed using Norman and Streiner calcuations.[42] In addition, linear regression models require a minimum of two subjects per variable to adequately estimate regression coefficients and confidence intervals.[43] Therefore, the sample size of 64 SCBT and 121 non-cancer controls provided adequate power for this analysis. Demographic data and baseline variables are reported using descriptive analyses based on variable type. Continuous variables reporting includes the mean (SD), and categorical variables are reported as numbers (%). Chi-square tests and independent samples t-tests were used to compare SCBT and non-cancer controls for categorical and continuous variables, respectively. To test for normality, the Shapiro-Wilk test was performed to account for non-normal distributions. To test for multicollinearity, the variance inflation factor (VIF) was used and predictor variables with a VIF of less than 5 were included in the regression models.[44] To handle missing data, multiple

imputation was performed.[45] To determine the association between the built environment and body mass measures, multivariable linear regression analysis was performed. BMI status was measured by using BMI percentiles. Measures of adiposity included total adiposity (BF%) and central adiposity (WHR and WHtR) as measurements. Age, sex, maternal ethnicity, the diagnosis of SCBT versus non-cancer control, annual family income, diet, screen time, maternal BMI, and the eight built environment domains were included as predictor variables within the regression model. The unstandardized regression coefficient (B) with a 95% confidence interval (CI) and p values are reported, with alpha set at 0.05.

To create dietary variables, 21 food items were included within a principal component analysis (PCA). Dietary patterns were measured by analyzing scree plots and eigenvalues > 1.0. After the patterns were extracted, they were rotated orthogonally through varimax rotation to achieve a structure with greater interpretability. The dietary items with absolute factor loadings ≥ 0.30 were considered items that significantly adhered to each dietary pattern.[46] The PCA generated factor scores that were recorded for each participant. SPSS version 28.0 was used to conduct all analyses.[47]

RESULTS

Table 1 reports the participants' characteristics. The participants enrolled included 64 SCBT (n=26 females, 40.60%) and 121 non-cancer controls (n=56 females, 46.30%). In the SCBT group, the brain tumor types included non-Neurofibromatosis-1 (n=25, 39.10%) and Neurofibromatosis-1 related low-grade glioma (n=10, 15.60%), medulloblastoma/primitive neuro-ectodermal (n=12, 18.80%), craniopharyngioma (n=2, 3.10%), ependymoma (n=2, 3.10%), choroid plexus papilloma (n=1, 1.60%), meningioma (n=1, 1.60%), atypical

teratoid/rhabdoid (n=1, 1.60%), central nervous system germ cell tumor (n=3, 4.70%), and other (n=7, 10.90%). The average time since diagnosis of a brain tumor was reported to be 5.60 ± 5.10 years. Treatment modalities included surgery (n=41, 64.10%), radiotherapy (n=22, 34.40%), chemotherapy (n=27, 42.20%), and observation (n=8, 12.50%).

SCBT and non-cancer controls had similar age, sex distribution, maternal ethnicity, annual family income, BMI, BMI percentiles, and BMI z-score distributions. The SCBT group was shorter (SCBT: 148.40 ± 25.90; non-cancer controls: 162.00 ± 15.10, $p<0.001$) and had lower weight (SCBT: 50.20 ± 24.80; non-cancer controls: 59.10 ± 20.10, $p=0.013$) versus the non-cancer controls.

Additionally, SCBT exhibited a trend for higher WHR than the non-cancer control group (SCBT: 0.87 ± 0.08; non-cancer controls: 0.82 ± 0.09, $p<0.001$).

Four dietary patterns including prudent, refined carbohydrate, high protein, and western emerged from the PCA as shown in Table 3. The prudent diet included items such as fruits and vegetables. The refined carbohydrate diet included items such as white bread and potato chips. The high protein diet included items such as red meat and eggs. The western diet included items such as fried foods and desserts. The SCBT and non-cancer controls illustrated similar built environment domain scores.

