ADIPOSITY IN CHILDHOOD BRAIN TUMORS

ADIPOSITY IN CHILDHOOD BRAIN TUMORS: PREVALENCE, PREDICTORS, AND CURRENT MANAGEMENT STRATEGIES

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TITLE: Adiposity in childhood brain tumors: prevalence, predictors, and current management strategies

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LAY ABSTRACT

Brain tumors are the most common solid tumors in children. The survival rates among children with brain tumors have increased significantly over the past four decades due to advances in early detection and treatment. However, these children are at increased risk of heart disease and type 2 diabetes, and early death. Evidence has suggested obesity and excess body fat as main reasons for cardiometabolic disorders in the general population, but it is not known if obesity and excess body fat contribute to diabetes and heart disease in survivors. Therefore, the current thesis aims to explore obesity and adiposity, their predictors and any existing treatments available to survivors of childhood brain tumors (SCBT) to see if outcomes can be improved.

The results show that while survivors of childhood brain tumors have similar overweight and obesity rates to the general population when measured by the most common clinical measure, called body mass index (BMI), they in fact have higher fat mass. Furthermore, we identified birth weight as a predictor of obesity while the location of the tumors and receiving radiation therapy as predictors of the fat mass in SCBT. The results also show the lack of current effective interventions to manage obesity in SCBT. This data is critical to consider in the design and implementation of strategies to reduce heat disease and diabetes in survivors to improve their quality of life and lifespan.

ABSTRACT

Introduction: The increased survival rates of children with brain tumors is the result of decades of advancement in diagnostic and therapeutic approaches, but brought the adverse long-term effects of the treatments and tumors on these children into focus. Survivors of childhood brain tumors (SCBT) are at an increased risk of cardiometabolic disorders and premature mortality. Obesity and excess adiposity are well-established risk factor for cardiometabolic risk in the general population, but its contribution to these outcomes in survivors is unknown. More recently, adiposity has emerged as a more robust predictor of cardiometabolic risk than body mass index, the most clinically used measure of obesity. The current thesis pursued four objectives: 1) to determine the prevalence of obesity and excess adiposity in SCBT 2) to explore adiposity and its determinants in SCBT 3) to investigate the determinants of obesity in SCBT and 4) to identify potentially effective interventions to manage obesity in SCBT.

Methods: Systematic reviews and meta-analyses were used to evaluate the prevalence and interventions for overweight and obesity in SCBT while the determinants of adiposity and obesity were explored using primary data and regression analyses. General health information and brain tumors information were collected with standardized questionnaires and review of medical records. The overweight or obesity status of subjects was determined by body mass index (BMI), and adiposity profile was evaluated using percent body fat (%FM), waist-to-hip ratio (WHR) and waist-to-height ratio (WHtR).

Results: The results show no difference between the overweight and obesity rates in SCBT and non-cancer controls. However, SCBT have higher total and central adiposity. Birth weight is found to be a predictor of future BMI in SCBT, while a higher total adiposity in SCBT is predicted by having supratentorial tumors and receiving radiotherapy. Lastly, not enough evidence is available to conclude the effectiveness of lifestyle interventions, pharmacotherapy, and bariatric surgery on managing obesity in SCBT.

Conclusions: Obesity, determined by BMI, is not enough to determine cardiometabolic risks in SCBT. Total and central adiposity should be measured as well to identify high-risk group. Special attention should be paid to SCBT with high birth weight, supratentorial tumors, and having received radiotherapy. Lastly, more randomized controlled trials are needed to provide high-quality evidence to determine the effectiveness of interventions to manage obesity and improve outcomes in SCBT.

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List of Abbreviations

SCBT: Survivors of Childhood Brain Tumors

BMI: Body Mass Index

Preface

I thank the children and families who participated in the study. I also thank my supervisor, Dr. M. Constantine Samaan and my committee members, Dr. Russell de Souza, Dr. Adam Fleming, and Dr. Lehana Thabane for all the inputs and supports. In addition, I thank all the collaborators who helped with subject recruitment and study progression including Dr. Sheila Singh, Dr. Donna Johnston, Dr. Shayna Zelcer, Dr. Shahrad Rassekh, Dr. Sarah Burrow, Dr. Katrin Scheinemann, Dr. Vicky Breaky, Dr. Steven Arora, and Dr. Vladimir Belostotsky. Lastly, I could not have finished the work without the financial supports from Canadian Institutes of Health Research (CIHR) Canadian Graduate Scholarship-Master's, Ontario Graduate Scholarship. The study was also funded by Pediatric Oncology Group of Ontario (POGO).

Authors' contributions for each scholarly work were described in each Chapter. Kuan-Wen Wang is the first author of all published or submitted papers. With support from other co-authors, committee members and supervisor, Kuan-Wen Wang defined the research questions, designed the methods, collected data, performed analyses, and interpreted results. She also drafted all the papers, which were then reviewed and approved by other co-authors.

All the scholarly works were included in the thesis with permission or under license.

Chapter 1: Introduction

Brain tumors are the most common solid tumors in children, whose survival rates have significantly improved due to advances in diagnostic and treatment modalities (Dolecek, Propp, Stroup, & Kruchko, 2012; Siegel et al., 2012; Woehrer et al., 2014). As more children surviving brain tumors reach their adulthood, it is becoming apparent that this group has increased risk of premature mortality and of developing cardiometabolic diseases such as cardiovascular disease and type 2 diabetes (Gurney et al., 2003; Heikens et al., 2000; Holmqvist et al., 2014; Mertens et al., 2001; Oeffinger et al., 2006; Prasad, Signorello, Friedman, Boice, & Pukkala, 2012).

In the general population, obesity is a well-established risk factor for cardiovascular diseases and type 2 diabetes (Mathers & Loncar, 2006; Murray & Lopez, 2013; Ng et al., 2014). However, it is unclear whether the same relationship exists between obesity and cardiometabolic outcomes in survivors of childhood brain tumors (SCBT). While obesity, classified by measuring body mass index (BMI), is the most clinically utilized measure, it does have limitations of stratifying cardiometabolic risk as it misses changes in boy composition in case of increased muscle mass. More recently, the search for more robust markers of cardiometabolic risk revealed that adiposity is a more robust measure of cardiometabolic risk than BMI (Lee, Huxley, Wildman, & Woodward, 2008; Phillips et al., 2013; Savva et al., 2000). There is an urgent need to assess adiposity and its determinants in survivors, so that interventions can be designed

to mitigate the cardiometabolic chronic health risks and improve the survivor's long-term health outcomes.

The present thesis aims to comprehensively assess the prevalence of obesity and adiposity in SCBT using a systematic approach. In already published work, the protocol of the systematic review is included in Chapter 2, and the full systematic review is included in Chapter 3.

In this thesis, the association between adiposity and potential tumor, treatment and lifestyle determinants are investigated in SCBT and compared to non-cancer controls. This paper is published and is included in Chapter 4.

One important predictor of future obesity in childhood and adulthood is birth weight (Qiao et al., 2015; Schellong, Schulz, Harder, & Plagemann, 2012). The association between birth weigh and obesity and other cardiometabolic outcomes was brought to attention by David Barker and the Dutch famine cohort in the 1990's (Barker, 1999a, 1999b; Lithell et al., 1996; Painter et al., 2006; Ravelli et al., 1998; Roseboom et al., 2000). The evidence led to the concept now known as the Developmental Origins of Health and Disease (DOHaD). It describes that an adverse intrauterine environment such as undernutrition results in fetal programing *in utero* that permanently shapes the body function, structure, and metabolism of the fetus to adapt to this environment (Nistala et al., 2011; Ornoy, 2011; Wadhwa, Buss, Entringer, & Swanson, 2009). However, this adaptation becomes counterproductive when the fetus is born and exposed to a different environment. The present thesis also examines birth weight as a

predictor of obesity in SCBT and the results are reported in Chapter 5. This paper has been submitted.

Lastly, Chapter 6 includes the published protocol for the systematic review to summarize current evidence on the effectiveness of interventions to manage obesity in SCBT. The published systematic review is included in Chapter 7.

Chapter 2: Evaluating overweight and obesity prevalence in survivors of childhood brain tumors: a systematic review protocol

Kuan-Wen Wang, Adam Fleming, Sheila K. Singh, Laura Banfield, Russell J. de Souza, Lehana Thabane and M. Constantine Samaan

MCS is the guarantor. The research question was defined by KWW, MCS, AF, SKS, RJdS, and LT. LB, KWW, RJdS, LT, and MCS contributed to the development of search strategy and determination of the eligibility criteria. Data abstraction form was designed by KWW and MCS. RJdS and LT provided the methodological support for this review. KWW and MCS drafted the manuscript, and the final version was reviewed and approved by all authors

Wang KW, Fleming A, Singh SK, Banfield L, de Souza RJ, Thabane L, et al. Evaluating overweight and obesity prevalence in survivors of childhood brain tumors: a systematic review protocol. Systematic Reviews. 2017;6(1):43.

The published version of the paper is included in Appendix 1.

INTRODUCTION

Recent advances in the management of pediatric brain tumors have significantly improved survival rates [1, 2]. However, the new record longevity noted in survivors of childhood brain tumors (SCBT) is being hindered by the emergence of new comorbidities including cardiometabolic diseases like hypertension, myocardial infarction, stroke and type 2 diabetes [3-12]. The current global overweight and obesity epidemic has been blamed for the rise of these cardiometabolic disorders in the general population, but the scale of overweight and obesity and its role in driving adverse outcomes in survivors is unknown.

Of note, SCBT have several risk factors that predispose them to overweight and obesity. These include impaired satiety signals, lower physical activity, impaired mobility and coordination, pain, disrupted sleep, mental health concerns, pituitary hormonal deficiencies and medications [14-17]. To further understand the contribution of overweight and obesity to cardiometabolic risk in SCBT, there is a need to determine its scale in SCBT. This will inform the design of interventions to target overweight and obesity and their risk factors to improve cardiometabolic outcomes, quality of life, and survival rates in this population.

In this systematic review, the epidemiological data on the prevalence of overweight and obesity in SCBT will be evaluated. The primary aim of this review is to determine whether SCBT have higher rates of overweight or obesity compared to non-cancer counterparts. The secondary aim of this review is to

evaluate whether SCBT have higher adiposity compared to the general population.

METHODS

This protocol is developed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis-Protocols (PRISMA-P) statement [18, 19] (Additional file 1).

Literature Search

Searches will be conducted in MEDLINE, CINAHL, EMBASE, Cochrane Database of Systematic Review, Cochrane Central Register of Controlled Trials, PubMed and Database of Abstracts of Reviews of Effect. The following concepts along with their synonyms will be used in the search: pediatric, brain tumors, overweight/obesity, and survivors. A search strategy will be developed in consultation with a senior Health Sciences Librarian with expertise in systematic reviews. We will not set any restrictions on publication date, but will restrict our search to English language publications. A full search strategy for MEDLINE is reported in Table 1.

To identify grey literature, we will search ProQuest Dissertations and Theses A&I and Web of Science. The search in the latter database will be limited to "Conference Proceedings Citation Index- Science-1990-present". We will then search for relevant publications from the first and last authors of the relevant conference abstracts to identify articles originating from the work presented in the abstracts. The reference lists of eligible studies and relevant reviews will also be

searched to identify any additional studies. Searches will be updated to capture recent publications by setting publication date restrictions.

The search results will be de-duplicated in EndNote X7 [20] and then exported into an excel file to screen for eligible titles and abstracts. The full texts of relevant records will then be retrieved to screen against the eligibility criteria.

Study Selection and Eligibility Criteria

Two independent reviewers, who will meet after each stage to resolve conflicts and achieve consensus, will screen the title and abstract of each record. A third reviewer will be consulted when disagreements persist. The two reviewers will then independently screen the full-text of the relevant studies identified from title and abstract screening.

This review will include SCBT diagnosed under 18 years of age. The following eligibility criteria will be applied: 1) Primary research articles with observational study design including longitudinal cohort, cross-sectional, or case-control studies 2) Sample size of ≥ 10 patients as previously described [21] 3) Assessment of prevalence of overweight or obesity and/or body composition using measures including body mass index (BMI), BMI z-score, BMI percentile, waist-to-hip ratio, waist-to-height ratio, body fat, and skinfold thickness. The screening process and results will be reported in a PRISMA flow diagram, as previously described [22-24] (Figure 1).

Data Collection

We developed a data abstraction form that will be piloted by two reviewers on two eligible studies. Comments will then be incorporated to finalize the form for this specific systematic review. The abstracted data will include publication information of title, authors' names, journal name, year of publication, as well as the city and country of publication. We will also collect study details including setting, study design, eligibility criteria, sample size, study duration, and funding source. Outcome measures, primary findings, and conclusions will be collected as well.

We will extract survivors' characteristics including age at diagnosis of brain tumor, age at study enrollment, and sex. We will also extract brain tumor details including brain tumor type, location, and treatment details such as treatment period, duration since treatment completion, and types of treatments received including radiotherapy, chemotherapy, and surgery or combinations therapies with these modalities. If the study has a non-cancer comparison group, we will document the type and source of non-cancer controls used, and abstract the same data except for tumor- and treatment-related variables.

Two reviewers will perform data abstraction independently, followed by discussion to resolve discrepancies. A third reviewer will intervene to resolve persisting differences. In studies that report the data from multiple cancer types as aggregates, data specific to the brain tumor group will be extracted either through published subgroup data, or by contacting the research team to acquire the data.

We will also contact the corresponding authors of published work in attempts to obtain any missing data.

The primary outcome for this review is the prevalence of overweight or obesity estimated by BMI, BMI z-score or BMI percentile. Secondary outcomes include waist-to-hip ratio, waist-to-height ratio, body fat percentage, and skinfold thickness.

Risk of Bias & Quality Assessment

Two reviewers will independently assess the risk of bias of the eligible studies using the Newcastle Ottawa Scale (NOS) for observational studies [25]. The NOS will be adapted from its original version by considering a previously used modified version [26], so that the scale is specific to this review. The reviewers will meet and discuss their decisions to include articles and to resolve any disagreement. In the case of persisting conflict, a third reviewer will be consulted.

This adapted NOS evaluates five items pertaining to risk of bias due to sample selection and classification (2 items), confounding factors (1 item), missing data (1 item), and measurement errors (1 item). For each item, the risk of bias is rated on a scale of 0 (high risk of bias), 1-2 (moderate risk of bias) to 3 (low risk of bias). The risk of bias is rated as unclear if not enough information is provided. Descriptions with examples for each level of risk of bias are provided (Additional file 2).

The overall risk of bias is rated as low when all five items have low risk of bias or high when one or more items have high risk of bias. The overall risk of bias is considered to be moderate when not all items have low risk of bias, but there are no items with high risk of bias. If one of the items is rated as unclear, the overall risk of bias will be unclear as well.

Furthermore, we will use the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) guideline [27] to evaluate the overall quality of evidence including the risk of bias, inconsistency, indirectness, imprecision, and publication bias to determine the overall quality of evidence for each outcome.

Statistical Analysis

We will perform meta-analysis if two or more studies of similar design and population characteristics can be identified for each outcome. We expect high heterogeneity across studies. The possible sources of heterogeneity include age at diagnosis, duration and types of treatment, brain tumor type and location. Therefore, we will perform meta-analysis using a random effects model if more than ten studies are eligible, and will perform both random effects and fixed effects models if less than ten studies are identified [28].

Dichotomous and continuous outcomes will be reported as pooled odds ratio and standardized mean difference with 95% confidence intervals, respectively. In studies where multiple measurements are done, we will include the outcomes measured with the longest follow-up reported.

Both inconsistency index (I^2) and *P* values from chi-square test for homogeneity will be considered to determine the level of heterogeneity among the included studies. The threshold set by the Cochrane Collaboration will be used to interpret I^2, with >75% representing considerable heterogeneity. A *P*-value of <0.10 will be used to determine statistical significance [29]. If meta-analysis is not appropriate, heterogeneity will be evaluated by describing and comparing the study samples, methods, and designs across studies. We will perform subgroup meta-analysis by sex and receipt of radiotherapy, chemotherapy, and surgery or combination therapies with these modalities if appropriate, as it has been reported that female SCBT are at higher risk of obesity than males [7, 8, 11]. In addition, to test the impact of outliers and studies with high risk of bias on the results, we will perform sensitivity analysis by excluding these studies if ten or more studies can be identified for an outcome.

To maintain the power of the results, we will not perform sensitivity analyses if less than ten studies are eligible. If ten or more studies are identified, we will use a contour-enhanced funnel plot to investigate publication bias [30]. The plot asymmetry will be determined by Egger's test and visual inspection [30]. Otherwise, we will estimate publication bias based on the number of relevant conference abstracts that did not have published articles originating from the work presented in the abstracts [31].

We will use Review Manager software version 5.3 (RevMan 5.3) [32] to conduct meta-analysis. If Egger's test is appropriate, Comprehensive Meta-

Analysis software version 3 (CMA 3.0) will be used instead [33]. A comprehensive table for summary of findings with narrative description will be reported when less than two studies of similar design and population are eligible and meta-analysis is not appropriate.

We will report the results of this systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines using the PRISMA checklist [22, 23]. We will also document the date and reasons for any amendments to the protocol.

DISCUSSION

While record numbers of children are surviving the diagnosis of brain tumors, this survival is burdened by the high rate of comorbidities and premature mortality [10, 12, 34]. To improve the quality of the cure, detailed understanding of the factors driving comorbidities in SCBT is likely to provide therapeutic entry points to improve outcomes.

Recent evidence suggests that new emerging risk factors may be contributing to mortality in this population. With increasing longevity, SCBT are at risk of type 2 diabetes and cardiovascular diseases that appear relatively early in life [3-6, 9]. This argues for a premature aging process, whereby diseases of old age are appearing earlier in life in SCBT. This may indicate that similar overweight or obesity levels may have a disproportionately negative impact on SCBT when compared to the general population, and interventions are needed to stem the occurrence of overweight and obesity and reduce their burden in survivors.

Notable limitations of this systematic review includes the restriction of the search strategy to English language publications only, as this may lead to missing information from non-English literature. In addition, if the heterogeneity of the studies is high, this will preclude the performance of a meta-analysis. Nevertheless, this review will identify gaps in knowledge and inform better clinical practice in identifying overweight and obesity, and will help inform the need for specifically designed interventions to tackle overweight and obesity in SCBT and improve outcomes.

Additional file 1: PRISMA-P checklist. This checklist includes recommended items to address in a systematic reviews protocol and where are they reported in this protocol. (DOCX 37KB)

Additional file 2: Adapted version of a modified Newcastle-Ottawa Scale (NOS) to evaluate overweight and obesity in survivors of childhood brain tumors. This form demonstrates the adapted version of the NOS to evaluate risk of bias of the included observational studies in this systematic review. (DOCX 17KB)

ABBREVIATIONS

SCBT: Survivors of Childhood Brain Tumors; PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis-Protocols; MEDLINE: Medical Literature Analysis and Retrieval System; CINAHL: Cumulative Index to Nursing and Allied Health Literature; EMBASE: Excerpta Medica Database; BMI: Body Mass Index; NOS: Newcastle Ottawa Scale; GRADE: Grading of Recommendations, Assessment, Development and Evaluation; RevMan 5.3: Review Manager software version 5.3; CMA 3.0: Comprehensive Meta-Analysis version 3; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

DECLARATIONS

Ethics approval and consent to participate: Not applicable

Consent for publication: Not applicable

Availability of data and materials: Not applicable

Competing interests: The authors declare no competing interests.

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Authors' contributions: MCS is the guarantor. Research question was defined by KWW, MCS, AF, SKS, RJdS, and LT. LB, KWW, RJdS, LT and MCS contributed to the development of search strategy and determination of the eligibility criteria. Data abstraction form was designed by KWW and MCS. RJdS and LT provided methodological support for this review. KWW and MCS drafted the manuscript, and the final version was reviewed and approved by all authors.

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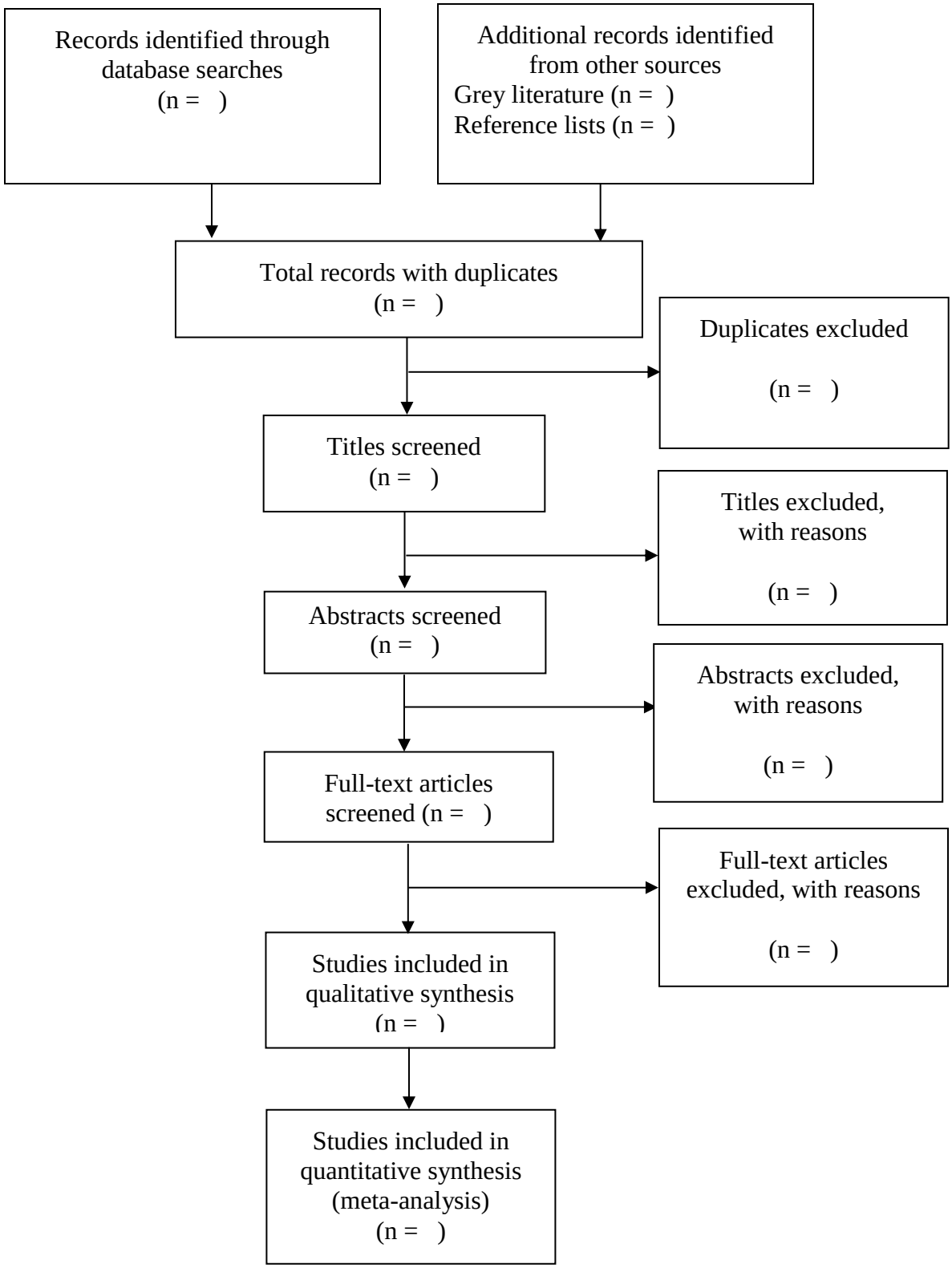
Table 1: Search Strategy for MEDLINE

#	Searches
1	exp Child/
2	child*.ab,ti,kf.
3	p?ediatric*.ab,ti,kf.
4	exp Adolescent/
5	adolescen*.ab,ti,kf.
6	youth*.ab,ti,kf.
7	teen*.ab,ti,kf.
8	kid*.ab,ti,kf.
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10	exp Brain Neoplasms/
11	exp Neuroectodermal Tumors/
12	exp Glioma/
13	glioma*.ab,ti,kf.
14	astrocytoma*.ab,ti,kf.
15	oligoastrocytoma*.ab,ti,kf.
16	astroglioma*.ab,ti,kf.
17	glioblastoma*.ab,ti,kf.
18	craniopharyngioma*.ab,ti,kf.
19	ependymoma*.ab,ti,kf.
20	subependymoma*.ab,ti,kf.
21	ependymoblastoma*.ab,ti,kf.
22	ganglioglioma*.ab,ti,kf.
23	medulloblastoma*.ab,ti,kf.
24	exp Germinoma/
25	germinoma*.ab,ti,kf.
26	Meningioma/
27	meningioma*.ab,ti,kf.
28	oligodendroglioma*.ab,ti,kf.
29	exp Neurofibromatoses/
30	neurofibromatos*.ab,ti,kf.
31	PNET*.ab,ti,kf.
32	neurocytoma*.ab,ti,kf.
33	choroid plexus papilloma*.ab,ti,kf.
34	((brain or central nervous system or CNS or brainstem or brain stem or cerebel* or cerebr* or hypothalam* or ventric* or intracranial or midline or

	choroid plexus or infratentorial or supratentorial or neuroectoderm* or germ cell*) adj5 (tumo?r* or neoplasm* or cancer*)).ab,ti,kf.
35	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
36	exp Obesity/
37	obes*.ab,ti,kf.
38	Overweight/
39	over weight.ab,ti,kf.
40	overweight.ab,ti,kf.
41	Body Weight/
42	exp Body Composition/
43	(body adj3 (mass* or size* or composition*)).ab,ti,kf.
44	(fat* adj3 (mass* or body or abdominal* or intra-abdominal* or viscera* or subcutane* or hepatic* or liver* or intramuscular* or intramyocellular*)).ab,ti,kf.
45	BMI*.ab,ti,kf.
46	Weight Gain/
47	exp "Body Weights and Measures"/
48	Anthropometry/
49	anthropometr*.ab,ti,kf.
50	grow*.ab,ti,kf.
51	overnutrition*.ab,ti,kf.
52	over nutrition*.ab,ti,kf.
53	malnutrition*.ab,ti,kf.
54	waist-height ratio*.ab,ti,kf.
55	waist to height ratio*.ab,ti,kf.
56	adipos*.ab,ti,kf.
57	((waist* or hip* or abdominal*) adj3 circumference*).ab,ti,kf.
58	(weight* adj3 (gain* or change* or fluctuat*)).ab,ti,kf.
59	waist-hip ratio*.ab,ti,kf.
60	waist to hip ratio*.ab,ti,kf.
61	skinfold thickness*.ab,ti,kf.
62	36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61
63	Survivors/
64	"Adult Survivors of Child Adverse Events"/
65	Disease-Free Survival/
66	surviv*.ab,ti,kf.

67	remission*.ab,ti,kf.
68	((post or off or after) adj5 (treatment* or therap*)).ab,ti,kf.
69	((treatment* or therap* or cancer* or disease* or event* or progression*) adj5 free).ab,ti,kf.
70	63 or 64 or 65 or 66 or 67 or 68 or 69
71	9 and 35 and 62 and 70
72	limit 71 to english language

Figure 1: Flow Diagram of Article Screening Process



Additional file 1: PRISMA-P Checklist

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	Not applicable
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	68
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	4-40
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	284-288
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☒	☐	208-209
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	279-282
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	279-282
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	282-283
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	70-84
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	85-89
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	102-103; 122-126
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	97-99; 104-108
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	Table 1

Section/topic	#	Checklist item	Information reported		Line number(s)
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	111-113
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	117-120
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	130-132;144-149
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	132-143
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	150-152
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	153-168
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	174-175
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	175-189
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	189-196
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	203-205
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	196-200
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	169-172

This checklist has been adapted for use with systematic review protocol submissions to BioMed Central journals from Table 3 in Moher D et al**:** Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

An Editorial from the Editors-in-Chief of *Systematic Reviews* details why this checklist was adapted - **Moher D, Stewart L & Shekelle P:** Implementing PRISMA-P: recommendations for prospective authors. *Systematic Reviews* 2016 **5**:15

Additional file 2: Adapted version of a modified Newcastle-Ottawa Scale to evaluate overweight and obesity prevalence in survivors of childhood brain tumors

0 = Definitely no
1 = Mostly no
2 = Mostly yes
3 = Definitely yes
Unclear = not enough information provided

Domain 1: Selection

Is the selection of study sample consecutive and representative of the population of interest?