Older children and adolescents exhibited lower BMI percentile and WHR (BMI percentile: B -0.591, 95% CI -1.110,-0.073, p value 0.025; WHR: B -0.075, 95% CI -0.129,-0.021, p value 0.007). Females had higher total body fat, but lower WHR compared to males (BF%: B 0.141, 95% CI 0.078,0.204, p value <0.001; WHR: B -0.015, 95% CI -0.028,-0.002, p value 0.021). Survivors had higher total body fat and WHR compared to non-cancer controls (BF%: B 0.067, 95% CI 0.003,0.131, p value 0.041; WHR: B 0.018, 95% CI 0.001,0.034, p value 0.035).

Maternal BMI was associated with increases in participants' BMI, total body fat, and WHtR (BMI percentile: B 0.980, 95% CI 0.353,1.607, p value 0.002; BF%: B 0.486, 95% CI 0.222,0.749, p value <0.001; WHtR: B 0.160, 95% CI 0.069,0.251, p value <0.001).

The results of the multivariable regression analyses illustrated no associations between each of the built environment characteristics in the NEWS tool and body mass measures (BMI percentile: residential density B 0.276, 95% CI -0.419,0.972, p value 0.436, land use mix diversity B -0.286, 95% CI -0.829,0.257, p value 0.301, land use mix access B 0.004, 95% CI -0.919,0.927, p value 0.993, street connectivity B 0.297, 95% CI -0.446,1.041, p value 0.431, walking/cycling facilities B 0.185, 95% CI -0.408,0.778, p value 0.540, neighborhood aesthetics B 0.270, 95% CI -0.542,1.082, p value 0.513, safety from traffic B -0.368, 95% CI -1.259,0.552, p value 0.418, and safety from crime B -0.074, 95% CI -1.321,1.172, p value 0.907; BF%: residential density B 0.031, 95% CI -0.292,0.354, p value 0.851, land use mix diversity B -0.082, 95% CI -0.326,0.163, p value 0.513, land use mix access B -0.036, 95% CI -0.434,0.363, p value 0.861, street connectivity B 0.309, 95% CI -0.007,0.626, p value 0.055, walking/cycling facilities B 0.109, 95% CI -0.167,0.385, p value 0.439, neighborhood aesthetics B 0.127, 95% CI -0.246,0.500, p value 0.503, safety from traffic B -0.047, 95% CI -0.462,0.368, p value 0.825, and safety from crime B -0.154, 95% CI -0.733,0.425, p value 0.601; WHR: residential density B -0.042, 95% CI -0.129,0.044, p value 0.362, land use mix diversity B 0.043, 95% CI -0.013,0.100, p value 0.131, land use mix access B -0.028, 95% CI -0.124,0.067, p value 0.558, street connectivity B -0.044, 95% CI -0.120,0.032, p value 0.252, walking/cycling facilities B 0.026, 95% CI -0.047,0.099, p value 0.476, neighborhood aesthetics B 0.062, 95% CI -0.020,0.143, p value 0.137, safety from traffic B -0.048, 95% CI -0.147,0.050, p value 0.336, and safety from crime B -0.083, 95% CI -0.223,0.056, p value 0.239; WHtR: residential density B

0.011, 95% CI -0.117,0.139, p value 0.865, land use mix diversity B 0.033, 95% CI -0.055,0.121, p value 0.462, land use mix access B -0.032, 95% CI -0.174,0.111, p value 0.662, street connectivity B 0.021, 95% CI -0.096,0.139, p value 0.720, walking/cycling facilities B 0.042, 95% CI -0.082,0.166, p value 0.493, neighborhood aesthetics B 0.018, 95% CI -0.115,0.151, p value 0.790, safety from traffic B -0.020, 95% CI -0.167,0.127, p value 0.789, and safety from crime B -0.086, 95% CI -0.283,0.111, p value 0.392). These non-significant results suggest that the built environment may not play as large of a role in driving body mass measures in comparison to the other predictor variables included in the model such as age, sex, diagnosis of SCBT versus control, and maternal BMI. To conclude, the multivariable regression analyses did not illustrate a significant relationship between the built environment and body mass measures in SCBT and non-cancer controls, further emphasizing the need to examine other biological variables that may play a larger role in driving body mass in this population such as the original tumors and their treatments. However, these results also suggest that future interventions should focus on incorporating lifestyle modifications such as walkable built environments in the treatment of obesity and its comorbidities. The multivariable linear regression analyses are shown in Table 2.

DISCUSSION

Although the survival rates of SCBT have improved over the past years, this improved survival is associated with high risk of comorbidities, resulting in adverse health outcomes such as diabetes mellitus and cardiovascular disease.[13,15,16]

This study investigated the impact of the built environment on measures of body mass and adiposity in SCBT compared to non-cancer controls. There was no association between the

factors that assessed the built environment and body mass measures. There is growing interest in the potential role of the environmental contributors to childhood obesity.[24,25] The built environment can aid in supporting healthy weight status by providing access to spaces where children can participate in physical activity on a regular basis.[26] Thus, this study emphasizes the role of factors other than the built environment as a potential contributor to obesity and suggests that modifying the built environment is only one factor that may improve physical activity and contribute to the management of obesity in SCBT and the general pediatric population.

In SCBT, the biology of tumors and treatments can cause hypothalamic-pituitary dysfunction and drive the development of obesity.[17-19] Specifically, survivors of suprasellar brain tumors are at higher risk of weight gain.[48] Hypothalamic obesity (HO) is a severe form of obesity that arises from damage to the hypothalamus and is commonly seen in patients after undergoing treatment for a brain tumor.[49]

The hypothalamus plays an integral role in regulating body weight through balancing the intake of food and energy expenditure, thus when impaired, this creates a disruption in the biological mechanisms that control satiety and hunger signals, leading to the development of HO.[50] As SCBT are prone to the development of HO, pharmacotherapy is likely needed to combat obesity. However, there is a lack of data on the safety and efficacy of anti-obesity pharmacotherapies in the general pediatric population,[49] further illustrating the need for research in this area.

As brain tumors and treatments likely drive the development of obesity and adiposity in SCBT, pharmacotherapies combined with lifestyle interventions such as walkable built environments may be one area to explore in the management and treatment of obesity. The built environment has the potential to be an effective childhood obesity intervention as safe neighborhood designs,

access to green spaces, and low local traffic, can support healthy weight trajectories in children.[51] However, this may not be the case in SCBT.

The built environment studies have also highlighted numerous factors that may lead to differences in the built environment that children experience. Often, social inequalities, such as low family income, play a role in driving obesity in children.[52] It is reported that childhood obesity disproportionately impacts children with low-income parents as they have been linked to higher BMI when compared to children from high-income households.[9] Importantly, food insecurity and poor diet quality and has been linked to children from low-income households, increasing the risk of childhood obesity.[53]

In addition, the built environment may differ in characteristics based on geographical location. Children from rural residential settings exhibit a higher likelihood of weight gain than children from urban areas.[54] Previous research has shown that children from rural areas often experience barriers to physical activity such as increased distance to schools or recreational facilities and the need to drive to activities.[55] In a population-based study in children living with cancer, those living in rural and low-income neighborhoods illustrated higher rates of mortality which may be influenced by neighborhood-level factors such as healthcare resources and community support, further contributing to lower survival rates.[56] It is also reported that childhood cancer is accompanied by significant economic burden to families, as the costs of cancer treatment and care are associated with poor financial outcomes, with low-income households often bearing the most socioeconomic consequences.[57,58] Furthermore, this illustrates that factors including annual family income, geographic location, and the financial burden of cancer care may characterize the type of built environments children live in, potentially influencing weight status and overall health.

One study strength is assessing non-cancer controls as a comparator. As expected, both SCBT and non-cancer controls exhibited similar built environment characteristics in this study; this allowed the testing of the impact of the built environment on body mass and adiposity measures in SCBT and the general pediatric population. As SCBT have increased adiposity with comparable BMI measures versus non-cancer controls,[21,22] it was possible to independently assess the effects of walkability on measures of adiposity between the two groups.