Low risk of bias: random sampling and consecutive recruitment from a representative population.

Moderate risk of bias: random sampling and consecutive recruitment from a non-representative population

High risk of bias: non-random sampling, non-consecutive recruitment

Recruitment is consecutive when explicit statement is provided or when all (or a random sample of) subjects during a given date range are included.

If there is a comparison group, are the selection of non-cancer control and classification of brain tumor status appropriate?

Low risk of bias: the non-cancer control is selected from the same community as the childhood brain tumors survivors and the brain tumor status is determined by medical records

Moderate risk of bias: the non-cancer control is selected from a different source and/or the brain tumor status is self-reported

High risk of bias: there is no description for the selection of non-cancer control and/or how classification is done

Domain 2: Comparability

Does the study identify and adjust for confounding factors in the analysis?

Low risk of bias: possible confounding factors are identified and adjusted for

Moderate risk of bias: possible confounding factors are identified but not adjusted for

High risk of bias: no confounding factors are identified when they are clearly present

Possible confounding factors include age, sex, the location and histology of brain tumors, types of treatment received for the brain tumors, years of survival, and the presence of other comorbidities such as endocrinolpathies.

Domain 3: Missing data

Are incomplete/missing data addressed adequately?

Low risk of bias: there are ≤10% incomplete/missing data

Moderate risk of bias: there are ≤25% incomplete/missing data and appropriate methods of addressing them are specified

High risk of bias: there are >25% incomplete/missing data or ≤25% incomplete/missing data and no methods are used to address them

Domain 4: Outcome

Are outcome measuring methods appropriate?

Low risk of bias: brain tumor treatment modalities are obtained from medical records and anthropometric measurements are done in duplicate with appropriate/justified methods

Moderate risk of bias: brain tumor treatment modalities are self-reported and/or anthropometric measurements are not done in duplicate but methods are appropriate or justified

High risk of bias: the methods used for anthropometric measurements are inappropriate or unjustified

Chapter 3: Overweight, obesity and adiposity in survivors of childhood brain tumors: A systematic review and meta-analysis

Kuan-Wen Wang, Adam Fleming, Donna L. Johnston, Shayna M. Zelcer, Shahrad Rod Rassekh, Salma Ladhani, Anna Socha, Jermin Shinuda, Shatha Jaber, Sarah Burrow, Sheila K. Singh, Laura Banfield, Russell J. de Souza, Lehana Thabane, M. Constantine Samaan

The research question was defined by KWW, AF, DLJ, SMZ, SRR, SB, SKS, RJdS, LT, and MCS. The search strategy and eligibility criteria was developed by all authors. Articles screening, data abstraction, and risk of bias and overall quality assessment were performed by KWW, SL, AS, JS, and SJ. RJdS and LT provided supports to methodology and statistical analysis. The manuscript was drafted by KWW and MCS, and reviewed by all authors. MCS was the guarantor.

Wang KW, Fleming A, Johnston DL, Zelcer SM, Rassekh SR, Ladhani S, et al. (in press). Overweight, obesity and adiposity in survivors of childhood brain tumors: A systematic review and meta-analysis. Clinical Obesity.

Introduction

Overweight and obesity are the main drivers of the epidemics of type 2 diabetes and cardiovascular diseases including hypertension, stroke and cardiovascular events, around the world.[1, 2] With record population growth and longevity, the increase in cardiometabolic disorders is one of the most significant health challenges of the 21st century.[1, 2] While these diseases impact the general population, certain subgroups are particularly vulnerable to obesity-driven cardiometabolic effects. One of these groups includes survivors of childhood brain tumors (SCBT).[3, 4]

The evidence of excess overweight and obesity in SCBT compared to non-cancer controls has been inconsistent, with some studies reporting an increase,[5, 6] while others finding no significant differences.[7, 8] The small sample size of some studies and the inclusion of different comparison groups including the general population or siblings may have contributed to these conclusions. Defining the estimates of overweight and obesity and their determinants in SCBT is critical, as this will allow targeted interventions to be implemented to lower cardiometabolic risk and improve outcomes.

The primary objective of this review is to compare the prevalence of overweight and obesity between SCBT and non-cancer controls. The secondary aim is to determine if SCBT have higher adiposity than non-cancer controls, as adiposity has been recognized as a more robust measure of metabolic health and outcomes compared to body mass index (BMI).[9, 10]

Methods

Literature Search

We searched databases including PubMed, EMBASE, MEDLINE, CINAHL, Database of Abstracts of Reviews of Effect, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews on October 14, 2016 using the following search terms and their synonyms: pediatric, brain tumors, overweight/obesity, and survivors. A full search strategy for MEDLINE was included in the protocol paper.[11]

Grey literature was searched in ProQuest Dissertations and Theses A&I and Web of Science. The searches were restricted to English language publications, but not publication date as described previously.[11] An updated search was conducted on June 3, 2017 to capture newly published studies where the same search strategy was used, and publication date was limited to October 2016-present.

Conference abstracts were excluded, but the publications from their first and last authors were searched to identify published results. Reference lists from the relevant review articles and eligible studies were also scanned for potentially eligible studies.

Study Selection

Title, abstract, and full-text screening was done by two independent reviewers. The two reviewers met after each screening stage to achieve consensus on the decisions of article selection. A third reviewer was consulted if conflict persisted.

This review included primary observational studies with SCBT diagnosed under 25 years of age. The age limit was set to be under 18 years of age at diagnosis in the protocol.[11] However, after conducting the literature search, we identified studies that included children along with adolescent and young adult (AYA), which was considered up to 25 years of age, and pediatric patients were often monitored up to 21 years of age by pediatric oncologists in the USA.[12] Therefore, we decided to broaden our age at diagnosis to include all relevant evidence.

Eligible studies included those with a sample size of ≥10 patients with assessment of BMI, BMI z-score, or BMI percentile to evaluate prevalence of overweight/obesity or adiposity measures including fat mass percentage (%FM), waist-to-hip ratio (WHR), and waist-to-height ratio (WHtR).

Data Abstraction

Two independent reviewers extracted data using pre-established data abstraction forms. Disagreements were resolved by a third reviewer. The primary outcome included the prevalence of overweight and obesity based on body mass measures including BMI, BMI z-score, or BMI percentile. The secondary outcome of adiposity included %FM, WHR, and WHtR.

In studies that included brain tumors with other cancer types, data specific to the brain tumor group were extracted if reported in the published work. In studies that published the data for multiple cancer types as aggregates, we contacted the principal investigators requesting specific data for the brain tumor

population. Some studies reported the same cohort with increased subject numbers over time; in this case, we included the largest reported sample size with the longest follow-up duration for the outcomes of interest.

Risk of Bias and Quality Assessment

Two reviewers evaluated the risk of bias for eligible studies and the overall quality of evidence for each outcome independently. Conflicts were resolved by consensus or arbitrated by a third reviewer. A modified version of the Newcastle-Ottawa Scale (NOS) was used to evaluate the risk of bias for eligible studies.[11]

We used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) guideline to assess the overall quality of evidence for outcomes including odds ratios (OR) of overweight, obesity, and combined overweight/obesity data between male and female SCBT as well as mean differences (MD) in %FM, WHR, and WHtR between SCBT and controls. The GRADE guideline is used to indicate how confident the researchers are to conclude that the estimate of effect is accurate, where a comparison group is involved.[13] Therefore, the outcome of prevalence of overweight/obesity in SCBT and non-cancer controls was not evaluated using GRADE since this is a single point of estimate rather than an estimate of effect between groups.

Statistical Analysis

For the primary outcome, to determine the prevalence of overweight and obesity in SCBT and non-cancer controls, a pooled prevalence for each group was

determined. The standard error (SE) of the prevalence was calculated with the following formula: SE = √((prevalence (1-prevalence)/sample size)).[14]

The prevalence of overweight and obesity among overall SCBT, patients with brain tumors other than craniopharyngioma, and patients with craniopharyngioma was summarized in separate groups, as craniopharyngioma patients are known to be at high risk of developing obesity.[15, 16] Therefore, analyzing the data from studies that focused on craniopharyngioma exclusively and studies that included other brain tumors types together will overestimate the prevalence of obesity in overall SCBT population. In studies reporting subgroup data by sex, a pooled OR was also calculated to compare overweight and obesity between male and female SCBT.

For the secondary outcome, to determine if SCBT have higher total and central adiposity than non-cancer controls, a pooled MD was calculated for %FM, WHR, and WHtR. In studies reporting median and range for adiposity measures, the mean and standard deviation were estimated using standardized formulae.[17]

Statistical heterogeneity was determined by inconsistency index (I^2) and P values from the chi-square test for homogeneity as previously described.[11] Higher I^2 values represent greater heterogeneity, with >75% indicating considerable heterogeneity and P <0.10 is the cut-off for statistical significance.

Meta-analyses were conducted using RevMan Software (version 5.3; Cochrane Collaboration). We used a random effects model due to high heterogeneity across studies. Publication bias was evaluated based on conference

abstracts without published results for pooled OR and MD because less than ten studies were included in the meta-analyses of these two outcomes.[11] More than ten studies can be found for some prevalence outcomes. However, publication bias was not applicable to this type of outcome because it was a single point of estimate while publication bias was comparing positive and negative outcomes, obtained from comparison, between published and unpublished works.[18]

Results

The full screening process and detailed exclusion criteria at each stage are reported in Fig. S1. After removing duplicates, we identified 4381 unique records from the literature searches. After title and abstract screening, 3901 and 305 were excluded at each stage, respectively. Of the remaining 175 records, 130 were excluded after full-text screening, resulting in 45 eligible studies for this systematic review.

Overweight and obesity in SCBT population

Among the 45 studies, 17 (n=2032 participants) reported prevalence of overweight and obesity among patients with various types of brain tumors,[5-8, 19-31] The study characteristics and results are described in Table 1. The age at diagnosis ranged from at birth to 24.8 year old. The age at study enrolment ranged from 6 months to 63.8 years, with a wide range of follow-up duration since diagnosis (3 months to 48.3 years).

Among the 17 studies, eight were retrospective cohort studies,[7, 21-24, 28, 29, 31] while three were longitudinal cohort studies,[19, 20, 26] and the remaining six were

cross-sectional studies.[5, 6, 8, 25, 27, 30] Nine studies[5-8, 25, 27, 29-31] included a non-cancer comparison group (by recruiting controls or comparing to national populations). However, only four studies[7, 8, 30, 31] reported sample sizes and were included in the meta-analysis to calculate estimation for non-cancer controls.

The pooled prevalence of overweight in overall SCBT was 22.3% (95% CI 13.5-31.1) and 26.4% (95% CI 18.5-34.3) in SCBT excluding craniopharyngioma (Fig. 1) while the pooled prevalence of overweight in non-cancer controls was 32.0% (95% CI 30.5-33.6) (Fig. S2).

The pooled prevalence of obesity was 23.8% (95% CI 15.3-32.2) in overall SCBT, 17.9% (95% CI 9.0-26.8) in SCBT excluding craniopharyngioma (Fig. 2), and 16.6% (95% CI 16.3-17.0) in non-cancer controls (Fig. S2).

The pooled prevalence of combined overweight or obesity was 42.6% (95% CI 30.1-55.1) in overall SCBT, 31.7% (95% CI 20.4-43.0) in patients with brain tumors other than craniopharyngioma (Fig. S3), and 40.4% (95% CI 34.0-46.8) in non-cancer controls (Fig. S2).

We also performed subgroup analysis to compare overweight and obesity between male and female SCBT in Fig. S4, as sex difference has been observed in previous reports.[32] Male SCBT were at higher odds of being overweight compared to female SCBT (OR 1.8, 95% CI 1.4-2.3). On the other hand, males had similar odds of obesity when compared to females (OR 1.2, 95% CI 0.6-2.2).

Taken together, these results indicate that SCBT had similar rates of overweight and obesity to non-cancer controls. Furthermore, sex difference was

observed for overweight but not obesity in SCBT, with male SCBT more vulnerable than female SCBT.

Overweight and obesity in craniopharyngioma

Twenty-six studies (n=1225 participants)[32-57] included patients with craniopharyngioma and evaluated their overweight and obesity profile. Fifteen studies were retrospective cohort studies,[32-37, 40, 42, 43, 45, 46, 49, 50, 55, 57] with three longitudinal cohort studies,[39, 48, 52] and eight cross sectional studies.[38, 41, 44, 47, 51, 53, 54, 56] None of these studies included a non-cancer control group appropriate for this systematic review. In addition, four studies[39, 44, 48, 57] reported the prevalence of severe or morbid obesity but not general obesity, and were not included in the final statistical analysis (Fig. S1).

Patients included in this group aged between 2.0-57.0 year old at study inclusion, with age at diagnosis ranging from 1 month-22 year old. The follow-up duration ranged from 2 months to 44.1 years.

The pooled prevalence of overweight in patients with craniopharyngioma was 24.2% (95% CI 13.7-34.8) (Fig. 1). This was lower, but not significant, than the overweight prevalence of non-cancer controls (Fig. S2). However, the pooled obesity prevalence was 54.4% (95% CI 48.0-60.9; Fig. 2), compared to 16.6% in non-cancer controls (Fig. S2).

The combined overweight and obesity prevalence in patients with craniopharyngioma was 68.1% (95% CI 56.1-80.1; Fig. S3). These results

indicate that in patients with craniopharyngioma, overweight and obesity affect almost two-third of patients.

Adiposity in SCBT

Two studies[58, 59] did not report the prevalence of overweight and obesity, yet included adiposity measures of SCBT. The characteristics of these two studies, along with the four studies that reported both the prevalence of overweight and obesity as well as adiposity measures, are described in Table 2.[30, 38, 51, 53, 58, 59]

Three cross-sectional studies including patients with various types of brain tumors reported adiposity measures along with a non-cancer comparison group.[30, 58, 59] The age at diagnosis of these patients was 6.8±3.5 years and their age at study evaluation was 14.9±4.7 years. Three cross-sectional studies[38, 51, 53] also reported adiposity measures in patients with craniopharyngioma; however, only one study[38] included a non-cancer control group. The age at diagnosis for these patients was 3.0-22.0 years, and age at evaluation was 7.7-57.0 years.

To explore adiposity in SCBT compared to non-cancer controls, the pooled average and mean difference of total adiposity and central adiposity between the groups were determined (Fig. S5-S8). The pooled total adiposity rates measured in %FM was higher in SCBT than non-cancer controls (26.5%, 95% CI 22.6-30.4 versus 21.7%, 95% CI 17.4-26.1). The pooled mean difference revealed that %FM was 4.1% higher in SCBT (95% CI 2.0-6.1) compared to controls.

The pooled WHR was higher in SCBT (0.87, 95% CI 0.85-0.88) than in non-cancer controls (0.78, 95% CI 0.70-0.86). The pooled mean difference

showed that SCBT had 0.07 higher WHR (95% CI 0.02-0.13) than non-cancer controls. Similarly, WHtR in SCBT was also higher (0.48, 95% CI 0.47-0.49) than non-cancer controls (0.43, 95% CI 0.39-0.46), with a pooled mean difference of 0.06 (95% CI 0.01-0.10). These results indicate that SCBT had higher total and central adiposity than non-cancer controls.

Risk of Bias and Overall Quality of Evidence

The overall risk of bias for each eligible study was reported in Table 1, with the detailed break- down of risk of bias for each category across studies reported in Table S1.

Five studies[7, 19, 20, 23, 24] including SCBT with different tumor types and nine studies[35, 43-45, 47, 49, 52, 56, 57] including patients with craniopharyngioma had moderate risk of bias. Nine studies had moderate risk of bias due to the use of unadjusted measures to determine overweight and obesity in pediatric population, such as BMI and relative weight.[7, 20, 23, 24, 47, 49, 52, 56, 57] As BMI in children and adolescents varies with age and sex,[60] using BMI cut-off points to determine overweight and obesity in children is biased by age and sex.

Three studies had >10% missing data mainly due to loss to follow-up,[19, 43, 52] while four studies[35, 43-45] did not use a reference population representative of the subjects to determine BMI z-score or BMI percentile.

Two studies had high risk of bias because it was reported that self-reported height and weight were used for calculation of BMI,[48, 54] which have shown to differ from measured values.[61] Twelve studies were rated to have unclear risk of

bias due to 1) unclear methods to classify overweight and obesity[21, 34, 39] 2) no specification as to which reference standards were used to calculate BMI z-score or BMI percentile[22, 28, 33, 39, 42, 50] and 3) insufficient information was provided to determine if sample selection was random and consecutive.[41, 51, 53, 59] One study was rated to have high risk of bias for adiposity outcomes because adiposity measures were not reported for 60% of participants.[53]

The overall quality of evidence was determined for overweight, obesity, and combined overweight and obesity between male and female SCBT as well as %FM, WHR, and WHtR between SCBT and non-cancer controls (Table S2). The risk of bias was not serious for all outcomes. This indicate that the results from these studies had internal validity.

Inconsistency was serious for WHR, and very serious for WHtR due to moderate or high heterogeneity, based on their I^2 values. Indirectness was serious for all adiposity measures because the primary objective of some studies was not comparing adiposity between SCBT and non-cancer controls.[58, 59] Imprecision was serious for obesity due to its low event rates and very serious for WHR due to its relatively small total sample size. Several conference abstracts were identified from the literature but published papers were not found after searching for publications of the first and last authors. Therefore, we suspect the presence of publication bias for reporting overweight and obesity in SCBT.

In summary, the overall quality of evidence was of moderate quality for overweight and combined overweight and obesity due to publication bias, and for

%FM due to indirectness. The obesity had overall low quality of evidence due to imprecision and publication bias, while the overall quality of evidence was downgraded to very low due to inconsistency, indirectness, and imprecision for WHR and WHtR.

Discussion

Children who survive brain tumors are at an increased risk of type 2 diabetes and cardiovascular disease and stroke.[3, 4] As obesity is a major risk factor for the development of these disorders,[2] it is imperative to determine its prevalence in this population to help identify those in need of targeted interventions to improve cardiometabolic outcomes. In this systematic review, the rate of combined overweight and obesity in overall SCBT was 42.6% versus 40.4% in non-cancer controls. This indicates that SCBT have similar overweight and obesity rates to the general population when BMI is used as a measure of body mass.

Our results also show that male SCBT have higher odds of being overweight than female SCBT, while the odds of obesity were similar in the two groups. This is consistent with the trends observed in the general population, where greater prevalence of overweight was observed in males in developed countries.[2, 62, 63] In contrast, obesity was reported to be higher in females than males in the general population.[2, 62, 63] Previous evidence suggested that female survivors had a higher risk of obesity than male SCBT.[32] However, this study included patients with suprasellar brain tumors with 28% craniopharyngioma

patients, while our analysis include patients with brain tumors of various types and locations, which may explain the differences in the results.

When looking at the risk of overweight and obesity in craniopharyngioma, patients with craniopharyngioma are at a particularly high risk of developing obesity as expected. The participants with craniopharyngioma had higher prevalence of obesity and combined overweight and obesity than SCBT and non-cancer controls.

Due to its location and biology, craniopharyngioma can invade the hypothalamus at the suprasellar region.[15] In addition, hypothalamic damage can occur due to treatment of these tumors by surgery or cranial irradiation.[15] Hypothalamic injury can impair satiety signals and disrupts insulin, leptin and ghrelin signalling resulting in hyperphagia.[15, 16] Hypothalamic damage can also lead to suppression of sympathetic activity with reduced epinephrine excretion.[15, 16, 64] The decreased sympathetic tone reduces adipose tissue lipolysis and basal metabolic rate, which contributes to weigh gain.[65, 66] In addition, reduced consumption of fruits and vegetables and increased fat intake,[67] along with lower physical activity caused by treatment-related cardiopulmonary dysfunction, tiredness, sleep disturbance, visual impairment, medications, motor imbalance and pain can contribute to obesity in SCBT.[68-71]

While the prevalence of overweight and obesity was similar between SCBT and non-cancer controls, there is evidence that the BMI tend to underestimate body mass in childhood cancer survivors.[72] As current evidence

suggests that SCBT have higher risk of cardiometabolic diseases compared to controls,[3, 4] perhaps having a similar mass is more detrimental to SCBT with the added burden of the tumor and its therapies when compared to controls. While BMI is the most widely used measure of obesity, recent evidence indicates that adiposity measures are more robust tools in stratifying cardiometabolic risk than BMI.[9, 10]

Our results demonstrate that SCBT has higher total and central adiposity than non-cancer controls. However, the impact of adiposity in survivors on their cardiometabolic outcomes remains unclear, as this is an emerging population. Longitudinal studies are warranted to provide evidence linking higher adiposity to increased risk of cardiometabolic diseases in SCBT.

Strengths and Limitations

There are several strengths to this systematic review. We used a comprehensive search strategy including hand-searching references of relevant reviews and eligible articles as well as publications from the first and last authors of the relevant conference abstracts. We also contacted the principal investigators in attempt to obtain unpublished data. We evaluated overweight and obesity in patients with craniopharyngioma separately and compared adiposity measures between SCBT and non-cancer controls. Using GRADE also allowed a comprehensive interpretation of the quality of evidence to identify gaps that can spur future studies.

There are several limitations in this review. We were not able to exclude craniopharyngioma from the brain tumor group for some studies.[5-7, 19, 22, 23, 25, 29, 31] Among these studies, only three studies[22, 23, 25] reported a breakdown of different brain tumor diagnoses, with 3.8-23.1% of subjects having craniopharyngioma. Furthermore, while all studies reported the estimation of the prevalence of overweight and obesity, only four studies[7, 8, 30, 31] were included in the meta-analysis for non-cancer controls. Other studies either did not have a non-cancer comparison group or compared the prevalence of overweight and obesity in SCBT to a reference population, without reporting the sample size of the control group.

The quality of evidence for obesity was low while WHR and WHtR had very low quality. Therefore, the results for these outcomes should be interpreted with caution. The later two outcomes had high heterogeneity across studies. Possible sources of heterogeneity include age at study evaluation or diagnosis, treatment protocols, endocrinopathies, tumor location and type, and duration of follow-up. All these factors have been reported to be risk factors for obesity in SCBT.[32, 73] These determinants will need further exploration.

Conclusions

This systematic review and meta-analysis provide a comparison of overweight, obesity and adiposity between SCBT and non-cancer controls. The results illustrate that the two groups are similar in overweight and obesity rates based on BMI measures, yet survivors have higher adiposity which may contribute to future cardiometabolic risks. More studies with longitudinal data are needed to

further elucidate the association between adiposity and future cardiometabolic outcomes in SCBT.

In our previous systematic review,[74] we described some intervention strategies to manage overweight and obesity in SCBT. These include lifestyle interventions to promote healthy diets and physical activity, appetite suppressant such as dexamphetamine, and bariatric surgery. However, these studies generated very low quality of evidence to make a definite conclusion on their effectiveness. Furthermore, Most of the studies used BMI to measure effectiveness while we discovered that adiposity might be the key contributor to increased cardiometabolic risks in SCBT. Future studies should include adiposity as one of the outcome measures to evaluate the effectiveness of these interventions in SCBT.

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Authors' Contributions: The research question was defined by KWW, AF, DLJ, SMZ, SRR, SB, SKS, RJdS, LT, and MCS. The search strategy and eligibility criteria was developed by all authors. Articles screening, data abstraction, and risk of bias and overall quality assessment were performed by KWW, SL, AS, JS, and SJ. RJdS and LT provided supports to methodology and statistical analysis. The manuscript was drafted by KWW and MCS, and reviewed by all authors. MCS was the guarantor.

Legends for tables and figures:

Figure 1. Prevalence of overweight in survivors of childhood brain tumors including all brain tumors, no craniopharyngioma, and craniopharyngioma only based on BMI measures

Figure 2. Prevalence of obesity in survivors of childhood brain tumors including all brain tumors, no craniopharyngioma, and craniopharyngioma only based on BMI measures

Table 1. Studies characteristics for prevalence of overweight and obesity

Table 2. Studies characteristics for adiposity measures

Supporting information:

Figure S1. Flow diagram of article screening process

Figure S2. Prevalence of overweight and obesity in external non-cancer controls based on BMI measures

Figure S3. Prevalence of overweight or obesity in survivors of childhood brain tumors including all brain tumors, no craniopharyngioma, and craniopharyngioma only based on BMI measures

Figure S4. Odds ratio of overweight and obesity in male and female survivors of childhood brain tumors based on BMI measures

Figure S5. Total adiposity in survivors of childhood brain tumors and external non-cancer controls

Figure S6. Mean difference of total adiposity between survivors of childhood brain tumors and external non-cancer controls

Figure S7. Central adiposity in survivors of childhood brain tumors and external non-cancer controls

Figure S8. Mean difference of central adiposity between survivors of childhood brain tumors and external non-cancer controls

Table S1. Evaluation of the risk of bias of included studies

Table S2. Overall quality of evidence using GRADE for studies

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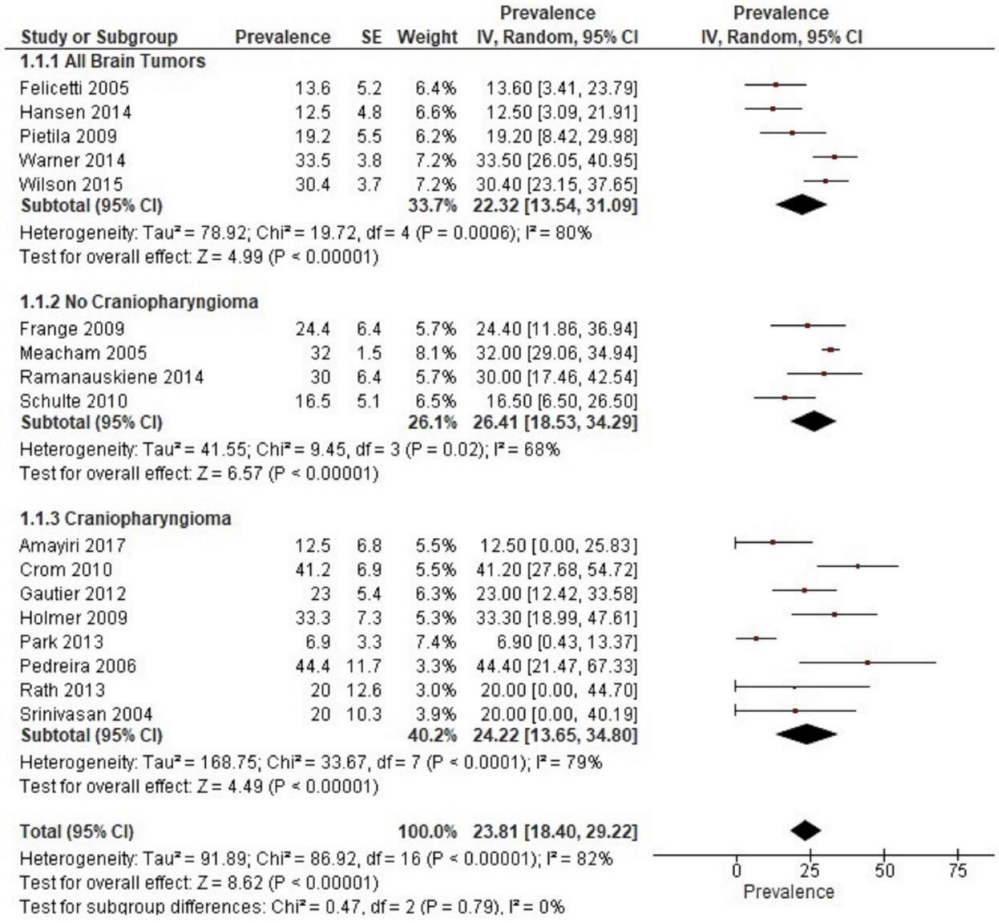
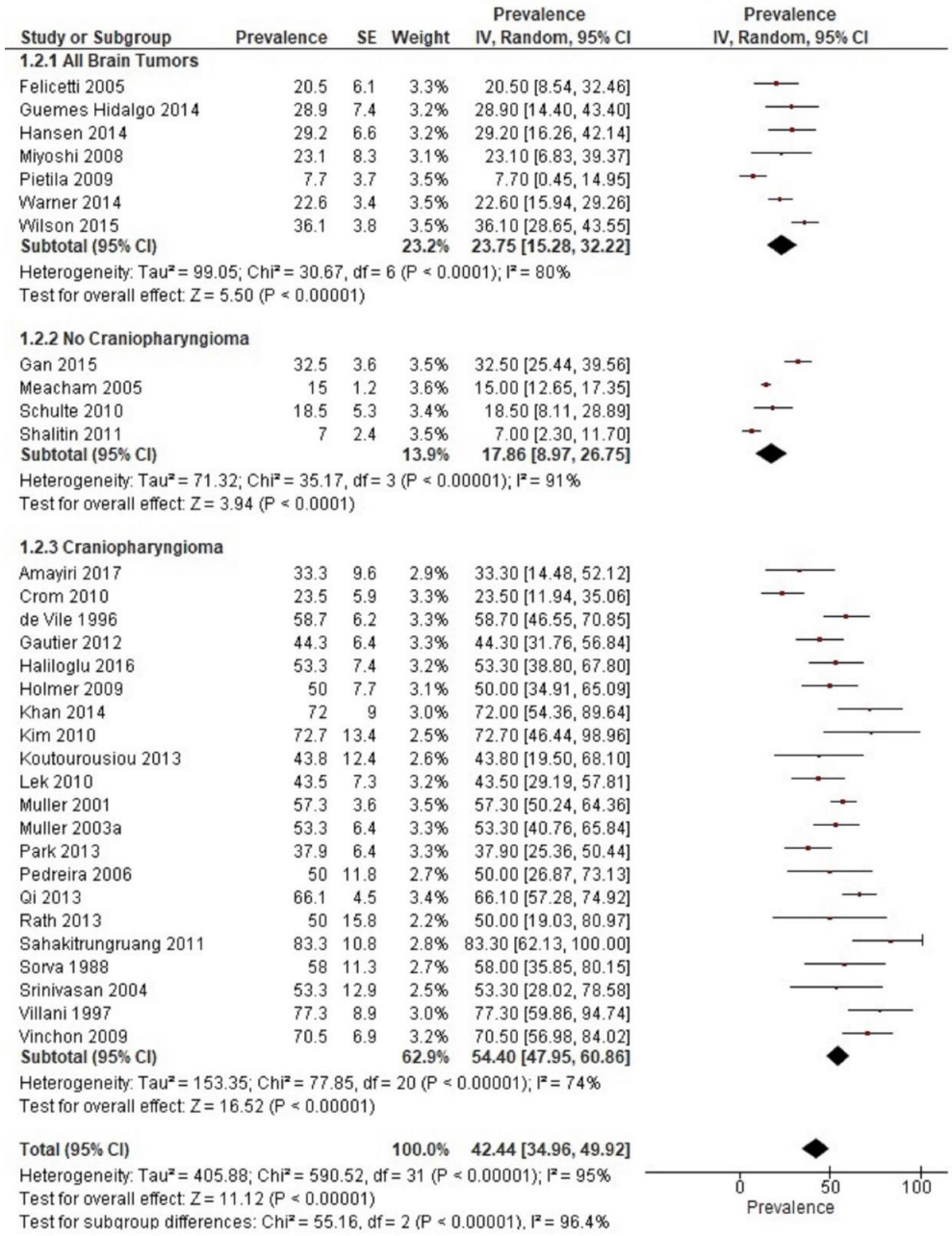
Figure 1. Prevalence of overweight in survivors of childhood brain tumors including all brain tumors, no craniopharyngioma, and craniopharyngioma only based on BMI measures



BMI: Body Mass Index; SE: Standard Error; IV: Inverse Variance; CI: Confidence Interval

Figure 2. Prevalence of obesity in survivors of childhood brain tumors including all brain tumors, no craniopharyngioma, and craniopharyngioma only based on BMI measures



BMI: Body Mass Index; SE: Standard Error; IV: Inverse Variance; CI: Confidence Interval

Table 1. Studies characteristics for prevalence of overweight and obesity

First author, Year, country	Study Design	Type of Control[a]	Sample size (n)	Age at study [b,c,d]	Age at Diagnosis [b,c,d]	Overweight/ obesity %[d]	Subgroups by sex/treatments	Risk of bias
% Overweight/Obesity in all brain tumor types								
Brouwer et al 2012 (Netherlands)	RC	External	47	20.0 (12.7-42.7)	9.3 (0.0-20.5)	OW/OB: 27.7	NR	Moderate
Felicetti et al 2015 (Italy)	L	None	44[e]	24.5±4.6	10.4±0.2	OW: 13.6 OB: 20.5	NR	Moderate
Güemes Hidalgo et al 2014 (Spain)	RC	Normative (NR)	38	10.3±3.1	5.3±3.1	OB: 28.9	NR	Unclear
Hansen et al 2014 (USA)	CS	Normative (CDC), External	48	15.1±1.8	8.3±3.7	OW: 12.5 OB: 29.2	NR	Low
Miyoshi et al 2008 (Japan)	RC	None	26	17.0 (4.0-36.0)	6.4 (0.0-15.0)	OB: 23.1	NR	Moderate
Pietilä et al 2009 (Finland)	CS	Normative (Finnish), External	52	14.2 (3.8-28.7)	6.0 (0.1-15.5)	OW: 19.2 OB: 7.7	OW/OB: RT+ 45.0, RT- 15.6	Low
van Santen et al 2015 (Netherlands)	RC	Normative (Dutch) and External	51	21.9 (7.0-46.8)	7.0 (0.0-18.0)	OW/OB: 41.2	NR	Low
Warner et al 2014 (USA)	RC	External	155	23.5 (18.0-40.0)	13.0 (0.0-20.0)	OW: 33.5 OB: 22.6	OW: M 39.8, F 25.4 OB: M 28.4, F 14.9	Low
Wilson et al 2015 (USA)	CS	Normative (CDC), External	158	32.4 (18.9-63.8)	7.2 (0.1-24.8)	OW: 30.4 OB: 36.1	OW: M 32.6, F 27.0 OB: M 37.9, F 33.3	Low
% Overweight/Obesity in brain tumors other than craniopharyngioma								
Meacham et al 2005 (USA)	CS	External	940	24.5 (20.0-47.0)	12.0 (0.0-20.0)	OW: 32.0 OB: 15.0	OW: M 38.1, F 24.9 OB: M 13.2, F 17.1	Low
Frange et al 2009 (France)	L	None	45[e]	25.2 (15.2-39.3)	8.8 (1.4-17.0)	OW/OB: 24.4	NR	Moderate
Gan et al 2015 (UK)	RC	None	166	15.5 (2.4-37.4)	4.9 (0.2-15.4)	OB: 32.5	NR	Unclear
Odagiri et al 2012 (Japan)	RC	None	22	17.4 (9.6-25.8)	11.5 (6.0-19.0)	OW/OB: 13.6	NR	Moderate
Ramanauskienė et al 2014 (Lithuania)	L	Normative (Lithuanian)	51	9.7 (0.50-27.8)	7.9 (0.25-17.2)	OW/OB: 30.0	NR	Low
Schulte et al 2010 (Canada)	CS	Normative (CDC) and External	54	13.7±3.0	7.4±3.4	OW: 16.5 OB: 18.5	NR	Low

Table 1. Studies characteristics for prevalence of overweight and obesity (continued)

First author, Year, country	Study Design	Type of Control[a]	Sample size (n)	Age at study [b,c,d]	Age at Diagnosis [b,c,d]	Overweight/ obesity %[d]	Subgroups by sex/treatments	Risk of bias
Shalitin et al 2011 (Israel)	RC	Normative (NR)	114	15.6±5.9	7.1±5.4	OB: 7.0	OB: CMT+ 9.0, CMT- 2.8	Unclear
Wang et al 2017 (Canada)	CS	Normative (CDC), External	56	14.7±7.1	9.1±4.9	OW/OB: 35.7	OW/OB: M 33.3, F 39.1	Low
% Overweight/Obesity in craniopharyngioma only								
Amayiri et al 2017 (Jordan)	RC	Normative (NR)	24	13.3 (2.0-25.5)	7.4 (0.9-16.4)	OW: 12.5 OB: 33.3	OW: M 8.3, F 16.7 OB: M 41.7, F 25.0 OW: RT+ 9.1, RT- 15.4 OB: RT+ 36.4, RT- 30.8	Unclear
Crom et al 2010 (USA)	RC	None	51	14.7 (6.2-38.9)	7.1 (1.2-17.6)	OW: 41.2 OB: 23.5	NR	Unclear
de Vile et al 1996 (UK)	RC	Normative (French)	63	16.6 (2.5-35.6)	7.0 (1.0-16.4)	OB: 58.7	NR	Moderate
Gautier et al 2012 (France)	RC	None	61[e]	26.1 (IQR=30.6)	9.0 (1.4-18.0)	OW: 23.0 OB: 44.3	NR	Low
Haliloglu et al 2016 (Turkey)[f]	RC	Normative (Turkish)	45	12.4 (3.8-25.72)	6.4 (0.50-13.8)	OB: 53.3	NR	Low
Holmer et al 2009 (Sweden)	CS	None[g]	42	28.0 (17.0-57.0)	12.0 (3.0-22.0)	OW: 33.3 OB: 50.0	OW: M 45.4, F 20.0 OB: M 40.9, F 60.0 OW: RT+ 40.0, RT- 27.3 OB: RT+50.0, RT- 50.0	Low
Khan et al 2014 (UK)	RC	Normative (British)	25	14.1 (7.3-22.3)	9.1 (2.3-17.3)	OB: 72.0	NR	Low

Table 1. Studies characteristics for prevalence of overweight and obesity (continued)

First author, Year, country	Study Design	Type of Control[a]	Sample size (n)	Age at study [b,c,d]	Age at Diagnosis [b,c,d]	Overweight/ obesity %[d]	Subgroups by sex/treatments	Risk of bias
Kim et al 2010 (USA)	CS	Normative (CDC)	11	11.2±1.7	NR	OB: 72.7	NR	Unclear
Koutourousiou et al 2013 (USA)	RC	Normative (NR)	16[e]	9.0 (4.0-18.0)	6.1 (3.1-13.1)	OB: 43.8	NR	Unclear
Lek et al 2010 (UK)[f]	RC	Normative (British)	46	11.4 (IQR=13.7)	7.5 (IQR=8.1)	OB: 43.5	OB: M 18.8, F 56.7	Low
Müller et al 2001 (Germany)	RC	Normative (French)	185[e]	16.2 (3.0-39.0)	8.6 (0.1-18.0)	OB: 57.3	NR	Moderate
Müller et al 2003a (Germany)	RC	Normative (French)	60	14.8 (2.1-24.0)	11.1 (0.1-17.5)	OB: 53.3	OB: M 47.1, F 61.5	Moderate
Park et al 2013 (Korea)	RC	Normative (Korean)	58	18.1±6.5	8.1±3.5	OW: 6.9 OB: 37.9	NR	Low
Pedreira et al 2006 (Australia)	CS	None[g]	18	21.2±6.7	8.4±3.3	OW: 44.4 OB: 50.0	NR	Moderate
Qi et al 2013 (China)	RC	Normative (Chinese)	109	15.6 (4.0-30.5)	8.2±3.9	OB: 66.1	NR	Moderate
Rath et al 2013 (Australia)	RC	Normative (NR)	10	16.2 (8.5-24.4)	8.9 (2.4-17.6)	OW: 20.0 OB: 50.0	NR	Unclear
Sahakitrungruang et al 2011 (Thailand)	CS	Normative (Thai)[g]	12	14.1 (7.7-18.1)	12.2 (6.7-17.1)	OB: 83.3		Unclear
Sorva 1988 (Finland)	L	None	19[e]	16.0 (6.6-23.0)	11.0 (1.6-18.0)	OB: 58.0	NR	Moderate
Srinivasan et al 2004 (Australia)	CS	Normative (Australian)[g]	15	12.2 (7.2-18.5)	7.1 (5.4-16.7)	OW: 20.0 OB: 53.3	NR	Unclear
Villani et al 1997 (Italy)	CS	None	22[e]	18.0 (8.0-35.0)	11.0 (6.0-16.0)	OB: 77.3	NR	High
Vinchon et al 2009 (France)	RC	Normative (French)	44[e]	20.1 (7.1-38.0)	8.9 (2.3-16.2)	OB: 70.5	NR	Low
Yano et al 2016 (Japan)	CS	None	26	27.4 (7.0-54.0)	7.3 (4.0-14.0)	OW/OB: 65.4	OW/OB: M 70.0, F 62.5	Moderate

Table 1. Studies characteristics for prevalence of overweight and obesity (continued)

First author, Year, country	Study Design	Type of Control[a]	Sample size (n)	Age at study [b,c,d]	Age at Diagnosis [b,c,d]	Obesity %[d]	Subgroups by sex/treatments	Risk of bias
% severe or morbid obesity in craniopharyngioma only								
Kalapurakal et al 2003 (USA)	L	Normative (NR)	25	16.0 (4.0-31.0)	6.0 (1.0-15.0)	Severe 32.0	NR	Unclear
Müller et al 2001 (Germany)	RC	Normative (French)	185[e]	16.2 (3.0-39.0)	8.6 (0.1-18.0)	Severe 44.3	NR	Low
Müller et al 2003b (Germany)	CS	Normative (French)	212	15.3 (2.3-42.9)	9.0 (0.1-18.0)	Severe 40.0	NR	Moderate
Poretti et al 2004 (Switzerland)	L	Normative (NR)	23[e]	20.6±7.3	9.0±4.5	Severe 60.9	NR	High
Sahakitrungruang et al 2011 (Thailand)	CS	Normative (Thai)[g]	12	14.1 (7.7-18.1)	12.2 (6.7-17.1)	Severe 75.0	NR	Unclear
Vinchon et al 2009 (France)	RC	Normative (French)	44[e]	20.1 (7.1-38.0)	8.9 (2.3-16.2)	Morbid 25.0	NR	Low
Yosef et al 2016 (Israel)	RC	None	27	14.8 (2.7-37.9)	7.3 (1.3-17.1)	Morbid 3.7	NR	Moderate

CS: cross-sectional; L: longitudinal; RC: retrospective cohort; OW: overweight; OB: obese; F: Female; M: Male; CMT+: survivors treated with chemotherapy; CMT-: survivors treated without chemotherapy; RT+: survivors treated with radiotherapy; RT-: survivors treated without radiotherapy; NR: not reported; CDC: Centers for Disease Control and Prevention; IQR: interquartile range.
[a]Normative controls are reference populations used to calculate BMI *z* score or percentile. External controls are healthy unrelated individuals or siblings for comparison. [b]Values were recorded as mean±standard deviation or mean/median (range) as reported. If not reported, the information was estimated based on the reported age at diagnosis, duration of follow-up, or age at study. [c]In studies including all childhood cancer survivors, the values were only reported for all childhood cancer survivors, unless information was provided for survivors of childhood brain tumors. [d]If values were reported in subgroups only, weighted average was calculated. [e]The values were the numbers of subjects that provide the outcomes of our interests and were less than the numbers of subjects reported in the studies due to missing data or lost to follow-up. [f]Studies included brain tumor types other than craniopharyngioma, but all have hypothalamic involvement.
[g]The external controls used in the studies were not applicable to our research question.

Figure S1. Flow diagram of article screening process

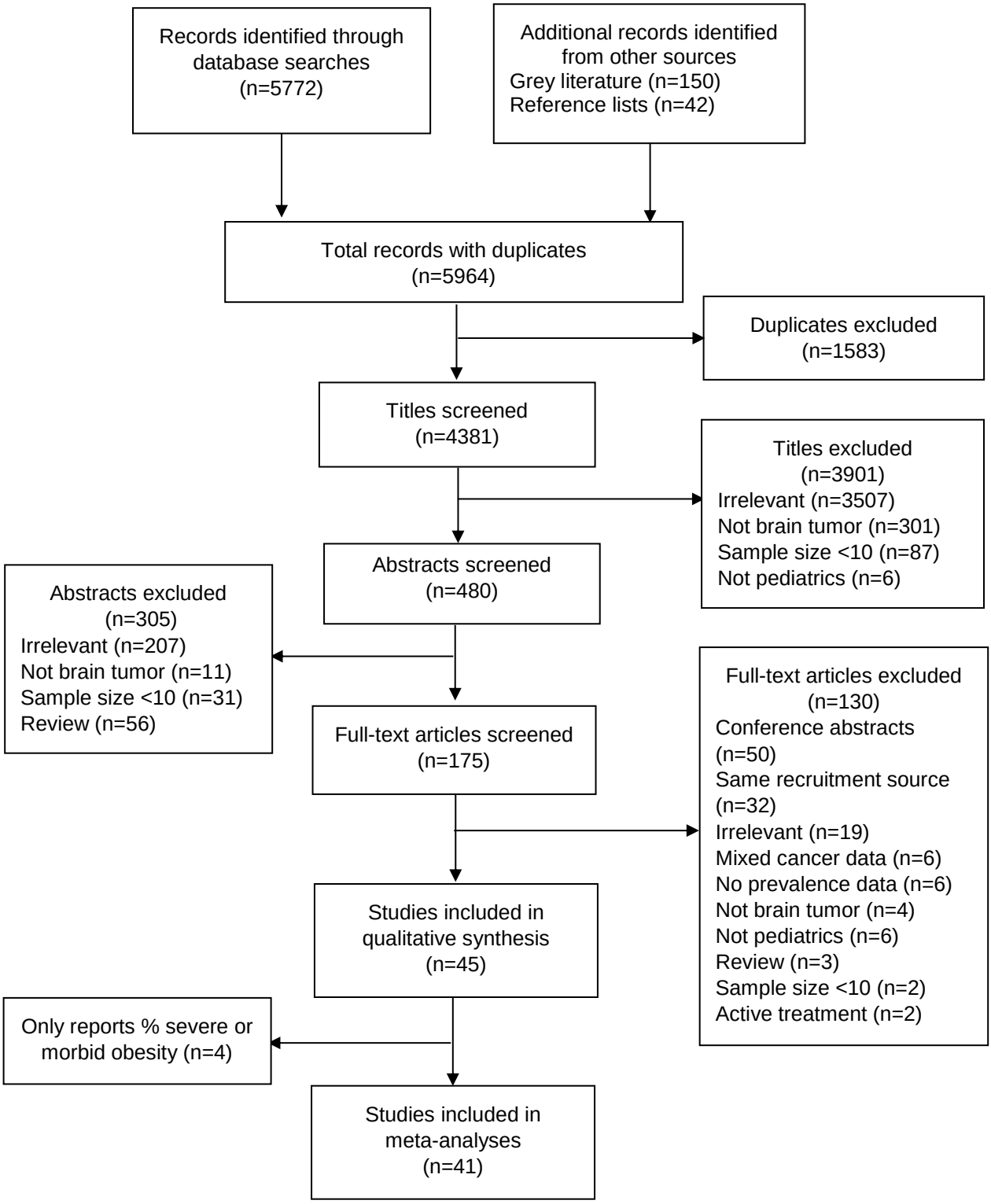
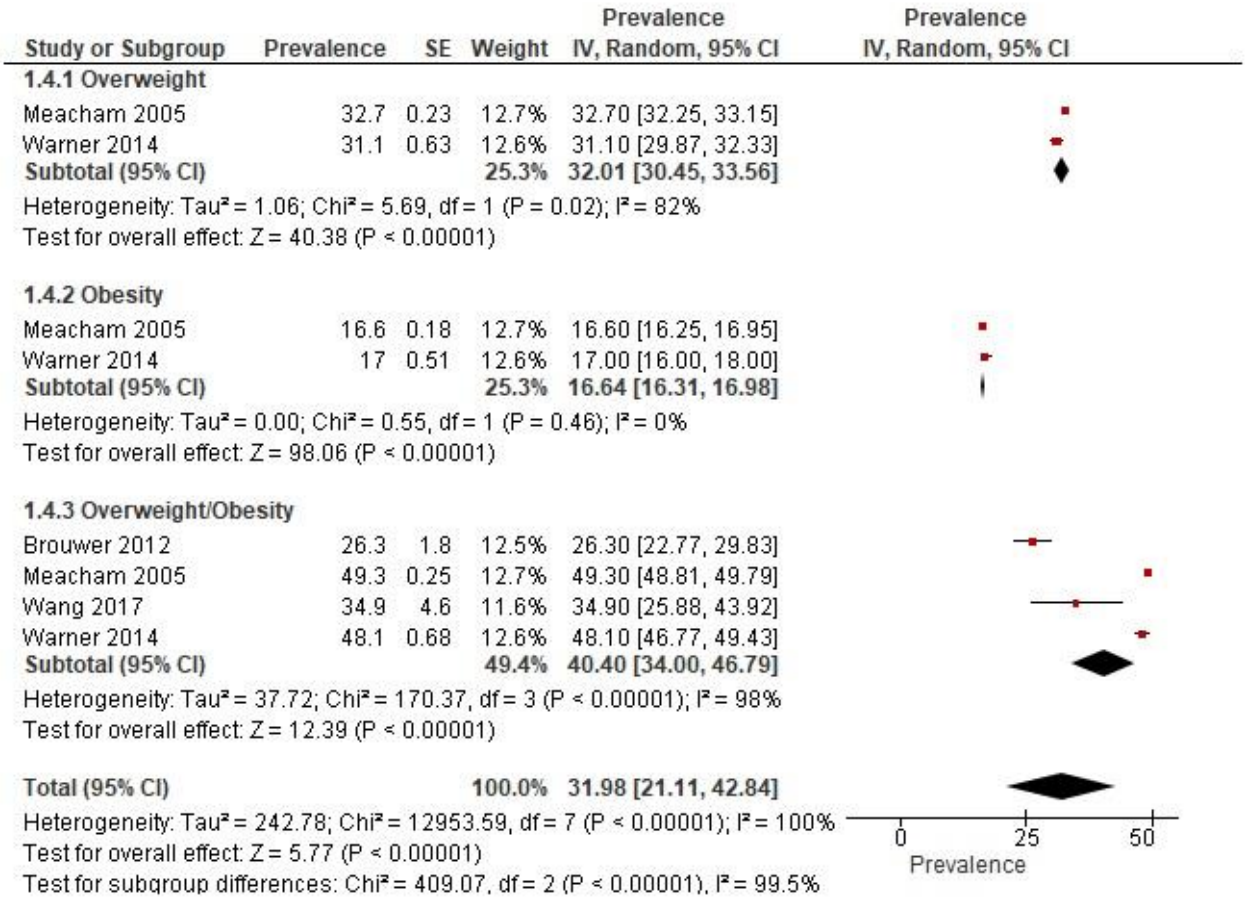
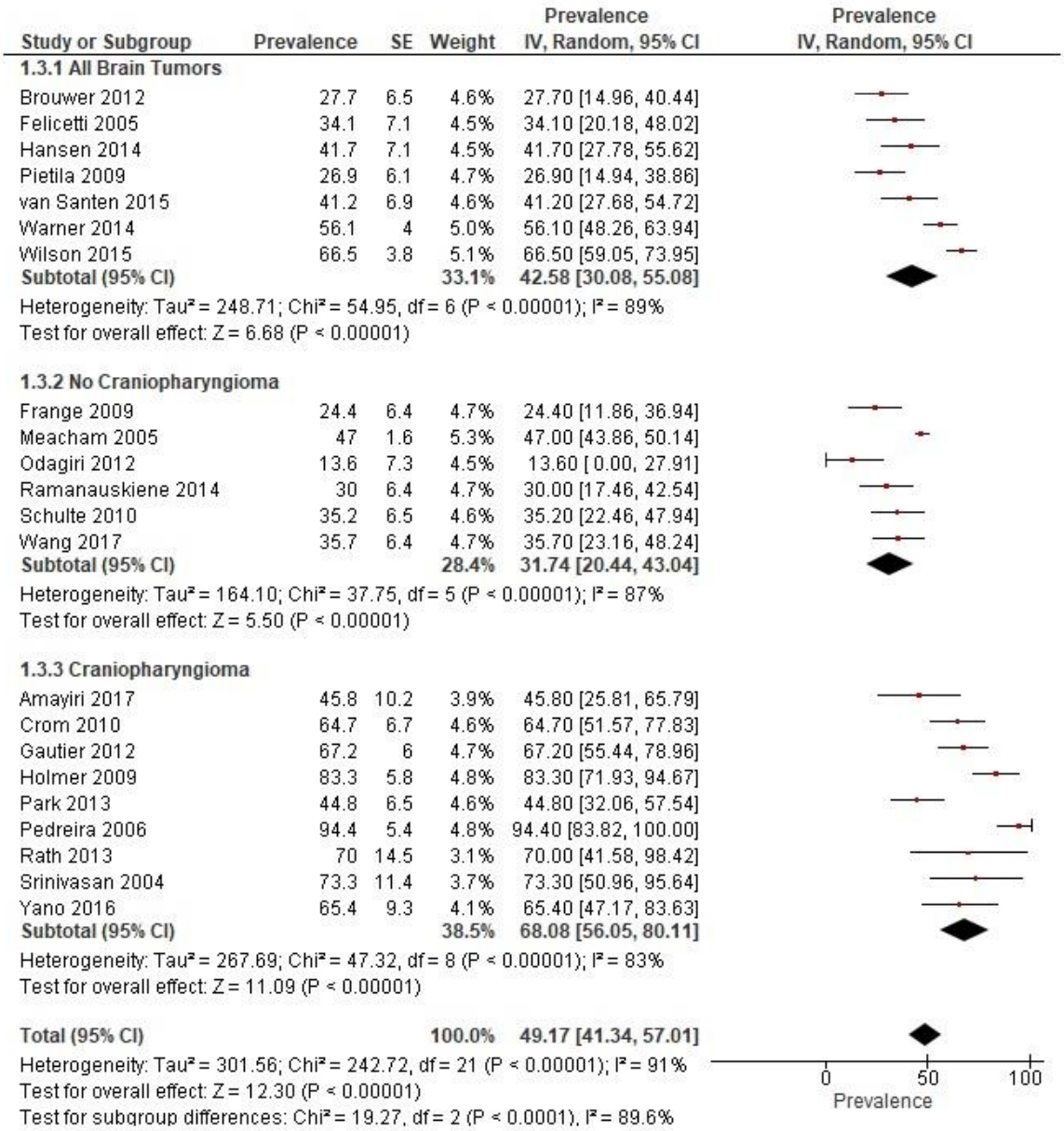


Figure S2. Prevalence of overweight and obesity in external non-cancer controls based on BMI measures