The cross-sectional design of this study is a limitation as this design does not allow the longitudinal assessment of body mass measures or changes in the built environment or lifestyle. Furthermore, the study did not include a large enough sample size of SCBT to perform a subgroup analysis in children of low-income families or by tumor subtype.

Data from the St. Jude Lifetime Cohort Study noted that survivors of pediatric cancer who lived in high deprivation neighborhoods had poorer diet and increased body fat percentage when compared to those with less deprivation.[59] Therefore, further analyses are required to study the effects of neighborhood-level characteristics regarding low-income families of survivors of childhood cancers and contributors to weight gain.

The design of neighborhoods and communities that integrate features of urban design that facilitate physical activity among children, such as accessibility to green spaces and recreational facilities have supported healthy weight trajectories among children.[25] As SCBT experience a higher risk of obesity and its associated comorbidities and with the built environment not being linked to their body mass or adiposity,[12-14] pharmacotherapeutic interventions may be required treatments in this population.

CONCLUSION

In conclusion, these findings suggest that lifestyle modifications including a walkable built environment may need to be combined with pharmacotherapy to treat and prevent obesity and excess adiposity in SCBT.

Future focus on the importance of lifestyle as well as pharmacotherapies to mitigate chronic diseases in children by shaping the spaces in which they live, learn, and play is crucial to ensure that the potential for combined therapies may have more impact on body mass measures and metabolism and mitigation of long-term cardiovascular and metabolic risks in SCBT.

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Disclosure

The authors report no conflicts of interest in this work.

Table 1. Baseline characteristics of study participants

Variables	SCBT (n=64) Mean (SD)	Controls (n=121) Mean (SD)	p value
Age at enrollment (years)	13.10 (5.10)	14.00 (2.80)	0.187
Sex, No. (%)			
Male	38 (59.40)	65 (53.70)	0.461
Female	26 (40.60)	56 (46.30)	
Maternal ethnicity, No. (%)			
European	51 (79.70)	97 (80.20)	0.938
Other	13 (20.30)	24 (19.80)	
Annual family income, No. (%)			
≤ $20,000-$34,999	17 (26.60)	28 (23.10)	0.254
$35,000-$79,999	15 (23.40)	37 (30.60)	
$80,000+	32 (50.00)	56 (46.30)	
Height (cm)	148.40 (25.90)	162.00 (15.10)	<0.001
Weight (kg)	50.20 (24.80)	59.10 (20.10)	0.013
BMI (kg/m^2)	21.20 (5.80)	22.10 (5.40)	0.333
BMI category, No. (%)			
BMI%ile < 85	43 (67.20)	79 (65.30)	0.762
BMI%ile ≥ 85	21 (32.80)	42 (34.70)	
BMI z-score	0.46 (1.20)	0.50 (1.10)	0.808
Waist-to-hip ratio	0.87 (0.08)	0.82 (0.09)	<0.001
Waist-to-height ratio	0.47 (0.07)	0.45 (0.08)	0.073
Body fat percentage (%)	25.60 (10.60)	22.70 (10.40)	0.075
Residential density	209.50 (51.30)	216.30 (68.00)	0.449
Land use mix diversity	2.90 (0.91)	3.10 (0.82)	0.290
Land use mix access	2.90 (0.59)	3.00 (0.54)	0.077
Street connectivity	2.80 (0.55)	2.80 (0.57)	0.803
Walking/cycling facilities	2.90 (0.77)	3.10 (0.73)	0.354
Neighborhood aesthetics	3.30 (0.53)	3.20 (0.62)	0.220
Safety from traffic	2.90 (0.56)	3.00 (0.51)	0.469
Safety from crime	3.50 (0.38)	3.40 (0.47)	0.149

Abbreviations: SCBT, survivors of childhood brain tumors; SD, standard deviation; BMI, body mass index; %ile, percentile.

Table 2. Multivariable regression analyses for the association of the built environment, annual family income, diet, screen time, and maternal BMI with body mass measures adjusted for age, sex, maternal ethnicity, and diagnosis in SCBT and non-cancer controls

	Model 1: BMI%ile		**Model 2: BF%**		**Model 3: WHR**		**Model 4: WHtR**	
Variables	**B (95% CI)**	**p**	**B (95% CI)**	**p**	**B (95% CI)**	**p**	**B (95% CI)**	**p**
Age (years)	-0.591 (-1.110,-0.073)	0.025	-0.132 (-0.367,0.103)	0.272	-0.075 (-0.129,-0.021)	0.007	-0.074 (-0.163,0.015)	0.104
Sex								
Male	1		1		1		1	
Female	0.081 (-0.055,0.216)	0.241	0.141 (0.078,0.204)	<0.001	-0.015 (-0.028,-0.002)	0.021	-0.001 (-0.022,0.020)	0.930
Maternal ethnicity								
Other	1		1		1		1	
European	0.0002 (-0.173,0.174)	0.998	-0.056 (-0.139,0.027)	0.180	-0.013 (-0.029,0.004)	0.126	-0.019 (-0.048,0.009)	0.186
Diagnosis								
Control	1		1		1		1	
SCBT	-0.038 (-0.184,0.107)	0.601	0.067 (0.003,0.131)	0.041	0.018 (0.001,0.034)	0.035	0.020 (-0.004,0.043)	0.098
Annual family income								
≤ $20,000-$34,999	1		1		1		1	
$35,000-$79,999	0.050 (-0.403,0.504)	0.800	0.028 (-0.157,0.213)	0.737	0.011 (-0.042,0.063)	0.639	0.014 (-0.079,0.106)	0.725
$80,000+	0.069 (-0.230,0.367)	0.619	0.016 (-0.153,0.186)	0.829	0.015 (-0.028,0.058)	0.434	0.014 (-0.048,0.076)	0.612
Dietary pattern								
Prudent diet	-0.014 (-0.081,0.054)	0.692	-0.010 (-0.043,0.023)	0.544	-0.0002 (-0.007,0.007)	0.951	-0.004 (-0.016,0.008)	0.500
Refined carbohydrate diet	0.026 (-0.035,0.087)	0.403	0.008 (-0.023,0.039)	0.607	0.003 (-0.003,0.009)	0.367	0.007 (-0.005,0.019)	0.254
High protein diet	0.029 (-0.035,0.094)	0.367	-0.020 (-0.053,0.013)	0.227	0.0002 (-0.006,0.006)	0.957	-0.0003 (-0.010,0.010)	0.951
Western diet	-0.018 (-0.096,0.061)	0.646	0.007 (-0.023,0.037)	0.658	0.003 (-0.003,0.009)	0.321	0.004 (-0.006,0.014)	0.409
Screen time (hours/day)	0.206 (-0.084,0.495)	0.163	0.030 (-0.108,0.168)	0.667	0.014 (-0.016,0.044)	0.352	0.036 (-0.009,0.082)	0.120
Maternal BMI (kg/m^2)	0.980 (0.353,1.607)	0.002	0.486 (0.222,0.749)	<0.001	0.013 (-0.054,0.080)	0.707	0.160 (0.069,0.251)	<0.001
Residential density	0.276 (-0.419,0.972)	0.436	0.031 (-0.292,0.354)	0.851	-0.042 (-0.129,0.044)	0.362	0.011 (-0.117,0.139)	0.865
Land use mix diversity	-0.286 (-0.829,0.257)	0.301	-0.082 (-0.326,0.163)	0.513	0.043 (-0.013,0.100)	0.131	0.033 (-0.055,0.121)	0.462
Land use mix access	0.004 (-0.919,0.927)	0.993	-0.036 (-0.434,0.363)	0.861	-0.028 (-0.124,0.067)	0.558	-0.032 (-0.174,0.111)	0.662
Street connectivity	0.297 (-0.446,1.041)	0.431	0.309 (-0.007,0.626)	0.055	-0.044 (-0.120,0.032)	0.252	0.021 (-0.096,0.139)	0.720
Walking/cycling facilities	0.185 (-0.408,0.778)	0.540	0.109 (-0.167,0.385)	0.439	0.026 (-0.047,0.099)	0.476	0.042 (-0.082,0.166)	0.493
Neighborhood aesthetics	0.270 (-0.542,1.082)	0.513	0.127 (-0.246,0.500)	0.503	0.062 (-0.020,0.143)	0.137	0.018 (-0.115,0.151)	0.790
Safety from traffic	-0.368 (-1.259,0.552)	0.418	-0.047 (-0.462,0.368)	0.825	-0.048 (-0.147,0.050)	0.336	-0.020 (-0.167,0.127)	0.789
Safety from crime	-0.074 (-1.321,1.172)	0.907	-0.154 (-0.733,0.425)	0.601	-0.083 (-0.223,0.056)	0.239	-0.086 (-0.283,0.111)	0.392