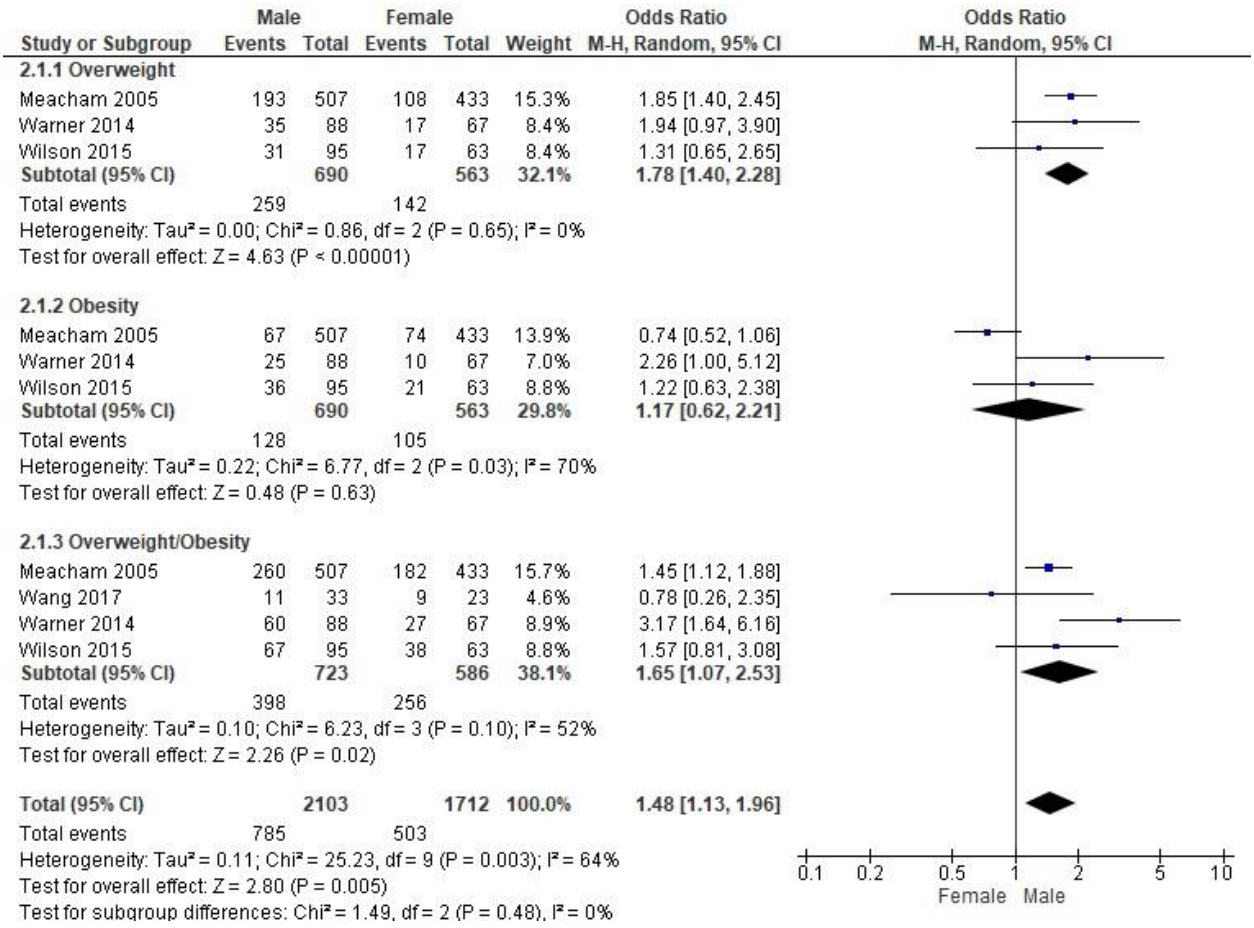
BMI: Body Mass Index; SE: Standard Error; IV: Inverse Variance; CI: Confidence Interval

Figure S3. Prevalence of overweight or obesity in survivors of childhood brain tumors including all brain tumors, no craniopharyngioma, and craniopharyngioma only based on BMI measures



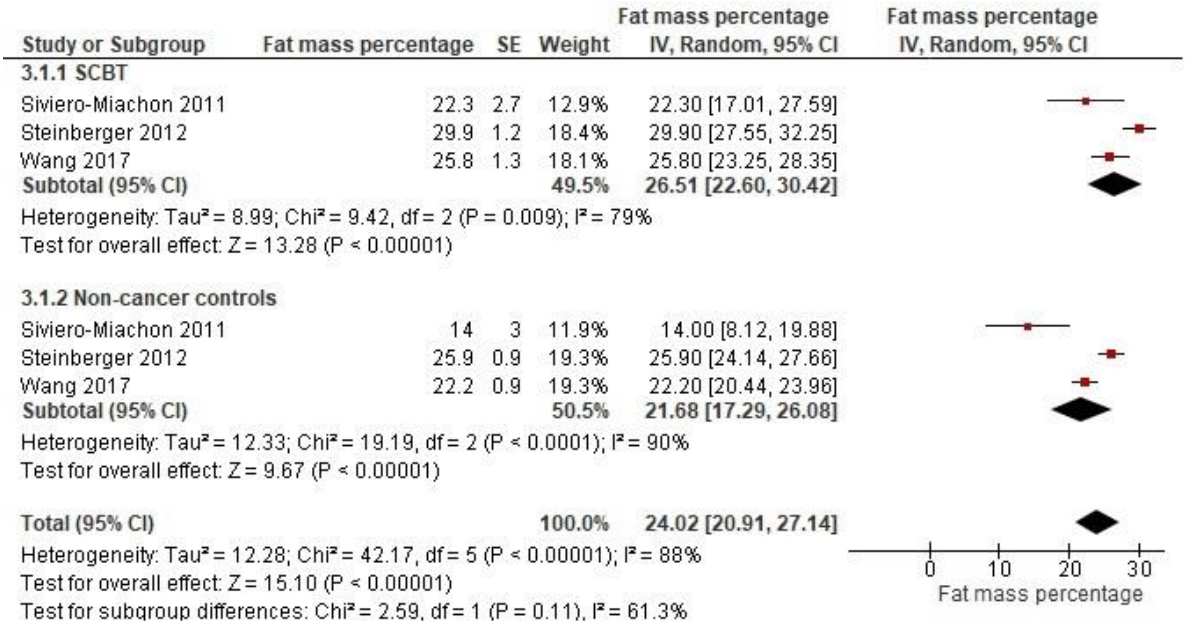
BMI: Body Mass Index; SE: Standard Error; IV: Inverse Variance; CI: Confidence Interval

Figure S4. Odds ratio of overweight and obesity in male and female survivors of childhood brain tumors based on BMI



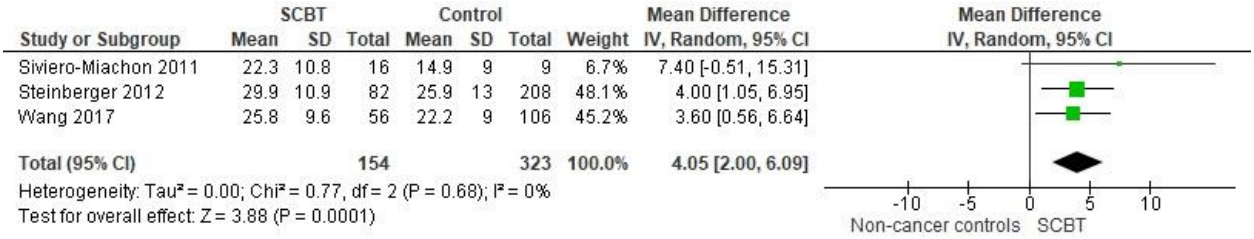
BMI: Body Mass Index; M-H: Mantel-Haenszel; CI: Confidence Interval

Figure S5. Total adiposity in survivors of childhood brain tumors and external non-cancer controls



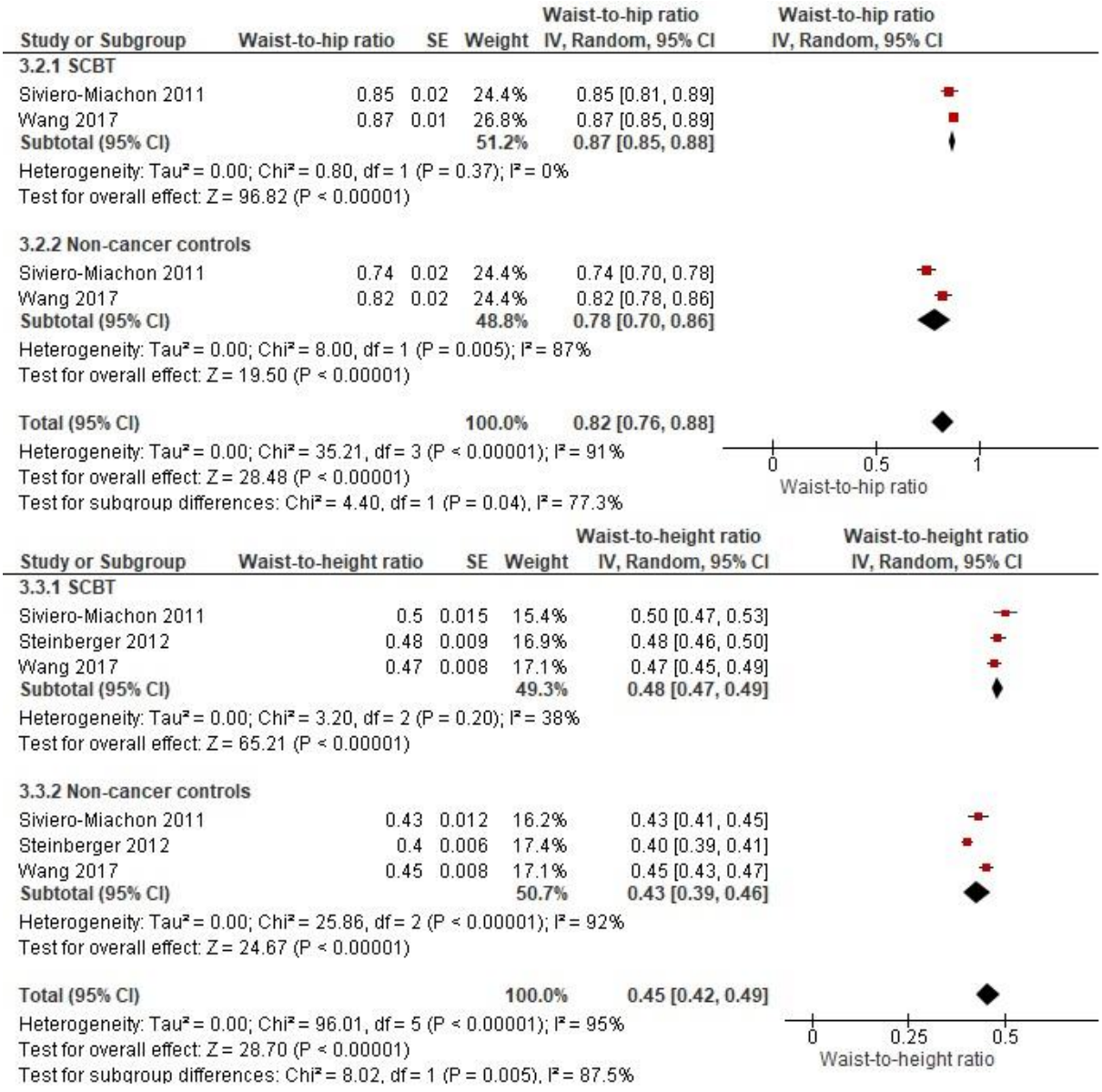
SE: Standard Error; IV: Inverse Variance; CI: Confidence Interval; SCBT: Survivors of Childhood Brain Tumors

Figure S6. Mean difference of total adiposity between survivors of childhood brain tumors and external non-cancer controls



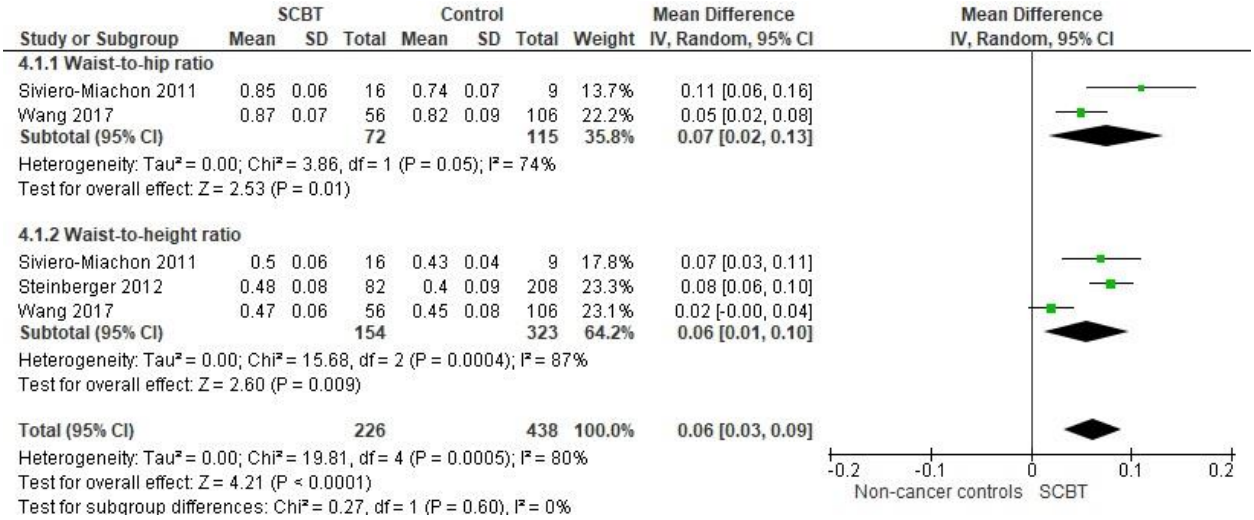
SE: Standard Error; IV: Inverse Variance; CI: Confidence Interval; SCBT: Survivors of Childhood Brain Tumors

Figure S7. Central adiposity in survivors of childhood brain tumors and external non-cancer controls



SE: Standard Error; IV: Inverse Variance; CI: Confidence Interval; SCBT: Survivors of Childhood Brain Tumors

Figure S8. Mean difference of central adiposity between survivors of childhood brain tumors and external non-cancer controls



SD: Standard Deviation; IV: Inverse Variance; CI: Confidence Interval; SCBT: Survivors of Childhood Brain Tumors

Table S1. Evaluation of the risk of bias of included studies

Author Year (Location)	Selection (cases)	Selection (controls)	Comparability	Missing data	Outcome	Overall rating
% Overweight/Obesity in all brain tumor types						
Brouwer et al 2012 (Netherlands)	Low	Low	Moderate	Low	Low	Moderate
Felicetti et al 2015 (Italy)	Low	N/A	Low	Moderate	Low	Moderate
Frange et al 2009 (France)	Low	N/A	Moderate	Low	Low	Moderate
Gan et al 2015 (UK)	Low	N/A	Unclear	Low	Low	Unclear
Güemes Hidalgo et al 2014 (Spain)	Low	Unclear	Low	Low	Low	Unclear
Hansen et al 2014 (USA)	Low	Low	Low	Low	Low	Low
Meacham et al 2005 (USA)	Low	Low	Low	Low	Low	Low
Miyoshi et al 2008 (Japan)	Low	N/A	Moderate	Low	Low	Moderate
Odagiri et al 2012 (Japan)	Low	N/A	Moderate	Low	Low	Moderate
Pietilä et al 2009 (Finland)	Low	Low	Low	Low	Low	Low
Ramanauskienė et al 2014 (Lithuania)	Low	Low	Low	Low	Low	Low
Schulte et al 2010 (Canada)	Low	Low	Low	Low	Low	Low
Shalitin et al 2011 (Israel)	Low	Unclear	Low	Low	Low	Unclear
van Santen et al 2015 (Netherlands)	Low	Low	Low	Low	Low	Low
Wang et al 2017 (Canada)	Low	Low	Low	Low	Low	Low
Warner et al 2014 (USA)	Low	Low	Low	Low	Low	Low
Wilson et al 2015 (USA)	Low	Low	Low	Low	Low	Low
% Overweight/Obesity in craniopharyngioma only						
Amayiri et al 2017 (Jordan)	Low	Unclear	Low	Low	Low	Unclear
Crom et al 2010 (USA)	Low	N/A	Unclear	Low	Low	Unclear
de Vile et al 1996 (UK)	Low	Moderate	Low	Low	Low	Moderate
Gautier et al 2012 (France)	Low	N/A	Low	Low	Low	Low
Haliloglu et al 2016 (Turkey)[e]	Low	Low	Low	Low	Low	Low

Author Year (Location)	Selection (cases)	Selection (controls)	Comparability	Missing data	Outcome	Overall rating
% Overweight/Obesity in craniopharyngioma only						
Holmer et al 2009 (Sweden)	Low	N/A	Low	Low	Low	Low
Khan et al 2014 (UK)	Low	Low	Low	Low	Low	Low
Kim et al 2010 (USA)	Unclear	Low	Low	Low	Low	Unclear
Koutourousiou et al 2013 (USA)	Low	Unclear	Low	Low	Low	Unclear
Lek et al 2010 (UK)[e]	Low	Low	Low	Low	Low	Low
Müller et al 2001 (German)	Low	Moderate	Low	Moderate	Low	Moderate
Müller et al 2003a (Germany)	Low	Moderate	Low	Low	Low	Moderate
Park et al 2013 (Korea)	Low	Low	Low	Low	Low	Low
Pedreira et al 2006 (Australia)	Low	N/A	Moderate	Low	Low	Moderate
Qi et al 2013 (China)	Low	Low	Moderate	Low	Low	Moderate
Rath et al 2013 (Australia)	Low	Unclear	Low	Low	Low	Unclear
Sahakitrungruang et al 2011 (Thailand)	Unclear	Low	Low	Low	Low	Unclear
Sorva 1988 (Finland)	Low	N/A	Moderate	Moderate	Low	Moderate
Srinivasan et al 2004 (Australia)	Unclear	Low	Low	Low	Low	Unclear
Villani et al 1997 (Italy)	Low	N/A	Unclear	Low	High	High
Vinchon et al 2009 (France)	Low	Low	Low	Low	Low	Low
Yano et al 2016 (Japan)	Low	N/A	Moderate	Low	Low	Moderate

Author Year (Location)	Selection (cases)	Selection (controls)	Comparability	Missing data	Outcome	Overall rating
Severe or morbid obesity in craniopharyngioma only						
Kalapurakal et al 2003 (USA)	Low	Unclear	Unclear	Low	Unclear	Unclear
Müller et al 2001 (German)	Low	Moderate	Low	Moderate	Low	Moderate
Müller et al 2003b (Germany)	Low	Moderate	Low	Low	Low	Moderate
Poretti et al 2004 (Switzerland)	Low	Unclear	Low	Low	High	High
Sahakitrungruang et al 2011 (Thailand)	Unclear	Low	Low	Low	Low	Unclear
Vinchon et al 2009 (France)	Low	Low	Low	Low	Low	Low
Yosef et al 2016 (Israel)	Low	N/A	Moderate	Low	Low	Moderate
Adiposity measures in all brain tumor types						
Siviero-Miachon et al 2011 (Brazil)	Low	Low	Low	Low	Low	Low
Steinberger et al 2012 (USA)	Unclear	Low	Low	Low	Low	Unclear
Wang et al 2017 (Canada)	Low	Low	Low	Low	Low	Low
Adiposity measures in craniopharyngioma only						
Holmer et al 2009 (Sweden)	Low	Low	Low	Low	Low	Low
Sahakitrungruang et al 2011 (Thailand)	Unclear	N/A	Low	Low	Low	Unclear
Srinivasan et al 2004 (Australia)	Unclear	N/A	Low	High	Low	High

N/A: not applicable

Table S2. Overall quality of evidence using GRADE for studies with comparison data

Quality assessment						Number of patients		Results	Quality
Study outcome	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Male**	**Female**		
Overweight N=3	Not serious	Not serious	Not serious	Not serious	Serious	259/690 (37.5%)	142/563 (25.2%)	**OR 1.78** (1.40-2.28)	⊕⊕⊕◯ MODERATE
Obesity N=3	Not serious	Not serious	Not serious	Serious	Serious	128/690 (18.6%)	105/563 (18.7%)	**OR 1.17** (0.62-2.21)	⊕⊕◯◯ LOW
Overweight /Obesity N=4	Not serious	Not serious	Not serious	Not serious	Serious	398/723 (55.0%)	256/586 (43.7%)	**OR 1.65** (1.07-2.53)	⊕⊕⊕◯ MODERATE
Quality assessment						**Number of patients**		**Results**	**Quality**
Study outcome	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**SCBT**	**Control**		
%FM N=3	Not serious	Not serious	Serious	Not serious	None	154	323	MD **4.05 % higher** (2-6.09)	⊕⊕⊕◯ MODERATE
WHR N=2	Not serious	Serious	Serious	Very serious	None	72	115	MD **0.07 higher** (0.02-0.13)	⊕◯◯◯ VERY LOW
WHtR N=3	Not serious	Very serious	Serious	Not serious	None	154	323	MD **0.06 higher** (0.01-0.1)	⊕◯◯◯ VERY LOW

GRADE: grading of recommendations assessment, development and evaluation; SCBT: Survivors of Childhood Brain Tumors; OR: Odds Ratio; MD: Mean Difference; WHR: Waist-to-Hip Ratio; WHtR: Waist-to-Height Ratio; %FM: Fat mass percentage

Chapter 4: Adiposity in childhood brain tumors: A report from the Canadian Study of Determinants of Endometabolic Health in Children (CanDECIDE Study)

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MCS is the guarantor. Study conception and design determined by MCS, KWW, RJdS, AF, SKS, DLJ, SMZ, SRR, SB, KS and LT. Subjects recruitment and data collection were done by KWW, with the support from MCS, AF, SKS, SB, and KS. Dietary data interpretation and analysis was completed by KWW, RJdS, and MCS. Other statistical analyses and data interpretation were completed by KWW, MCS, RJdS, AF, SKS, DLJ, SMZ, SRR, SB, KS, and LT. KWW and MCS drafted the manuscript. All authors provided critical revisions of the manuscript and approved the final submitted version.

Wang KW, Souza RJ, Fleming A, Singh SK, Johnston DL, Zelcer SM, et al. Adiposity in childhood brain tumors: A report from the Canadian Study of Determinants of Endometabolic Health in Children (CanDECIDE Study). Scientific Reports. 2017;7:45078.

The published version of the paper is included in Appendix 2.

INTRODUCTION

Brain tumors are the most common pediatric solid tumors[1]. Groundbreaking discoveries in tumor biology and advances in diagnosis and therapy have significantly improved the survival of many of these children[2]. As the number of survivors has risen, it has become evident that this group is at risk of developing chronic morbidities[3,4] and premature mortality[5,6].

Recent evidence suggests that adult survivors of childhood brain tumors are at risk of cardiovascular disease and type 2 diabetes[7-10]. As obesity is an independent risk factor for cardiometabolic disorders in the general population, it may provide an explanation of the added cardiometabolic risk in survivors[11]. However, when obesity rates are measured by using body mass index (BMI), children with brain tumors (CBT) are reported to have BMI levels that are either close to or slightly higher than rates in the general population[12-14].

While BMI is the most widely used clinical measure of obesity, it does not distinguish the relative contribution of fat, muscle, or bone to body mass, which are considerably variable in growing children[15].

Adiposity is defined as the presence of fat in and outside the adipose tissue, including muscle and hepatic fat depots. The adipose depot is composed of a subcutaneous compartment, which is considered protective against cardiometabolic risk[16,17]. On the other hand, the visceral adipose compartment

secretes inflammatory cytokines which can lead to insulin resistance, and is linked to adverse cardiometabolic outcomes[18].

Measures of total adiposity (fat mass percentage; %FM) and central adiposity, including waist- to-hip ratio (WHR) and waist-to-height ratio (WHtR), have been shown to be more robust predictors of cardiometabolic health and risk compared to BMI[19-25], with WHtR emerging as a strong indicator of intra-abdominal fat[26].

However, adiposity is not routinely measured in children, including pediatric cancer patients. While brain tumors are a heterogeneous group, a common tumor classically reported to be associated with obesity is craniopharyngioma[27]. There have been very few reports on the evaluation of obesity in other brain tumor subtypes and beyond hypothalamic obesity[28,29].

As BMI-based obesity rates are similar between CBT and controls yet CBT have high risk of cardiometabolic disorders, we hypothesized that CBT, excluding craniopharyngioma, have higher adiposity when compared to non-cancer controls. This excess adiposity may contribute to adverse cardiometabolic outcomes and premature mortality. A secondary aim of this study was to investigate the determinants of adiposity in CBT.

RESULTS

We included 56 CBT (n=23 female) and 106 non-cancer controls (n=51 female) in this study. The characteristics of the study population are reported in Table 1.

The two groups were similar in terms of age (CBT: 5.20-42.70 years; controls: 5.40-18.80 years; p-value 0.59) and sex distribution (p-value 0.39). The CBT group had more participants in prepubertal stage (n=19, 33.90%) versus controls (n=16, 15.10%). Age of diagnosis of brain tumor was 9.10±4.90 years, and average time since diagnosis was 5.60±5.10 years.

As reported previously[30], CBT were shorter (150.60±25.20 versus 161.70±15.30 cm, p-value=0.002) and weighed less (52.40±24.10 versus 59.00±20.80 kg, p-value=0.02) than the control group.

The %FM correlated with central adiposity (Spearman's rho test WHR 0.31, p-value<0.001; WHtR 0.73, p-value<0.001). Central adiposity measures were highly correlated with each other as well (Spearman's rho test 0.67, p-value<0.001).

The total screen time and sleep duration were similar between the two groups (Table 1). The most common tumor subtypes in participants included gliomas (n=34, 60.70%) and Primitive Neuroectodermal tumors (PNET)/medulloblastoma (n=11, 19.60%) (Table 2). The tumors were distributed between supratentorial (n=26, 46.40%) and infratentorial regions (n=30, 53.60%) (Table 2), with only 7 patients (12.50%) having tumors involving the hypothalamus. The therapeutic modalities were used in the management of brain tumors are shown in Table 2. Surgery alone was the most common treatment modality (n=18, 32.10%), followed by a combination of surgery, chemotherapy and radiotherapy (n=15, 26.80%). Chemotherapy alone was noted in five cases

(8.90%), and radiotherapy alone was implemented in one patient (1.80%). Four patients (7.10%) received surgery and chemotherapy, and four (7.10%) received surgery and radiotherapy; one received radiotherapy and chemotherapy (1.80%).

In the 22 participants who received radiotherapy, the radiotherapy dosage was 47.10±12.40 Gy. Sixteen participants received craniospinal irradiation (72.70%), and six received cranial irradiation (27.30%). Eight patients were being managed with watch-and-wait strategy (14.30%).

Post-therapy endocrinopathies were observed in 14 (26.80%) CBT participants. Among this group, a single diagnosis was made in seven patients including hypothyroidism (n=3, 21.40%), growth hormone deficiency (n=2, 14.30%), hypogonadism (n=1, 7.10%), and precocious puberty (n=1, 7.10%). The other seven patients had multiple hormonal deficiencies including hypothyroidism (n=5, 35.70%), growth hormone deficiency (n=6, 42.90%), hypogonadism (n=4, 28.60%), adrenocorticotropic hormone deficiency (n=4, 28.60%), diabetes insipidus (n=3, 21.40%), and precocious puberty (n=1, 7.10%). All endocrinopathies were treated appropriately.

Adiposity patterns in CBT and controls

To determine if CBT have enhanced adiposity compared to non-cancer controls, we used logistic regression analysis.

CBT had higher total adiposity compared to controls (%FM 25.50±9.60% versus 22.40 ± 9.30%; β=1.51, 95% CI=1.08, 2.10, p-value=0.016). CBT also had higher central adiposity compared to controls including higher WHR (0.87±0.07

versus 0.82±0.09; β=7.53, 95% CI=2.30, 24.64, p- value=0.001) and a trend of higher WHtR (0.47±0.06 versus 0.45±0.08; β=0.34, 95% CI=0.12, 1.02, p-value=0.053).

Importantly, and in confirmation of previous reports, there were no differences in BMI and overweight/obesity rates between CBT and non-cancer controls (Table 1). BMI correlated with total adiposity (%FM) in CBT and controls (Spearman's rho test CBT 0.50, p-value<0.001; controls 0.76, p-value<0.001). BMI also correlated with WHR in controls but not in CBT (Spearman's rho test CBT 0.41, p-value 0.12; controls 0.17, p-value 0.038). Furthermore, BMI correlated with WHtR in CBT and controls (Spearman's rho test CBT 0.51, p-value<0.001; controls 0.73, p-value<0.001). These results demonstrate that CBT have higher total and central adiposity compared to non-cancer controls, in the presence of similar obesity rates based on BMI measurements.

Determinants of adiposity in survivors and controls

To define the determinants of adiposity, we conducted separate exploratory subgroup analyses using multivariate linear regression for CBT and controls (Table 3 for CBT; Supplementary Table S1 for controls). Dietary data are included in Table 4.

As noted in the general pediatric population[31], females in the control group had higher total adiposity, while males had increased WHR, and puberty was associated with all measures of adiposity. These trends were not noted in CBT.

CBT with Supratentorial tumors had increased total adiposity (β -1.83, SE 0.80, p-value 0.028), with trended association with central adiposity (WHR β -0.37, SE 0.21, p-value 0.08; WHtR β -0.53, SE 0.27, p-value 0.06) (Table 3).

CBT who received radiotherapy had higher %FM (β=1.65, SE 0.79, p-value=0.046). However, radiotherapy type (craniospinal versus cranial irradiation) and radiation dose did not correlate with %FM (Spearman's rho test radiotherapy type r 0.13, p-value 0.57; Dose r 0.24, p-value 0.36), WHR Spearman's rho test radiotherapy type r 0.18, p-value 0.43; Dose r 0.33, p-value 0.17), or WHtR (Spearman's rho test radiotherapy type r 0.10, p-value 0.67; Dose r 0.24, p-value 0.3).

While 27 (48.2%) CBT were treated with corticosteroids, there was no association between steroid use and %FM (β=0.68, SE 0.62, p-value=0.28), WHR (β= 0.04, SE 0.19, p-value=0.81), or WHtR (β=0.21, SE 0.21, p-value=0.32) (Table 3).

When examining the contribution of lifestyle factors (diet, physical activity, screen time, sleep duration) to adiposity in controls, physical inactivity trended with WHR, while screen time was associated with WHtR. Diet and sleep duration were not associated with adiposity measures. None of the lifestyle factors were associated with total or central adiposity measures in CBT (Table 3 for CBT; Supplementary Table S1 for controls; Diet data Table 4).

DISCUSSION

The improved survival rates of children with brain tumors have been hindered by premature mortality and the development of morbidities. Of particular importance, recent evidence confirms that survivors are at risk of type 2 diabetes and cardiovascular disease[7-10]. In this study, we demonstrate that adiposity, one of the most important determinants of cardiometabolic risk, is enhanced in CBT when compared to non-cancer controls.

Importantly, the adipose phenotype noted in CBT is evident with equivalent overweight/obesity rates to controls based on BMI measurements.

It has been reported that BMI can underestimate the prevalence of obesity in childhood cancer survivors, including survivors of brain tumors[19]. Until further understanding of the potential role of early excess adiposity in programming future cardiometabolic risk in CBT, there is a need to measure both BMI and adipose depots, and to continue to attempt to define their determinants. Our data are consistent with studies that used dual X-ray absorptiometry (DXA) scans[13,32], and reported the presence of higher total adiposity in cancer survivors who were treated with cranial irradiation[13,32]. The first study identified impaired mobility as an association of adiposity; the second study recruited patients with different cancers including brain tumors, and used siblings as a control group. The latter study identified male sex and screen time as risk factors of adiposity[32]. Our study population included CBT exclusively, with non-cancer controls as a comparison

group. This may explain why the previously identified risk factors were not linked to adiposity in our study.

An important contribution of our study is that it provides evidence for the use of clinically feasible measures to determine adiposity in CBT. This has important implications for settings where access to DXA is not practical or possible, allowing clinicians to estimate the adiposity patterns in their survivor populations.

Our data also demonstrate that tumor location and radiotherapy have important associations with adiposity. Supratentorial tumors were associated with enhanced total and central adiposity, while radiotherapy was associated with excess total adiposity.

While tumors and their treatment can lead to anatomical or functional hypothalamic-pituitary damage with pituitary hormonal deficiencies[33], disruption of hypothalamic satiety signaling and reduced basal metabolic rate that can drive obesity[27], these factors may also contribute to excess adiposity.

Our results did not corroborate previous evidence of the association of higher doses of radiotherapy with obesity in childhood cancers, including brain tumors[34,35]. While these studies used BMI to measure obesity, our results suggest that adiposity may be associated with radiotherapy regardless of dosage. Clarifying the effect of radiotherapy type, dosing and fractionation on adiposity is an important question to address in CBT.

Endocrinopathies have been reported to increase the risk of higher BMI, but their effect on adiposity patterns in CBT early on requires further study, as these effects may become more apparent as CBT age. While radiation dosage is important in causing hormonal abnormalities in cancer survivors, our population was treated for existing endocrinopathies and this may mask the effect of radiation dose to adiposity[36].

It has been reported that certain tumors including craniopharyngiomas, pilocytic astrocytomas, and medulloblastomas are associated with elevated BMI[35]. We purposefully excluded craniopharyngiomas, which is an important strength for this study to determine the contribution of other tumors to the adipose phenotype in CBT. A larger sample size is needed to clarify whether adiposity is driven by specific tumor types.

Several lifestyle factors are associated with obesity in the general pediatric population, Including excess caloric intake from sugar-sweetened beverages, prolonged screen time, and short sleep duration. Physical inactivity has been a controversial determinant of obesity in children[37-41].

While biological (sex), hormonal (puberty) and lifestyle factors were associated with adiposity in controls, none emerged as an explanation of the enhanced adiposity profile in CBT, which was associated with tumor location and radiotherapy.

The lack of association of diet with adiposity in our study is consistent with a study in craniopharyngioma patients, which revealed that physical

inactivity, and not nutritional factors, were associated with higher adiposity[42]. As our study is cross-sectional, one caveat is that the dietary patterns may have changed from the time of diagnosis onwards. Longitudinal studies are needed to clarify the link between diet and adiposity in CBT.

The association of physical inactivity with childhood obesity and its use as a treatment for Obesity has yielded inconsistent results[43-46]. In CBT, physical inactivity can be driven by treatment-related pulmonary and cardiac dysfunction[47,48], reduced muscle strength and fitness[49], fatigue, sleep disturbance[50], mental health issues, visual impairment, imbalance and pain[13,51,52]. Further studies on the association of physical activity with adiposity, and fat mass modification by targeted interventions in CBT are needed.

Our data suggest that within few years from having a brain tumor, CBT are following the secular lifestyle trends noted in the general population. However, the effect of adopting these trends on adiposity and cardiometabolic risk in CBT can be disproportionate, due to the added burden of the tumor and its treatment. Multipronged, personalized, and sustained interventions are needed in CBT, as adiposity is only one of many risk factors that may respond to lifestyle alteration.

There are several limitations to our study. While the WHR and WHtR demonstrated the presence of excess central adiposity in CBT, it is not clear if this is due to subcutaneous or visceral fat depot expansion. It is also unclear yet if these adiposity patterns will be sustained as CBT age. In addition, due to the cost

and logistics involved we did not measure other fat depots including hepatic and intermyocellular fat. Larger sample size and longitudinal studies of the fat depots are needed starting at diagnosis, to elucidate the evolution of the adiposity patterns in CBT.

As the questionnaires were self-administered, the presence of recall bias is possible. However, this is less likely, as the data collected were related to recent lifestyle factors, and the clinical data related to the tumor and its treatment were collected from the medical records.

CONCLUSIONS

In summary, our study reveals that excess total and central adiposity are present in non- craniopharyngioma population of CBT compared to controls. Adiposity, especially central adiposity, is an important cardiometabolic risk marker that appears in CBT within few years of their diagnosis. Tumor location and radiotherapy are important determinants of the noted adipose phenotype in these patients.

There is a need to understand the determinants of adiposity so that new therapies and prevention strategies can be developed to mitigate premature cardiovascular disease and type 2 diabetes and improve outcomes in CBT.

METHODS

Participants

The participants in this study were recruited into the Canadian Study of Determinants of Endometabolic Health in Children (CanDECIDE Study). This is a cohort study based at McMaster Children's Hospital, a tertiary pediatric academic center in Hamilton, Ontario, Canada. The study protocol and feasibility have been published[53,54]. The data reported are cross-sectional data collected at recruitment into the study.

We consecutively recruited CBT from the neurooncology clinics, and non-cancer controls were recruited from orthopedic clinics at the hospital and from the community. The orthopedic clinic controls included healthy children who suffered fractures or sprains and were seen for evaluation. These participants were approached while in clinic to request their participation in the study. Importantly, all study measures were performed after the fractures or sprains have healed, and participants had returned to their usual lifestyle before the injury. The recruitment period lasted from November 2012-March 2016.

We recruited boys and girls, 5 years and older, who were free of infection for 15 days prior to participation in the study, with no history of autoimmune diseases and not receiving immunosuppressive therapy for 15 days prior to inclusion. The exclusion criteria included active infection, autoimmune diseases, pregnancy or inability to provide informed consent.

Consent

The Hamilton Integrated Research Ethics Board approved this study. Consent forms were signed by parents if the participants were less than 16 years old, or by the participants if they were 16 years or older[55]. Children 7-15 years of age also signed an additional assent form. Informed consent was obtained from all participants. The study was conducted in accordance with appropriate clinical practice guidelines and national legal requirements.

Sociodemographic and clinical data

Data collected during the initial encounter with potential participants included self-reported age and sex, and this was confirmed from the medical records. Additional data collected from the medical records included age at diagnosis, tumor type, location, details of treatments received, and associated endocrinopathies and their treatment. Pubertal staging was assessed by pictorial Tanner pubertal staging in girls (>8 year old) and boys (>9 year old)[56].

Height and weight were measured to the nearest one tenth of a centimeter and one tenth of a kilogram using a stadiometer and an electronic weighing scale (Seca, USA), respectively. Body mass index (BMI) was calculated as kg/m^2. BMI percentile was obtained using the Children's BMI Tool for Schools[57] and BMI z-score were determined from the Centers for Disease Control and Prevention (CDC) growth chart[58]. Sitting systolic and diastolic blood pressures were

measured twice using the right arm with an automated blood pressure monitor (Welch Allyn, Inc., USA).

The two commonly used methods to measure body fat include Dual-energy X-ray absorptiometry (DXA) scan and bioelectrical impedance analysis (BIA)[59]. The latter is less expensive, easier to access and perform than DXA. In this study, we used BIA to measure %FM to determine total adiposity. This method has been validated against DXA scans, and the two measures are highly correlated[59]. While the Tanita body fat monitor (Tanita Corporation, Illinois, USA) is portable, it cannot be used on those 18 years and older. In this case, the InBody520 body composition analyzer (Biospace Co., Ltd, Korea) was used to measure %FM. High correlations were established between the Tanita body fat monitor and the InBody520 body composition analyzer when tested on 5-17 year old children (r=0.988; p-value=0.001).

Waist and hip circumferences were measured to the nearest one tenth of a centimeter, using a spring-loaded measuring tape (OHAUS Corporation, Canada)[60]. Central adiposity was determined by calculating the WHR and WHtR[22].

Diet

Dietary intake was assessed as we previously reported[54]. Briefly, we used items from the Youth and Adolescent Food Frequency Questionnaire[54,61,62]. This is a questionnaire developed in a US pediatric cohort, and includes questions

about food intake based on average portion sizes of different dietary constituents. The number of servings per day was calculated from the questionnaire by multiplying the frequency of consumption by portion size.

Principal component analysis was used to analyze the dietary patterns in participants. This analysis revealed four dietary patterns including prudent, western, high-protein and refined carbohydrate diets (Table 4). The prudent diet included high intake of fruits and vegetables. The western diet included high intake of fried foods, desserts, baked goods, and refined foods (e.g., chips, snacks, candies). The high-protein diet included high intake of meat and eggs. The refined carbohydrate diet included high intake of white bread and low intake of dark (whole grain) bread.

Physical activity

Physical activity was measured using the Habitual Activity Estimation Scale (HAES)[63]. The participants were asked to indicate their overall physical activity level as very inactive, inactive, somewhat inactive, somewhat active, active, or very active. This data were used to report physical activity levels. The levels were dichotomized into active and inactive for statistical analyses.

Sleep

Sleep duration (hours/day) was calculated from the difference between the self-reported time the participant went to bed and woke up the next morning. Sleep duration calculated with this method has been shown to correlate well with objective sleep quantification methods[64].

Screen time

Total screen time (hours/day) was calculated from the sum of self-reported time spent watching television, using cell phone, computer, computer games, and tablets.

Statistical analysis

All analyses were performed with SPSS version 20 software[65]. Kolmogorov-Smirnov test was used to test for normality, and variables with non-normal distribution were log-transformed. Age log-transformation revealed no outliers.

We used variance inflation factor to test for collinearity of variables, and found none that were collinear. Multiple imputations were used to handle missing data.

Continuous variables are reported as mean±SD, and categorical variables are reported as counts (%). Chi-square tests and independent sample t-tests were used to compare brain tumor survivors and controls for categorical and continuous variables, respectively. We used Spearman's test to assess the correlation of adiposity measures with BMI and with each other in this study.

To assess the association of adiposity with brain tumor status, we used binary logistic regression. The dependent variable (event) was the cancer case status, with 56 events included in the analysis and 106 controls (non-events). Age, sex, %FM, WHR, and WHtR were included as the predictor variables in the analysis. We rescaled the WHR and WHtR coefficients by multiplying the log-

transformed data by $10^{66,67}$. Logistic regression was conducted based on the assumption that ten events per predictor variable are needed for the analysis. As there are five predictor variables included in the analysis, our study is sufficiently powered to answer the main study question.

To explore the determinants of the adiposity patterns in CBT and controls, we performed exploratory subgroup analyses of the cancer cases and controls separately with multivariate linear regression analysis. The dependent variables included %FM, WHR, and WHtR.

The predictor variables of interest in CBT included age, sex, puberty, brain tumor histopathology, tumor location, and treatments including surgery, radiotherapy, chemotherapy, and steroids. In addition, we included lifestyle factors encompassing diet, physical activity, screen time, and sleep duration in the analysis. For controls, we included age, sex, puberty, diet, physical activity, screen time, and sleep duration in the analysis. The sample size of 56 events and 106 non-events provide adequate power for this analysis, as two events per variable are required in linear regression analyses to address the question of adiposity determinants in CBT and controls[68]. To analyze the dietary patterns in participants, we used principal component analysis. Twenty-two food items were included in the factor analysis. The number of dietary patterns retained was determined by visual inspection of scree plots in conjunction with eigenvalues (>1.0) and principal component interpretability. The factors were orthogonally transformed by using the varimax rotation to ensure the independence of factors

in the structure. Dietary patterns were characterized based on dietary items with their factor loadings ≥ |0.30|. The PCA scores for each pattern obtained for each individual represented how closely their food choices reflected one of the empirically-derived dietary patterns, with higher scores reflecting a greater degree of adherence to that dietary pattern[69].

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AUTHOR CONTRIBUTIONS

M.C.S. is the guarantor. Study conception and design determined by M.C.S., K.W.W., R.J.d.S., A.F., S.K.S., D.L.J., S.M.Z., S.R.R., S.B., K.S. and L.T. Subjects recruitment and data collection was done by K.W.W., with the support from M.C.S, A.F., S.K.S., S.B., and K.S. Dietary data interpretation and analysis was completed by K.W.W., R.J.d.S., and M.C.S. Other statistical analyses and data interpretation was completed by K.W.W., M.C.S., R.J.d.S., A.F., S.K.S., D.L.J., S.M.Z., S.R.R., S.B., K.S., and L.T. K.W.W. and M.C.S. drafted the manuscript. All authors provided critical revisions of the manuscript and approved the final submitted version.

ADDITIONAL INFORMATION

Competint financial interests: In the last five years, Dr. de Souza has served as an external resource person to the World Health Organization's Nutrition Guidelines Advisory Group on trans fats and saturated fats. The WHO paid for his travel and accommodation to attend meetings from 2012-2015 to present and discuss this work. He has also done contract research for the Canadian Institutes of Health Research's Institute of Nutrition, Metabolism, and Diabetes, Health Canada, and the World Health Organization for which he received remuneration. He has held a grant from the Canadian Foundation for Dietetic Research as a principal investigator, and is a co-investigator on several funded team grants from Canadian Institutes of Health Research. The other authors declare no conflict of interest.

Table 1. Characteristics of study population

Variables	Non-cancer controls (n=106)			CBT (n=56)		
	Total Mean (SD)	**Male Mean (SD)**	**Female Mean (SD)**	**Total Mean (SD)**	**Male Mean (SD)**	**Female Mean (SD)**
Age (years)	14.00 (2.80)	14.00 (2.60)	14.00 (3.00)	14.70 (7.10)	14.80 (5.50)	14.50 (9.00)
Sex, No. (%)						
Female	51.00 (48.10)	-	-	23.00 (41.10)	-	-
Male	55.00 (51.90)	-	-	33.00 (58.90)	-	-
Height (cm)	161.70 (15.30)	166.00 (16.80)	157.20 (11.90)	150.60 (25.20)	155.90 (26.10)	143.00 (22.30)
Weight (kg)	59.00 (20.80)	64.30 (25.00)	53.50 (13.30)	52.40 (24.10)	55.20 (23.00)	48.50 (25.50)
BMI (kg/m2)	22.10 (5.60)	22.80 (6.60)	21.40 (4.10)	21.60 (5.50)	21.40 (4.40)	21.80 (6.80)
BMI z-score	0.49 (1.16)	0.58 (1.27)	0.41 (1.02)	0.41 (1.15)	0.32 (1.26)	0.55 (0.96)
BMI category, No. (%)						
BMI%ile<85	69.00 (65.10)	34.00 (61.80)	35.00 (68.60)	36.00 (64.30)	22.00 (66.70)	14.00 (60.90)
BMI%ile≥85	37.00 (34.90)	21.00 (38.10)	16.00 (31.40)	20.00 (35.70)	11.00 (33.30)	9.00 (39.10)
%FM	22.20 (9.00)	19.10 (9.00)	25.60 (7.80)	25.80 (9.60)	23.00 (9.40)	29.90 (8.60)
WHR	0.82 (0.09)	0.84 (0.08)	0.80 (0.10)	0.87 (0.07)	0.86 (0.07)	0.88 (0.08)
WHtR	0.45 (0.08)	0.45 (0.09)	0.44 (0.07)	0.47 (0.06)	0.47 (0.06)	0.48 (0.07)
Sys BP (mmHg)	107.20 (10.60)	110.40 (10.60)	103.70 (9.60)	104.00 (11.50)	104.10 (11.60)	103.90 (11.80)
Dia BP (mmHg)	67.60 (9.60)	67.10 (10.00)	68.10 (9.10)	66.30 (8.50)	66.20 (8.50)	66.40 (8.80)
Physical activity, No. (%)						
Active	97.00 (91.50)	48.00 (87.30)	49.00 (96.10)	43.00 (76.80)	25.00 (75.80)	18.00 (78.30)
Inactive	9.00 (8.50)	7.00 (12.70)	2.00 (3.90)	13.00 (23.20)	8.00 (24.20)	5.00 (21.70)
Screen time (hours/day)	4.30 (2.60)	4.80 (2.70)	3.80 (2.50)	4.50 (2.70)	4.80 (2.60)	3.90 (2.70)
Sleep duration (hours/day)	9.50 (1.40)	9.70 (1.70)	9.40 (1.10)	9.60 (1.20)	9.40 (1.20)	9.70 (1.10)

Abbreviations: SD, Standard Deviation; BMI, Body Mass Index; %tile, percentile; %FM, fat mass percentage; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio; Sys BP, systolic blood pressure; Dia BP, diastolic blood pressure; mmHg, millimeter Mercury.

Table 2. Brain tumor type, location, and treatments

Variables	No. (%)
Brain tumor type	
CNS germ cell tumors	5(8.90)
PNET/Medulloblastoma	11(19.60)
Ependymoma	2(3.60)
Subependymal giant cell astrocytoma	3(5.40)
Meningioma	1(1.80)
NF-1, low grade glioma	10(17.85)
Non-NF-1, low grade glioma	24(42.85)
Brain tumor location	
Supratentorial	26(46.40)
Infratentorial	30(53.60)
Brain tumor treatments	
Surgery	41(73.20)
Radiotherapy	22(39.30)
Chemotherapy	27(48.20)
No treatment	8(14.30)
Steroids	27(48.20)

Abbreviations: PNET, Primitive Neuroectodermal Tumor; NF-1, Neurofibromatosis Type 1.

Table 3. The determinants of adiposity in participants with brain tumors

Variables	%FM		WHR		WHtR	
	β (SE)	P-value	β (SE)	P-value	β (SE)	P-value
Age	-0.12 (0.10)	0.23	-0.28 (0.03)	0.29	-0.02 (0.03)	0.50
Sex	0.55 (0.52)	0.30	-0.13 (0.14)	0.36	-0.13 (0.18)	0.46
Puberty	1.11 (0.99)	0.28	0.28 (0.26)	0.29	0.35 (0.34)	0.32
Brain tumor type	-0.33 (0.44)	0.46	-0.06 (0.11)	0.58	0.08 (0.15)	0.61
Brain tumor location	-1.83 (0.80)	0.028	-0.37 (0.21)	0.08	-0.53 (0.27)	0.06
Surgery	0.91 (0.81)	0.27	0.08 (0.21)	0.69	0.20 (0.28)	0.47
Radiotherapy	1.65 (0.79)	0.046	0.08 (0.21)	0.69	0.22 (0.27)	0.43
Chemotherapy	-0.86 (0.74)	0.25	0.06 (0.19)	0.77	-0.02 (0.25)	0.93
Steroids	0.68 (0.62)	0.28	0.04 (0.16)	0.81	0.21 (0.21)	0.32
Prudent diet	0.13(0.33)	0.68	0.06 (0.08)	0.44	0.06 (0.11)	0.62
Western diet	0.15 (0.33)	0.64	0.04 (0.09)	0.64	0.17 (0.11)	0.13
High-protein diet	-0.19 (0.27)	0.48	-0.02 (0.07)	0.76	-0.09(0.09)	0.33
Refined carbohydrate diet	0.38 (0.29)	0.20	0.06 (0.08)	0.43	0.07(0.10)	0.45
Physical inactivity	-0.89 (0.57)	0.12	-0.12 (0.15)	0.42	-0.26 (0.19)	0.19
Screen time	1.08 (1.33)	0.42	0.14 (0.34)	0.68	0.42 (0.46)	0.37
Sleep duration	6.41 (7.24)	0.38	1.77 (1.87)	0.35	1.44 (2.49)	0.57

Abbreviations: %FM, Percent Fat Mass; WHR, Waist-to-Hip Ratio; WHtR, Waist-to-Height Ratio; SE, standard error.

Table 4. Factor loading matrix for dietary patterns in participants

Items	Factor loadings			
	Prudent	Western	High-protein	Refined carbohydrate
Fruits	**0.73**	-	-	-
Vegetables	**0.70**	-	-	-
Water	**0.57**	-	-	-
Crackers	**0.52**	-	-	-
Grain	0.49	-	-	-
Juice	-	-0.18	-	-
Fried Foods	-	**0.68**	-	-
Desserts	-	**0.61**	-	-
Baked Goods	-	**0.56**	-	-
Chips	-	**0.53**	-	-
Snacks	-	**0.53**	-	-
Candies	-	**0.51**	-	-
Poultry	-0.31	-	**0.67**	-
Red Meat	-	-	**0.63**	-
Eggs	-	-	**0.57**	-
Soft Drinks	-0.39	-	0.40	-
Peanut/other nuts	0.30	-0.31	0.38	-
White Bread	-	0.30	-	**0.71**
Dark Bread	0.35	-	0.34	**-0.67**
Gelatin	-	-	-	**0.66**
Fish	-	-	-	0.37
Dairy	-	-	-	0.35
Total variance explained (%)	15.7	10.1	8.4	7.1

Absolute values <0.30 were not listed in the table, except for juice whose highest value of factor loading is shown.
Absolute values >0.50 were bolded to emphasize strength of association and determination of dietary patterns.

Supplementary Table S1. Factors associated with adiposity patterns in non-cancer controls.

Variables	%FM		WHR		WHtR	
	β (SE)	P-value	β (SE)	P-value	β (SE)	P-value
Age	0.14 (0.11)	0.19	0.01 (0.02)	0.59	0.05 (0.04)	0.25
Sex	1.54 (0.41)	<0.001	-0.24 (0.09)	0.01	-0.04 (0.15)	0.78
Puberty	-1.53 (0.78)	0.052	-0.47(0.18)	0.01	-0.68 (0.29)	0.02
Prudent diet	-0.14 (0.20)	0.50	0.07 (0.05)	0.12	-0.02 (0.08)	0.81
Western diet	-0.13 (0.20)	0.50	0.07 (0.04)	0.10	-0.04 (0.07)	0.56
High protein diet	-0.19 (0.20)	0.34	0.007(0.05)	0.88	-0.007 (0.07)	0.93
Refined carbohydrate diet	0.09 (0.20)	0.65	0.01(0.05)	0.80	0.13 (0.07)	0.09
Physical inactivity	0.04 (0.72)	0.95	0.30 (0.16)	0.07	0.10 (0.27)	0.70
Screen time	0.31 (0.80)	0.70	0.31 (0.18)	0.09	0.65 (0.29)	0.03
Sleep duration	0.83 (3.60)	0.82	0.62 (0.82)	0.49	-0.25 (1.33)	0.85

Abbreviations: CBT, Children with Brain Tumors; %FM, Percent Fat Mass; WHR, Waist-to-Hip Ratio; WHtR, Waist-to-Height Ratio; CI, Confidence Interval.

Chapter 5: Birth weight as a predictor of body mass in children with brain tumors: A cross-sectional study

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MCS is the guarantor. Research question and study design were defined by KWW, RJdS, AF, DLJ, SMZ, SRR, SB, LT and MCS. KWW performed subject recruitment and data collection, supported by AF and SB. RJdS and LT provided supports to research methods and statistical analyses. Data interpretation was completed by KWW, RJdS, AF, DLJ, SMZ, SRR, SB, LT and MCS. The manuscript was drafted by KWW and MCS and reviewed by all authors, who agreed with its content.

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Introduction

Brain tumors are the most common cause of cancer-related death in children, despite the diversity in tumor subtypes and the aggressiveness of some subtypes, advancements in management, including imaging and therapeutic breakthroughs, have increased the number of children surviving these tumors[1,2]. This important milestone has been offset by the emergence of co-morbidities and premature mortality in survivors[3-7]. While traditional outcome determinants included tumor recurrence and secondary tumors, recent evidence suggests that children with brain tumors (CBT) are at higher risk of premature cardiovascular diseases including hypertension, cerebrovascular and cardiovascular events and type 2 diabetes compared to non-cancer controls[8-10]. While the mechanisms leading to these cardiometabolic disorders are incompletely understood, the combined burden of the tumor and treatment with these emerging chronic disorders will increasingly contribute to adverse outcomes in CBT as they get older.

The global obesity epidemic is the main catalyst of cardiometabolic disorders in the general population[11-14], and the association of obesity with future type 2 diabetes and cardiovascular diseases has been tracked to childhood[15]. Defining the determinants of obesity and cardiometabolic outcomes in CBT will help identify those at risk, and may allow the prioritization of which children need early intervention to prevent obesity and cardiometabolic disorders, and improve survivors' quality of life and lifespan.

Over the past two decades, evidence has validated the role of birth weight as a predictor of obesity and cardiometabolic disorders in adults[16,17]; however, it is unclear if birth weight in CBT predicts obesity during childhood. The primary aim of this paper was to explore if birth weight predicts body mass in CBT during childhood, compared to non-cancer controls.

Results

Population characteristics:

We included 78 CBT (n= 33 females (42.3%)) and 133 non-cancer controls (n= 60 females, (45.1%)) in this study. The characteristics of the study population are shown in Table 1.The two groups were similar in terms of age, sex, ethnicity, body mass index (BMI), BMI z-score, and birth weight distribution. However, the controls were taller and weighed more than CBT. On the other hand, CBT had higher fat mass percentage (%FM) (CBT 25.80±9.60% versus controls 22.40±9.80%). There were equal proportions of participants who were overweight or obese in both groups.

Participants born at full-term comprised the largest groups (CBT n= 45 (57.70%); controls n= 65 (48.90%)). More controls were born pre-term (CBT n= 3 (3.80%); controls n= 21 (15.80%)) and early-term (CBT n= 10 (12.80%); controls n= 24 (18.00%)) compared to CBT, while more CBT were born at late-term (CBT n= 20 (25.60%); controls n= 23 (17.30%)).

The majority of both CBT and controls were born appropriate for gestational age (AGA) (CBT n= 60 (76.90%); controls n= 90 (67.70%)). A larger

proportion of CBT were born small for gestational age (SGA) compared to non-cancer controls (CBT n= 11 (14.10%); controls n= 12 (9.00%)) while large for gestational age (LGA) was more common in controls (CBT n= 7 (9.00%); controls n= 31 (23.30%)). Maternal gestational diabetes was reported in two CBT (2.60%) and in one control (0.80%), while preeclampsia was reported in five CBT (6.40%) and 10 controls (7.50%).

The majority of the subjects had normal birth weight (CBT n= 62 (79.50%); controls n= 104 (78.20%)). Six CBT (7.70%) and six controls (4.50%) were born with a low birth weight (<2500 grams). High birth weight (>4000 grams) were found in ten CBT (12.80%) and 23 controls (17.30%).