Abbreviations: BMI, body mass index; %ile, percentile; B, unstandardized regression coefficient; BF%, body fat percentage; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio; CI, confidence interval; SCBT, survivors of childhood brain tumors.

Table 3. Factor loading matrix for dietary patterns in study participants

Items	Factor Loadings			
	Prudent	**Refined carbohydrate**	**High protein**	**Western**
Red Meat	–	–	0.71	–
Poultry	–	–	0.77	–
Fish	–	–	0.13	–
Fried Foods	–	–	–	0.78
Eggs	–	–	0.61	–
Snacks	–	–	–	0.35
Desserts	–	–	–	0.63
Dairy	–	0.51	0.38	–
Fruits	0.83	–	–	–
Grain	0.57	–	–	–
Potato Chips	–	0.77	–	0.32
Gelatin	–	0.89	–	–
Candies	–	–	–	0.51
Crackers	0.19	–	–	–
Peanut/other nuts	0.42	–	0.30	-0.34
White Bread	–	0.43	–	–
Dark Bread	–	–	0.34	–
Baked Goods	–	–	0.18	–
Water	0.62	–	–	–
Vegetables	0.79	0.32	–	–
Soft Drinks	-0.15	–	–	–
Total Variance (%)	13.6	12.1	8.7	8.1

Notes: Absolute values < 0.30 were not listed in the table, except for items including fish, crackers, baked goods, and soft drinks in which the highest value of factor loading is illustrated.

Chapter 3: Discussion

3.1 The Built Environment and Body Mass Measures in SCBT

While children with a diagnosis of brain tumors are surviving at high rates, the aftereffects of treatment including cardiometabolic disorders that can impact outcomes. We aimed to assess the impact of the built environment on their body mass measures.

In this study, there were no significant associations between the built environment and body mass measures including BMI percentile, BF%, WHR, and WHtR. However, age and maternal BMI were associated with BMI percentile. Female sex, the diagnosis of SCBT versus non-cancer control, and maternal BMI were associated with BF%. Age, female sex, and the diagnosis of SCBT were associated with WHR. Lastly, maternal BMI was associated with WHtR.

The results of this study are not consistent with the original hypothesis that the walkability of neighborhoods is associated with favorable body mass measures among SCBT and non-cancer controls. The results of our study are consistent with current evidence regarding the built environment and childhood weight status. A systematic review investigating the built environment as a determinant of childhood obesity found limited evidence of neighborhood walkability decreasing BMI-derived outcomes.[24] Future studies need to investigate the factors which may contribute to the health inequalities among children and impact the relationship between the built environment characteristics and weight status.[24]

This study also highlights that there are several variables that play a role in driving body mass measures in children. Maternal BMI is often reported as a contributor to a child's weight status, with studies reporting that the risk of developing childhood obesity is associated with parental weight status.[60-62] The reasons for the association of children's body mass measures with parental measures include biological or environmental factors, such as genetic contributors or impacts of the shared environment including eating similar meals and engaging in physical activity.[63]