Tumor characteristics & treatments:

Brain tumor characteristics and therapeutic modalities are reported in Table 2. The most common tumors in this study population were low-grade gliomas (n= 45 (57.70%)). Brain tumors were equally distributed between supratentorial and infratentorial regions. The treatments used in participants included surgery alone (n= 25 (32.00%)), and a combination of surgery, radiotherapy, and chemotherapy (n= 24 (30.80%)). In addition, other treatment options included radiotherapy alone (n= 2 (2.60%)), chemotherapy alone (n= 7 (9.00%)), and combinations of surgery and radiotherapy (n= 6 (7.70%)); surgery and chemotherapy (n= 5 (6.40%)); radiotherapy and chemotherapy (n= 1 (1.30%)). Eight CBT (10.20%) were managed conservatively at the time of inclusion into the study.

The association of birth weight and body mass:

To explore the association of birth weight with body mass, we performed multivariable regression analyses in CBT, adjusted for age, sex, puberty, and %FM. Birth weight was positively associated with BMI (β= 0.18; 95%CI 0.03,0.33; p= 0.02) and BMI z-score (β= 3.69; 95%CI 1.12,6.25; p= 0.006) in CBT and controls (BMI β= 0.17; 95%CI 0.07,0.27; p= 0.001; BMI z-score β= 2.15; 95%CI 0.75,3.55; p= 0.003).

To determine if the association between birth weight and body mass differs between CBT and controls, an interaction term (birth weight*brain tumor status) was introduced (Table 3). This analysis reveals that birth weight is associated with body mass, and that the effect of birth weight on future body mass is similar in CBT and controls (BMI β= 0.02; 95% CI -0.15, 0.20; p= 0.80; BMI z-score β= 2.02; 95% CI -0.62,4.67; p= 0.13).

Discussion

The emergence of cardiovascular diseases and type 2 diabetes in survivors of childhood brain tumors are likely to contribute to adverse prognoses, and there is an urgent need to identify the drivers of these outcomes to mitigate their effects on life span and quality of life. In this study, we demonstrate that birth weight can predict body mass in CBT during childhood, and this relationship was similar to that noted in non-cancer controls.

The influence of the in- and ex-utero environments on the risk of obesity and cardiometabolic risk is an important determinant of health outcomes, based

on evidence from studies in the general population[18]. One of the potential early and feasible measures that forecast these outcomes is birth weight.

Birth weight is driven by several factors, including genes that determine body size and growth, and the intrauterine environment[19]. It is estimated that 10-40% of birth weight is driven by genetic factors, with several loci identified to suggest genetic links with body weight and mass[19,20]. In addition, fetal metabolic programing *in utero* in response to the intrauterine environment contributes to cardiometabolic health postnatally through epigenetic and other mechanisms[21].

The exposure of an embryo to an adverse intrauterine environment and excess metabolic stress leads to the re-programming of the metabolic pathways, to adapt to in-utero scarcity or excess of nutrients[18,22]. Clinically, this manifests with infants being born small or large for gestational age[23]. However, it is likely that at intermediate stages of metabolic stress, some babies may have a birth weight within the normal range, but have been exposed to an environment that can alter their metabolic trajectory[24].

The evidence for the association of certain categories of birth weight with adult BMI and cardiometabolic disorders was highlighted in studies from David Barker and the Dutch famine cohort and others, and showed that birth weight and maternal-fetal undernutrition was linked to low birth weight that was associated with adult obesity and adverse cardiometabolic outcomes[25-30].

In addition, the link between birth weight and obesity has been highlighted in previous reports showing that those born SGA or LGA to be at risk of adult

obesity[18]. However, recent studies report that in those with a birth weight that is sometimes within the normal range, or who have high birth weight (>4000 grams), are at risk of adult obesity[24,31,32]. Contrary to previous evidence[33-35], some studies did not show linear, J-shaped or U-shaped associations of birth weight with adult obesity[31,32].

Our data show a positive relationship between birth weight and body mass measures in CBT and controls in childhood. This is congruent with recent large-scale studies that have provided further evidence of similar results in the general pediatric population[23,36,37]. Birth weight may help identify those CBT who are at risk of adult obesity. Detailed study of growth paths and longer follow-up period are needed to determine if birth weight predicts obesity in CBT as they reach adulthood.

While available evidence suggest that obese children are at risk of becoming obese adults[38-40], the association between birth weight, childhood BMI and future cardiometabolic risk is more complex[41]. It has been reported that birth weight below 3.4 kg, which is still considered appropriate for gestational age, and high BMI during childhood were independently associated with increased risk of coronary heart disease[42]. The association between low birth weight and type 2 diabetes was also reported[43,44]. The evidence indicates that both birth weight and BMI need to be scrutinized in CBT and controls to identify subjects who are at an increased risk of cardiometabolic disorders, as they appear to be independently linked to these outcomes.

While pediatric obesity is associated with adult obesity[38-40], it is less clear how a normal birth weight affect this trajectory of adult obesity and cardiometabolic outcomes in CBT as most of our sample consisted of children with a birth weight within the normal range. In order to determine the contribution of a higher birth weight that is still within the normal range to future BMI in adulthood and its association with cardiometabolic outcomes in CBT, the analysis of prospective data sets is required.

One of the strengths of our study is the inclusion of non-cancer controls to provide a comparison group. Our data show that in CBT, having a higher birth weight is linked with having a higher body mass during the early years after surviving the brain tumor.

It has been shown that CBT have increased adiposity early in life post completion of therapy, and are at higher risk of cardiovascular diseases and diabetes compared to the general population, despite having similar BMI to controls[9,45,46]. CBT can have disproportionate effects of their tumor and its treatment on cardiometabolic outcomes at a similar obesity rate, and birth weight may be a potential predictor of these outcomes[46-48].

There are several limitations in this study. We did not have sufficient power to determine the association of birth weight with young adult BMI, as the number of young adult subjects in our study is small. While we demonstrate that birth weight is positively associated with body mass measures in adolescence, our data does not distinguish whether this is a result of the expansion of lean body

mass or fat mass, as BMI is a measure of total body mass. A recent study showed that birth weight was associated with fat-free mass, but not with fat mass among children and adolescents[49]. This will require further clarification in future studies.

In addition, this analysis is cross-sectional and therefore it is not clear if subjects were overweight or obese before their brain tumor diagnoses. Prospective collection of data from diagnosis onwards and correlating growth data with those from earlier time points may help define growth patterns of those survivors at risk of obesity.

In conclusion, cardiometabolic disorders are occurring at a relatively young age in CBT, and are emerging as significant morbidities and as potential determinants of longevity[5,9,45]. Our results suggest that birth weight predicts body mass in CBT in the early years post treatment. Future studies need to focus on determining the early origins of obesity and cardiometabolic risk in survivors. This will help identify survivors who are at particular risk of these complications, and birth weight may be one of the risk markers used to stratify cardiometabolic risk in CBT.

Methods

Participants:

Participants in this study were recruited into the Canadian Study of Determinants of Endometabolic Health in Children (CanDECIDE) Study. This is a cohort study conducted at McMaster Children's Hospital in Hamilton, Ontario, Canada[50,51].

Briefly, we recruited participants who were 5 years and older, with no history of autoimmune diseases or infection, and have not received immunosuppressive therapy for at least 15 days prior to enrollment. Participants were consecutively recruited and the study recruitment took place between November 2012-March 2017. The Hamilton Integrated Research Ethics Board approved the study, and participants provided written informed consent. The study procedures were carried out in accordance with relevant guidelines and legal regulations.

Clinical Data and Anthropometric measures:

The collected data included age, sex, ethnicity, puberty, pregnancy gestation, maternal gestational diabetes and preeclampsia, and reported birth weight using standardized questionnaires[50,51]. While reported birth weight correlates with measured birth weight[52], the reported birth weight was verified from the medical records. In CBT, we also collected data regarding tumor type, location, sidedness and treatment modalities.

Gestation was defined for those born at less than 37 weeks as preterm, between 37-38+6/40 weeks as early term, 39-40+6/40 weeks as full term, and 41-41+6/40 weeks as late term gestations[53]. Normal birth weight was defined to be between 2500-4000 grams[54]. Infants born SGA were defined as those with a birth weight below the10th percentile, AGA as 10th-90th percentile, and LGA as above 90th percentile using Canadian reference ranges[55].

Anthropometric measurements performed included height measured to 0.1 cm using a stadiometer, and weight measured using an electronic weighing scale (Seca, USA) and measured to the closest 0.1 kg. BMI was calculated in kg/m^2 for all subjects. For those under 20 years of age (CBT n= 62, controls n= 133), BMI percentile and BMI z-scores were also obtained based on the Children's BMI Tool for Schools[56] and the Centers for Disease Control and Prevention (CDC) growth chart[57], respectively. Subjects with BMI $\geq 85^{th}$ – $<95^{th}$ percentile were classified as overweight, and those above 95^{th} percentile were classified as obese[58].

Adiposity was determined by measuring fat mass percentage (%FM) using the Tanita body fat monitor (Tanita Corporation, Illinois, USA) for those under 18 years of age, and with the InBody520 body composition analyzer (Biospace Co., Ltd, Korea) for those 18 years and older as previously reported[46].

Statistical Analysis:

All analyses were performed using PASW version 18 statistical package.[59] Kolmogorov-Smirnov test was used to assess the normality of data distribution, and data were log-transformed if they were non-normally distributed. Outliers were examined with box plot and visual inspection of extreme values. Missing data were imputed. Mean and standard deviation (SD) were reported for continuous variables, while the categorical variables were reported as counts with percentages.

To explore the association between birth weight and body mass measures in CBT, multivariable linear regression analysis was performed in this group. The

dependent variables included BMI and BMI z-scores in separate models. The independent variables included birth weight, age, sex, puberty, and %FM.

The relationship between birth weight and body mass in CBT and non-cancer controls was explored by adding an interaction term (birth weight*brain tumor status). Both CBT and non-cancer controls were included in the regression analysis.

Results were presented as estimated β coefficients, 95% confidence intervals (CI), and associated p-value. The criterion for statistical significance was set at alpha = 0.05.

Data Availability

The dataset used for statistical analysis for the current study is available from the corresponding author.

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Author Contributions:

M.C.S. is the guarantor. Research question and study design were defined by K.W.W., R.J.d.S., A.F., D.L.J., S.M.Z., S.R.R., S.B., L.T. and M.C.S. K.W.W. performed subject recruitment and data collection, supported by A.F. and S.B. R.J.d.S. and L.T. provided supports to research methods and statistical analyses. Data interpretation was completed by K.W.W., R.J.d.S., A.F., D.L.J., S.M.Z., S.R.R., S.B., L.T. and M.C.S. The manuscript was drafted by K.W.W. and M.C.S. and reviewed by all authors, who agreed with its content.

Additional Information

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Table 1. Characteristics of study population.

Variables	Control	CBT
	Total (n=133) Mean±SD	**Total (n=78) Mean±SD**
Age at enrollment (years)	14.10±2.70	15.10±7.30
Sex, No. (%)		
Female	60 (45.10)	33 (42.30)
Male	73 (54.90)	45 (57.70)
Ethnicity, No. (%)		
European	91 (68.40)	59 (75.60)
Others	42 (31.60)	19 (24.40)
Puberty, No. (%)		
Pre-pubertal	17 (12.80)	24 (30.80)
Pubertal	116 (87.20)	54 (69.20)
Height (cm)	162.70±15.00	151.00±25.20
Weight (kg)	60.00±21.40	53.40±24.90
BMI (kg/m^2)	21.70±4.20	21.40±4.70
BMI z-score	0.49±1.10	0.47±1.10
BMI category, No. (%)		
BMI%ile<85 or BMI<25	88 (66.20)	49 (62.80)
BMI%ile≥85 or BMI≥25	45 (33.80)	29 (37.20)
Fat mass percentage (%)	22.40±9.80	25.80±9.60
Birth weight (g)	3491.30±487.40	3436.60±516.50
Pregnancy gestation (weeks)	38.90±2.30	39.90±1.80

Abbreviations: CBT, Children with Brain Tumors; SD, Standard Deviation; BMI, Body Mass Index

Table 2. Brain tumor type, location, and treatments (n=78)

Variables	No. (%)
Brain tumor type	
Non-NF-1, low grade glioma	34 (43.60)
PNET/Medulloblastoma	17 (21.80)
NF-1, low grade glioma	11 (14.10)
CNS germ cell tumors	6 (7.70)
Subependymal giant cell astrocytoma	3 (3.80)
Ependymoma	2 (2.60)
Craniopharyngioma	2 (2.60)
Meningioma	1 (1.30)
Atypical teratoid/rhabdoid tumor	1 (1.30)
Choroid plexus papilloma	1 (1.30)
Brain tumor location	
Supratentorial	36 (46.20)
Infratentorial	42 (53.80)
Brain tumor treatments	
Surgery	60 (76.90)
Radiotherapy	33 (42.30)
Chemotherapy	37 (47.40)
No treatment	8 (10.30)

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

Table 3. Interaction analysis of body mass measures and birth weight in CBT and non-cancer controls

BMI				
Variables	**Main Effect**		**Interaction**	
	Estimated β (95% CI)	p-value	Estimated β (95% CI)	p-value
Birth weight	0.18 (0.09,0.27)	<0.001	0.17 (0.06,0.28)	0.003
Brain tumor status	-0.03 (-0.04,-0.01)	<0.001	-0.11 (-0.73,0.51)	0.73
Interaction[a]	-	-	0.02 (-0.15,0.20)	0.80
BMI z-score				
Variables	**Main Effect**		**Interaction**	
	Estimated β (95% CI)	p-value	Estimated β (95% CI)	p-value
Birth weight	2.81 (1.54,4.09)	<0.001	2.10 (0.52,3.68)	0.009
Brain tumor status	-0.33 (-0.51,-0.14)	0.001	-7.48 (-16.83,1.86)	0.12
Interaction[a]	-	-	2.02 (-0.62,4.67)	0.13

Abbreviations: CBT, Children with Brain Tumors; BMI, Body Mass Index; CI, Confidence Interval. Models were adjusted for age, sex, puberty, fat mass percentage.

[a]The interaction term was birth weight*brain tumors status (yes/no).

Chapter 6: The effectiveness of interventions to treat obesity in survivors of childhood brain tumors: a systematic review protocol

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MCS is the guarantor. The research question was defined by MCS, AF, SKS, SB, and LT. Search strategy and eligibility criteria were developed by KWW, MV, RC, LB, and MCS. Data abstraction form was designed by KWW, MV, RC, and MCS. Quality and risk of bias assessments were conducted by KWW and RC. Methodological support was provided by RJdeS and LT. KWW, RC, AF, SKS, SB, LT, LB, and MCS drafted the manuscript. All authors reviewed, edited, and approved the final version of the manuscript.

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The published version of the paper is included in Appendix 3.

INTRODUCTION

Brain tumors are the most common solid tumors in children and constitute up to 20% of childhood cancers [1]. Significant breakthroughs in understanding the hallmarks of cancer biology, coupled with advances in diagnostic imaging and improved therapies, have enhanced the survival rates of these children [2, 3].

As the number of survivors of childhood brain tumors (SCBT) increased, it has become apparent that survivors remain at risk of premature mortality [4-6], and the development of multiple comorbidities [7, 8]. Many SCBT develop chronic health conditions within years of their initial diagnosis [9], and one such morbidity is obesity [10-13]. In one study, obesity was reported in 36.5% of SCBT, compared to 29% in the general population [14, 15]. In the general population, the annual health care expenditures of obese individuals are about US$1,360 higher than for their non-obese counterparts [16], and this is likely to be replicated in SCBT.

Addressing obesity in SCBT is crucial, as it increases the risk of cardiometabolic disorders in a similar fashion to the general population, and may contribute to premature mortality [17, 18]. Obesity is an independent risk factor for decreased survival in some children with brain tumors [19]. Understanding the drivers of obesity in SCBT will allow the development of precision-based strategies for reducing the risk of obesity and its cardiometabolic comorbidities, which in turn may improve the quality of life and lifespan of SCBT.

Obesity in SCBT is multifactorial, and can be related to altered energy intake [20, 21], reduced mobility and physical activity [22-25], hypothalamic-pituitary damage [11], pituitary hormone deficiencies [26], sleep problems [27], vision problems, imbalance and pain [8, 28], mental health issues and medications e.g. antidepressants [29].

As obese children are likely to become obese adults [30-34], it is important to develop effective interventions to manage obesity from an early age. The purpose of this systematic review is to evaluate current evidence of effectiveness of interventions to manage obesity in SCBT.

Research Question

In survivors of childhood brain tumors, are the current interventions including lifestyle intervention, pharmacotherapy, and bariatric surgery effective in managing obesity?

Study Objectives

1) Measure the effectiveness of lifestyle interventions, pharmacotherapy and bariatric surgery in the treatment of obesity in SCBT
2) Conduct a meta-analysis of primary studies, if appropriate, to gain a more precise estimate of the effectiveness of different strategies in managing obesity
3) Critically appraise existing evidence and identify gaps in the literature to provide future research directions

METHODS

The protocol for this systematic review is developed and reported with guidance from the Preferred Reporting Items for Systematic Review and Meta-Analysis-Protocols (PRISMA-P) statement (Additional file 1) [35].

Eligibility Criteria

This review will include studies involving boys and girls who are overweight or obese (BMI z-score $\geq 85^{th}$ percentile) [36], with a diagnosis of brain tumor made under the age of 18 years. Randomized Controlled Trials (RCTs), quasi-RCT, prospective or retrospective cohort study, case-control study, cross-sectional study, and controlled or uncontrolled studies with before-and-after comparisons will be included [37].

There will be no restriction to the language or timing of publication. Conference proceedings, congress reports, and editorials will be hand searched for suggested relevant studies. We will exclude interim analyses, case reports, and pilot studies.

In studies where SCBT are included in an intervention with other cancer types, we will extract data for the brain tumor subgroup. If the data from subgroups are not published or pooled with data from survivors of other cancers, we will attempt to contact the authors to obtain the subgroup data.

The interventions included in the study are:

- Life style intervention: Any form of modifications in subjects' daily life including their dietary patterns, physical activity, and eating behaviors
- Pharmacotherapy: Any administration of medications
- Bariatric surgery: Any surgical approach performed with the intention of treating obesity, including adjustable gastric banding, sleeve gastrectomy, biliopancreatic diversion with duodenal switch and gastric bypass

Studies that are entered into the databases up to February 1st, 2016 will be screened for eligibility. The search will be updated to capture recently published literature.

Outcome measures

Primary outcome: The primary outcome in this review is BMI z-score change from baseline to the end of the intervention and/or at follow-up.

Secondary outcomes: Secondary outcomes include changes in waist and hip circumference, waist-to-hip ratio, waist-to-height ratio, body fat percentage, and blood pressure as reported. We will also report changes in diabetes status, insulin resistance, and non-alcoholic fatty liver disease, if available. In addition, we will document changes in lipid levels including high-density lipoprotein, low-density lipoprotein, cholesterol, and triglycerides, if reported. We will also abstract any adverse events observed during the study. Adverse events for the commonly used pharmacological agents include insomnia, headaches, hypertension, and others [38]. Adverse outcomes for bariatric surgery include surgical complications,

perioperative outcomes, and mortality as defined previously [39]. Adverse events directly related to lifestyle interventions include back and shoulder pain, musculoskeletal injuries, episodes of angina, and others [40, 41]. Additional adverse events will be included as reported.

Search Strategy

We will consult a Health Sciences librarian with expertise in systematic reviews when designing the search strategy. A proposed search strategy for Medline is described in Table 1. Searches will be conducted in PubMed, Medline, EMBASE, PsycINFO, Sport Discus, CINAHL, Cochrane Database of Systematic Review, Cochrane Central Register of Controlled Trials (CENTRAL), and Database of Abstracts of Reviews of Effect (DARE). We will search ClinicalTrials.gov and ProQuest Dissertations and Theses A&I to identify relevant grey literature. We will also search the reference lists of articles deemed eligible for inclusion in the analysis for relevant studies.

Data Management

Two independent reviewers will perform data abstraction and quality assessment. Disagreement between the two reviewers will be resolved by discussion, with subsequent involvement of a third reviewer to arbitrate disagreements. Excel spreadsheets will be used to manage study records during the screening process. We will use the Grading of Recommendations Assessment, Development and Evaluation Profiler (GRADEpro) software to create tables for summary of findings and quality assessment [42].

Data Screening

Duplicates will be removed, followed by screening of titles and abstracts. Full text articles that meet the inclusion criteria will be retrieved and screened. Screening at all steps will be conducted independently by two reviewers, who will meet after each step to ensure consistency and to resolve conflicts. In the case of persisting disagreement, a third reviewer will be consulted. A flow diagram will be included to report the screening process (Figure 1) [43, 44].

Data Abstraction

Data will be extracted independently by two reviewers, using a data abstraction form specifically designed for this systematic review. Details to be collected include title, authors, publication date, journal name, setting, country, funding source, study design, study duration, eligibility criteria, sample size, and methods used for brain tumor diagnosis including imaging, histology, and clinical assessment.

Participants' characteristics include age at diagnosis of brain tumor and at study enrollment, sex, ethnicity, and brain tumor location and laterality. Treatment details include radiotherapy type (fractionated or non-fractionated) and dose, chemotherapy type, dose and duration, and surgery details (total resection, partial resection, shunting, ventriculostomy, other).

Detailed description of the obesity interventions will be recorded including study design, components, duration and adverse events. We will document primary and secondary outcomes of the studies. Adjustment for confounders and

details of the statistical analyses performed will be extracted as well as study results. We will attempt to retrieve incomplete data by contacting the corresponding authors of published work.

Quality Assessment

The Risk of Bias Assessment Tool from the Cochrane Collaboration will be used to assess RCT [45]. This tool includes six domains: sequence generation, allocation concealment, blinding, incomplete data, selective reporting outcomes, and other sources of bias. Each RCT will be rated as having either a high, low, or unclear risk of bias.

The Risk of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool will be used for non-randomized studies such as cohort studies [46]. This tool includes three domains: pre-intervention, at-intervention, and post-intervention.

In the pre-intervention domain, bias due to confounding and participant selection are evaluated. Possible confounding factors include brain tumor location, type, treatments, years of survival, age, sex, pubertal stage, baseline body composition, and presence of comorbidities such as metabolic syndrome and hormonal deficiency. Bias due to misclassfication of the intervention status is assesed in the at-intervention domain. The post-intervention domain include bias due to departures from the intended interventions, missing data, methods of outcome measurements and selective reporting outcomes. In particular, co-interventions between lifestyle interventions, pharmacotherapy, and bariatric

surgery can contribute to bias during the post-intervention domain. For example, participants may take anti-obesity agents while they are on diet restriction. Each non-randomized study will be rated as having either a low, moderate, serious, critical or unclear risk of bias.

The quality of uncontrolled studies will be assessed with a checklist developed by the University of Alberta Evidence-based Practice Center (UAEPC) [47]. This checklist evaluates selection bias, incomplete data, and the methods of outcome assessments. We will tabulate risk of bias for all included studies and discuss its impact on the meta-analysis.

The quality of evidence will be assessed using the Grading quality of evidence and strength of recommendations (GRADE) guidelines [48]. The GRADE guideline covers risk of bias, inconsistency, indirectness, imprecision, and publication bias. The overall quality of evidence is reported by each outcome measure as high, moderate, low or very low.

Data Analysis

Detailed characteristics of the included studies will be provided, in addition to a meta-analysis if applicable. We will analyze each intervention separately, and outcomes will be analyzed separately based on study designs. We will perform meta-analysis if two or more studies are identified per intervention.

Dichotomous outcomes will be reported as odds ratio, while continuous outcomes will be reported as standardized mean differences and 95% confidence intervals. Expecting high levels of heterogeneity, our primary approach will

emphasize the random-effects estimate if more than ten studies can be identified [49]. Otherwise, both random effect and fixed effect models will be presented.

Inconsistency index (I^2) and *P* values will be used to quantify heterogeneity. The interpretation of the I^2 will be based on the threshold set by the Cochrane Collaboration [50]. If appropriate, a stratified analysis by sex will be pursued to identify a source of heterogeneity, as female SCBT are more at risk of developing obesity than males [8, 10].

If sufficient studies are identified for an outcome (≥10), we will perform sensitivity analysis by excluding outlier, small-sized, or highly biased studies to determine the impact of these studies on the meta-analysis result. To investigate publication bias, we will create a contour-enhanced funnel plot and use Egger's test and visual inspection to determine plot asymmetry, if there are ten or more studies for an outcome [51].

All meta-analyses will be conducted using Review Manager software version 5.3 (RevMan 5.3) [52] while Comprehensive Meta-Analysis software version 3 (CMA 3.0) will be used for Egger's test [53]. When meta-analysis is not appropriate, a table for summary of findings will be created using GRADEpro software, and a narrative summary will be reported. The results of this systematic review will be presented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [43, 44]. When amendments of the protocol are needed, we will document the date and the rationale for these changes.

DISCUSSION

As the number of SCBT increased over time, it has become apparent that the burden of surviving a brain tumor is significant [4, 6, 12, 13]. Obesity is a critical comorbidity to address in survivors, as it drives the risk of cardiovascular diseases, type 2 diabetes, metabolic syndrome and hypertension [7, 8, 17-19]. This reduces quality of life and lifespan of the survivors, and increases healthcare system utilization.

In order to improve health outcomes in SCBT, it is important to develop evidence-based interventions to treat and prevent obesity and its cardiometabolic comorbidities.

The findings from this systematic review will have important implications for SCBT, as it will provide insights into the current best form of obesity intervention for these patients. The review will also define gaps in knowledge and help improve the quality of life and lifespan of SCBT by guiding the design of new interventions to target obesity and its cardiometabolic comorbidities.

Additional file 1: PRISMA-P checklist. This checklist includes recommended items to address in a systematic reviews protocol and where are they reported in this protocol.

Abbreviations: SCBT: Survivors of Childhood Brain Tumors; PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis; BMI: Body Mass Index; RCT: Randomized Controlled Trial; EMBASE: Excerpta Medica DataBase; CINAHL: The Cumulative Index to Nursing and Allied Health Literature; CENTRAL: Cochrane Central Register of Controlled Trials; DARE: Database of Abstracts of Reviews of Effect; GRADE: Grading of Recommendations Assessment, Development and Evaluation; ROBINS-I: Risk of Bias In Non-randomized Studies – of Interventions (ROBINS-I); UAEPC: University of Alberta Evidence-based Practice Center; RevMan 5.3: Review Manager software version 5.3; CMA 3.0: Comprehensive Meta-Analysis version 3.

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Authors' contributions

MCS is the guarantor. Research question defined by MCS, AF, SKS, SB, LT. Search strategy and eligibility criteria developed by KWW, MV, RC, LB, and MCS. Data abstraction form designed by KWW, MV, RC, MCS. Quality and risk of bias assessments were conducted by KWW and RC. Methodological support provided by RJdeS and LT. KWW, RC, AF, SKS, SB, LT, LB and MCS drafted the manuscript. All authors reviewed, edited, and approved the final version of the manuscript.

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53. Comprehensive Meta-Analysis (CMA) [Computer program]. Version 3. Englewood NJ: Biostat.

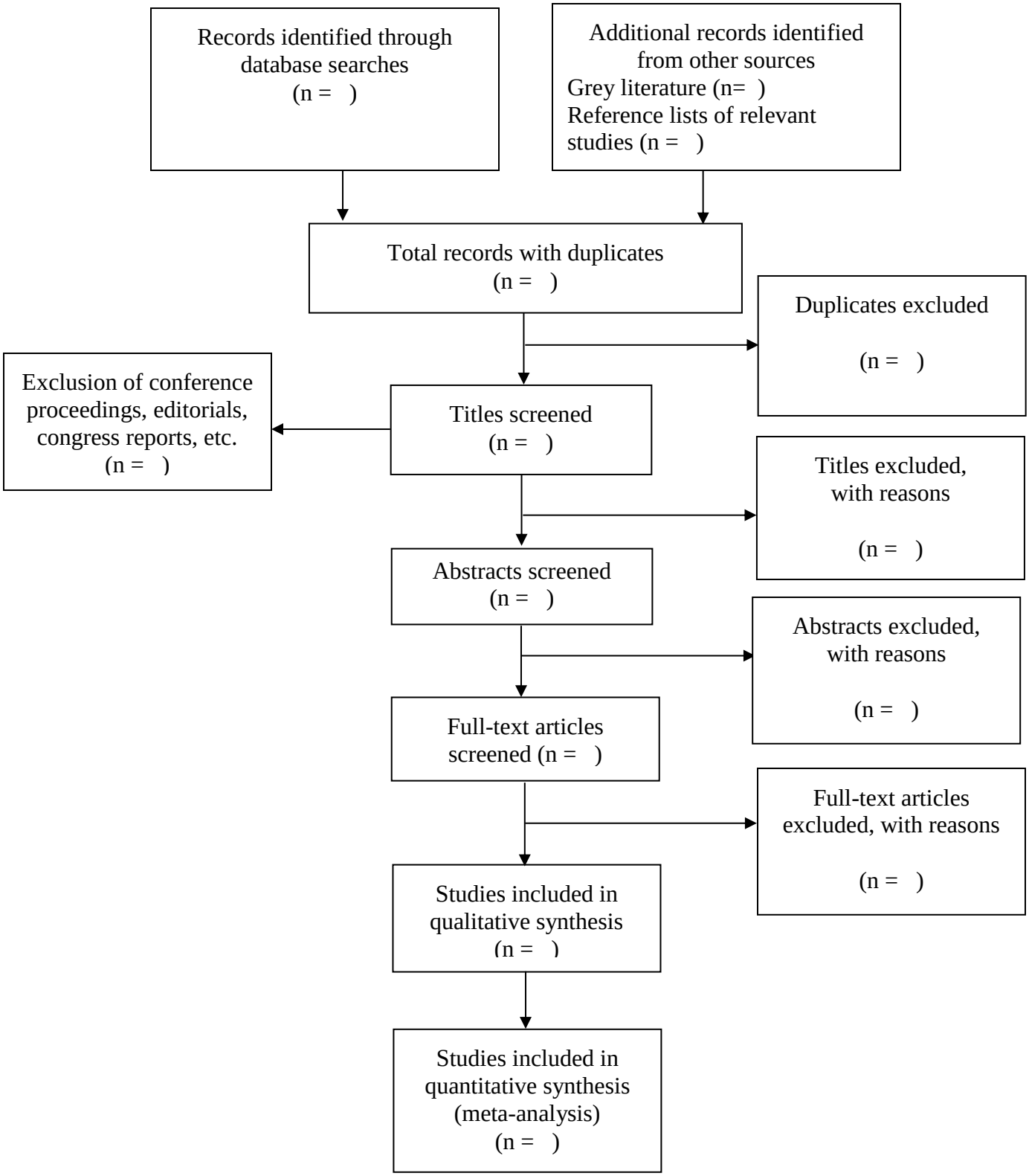
Table 1: Search Strategy for Medline

1	exp Child/
2	child*.mp.
3	p?ediatric*.mp.
4	exp Adolescent/
5	adolescen*.mp.
6	youth*.mp.
7	exp Adult/
8	adult*.mp.
9	Young Adult/
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11	exp Brain Neoplasms/
12	exp Cranial Nerve Neoplasms/
13	exp Neuroectodermal Tumors/
14	cerebroma*.mp.
15	exp Glioma/
16	glioma*.mp.
17	astrocytoma*.mp.
18	oligoastrocytoma*.mp.
19	astroglioma*.mp.
20	glioblastoma*.mp.
21	retinoblastoma*.mp.
22	pinealoma*.mp.
23	pineoblastoma*.mp.
24	pinealoblastoma*.mp.
25	pinealblastoma*.mp.
26	pineal blastoma*.mp.
27	pineocytoma*.mp.
28	pinealocytoma*.mp.
29	craniopharyngioma*.mp.
30	ependymoma*.mp.
31	subependymoma*.mp.
32	ependymoblastoma*.mp.
33	gangliioglioma*.mp.
34	gliosarcoma*.mp.
35	medulloblastoma*.mp.

36	exp Germinoma/
37	germinoma*.mp.
38	Meningioma/
39	meningioma*.mp.
40	oligodendroglioma*.mp.
41	exp Neurofibromatoses/
42	neurofibromatos*.mp.
43	PNET*.mp.
44	neurocytoma*.mp.
45	choroid plexus papilloma*.mp.
46	exp Neoplasms/
47	cancer*.mp.
48	tumo?r*.mp.
49	neoplasm*.mp.
50	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49
51	exp Obesity/
52	obes*.mp.
53	Overweight/
54	over weight.mp.
55	overweight.mp.
56	51 or 52 or 53 or 54 or 55
57	life style*.mp.
58	lifestyle*.mp.
59	exp Diet/
60	diet*.mp.
61	exp Nutrition Therapy/
62	nutrition.mp.
63	behavi*.mp.
64	exp Exercise Therapy/
65	kinesiotherap*.mp.
66	physical activ*.mp.
67	exp Exercise/
68	exercis*.mp.
69	walk*.mp.
70	jog*.mp.
71	run*.mp.
72	swim*.mp.
73	exp Bariatrics/
74	bariatric*.mp.

75	bariatric surger*.mp.
76	gastrojejunostomy.mp.
77	gastric bypass.mp.
78	stomach bypass.mp.
79	jejunoileal bypass.mp.
80	lipectomy.mp.
81	gastroplasty.mp.
82	stomach stapling.mp.
83	drug*.mp.
84	pharm*.mp.
85	exp Weight Reduction Programs/
86	((weight reduc* or weight los*) adj5 surger*).mp.
87	((weight reduc* or weight los*) adj5 program*).mp.
88	57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87
89	Body Weight/
90	body mass*.mp.
91	BMI.mp.
92	exp Body Weight Changes/
93	exp Body Weights and Measures/
94	body fat.mp.
95	waist-height ratio*.mp.
96	waist to height ratio*.mp.
97	adipos*.mp.
98	body size*.mp.
99	waist circumference*.mp.
100	hip circumference*.mp.
101	weight*.mp.
102	height*.mp.
103	waist-hip ratio*.mp.
104	waist to hip ratio*.mp.
105	skinfold thickness*.mp.
106	89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105
107	10 and 50 and 56 and 88 and 106

Figure 1: Flow Diagram of Article Screening Process



PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page No	Total Line No
ADMINISTRATIVE INFORMATION				
Title:				
Identification	1a	Identify the report as a protocol of a systematic review	1	1-2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2	66
Authors:				
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1 11-12	4-29 282-298
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	12	271-277
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	10	235-237
Support:				
Sources	5a	Indicate sources of financial or other support for the review	11	269
Sponsor	5b	Provide name for the review funder and/or sponsor	11	269
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A	N/A
INTRODUCTION				
Rationale	6	Describe the rationale for the review in the context of what is already known	3-4	70-95
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4	96-105
METHODS				
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	4-5	110-129
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	5 6	130-131 147-154
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Table 1	Table 1

Section and topic	Item No	Checklist item	Page No	Total Line No
Study records:				
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6-7	156-162
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7	163-168
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7 8	169-171 182-183
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7	171-181
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	5-6	132-145
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8-9	184-206
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	9	211-215
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	9	216-222
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9	223-227
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	10	232-233
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9-10	227-229
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	9	207-210

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Chapter 7: The effectiveness of interventions to treat hypothalamic obesity in survivors of childhood brain tumors: a systematic review

Kuan-Wen Wang, Ruth Chau, Adam Fleming, Laura Banfield, Sheila K. Singh, Donna L. Johnston, Shayna M. Zelcer, Shahrad Rod Rassekh, Sarah Burrow, Marlie Valencia, Russell J. de Souza, Lehana Thabane, M. Constantine Samaan

MCS is the guarantor. The research question was defined by MCS, KWW, AF, SKS, SB, RJdS and LT. The search strategy and eligibility criteria were developed by KWW, RC, LB, MV, RJdS, DLJ, SMZ, SRR, LT and MCS. Title, abstract and full-text screening was performed by KWW, RC and MV. Data abstraction was completed by KWW, RC and MV. Quality and risk of bias assessments were conducted by KWW and RC. Methodological and statistical support was provided by MCS, RJdS and LT. KWW and MCS drafted the manuscript, and all authors reviewed, edited and approved the final version of the manuscript.

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The published version of the paper is included in Appendix 4.

Introduction

Brain tumours account for up to 20% of all childhood cancers and are the most common solid tumours in children. While survival rates of children with brain tumours have improved over the past three decades, these tumours remain a leading cause of childhood mortality after accidents (1–4). In addition, it has become clear that these children are at an increased risk of significant comorbidities and premature mortality (5–9).

Traditionally, the most common causes of death in survivors were the recurrence of the primary tumour, and the development of secondary tumours. However, emerging adverse cardiometabolic outcomes may contribute to the risk of premature mortality in survivors. Recent evidence suggests that survivors of childhood brain tumours (SCBT) have approximately a two-fold higher risk of developing type 2 diabetes compared to the general population (10). In addition, cardiovascular diseases including hypertension, cardiac events and stroke are also more frequent in survivors (11–13).

While type 2 diabetes and cardiovascular diseases are driven by the global obesity epidemic in the general population (14–17), it is unclear if obesity contributes to the elevated cardiometabolic burden and outcomes in survivors.

The most commonly reported obesity phenotype in SCBT is noted with lesions in the hypothalamus, e.g. craniopharyngioma (18). These tumours and their treatment cause hypothalamic damage and disruption of satiety signalling, decreased basal metabolic rate and pituitary hormonal deficiencies (19–21). As

hypothalamic injury is multifactorial, treating patients with hypothalamic obesity is challenging, as they often do not respond to conventional lifestyle modifications (18).

Intriguingly, recent data suggest that SCBT have comparable rates of obesity to populationbased controls (9,12). There is currently no complete explanation for the excess cardiometabolic risk in survivors compared with the general population at equivalent body mass index (BMI), and further studies to define the determinants of cardiometabolic risk and their contribution to outcomes are needed.

While there is limited understanding of the pathogenesis of cardiometabolic diseases in SCBT, managing obesity, including hypothalamic obesity, is a prudent strategy to improve the quality of life and lifespan of survivors (22,23). In this systematic review, our goal was to determine the current evidence base for interventions designed to manage obesity, including hypothalamic obesity, in SCBT.

Research question

In SCBT, are lifestyle interventions, pharmacotherapy or bariatric surgery effective in treating obesity, including hypothalamic obesity?

Methods

The protocol for this systematic review was previously published (24) and registered with the International Prospective Register of Systematic Reviews (PROSPERO; CRD42015025909).

Eligibility criteria

This systematic review included studies of overweight (BMI z-score ≥85th to <95th percentile) and obese (BMI z-score ≥ 95th percentile) SCBT (25), whose brain tumour diagnosis was made before 18 years of age. Randomized controlled trials (RCTs), quasi-RCTs, prospective and retrospective cohort studies, case–control studies, cross-sectional studies and uncontrolled studies with before-and-after comparisons were all eligible for inclusion. Case reports, interim analyses and pilot/feasibility studies were excluded. We included a comprehensive list of interventions in the search strategy including lifestyle-based interventions, pharmacotherapy and bariatric surgery. Lifestyle interventions involved any form of modification to the subjects' daily life such as diet and physical activity. Pharmacotherapy and bariatric surgery referred to the use of medications and surgical approaches with the intention of treating obesity, respectively. For bariatric surgery, surgical approaches incorporated laparoscopic adjustable gastric banding (LAGB), gastric bypass, sleeve gastrectomy and biliopancreatic diversion with duodenal switch (26).

Search strategy

Searches were conducted in PsycINFO, CINAHL, Cochrane Central Registry of Controlled Trials, Cochrane Database of Systematic Review, Database of Abstracts and Reviews of Effect, Medline, SPORTDiscus, EMBASE and PubMed. The grey literature was searched in ClinicalTrials.gov and ProQuest Dissertations and Theses A&I. The searches included all publications in these

databases up to September 1st, 2016. The reference lists of eligible articles were scanned for potentially eligible records. Publications from the first and last authors of the relevant articles were also reviewed. A finalized search strategy for Medline was reported in the protocol paper (24).

Study selection

Article screening was conducted by two reviewers independently at all steps including titles, abstracts and full texts. The reviewers met after each step to compare the results and resolve conflicts through discussion. A third reviewer arbitrated persistent disagreements.

Quality assessment

Two reviewers independently assessed the study's risk of bias. The risk of bias in RCTs was assessed using the Risk of Bias Assessment Tool from the Cochrane Collaboration (27). Non-randomized studies were assessed using the Risk of Bias In Non-randomized Studies – of Interventions assessment tool (ROBINS-I) (28). Uncontrolled studies were evaluated using a checklist developed by the University of Alberta Evidence-based Practice Center (29). The overall quality of evidence was determined using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) guidelines (30). Discrepancies in assessments were resolved by discussion, and if no agreement could be reached, a third reviewer helped the reviewers resolve disagreements.

Data abstraction and synthesis

Two reviewers using a pre-established data abstraction form extracted data independently. The primary outcome for this review was BMI z-score (reported at times as BMI SDS) change from baseline to the end of the intervention and/or follow-up if available. Secondary outcomes included changes in adiposity measures including waist-to-hip ratio, waist-to-height ratio and fat mass percentage. We also aimed to examine changes in blood pressure, diabetes status, insulin resistance, non-alcoholic fatty liver disease and lipid profiles, when available. We documented the adverse events reported during the studies. Data were analysed separately on the basis of intervention types and study designs.

For any intervention type, a meta-analysis was deemed appropriate if two or more eligible studies with similar study design and patient populations were identified. If such conditions were satisfied, odds ratios would be used as the summary measure for dichotomous outcomes, and standardized mean differences with 95% confidence intervals for continuous outcomes.

Heterogeneity was quantified by using the inconsistency index (I^2) and interpreted using the threshold set by the Cochrane Collaboration (31). Publication bias would be assessed by visual inspection of a contour-enhanced funnel plot and by Egger's test, if more than 10 studies were available for an outcome (32).

Results

Search results

The literature screening process is reported in Fig. 1. The literature search identified 17,854 unique records from all databases, including grey literature and reference lists of relevant studies. After evaluating the titles, 16,205 records (16,003 records of title review and 202 conference proceedings, editorials and congress reports) were excluded with an agreement rate of 96.9%. The most common reason for exclusion was that the paper was not relevant to obesity interventions. Out of the 1,649 abstracts screened, 1,609 were excluded mostly because the participants were not brain tumour survivors. The agreement rate for abstract screening was 95.7%.

Following title and abstract screening, 40 articles were retrieved for full-text screening, and 21 were excluded owing to the non-inclusion of brain tumour populations (n = 6), brain tumours diagnosed >18 years (n = 1), only one subject was <18 years old (n = 1), case reports (n = 2), pilot studies (n = 1), interventions not related to obesity management (n = 1) and conference abstracts (n = 9). In addition, five trials identified from ClinicalTrials.gov were in the recruitment stage and were not included in this systematic review. Three completed trials identified from ClinicalTrials.gov did not have published results, and their data could not be retrieved after contacting the principal investigators.

One study was reported as a pilot study in the title, yet it was included in this systematic review, as on reviewing the paper, the report was more consistent

with a trial design and not a pilot study (33). Another RCT included two subjects with acute lymphoblastic leukaemia in addition to SCBT and was included in this review (34).

In total, 11 records were included in this review, and the references of the excluded articles at full-text screening are listed in Table S1. No meta-analysis was performed owing to high heterogeneity and risk of bias across published studies.

Table 1 includes data describing the interventions reported, while Table 2 reports on the change in obesity measures with the different interventions. Table 3 reports on effects of interventions on diabetes, insulin resistance status and lipid profiles in studies that report these variables.

Lifestyle interventions (Tables 1–3)

Two studies examined lifestyle interventions (35,36). The first study included 39 subjects (n=23 female) with the majority of patients having a diagnosis of craniopharyngioma (n = 33), and including participants with other types of brain tumours including germinoma (n = 3), lipoma (n = 1), hamartoma (n = 1) and glioma (n = 1) (35). The intervention was delivered in a hospital clinic setting and involved goal setting for healthy dietary intake and physical activity. Nine subjects also received pharmacological agents including metformin. Subjects attended the clinic every 1–6 months, with a mean follow-up duration of 0.97 ± 0.92 years. Thirty-one subjects were already managed at the endocrine clinic in

the hospital before starting the programme. In the absence of a control group, before-and-after comparisons were performed for weight and metabolic variables.

The study reported significant reduction in BMI and weight changes post-intervention, with increased high-density lipoprotein (HDL; 1.09 ± 0.33 vs 1.24 ± 0.04 mmol L^{-1}, p = 0.03), but no significant changes in BMI z-score, low-density lipoprotein (LDL), triglycerides (TG) or fasting glucose (35).

The German study was a retrospective cohort study, with 108 craniopharyngioma patients. Thirty-one were treated with rehabilitation programme and 77 were non-treated controls (36). The participants were involved in a rehabilitation programme promoting healthy lifestyle and psychological well-being.

The median duration of the programme was 39 days (range, 20–135 days), with varying numbers of visits. The subjects were monitored from the initial brain tumour diagnosis with a broad range of follow-up duration (9.8–36.4 years). The results revealed higher BMI z-score in the intervention group at follow-up, which may be explained by its significantly higher baseline BMI z-score when compared with that of the control group. Neither study reported on adverse events during the conduct of the interventions.

Pharmacotherapy (Tables 1–3)

Six studies using pharmacotherapies to manage obesity in patients with brain tumours were identified (33,34,37–40). All were small (n = 5–12), with the majority of pooled participants having hypothalamic obesity. The participants

included 32 patients with craniopharyngioma, eight patients with astrocytoma and two patients with glioma.

Only two studies were RCTs and reported the use of the appetite suppressant sibutramine (10–15 mg d^{-1}, 20 weeks) (37) and somatostatin analogue octreotide (5–15 μg kg^{-1} d^{-1}, 6 months) (34). In the Subutramine study, while 10 recruited patients were classified as having central nervous system damage, two were excluded as one had Prolactinoma, while the second participant had Histiocytosis X. Of the remaining eight subjects, three did not complete the study due to craniopharyngioma recurrence. The data reported in Table 1 are based on data provided by the author to our team having contacted the author directly. Of the five eligible participants remaining in the study, sibutramine did not significantly lower BMI z-score. Octreotide was shown to stabilize weight and BMI gain in SCBT.

Two uncontrolled studies reported using another appetite suppressant, dexamphetamine (5 mg twice daily, 6–63 months (38); 5 mg d^{-1} starting dose, and titrated up to a mean dose of 16 ± 2 mg d^{-1}, with a total treatment duration of 24 months) (40). The first study revealed that using dexamphetamine reduced BMI z-score (0.7 in male and 0.4 in female) (38), while the second study revealed no alteration in BMI with the treatment but reduced the rate of weight gain (before 2.0 ± 0.3 kg $month^{-1}$ versus after 0.4 ± 0.2 kg $month^{-1}$, $p = 0.009$) (40).

Another uncontrolled study used exenatide, a glucagon-like peptide-1 receptor agonist, at 5 μg per dose for 8 weeks and then 10 μg per dose twice daily,

for a total duration of 50 weeks of treatment. Exenatide therapy resulted in weight reduction in SCBT (before 158.1 ± 59.01 kg versus after 155.6 ± 57.6 kg, n = 3 from data provided by the author upon contact by our team for eligible participants, no reported p-value due to small sample size) (33).

One study adopted a combination therapy of the insulin sensitizer metformin (500–1,500 mg d^{-1}, 6 months) with micronized fenofibrate (160 mg d^{-1}, 6 months) as a lipid-modulating therapy (39). Metformin with micronized fenofibrate treatment did not alter BMI z-score (39).

In evaluating glucose homeostasis and lipid profiles with these therapies, the impact of sibutramine could not be evaluated owing to small sample size (Table 3) (37). Neither octreotide nor dexamphetamine had a significant impact on fasting glucose, insulin or lipid profiles (34,40). No significant changes in metabolic parameters were reported with the use of exenatide (33).

As expected with combination therapy, metformin lowered insulin resistance measured by the homeostatic model assessment insulin resistance index (HOMA-IR) from a median of 8.64 (range, 5.08–12.65) to a median of 4.68 (range, 0.7–7.9), with three out of six participants having a HOMA-IR below the insulin resistance cut-off levels (39). Furthermore, fenofibrate lowered triglycerides (median 263.5 vs 154 mg dL^{-1}) (39). Both dexamphetamine and combination therapy of metformin and micronized fenofibrate did not alter total cholesterol (39,40). Adverse events attributed to pharmacotherapy included nausea/ vomiting, joint pain, injection site reaction, nephrolithiasis (33),

diarrhoea, cholelithiasis, mild glucose intolerance, dia-betes (34), insomnia (37,38), fluctuation in mood (33,37), constipation, fatigue, depression (37) and headache (40) (Table 2).

Bariatric surgery (Tables 1 and 2)

Two studies reported the use of bariatric surgery to treat hypothalamic obesity in craniopharyngioma (41–43), and survivors of other brain tumour types were not included in the study. In one study, the short-term and long-term surgical outcomes were reported in separate papers (41,42). A total of nine women and three men were included in the two studies. Weismann et al. also included a group of obese non-cancer subjects (n = 143) treated with the same type of bariatric surgery, and comparisons were made between the survivors and the non-cancer participants (43).

The most commonly implemented surgical procedure was LAGB. Muller et al. reported weight reduction with LAGB in obese patients with craniopharyngioma with short-term follow-up (<5 years) (41), but that effect disappeared with long-term follow-up (>5 years) (42). Weismann et al. reported that LAGB was effective in non-cancer controls but not in craniopharyngioma-related obesity (43). Sleeve gastrectomy was not effective in patients with craniopharyngioma, while gastric bypass achieved similar weight reductions in both craniopharyngioma patients and controls (43).

Risk of bias assessments

The risk of bias for the seven uncontrolled studies that included different interventions (33,35,38–43) was evaluated using the University of Alberta Evidence-based Practice Center checklist (Table S2) (29). Of these, five had consecutive recruitment (33,35,39,40,43), one did not have consecutive recruitment (41,42) and one did not clearly report this parameter (38). Although six studies addressed incomplete outcome reporting adequately (35,38–43), one study had 40% dropout rate among SCBT and may be biased by incomplete outcome reporting (33). Six studies did not clearly describe who collected the outcome measures (33,35,39–43), and one had the treatment provider collecting the outcomes (38).

One retrospective cohort study compared a lifestyle intervention group with a non-intervention group (36), and ROBINS-I tool was used to evaluate risk of bias of this study (Table S3) (28). Sample selection, outcome measurements and missing data were rated to have low risk of bias for this study. It was classified as having a high risk of bias as potential confounders were not accounted for in the design or analysis. Insufficient data were available to assess risk of bias owing to participant selection, intervention measurement or treatment infidelity. Overall, this study was assessed as having serious risk of bias.

The Risk of Bias Assessment Tool from the Cochrane Collaboration (27) was used to evaluate the two RCTs identified in this review (Table S4) (34,37). The RCT using sibutramine had appropriate sequence generation, allocation

concealment and blinding. The risk of bias due to incomplete outcome data and selective outcome reporting were also low. Therefore, the overall risk of bias for this RCT is low. The RCT using octreotide did not provide sufficient information on how the randomization sequence was generated, or how the allocation was concealed. The overall risk of bias for this RCT was determined to be unclear.

Overall quality of evidence assessment

We used the GRADE guidelines to evaluate the overall quality of evidence (30). The studies produced a low quality evidence (44), and the risk of bias, inconsistency, indirectness, and imprecision were all rated as serious or very serious. This eventually led to downgrading the overall quality of evidence to very low (Table S5).

The risk of bias was considered serious because of the lack of consecutive recruitment (38,41,42), unclear or inappropriate outcome measurement method in all of the uncontrolled studies (33,35,38–43), or very serious owing to the unadjusted confounding factors in the cohort study of the population in a rehabilitation program (36). Inconsistency was also serious across studies as opposite results were reported.

Indirectness was rated as very serious owing to differences across studies even within the same intervention type. Although the interventions can be generally categorized into lifestyle interventions, pharmacotherapy and bariatric surgery, some involved combined approaches to therapy, with one study implementing lifestyle intervention and the use of metformin (35). Studies on

pharmacotherapy used different drugs, and even when the drugs were similar (e.g. dexamphetamine), the doses and durations of treatment were different (33,34,37–40). In the bariatric surgery group, the number of surgeries in survivors was small, with some patients receiving multiple bariatric surgery procedures (43), while others had only one procedure performed (41,42).

Imprecision was quantified to be mostly very serious owing to small sample size in the studies. The presence of publication bias could not be determined with funnel plot or Egger's test, as there were less than 10 eligible studies in each intervention type.

Importantly, several trials using pharmacologic agents registered in ClinicalTrials.gov were unpublished after the completion of the studies. Although attempts were made to contact the study investigators, data from these trials could not be retrieved. Therefore, we suspect that publication bias is present at least for the pharmacologic interventions. One of the completed trials from ClinicalTrials.gov reported an adverse event of venous thromboembolism with beloranib, while another study using octreotide depot was discontinued owing to low efficacy (45,46). Selective reporting was also noted in studies on exenatide, dexamphetamine and combined metformin plus micronized fenofibrate therapy, where certain outcomes were reported as insignificant, without actual data (33,39,40).

Discussion

Although a substantial evidence base for effective obesity management has been developed from adult cancer survivorship studies (47–49), there is a dearth of evidence for the paediatric population. When paediatric data are available, much of the evidence on obesity management is focused on survivors of leukaemia (50,51).

In addition, while obesity interventions have short-term benefits in obese non-cancer children (52–54), the short-term and long-term benefits of these interventions in brain tumour survivors are unclear. This systematic review has focused on synthesizing current evidence for managing obesity in brain tumour survivors. Although the goal of the review was to summarize the evidence for managing hypothalamic and non-hypothalamic obesity in this population, almost all participants included in these studies had craniopharyngioma or hypothalamic involvement of their tumour. Therefore, the current evidence of managing obesity in SCBT included in this review is concentrated on managing hypothalamic obesity.

There was a small number of studies identified and a high level of heterogeneity across the studies. Lifestyle interventions differed in the composition of diet and the exercise or activity regimens recommended to the participants (35,36), while studies on pharmacotherapy used different

drugs with different dosages, frequencies and durations (33,34,37–40). In the two bariatric surgery studies identified, the type and number of surgical procedures were different among participants (41–43).

In addition, there was a wide variation in the obesity-related outcomes measured including absolute weight lost (33,34,36–42), weight gain per year or month (35,40) or weight change percentage (35,43). Another source of heterogeneity was the broad range of the follow-up period, which ranged from weeks to years (35–37,42).

Lifestyle interventions

Obesity in SCBT can be partly attributed to lifestyle changes including sedentary behaviours coupled with increased caloric intake (55–57). The goal of lifestyle intervention is to trigger behavioural change in diet and physical activity to manage obesity, but the long-term effect of these interventions is unknown. In addition, patients with hypothalamic obesity are not likely to respond to lifestyle interventions because of the multiple pathways through which hypothalamic injury contributes to obesity in SCBT (18).

Studies on lifestyle intervention identified in this review have reported different results, with some studies reporting less weight gain per year over months to years of follow-up (35), while other studies failed to show an effect (36). In addition, studies have not reported on adverse events in the study populations.

Paediatric bariatric programmes report short-term benefits related to lifestyle interventions for up to 1 year (58). However, long-term efficacy data are lacking, and young children seem to benefit more than adolescents (59). This argues for the need for further research to understand the determinants of hypothalamic and non-hypothalamic obesity in survivors, and to re-think the approaches used in lifestyle-based obesity intervention programmes. There may be a need to pursue combination therapies, with lifestyle being one component of the intervention. In addition, renewed focus on the development of sustainable methods of delivery of long-term interventions is needed, to improve obesity management and cardiometabolic outcomes in survivors.

Pharmacotherapy

The mechanisms of action of anti-obesity drugs are centred on hunger and satiety signalling (60). The drugs used in these studies target obesity mainly by appetite suppression (e.g. sibutramine (37) and dexamphetamine (38,40)). One alternative and interesting approach involved the combined use of insulin sensitization and lipid-lowering therapy to mitigate the adverse effects of obesity on glucose and lipid metabolism rather than targeting obesity per se (39).