Although there was no association with screen time and body mass measures in this study, this finding is not consistent. Adolescents who engage in more screen time are at risk of developing obesity.[64] In addition, a systematic review and meta-analysis highlighted that children and adolescents with higher screen time exhibited higher waist circumference when compared to lower screen time.[65]

Healthy diets are essential for maintaining a healthy body mass and mitigating obesity and its associated comorbidities, with studies identifying a high intake of sugary beverages and fast food to be the main dietary risk factors for obesity in children and adolescents.[66]

3.2 Biological Mechanisms of Obesity and Adiposity in SCBT

As this study investigated the impact of the built environment on body mass and adiposity measures in SCBT, it also highlighted the biological mechanisms associated with excessive weight gain in this population. In SCBT, excessive weight gain is often driven by hypothalamic-pituitary damage caused by tumors and their treatments.[17-19] As SCBT illustrate increased adiposity compared to non-cancer controls,[21,22] it is important to highlight the metabolic disturbances that may cause rapid weight gain. Radiotherapy can result in the alteration of the hypothalamic-pituitary-glandular axes in SCBT and drive obesity and the metabolic syndrome.[67] In addition, it is reported that children with tumors of the suprasellar region are at higher risk of obesity compared to tumors in other regions.[48] Therefore, the role of the biology of tumors and treatments are highlighted as one of the main drivers of obesity and adiposity in SCBT.

3.3 Future Considerations

As this study found no evidence that the built environment impacts body mass measures in SCBT, it is still important to emphasize the role of lifestyle modification in maintaining health and wellbeing in children. Also, the use of lifestyle modification may need to be combined with pharmacotherapies as a potential treatment for obesity treatment and prevention in this population. As there may be biological drivers of weight gain in SCBT, future studies need to investigate interventions to manage obesity, and especially focus on addressing the higher levels of adiposity in this population. As the pathogenesis of obesity in SCBT is more likely to be driven by the tumors and their treatments, pharmacotherapy interventions may be an approach in combination with lifestyle interventions to manage obesity. Studies that have examined the use of pharmacotherapies to treat obesity among SCBT were often of short duration, which in turn may lead to undetected long-term benefits and adverse outcomes, highlighting the need for further research in the pharmacotherapies that can be used in this population.[68]

There is a lack of pharmacotherapeutic interventions to treat obesity in the pediatric population, further emphasizing the need for research in this area to establish the efficacy of these treatments.[49] Therefore, as the use of pharmacotherapy may also be needed to prevent the rapid acceleration of weight gain in SCBT, future studies should incorporate the use of lifestyle modifications such as walkable built environments to aid in the treatment and prevention of obesity.

The built environment can drive healthy weight trajectories in children through the implementation of safe neighborhood designs, greenspaces, and low local traffic.[51]

It is important to highlight that the social determinants of health may also play a part in increasing the risk of obesity in survivors and controls. The cost of cancer treatments in some

parts of the world, and the disruption to parental ability to work can drive adverse socioeconomic outcomes when children are diagnosed with cancer. A systematic review of the impact of childhood cancer on parental socioeconomic status revealed that families of lower socioeconomic status were particularly impacted by cancer diagnoses.[58] Therefore, future studies in SCBT need to focus on the socioeconomic consequences of childhood cancer on the family and their impacts on weight trajectories in children.

Geographical location among cancer survivors has also been highlighted as a potential risk factor for weight gain, as survivors living in rural areas with lower neighborhood socioeconomic status were at higher risk of having increased body fat percentage.[59]

In conclusion, the built environment was not associated with body mass measures in SCBT and controls, highlighting the impact of the tumors and their treatments on body mass. The combination of pharmacotherapies and lifestyle modifications that include walkable built environments may be a potentially effective intervention for the treatment and prevention of obesity and adiposity in SCBT that deserve further assessment.

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