Dexamphetamine lowered BMI z-score and had favourable effects on body composition in one study (38) and slowed weight gain in another study (40). A dualpronged approach using metformin and micronized fenofibrate had favourable metabolic effects on glucose homeostasis and the lipid profile but did not affect BMI z-score (39). One of the RCTs in this field used sibutramine, and

this appetite suppressant had no effect on BMI z-score in the subgroup of participants eligible for this review (37). In addition, sibutramine was recently withdrawn from the market owing to serious side effects of increased risk of stroke and myocardial infarction (61).

We also included another RCT that used octreotide to manage hypothalamic obesity. (34) This study included two survivors of leukaemia, and having contacted the authors, we could not obtain the brain tumour subgroup data to analyse them separately. This RCT demonstrated beneficial effects of octreotide on lowering insulin and stabilizing weight and BMI gain in paediatric hypothalamic obesity, although the results were not exclusive to SCBT.

In addition, a recent study on exenatide showed no significant weight loss in patients with hypothalamic obesity, but stabilization of weight gain (33). Exenatide may be a promising therapeutic option for hypothalamic obesity in SCBT, but it requires further validation especially if used in combination with additional modalities including lifestyle intervention.

Adverse events in all pharmacotherapy-based studies were reported to be mild and tolerable (33,34,37–40). However, these studies were of short duration, and may fail to detect long-term adverse events or benefits of these interventions. Therefore, it is still unclear whether anti-obesity agents will be well tolerated with long-term use in SCBT, which is an area for further research.

Bariatric surgery

The potential mechanisms by which bariatric surgery induces weight loss may involve the induction of satiety, gut–brain axis effects, reduction of gastric volume, changes in gastrointestinal hormones, the microbiome and reduced nutrient absorption (62–64). The efficacy of bariatric surgery also varies by procedure and tumour type, with gastric bypass having a greater effect in craniopharyngioma, but not in other brain tumour types (63).

The most common procedure used in SCBT is LAGB. Although LAGB has low mortality risk and few metabolic complications, it has the highest (>50%) long-term failure rate among bariatric procedures, and re-intervention is very common (65).

The small sample size and high risk of selection bias (41–43) preclude a definite conclusion on the utility of surgery in survivors as a therapeutic modality for obesity.

Strengths and limitations

One of the strengths of this review is the comprehensive search strategy, with inclusion of papers published in languages other than English. This allowed the inclusion of an eligible study published in German (36). Furthermore, the rigour of the search strategy was standardized through a three-step development process (24). An initial limited search in Medline was conducted, followed by examination of the index terms used to describe the articles. The search strategy was then finalized including all the identified keywords and index terms (24).

Lastly, the reference lists of the relevant articles were examined, and publications from the first and last authors of the relevant articles were sought. Another strength of this review is the use of an inclusive search strategy of brain tumour survivors with and without craniopharyngioma, whereby hypothalamic obesity in the latter diagnosis is commonplace, and for which interventions are usually geared. This inclusive approach highlights the limited current evidence in managing non-hypothalamic obesity in SCBT. Finally, this review used the GRADE approach to assess the confidence in the findings, which provides a comprehensive interpretation of the overall quality of evidence.

Some of the limitations of this review include our inability to perform meta-analysis owing to lack of studies with low risk of bias and high levels of heterogeneity across studies. In addition, when we separated data for patients with brain tumours from other cancer types, the sample size was reduced substantially, and the results may be insignificant owing to insufficient study power to detect meaningful differences. Furthermore, almost all the studies included in this systematic review were uncontrolled studies with before-and-after comparisons. The lack of randomization and absence of control groups downgraded the quality of the evidence. In addition, most studies did not report long-term follow-up data. Therefore, the long-term outcomes of these interventions in survivors remain unclear.

Conclusions

This systematic review demonstrates that the interpretation of intervention effectiveness in SCBT is limited by small sample size, uncontrolled study design, absent long-term follow-up data, lack of randomization and the absence of control groups.

This highlights the limited evidence base to derive effective management strategies of hypothalamic obesity in SCBT, which has a direct impact on outcomes. The a priori design of RCT will allow sample size calculation to create studies that are sufficiently powered to measure meaningful differences in obesity management outcomes in SCBT.

In addition, as few centres will have sufficient power to conduct single centre studies, and creating multicentre studies appears to be an appropriate recommendation. Recently, there has been considerable advocacy for the performance of well-designed trials on children (66,67). We believe that this is an opportunity to create collaborations to improve cardiometabolic outcomes in survivors. These interventions may include already available interventions, e.g. exenatide, and utilize novel or combined therapeutic strategies.

For many rare paediatric conditions (e.g. cancer and intensive care patients), multicentre RCT is the norm in creating high-quality evidence, and this approach is applicable to the study of interventions aimed at improving cardiometabolic outcomes in the brain tumour population.

Conflict of interest statement

K-W. W. received student scholarships from Ontario Graduate Scholarship Program and Canadian Institutes of Health Research. M. C. S. received a grant from Pediatric Oncology Group of Ontario Research Unit.

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Authors' contributions

M. C. S. is the guarantor. The research question was defined by M. C. S., K-W. W., A. F., S. K. S., S. B., R. J. d. S. and T. The search strategy and eligibility criteria were developed by K-W. W., R. C., L. B., M. V., R. J. d. S., D. L. J., S. M. Z., S. R. R., L. T. and M. C. S. Title, abstract and full-text screening was performed by K-W. W., R. C. and V. Data abstraction was completed by K-W. W., R. C. and M. V. Quality and risk of bias assessments were con-ducted by K-W. W. and R. C. Methodological and statistical support was provided by M. C. S., R. J. d. S. and L. T. K-W. W. and M. C. S. drafted the manuscript, and all au-thors reviewed, edited and approved the final version of the manuscript.

Supporting information

Table S1. References of the excluded articles at full-text screening.

Table S2. Evaluation of methodological quality of uncontrolled studies using the UAEPC checklist.

Table S3. Evaluation of methodological quality of cohort studies using ROBINS-I tool.

Table S4. Evaluation of methodological quality of RCTs using the Risk of Bias Assessment Tool from the Cochrane Collaboration.

Table S5. Overall quality of evidence using GRADE for weight-related outcomes.

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Figure 1 Flow diagram of article screening process.

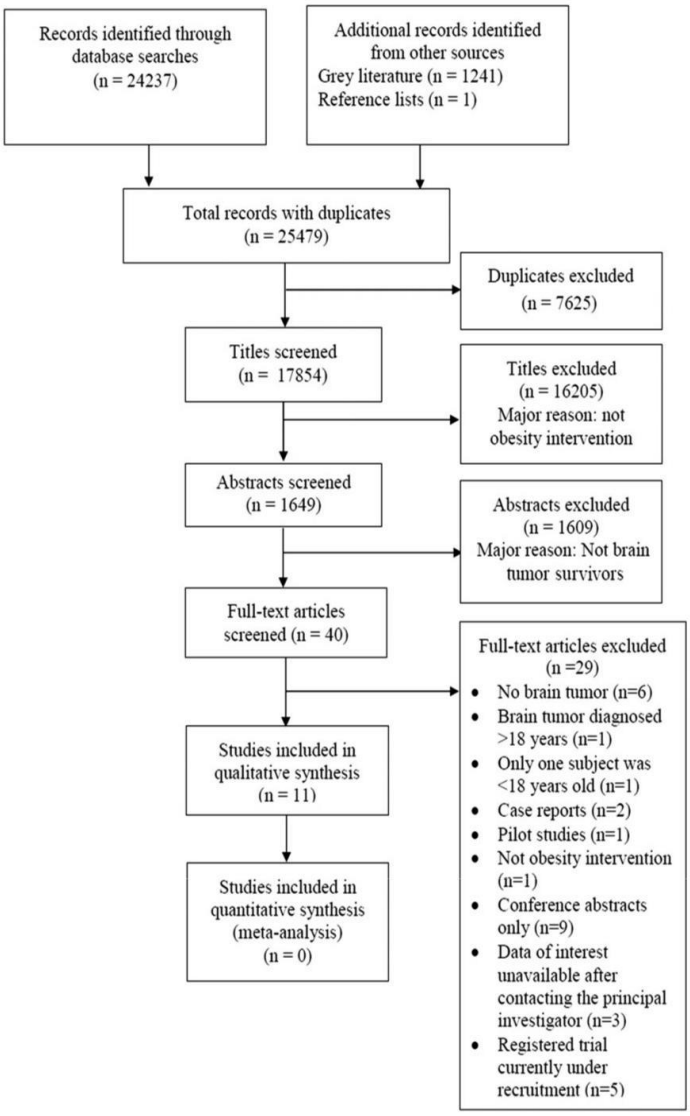

Table 1: Characteristics of included studies

Author (country, year, study design)	Population	Intervention	Outcomes	Duration	Notes
		Lifestyle Intervention			
Rakhshani et al. (Canada, 2010, uncontrolled before-after)	• Brain tumors (n=39, 23 females) • CP (n=33), germinoma (n=3), lipoma (n=1), hamartoma (n=1), glioma (n=1) • Median age 7.6 (range 2.2–15.9) years at brain tumor diagnosis • 71.8% surgery, 20.5% radiation, 20.5% chemotherapy • Pituitary hormone dysfunction (n=34) • 24 growth hormone deficiency (20 treated)	Comprehensive care clinic • Modification on diet and physical activity • Pharmacological agents such as metformin in certain cases	Change in %BMI/year, BMI z-score, % ideal body weight/year, % weight gain, blood pressure, fasting glucose, HDL, LDL, triglycerides from baseline to follow-up	• Frequency of once per month up to every 6 months at patients' choices • Patients attended mean of 3.3±2.2 visits • Duration of follow-up mean 0.97±0.92 years (range 3-41 months)	31 patients were already treated at the Endocrine Clinic before attending the program.
Sterkenburg et al. (Germany, 2014, retrospective cohort)	• CP (n=108, 58 females) Intervention group (n=31,1 9 females) • Median age 9.2 (range 1.9-17.4) years at brain tumor diagnosis • 55% had complete resection Control group (n=77, 39 females) • Median age 7.8 (range 0.05-18.8) years at brain tumor diagnosis • 35% had complete resection	Rehabilitation program Training eating habits, promoting physical activity and improve psychological well-being	Change in BMI z-score, from diagnosis to follow-up and comparison between intervention and control groups	• Duration of each program median 39 days (range 20-135 days), with varying frequency of attendance • Follow-up period median 16.3 years (range 9.8-36.4) from diagnosis to last evaluation	21 patients from the intervention group had life-threatening co-morbidities associated with a metabolic syndrome, hyperphagia, and conduct disorders.
		Pharmacotherapy			
Danielsson et al. (Sweden, 2007, RCT)	• Brain tumors (n=5, 3 females) • CP (n=4), astrocytoma (n=3), optic glioma (n=1), prolactinoma (n=1), Histocytosis X (n=1) • Median age 5 (range 2-11) years at brain tumor diagnosis • All undergone surgical resection	Sibutramine (10 mg/day) • The daily dose was increased to 15 mg if weight reduction of at least 4 kg was not observed within 8 weeks	Change in BMI z-score, total body fat percentage, fasting glucose and insulin levels, and non-fasting cholesterol and triglyceride levels from baseline to end of trial	20 weeks each for intervention phase and placebo phase.	The sibutramine-placebo group received sibutramine at baseline and crossed-over to placebo at week 20.
Ismail et al. (Australia, 2006, uncontrolled before-after)	• Invasive hypothalamic lesions (n=12, 7 females) • CP (n=9), astrocytoma (n=2), glioma (n=1) • Median age 9.4 (range 4.4-13.1) years at brain tumor diagnosis • Total resection (n=6), partial resection (n=4), drainage (n=2), adjuvant radiotherapy >51Gy (n=7) • Pituitary hormone deficiency (treated)	Dexamphetamine (5 mg twice/day)	Change in weight and BMI z-score, from baseline to follow-up	• Duration of treatment median 13 months (range 7-63) in males and 15 months (range 6-48) in females • Followed up every 3-6 months	
Kalina et al. (Poland, 2015, uncontrolled before-after)	• CP (n=22, 12 females) • Median age 10.5 (range 0.2-16.8) years at brain tumor diagnosis • Gross total resection (n=8), subtotal/partial resection (n=14), radiotherapy (n=18) for tumor residue or progression • Short stature, lack of pubertal progression, hypothyroidism, adrenal insufficiency (treated)	Metformin with micronized fenofibrate (n=10) • Metformin hydrochloride: 500-1500 mg/day • Micronized fenofibrate: 160 mg/day	Change in BMI z-score, total cholesterol, triglycerides, HOMA-IR from baseline to follow-up	• Duration of treatment 6 months • Evaluation at baseline and at 6 months	Ten out of 22 patients received pharmacotherapy to treat obesity, after unsuccessful lifestyle intervention.

Table 1: Characteristics of included studies (Contd.)

Author (country, year, study design)	Population	Intervention	Outcomes	Duration	Notes
		Pharmacotherapy			
Lomenick et al. (USA, 2016, uncontrolled before-after)	• Brain tumors (n=5, 4 females) • CP (n=3), astrocytoma (n=1), hypothalamic tumor of unknown origin (n=1) • Median age 8 (range 5-14) years at brain tumor diagnosis • All received surgical resection, one of them also received radiation and chemotherapy • Multiple pituitary hormone deficiency (treated)	Exenatide • Subcutaneously twice a day • Dosage started at 5mcg/dose and increased to 10 mcg/dose after 8 weeks, unless an adverse reaction occurred	Change in weight, glucose and insulin levels from baseline to follow-up	• Duration of treatment: 50 weeks • Followed up at 0-2 weeks (baseline) and 50-52 weeks (during treatment)	• Out of the ten subjects enrolled in the study, only five had a brain tumor diagnosed under 18 years of age. • Among the five subjects eligible for this review, two withdrew due to adverse events including mood swing and kidney stones
Lustig et al. (USA, 2003, RCT)	Treatment group (n=10, 4 females) • CP (n=6), hypothalamic astrocytoma (n=2), acute lymphoblastic leukemia (n=2) • Mean age 13.8 ± 1.2 years at start of the study protocol • Surgery (n=8), radiotherapy (n=10), chemotherapy (n=2) • Pituitary hormone deficiency (treated) Placebo group (n=10, 5 females) • CP (n=7), hypothalamic astrocytoma (n=1), germinoma (n=1), optic pathway glioma (n=1) • Mean age 14.2 ± 0.9 years at start of the study protocol • Surgery (n=8), radiotherapy (n=10), chemotherapy (n=2) • Pituitary hormone deficiency (treated)	Octreotide • Dosage started with 5μg/kg·d, and increased bimonthly by 5μg/kg·d to a maximum of 15μg/kg·d • Each dosage was divided into 3 daily doses	Change in weight, BMI, fasting glucose and insulin, and leptin from baseline to follow-up	• Duration of treatment: 6 months • Followed up bimonthly	Two subjects, one from each group, withdrew from the study due to tumor recurrence or the development of diabetes hyperosmolar nonketotic coma
Mason et al. (USA, 2002, uncontrolled before-after)	• CP (n=5, 2 females) • Median age 8.5 (range 6-9.8) years at start of the study protocol • All had surgical resection • Multiple pituitary hormone deficiency (treated)	Dexamphetamine • Dosage started at 5 mg/day and was increased by 2.5 mg weekly until either an outcome, or an adverse reaction occurred • Maximal daily dosage was mean 16 ± 2 mg, divided into 3 doses	Change in weight, BMI, insulin, IGF-1, and IGFBP-3 from baseline to follow-up	• Duration of treatment: 24 months • Followed up at 1, 3, 6, 9, 12, 18, 24 months of therapy	

Table 1: Characteristics of included studies (Contd.)

Author (country, year, study design)	Population	Intervention	Outcomes	Duration	Notes
		Bariatric Surgery			
Muller et al. (Germany, 2007 & 2011, uncontrolled before-after)	• CP (n=3, 2 females) • Brain tumor diagnosed at 2, 11, 12 years • Age 14, 17.5, 21 at the time of LAGB • All received surgical resection, one of them also had radiation • Hypopituitarism (treated)	Adjustable LAGB	Change in BMI z-score, from baseline to follow-up	2007: Follow-up period 4.5, 1.5, 3 years 2011: Follow-up period 9.1, 5.3, 7.1 years	The subjects previously had unsuccessful treatment efforts in weight control and insisted on receiving LAGB.
Weismann et al. (Germany, 2013, uncontrolled before-after)	• CP (n=9, 7 females) • Non-cancer control (n=143) • Median age 10 (range 1-21) years at brain tumor diagnosis • Median age 17 (range 12-30) years at bariatric surgery • Hypopituitarism (treated)	• LAGB (n=6) • SG (n=4) • GB (n=2)	Difference of % weight change between obese CP and non-cancer control at baseline and at follow-up	Median follow-up (CP, control) years • LAGB (5.5, 3) • SG (2, 1) • GB (3, 2)	Patients received different surgeries at different centers and often receive multiple times of bariatric surgeries.

CP: craniopharyngioma; CCC: comprehensive care clinic; RCT: randomized controlled trials; LAGB: laparoscopic gastric banding; SG: sleeve gastrectomy; GB: gastric bypass; BMI: body mass index (kg/m^2); HDL: high-density lipoprotein; LDL: low-density lipoprotein; IGF: insulin-like growth factor; IGFBP: insulin-like growth factor binding protein; HOMA-IR: homeostatic model assessment insulin resistance index (Fasting insulin (μU/L) x fasting glucose (nmol/L))/22.5).

Table 2: Effects of interventions on BMI, BMI z-score or weight change

Publication (country, year)	BMI, BMI SDS, Weight		p-value[1]	Adverse Events
	Baseline	Follow-up		
Lifestyle Interventions				
Rakhshani et al. (Canada, 2010)	Median (range) Change from brain tumor diagnosis to first visit • % BMI change/year 8.4 (−3.1 to 28.1)% • BMI z-score change 0.4 (−2.1 to 2.2) • % IBW change/year 19.9 (−18.7 to 149.2)% • % weight gain/year before clinic entry 21.4 (15.8–32.0)%	Median (range) Change from first to last visit • % BMI change/year 4.5 (−17.8 to 8.4)% • BMI z-score change 0.0 (−5.2 to 0.5) • % IBW change/year −4 (−141.7 to 34)% • % weight gain/ year during CCC 8.5 (3.4-14.0)%	p<0.01 ns p=0.003 p<0.05	Not reported
Sterkenburg et al. (Germany, 2014)	Intervention: Median BMI z-score +1.3 (-1.1 to +7.0) Control: Median BMI z-score +0.2 (-2.7 to +7.0) p=0.000[2]	Intervention: Median BMI z-score +4.9 (-0.2 to +13.13) Control: Median BMI z-score +2.1 (-1.5 to +10.2) p=0.039[2]	Not reported	Not reported
Pharmacotherapy				
Danielsson et al. (Sweden, 2007)	Sibutramine-Placebo group (n=3) Mean BMI z-score 4.8 ± 1.3 Placebo-Sibutramine group (n=2) Mean BMI z-score 4.9 ± 2.8	Sibutramine-Placebo group (n=3) Mean BMI z-score (sibutramine, placebo) 4.4 ± 1.3, 4.4 ± 1.2 Placebo-Sibutramine group (n=2) Mean BMI z-score (placebo, sibutramine) 5.1 ± 2.7, 4.7 ± 2.7	Not reported Not reported	Fluctuation in mood (n=2), constipation (n=1), fatigue (n=1), insomnia (n=1), depression (n=1)
Ismail et al. (Australia, 2006)	Mean weight 106.2 kg	Mean weight 101.4 kg Median BMI z-score reduction 0.7 in males (n=5); 0.4 in females (n=5)	Not reported	Insomnia (n=1), tumor recurrence (n=1)
Kalina et al. (Poland, 2015)	Median BMI z-score 1.91 (1.2 to 2.7)	Median BMI z-score 1.87 (1.3 to 2.6)	ns	None
Lomenick et al. (USA, 2016)	Mean weight (n=3) 158.1 ± 59.01 kg	Mean weight (n=3) 155.6 ± 57.6 kg	Not reported	Among all ten subjects: nausea/vomiting (n=7), joint pain (n=3), injection site reaction (n=3), mood swing (n=1), nephrolithiasis (n=1)
Lustig et al. (USA, 2003)	Octreotide group (n=9) Mean weight 98.5 ± 9.2 Mean BMI 37.4 ± 2.5 Placebo group (n=9) Mean weight 102.7 ± 6.8 Mean BMI 36.8 ± 1.2	Octreotide group (n=9) Mean weight 100.0 ± 9.5 Mean BMI 37.2 ± 2.5 Placebo group (n=9) Mean weight 111.9 ± 7.5 Mean BMI 39.0 ± 1.4	p<0.001[3]	Abdominal discomfort and diarrhea (n=9), cholelithiasis (n=4), mild glucose intolerance (n=2), diabetes (n=1)
Mason et al. (USA, 2002)	Mean BMI 32 ± 2.8 Mean monthly weight gain (from brain tumor diagnosis to the start of protocol) 2 ± 0.3 kg/month	Mean BMI 31 ± 3.3 Mean monthly weight gain (from start to the end of protocol) 0.4 ± 0.2 kg/month	ns p=0.009	Headache (n=1), cyst enlargement (n=1)

Table 2: Effects of interventions on BMI, BMI z-score or weight change (Contd.)

Publication (country, year)	BMI, BMI SDS, Weight		p-value[1]	Adverse Events
	Baseline	Follow-up		
Bariatric Surgery				
Muller et al. (Germany, 2007)	BMI z-score at diagnosis: +0.9, +4.45, +4.7 BMI z-score at LAGB: +13.9, +10.3, +11.4	BMI z-score at latest visit: +9.9, +9.7, +9.5	Not reported	None
Muller et al. (Germany, 2011)	BMI z-score at diagnosis: -0.9, +4.45, +4.7 BMI z-score at LAGB: +10.9, +10.4, +11.4	Lowest BMI z-score after LAGB: +6.9, +9.4, +7.5 BMI z-score at latest visit: +10.2, +13.9, +10.2	Not reported	
	Brain tumor group	**Non-cancer control group**	**p-value[4]**	**Adverse Events**
Weismann et al. (Germany, 2013)	Estimated % weight change in[4]: • LAGB (n=6) ~ +5% • SG (n=4) ~ +3% • GB (n=2) ~ -28%	Estimated % weight change in[5]: • LAGB (n=40) ~ -17% • SG (n=49) ~ -32% • GB (n=54) ~ -31%	<0.01 <0.05 Ns	Suspected acute adrenal insufficiency (n=1), transient increased of hydrocortisone (n=2)

BMI: body mass index (kg/m^2); IBW: ideal body weight; LAGB: laparoscopic gastric banding; SG: sleeve gastrectomy; GB: gastric bypass.
[1]Comparison between baseline and last evaluation
[2]Comparison between treated and untreated groups
[3]Comparison of changes from month 0 to month 6for weight and BMI between octreotide and placebo groups with two-sided t test
[4]Comparison between non-cancer controls and brain tumors
[5]Values were estimated from graphs where exact values were not reported

Table 3: Effects of interventions on diabetes, insulin resistance status, and lipid profiles

Publication (country, year)	Diabetes or insulin resistance status			Lipid profiles		
	Baseline	Follow-up	p-value	Baseline	Follow-up	p-value
Lifestyle Interventions						
Rakhshani et al. (Canada, 2010)	Mean±SD Fasting glucose 4.8 ± 0.8 mmol/l	Mean±SD Fasting glucose 4.4 ±0.6 mmol/l	0.06	Mean±SD • HDL: 1.1 ± 0.3 mmol/l • LDL: 2.8 ± 0.9 mmol/l • Triglyceride: 1.5 ± 0.6	Mean±SD • HDL: 1.2 ± 0.04 mmol/l • LDL: 2.9 ± 0.2 mmol/l • Triglyceride: 1.5 ± 0.7	0.03 ns 0.9
Pharmacotherapy						
Danielsson et al. (Sweden, 2007)	Sibutramine-Placebo group (n=3) Mean±SD • Fasting glucose 4.6 ± 0.06 mmol/L • Fasting insulin 87.7± 51.7 pmol/L	Sibutramine-Placebo group (n=3) Mean±SD (sibutramine, placebo) • Fasting glucose 4.6 ± 0.3, 4.4 ± 0.3 mmol/L • Fasting insulin 77 ± 45.0, 92.7 ± 61.4 pmol/L	Not reported	Sibutramine-Placebo group (n=3) Mean±SD • Cholesterol 5.5 ± 0.1 mmol/ • Triglyceride 1.5 ± 0.75 mmol/L	Sibutramine-Placebo group (n=3) Mean±SD (sibutramine, placebo) • Cholesterol 5.5 ± 0.1, 5.6 ± 0.1 mmol/L • Triglyceride 1.5 ± 0.2, 1.5 ± 0.6 mmol/L	Not reported
	Placebo-Sibutramine group (n=2) Mean±SD • Fasting glucose 4.7 ± 0.3 mmol/L • Fasting insulin 116 ± 28.3 pmol/L	Placebo-Sibutramine group (n=2) Mean±SD (placebo, sibutramine) • Fasting glucose 5.1 ± 0.5, 5.8 ± 1.1 mmol/L • Fasting insulin 172.5 ± 116.7, 331 pmol/L	Not reported	Placebo-Sibutramine group (n=2) Mean±SD • Cholesterol 4.3 ± 0.1 mmol/L • Triglyceride 1.8 ± 0.4 mmol/L	Placebo-Sibutramine group (n=2) Mean±SD (placebo, sibutramine) • Cholesterol 4.1 ± 0.5, 3.6 ± 0.1 mmol/L • Triglyceride 2.6 ± 0.8, 2.7 mmol/L	Not reported
Kalina et al. (Poland, 2015)	Median HOMA-IR 8.6 (5.1 to 12.7)	Median HOMA-IR 4.7 (0.7 to 7.9)	<0.05	• Median cholesterol 230 (199 to 274) mg/dl • Median triglyceride 263.5 (171-362) mg/dl	• Median cholesterol Not reported • Median triglyceride 154 (102-183) mg/dl	ns <0.05
Lustig et al. (USA, 2003)	Octreotide group (n=9) Mean±SD • Fasting insulin 29.2 ± 4.9 μU/mL • Fasting glucose 78.7 ± 4.5 mg/dl Placebo group (n=9) Mean±SD • Fasting insulin 36.9 ± 6.8 μU/mL • Fasting glucose 70.4 ± 7.7 mg/dl	Octreotide group (n=9) Mean±SD • Fasting insulin 27.7 ± 11.8 μU/mL • Fasting glucose 94.0 ± 6.7 mg/dl Placebo group (n=9) Mean±SD • Fasting insulin 27.9 ± 4.6 μU/mL • Fasting glucose 71.6 ± 4.1 mg/dl	ns[1] p=0.076[1]	Octreotide group (n=9) Mean±SD • Leptin 45.3 ± 8.2 ng/mL Placebo group (n=9) Mean±SD • Leptin 34.7 ± 4.7 ng/mL	Octreotide group (n=9) Mean±SD • Leptin 32.8 ± 5.1 ng/mL Placebo group (n=9) Mean±SD • Leptin 29.1 ± 4.4 ng/mL	ns[1]
Mason et al. (USA, 2002)	Mean±SD • Fasting insulin 43.8 ± 4.6 μU/mL • IGF-1 99.8 ± 43.5 ng/mL • IGFBP-3 1.8 ± 0.3 mg/L • Fasting glucose Not reported	Mean±SD • Fasting insulin 49.4 ± 11.8 μU/mL • IGF-1 49.8 ± 38.4 ng/mL • IGFBP-3 1.7 ± 0.4 mg/L • Fasting glucose Not reported	0.32 0.005 0.91 ns	Cholesterol Not reported	Cholesterol Not reported	ns

SD: standard deviation; HDL: high-density lipoprotein; LDL: low-density lipoprotein; IGF: insulin-like growth factor; IGFBP: insulin-like growth factor binding protein; HOMA-IR: homeostatic model assessment insulin resistance index (Fasting insulin (μU/L) x fasting glucose (nmol/L))/22.5; ns: non-significant (exact value not reported).

[1]Comparison of changes from month 0 to month 6 between octreotide and placebo groups with a two-sided t test

Table S1: References of the excluded articles at full-text screening

Publications	Reasons of Exclusion
Azar M, Reuveny R, Yalon M, Koren A, Constantini N. The effect of physical activity on the mental and physical health of childhood cancer survivor (Abstracts). *Br J Sports Med*. 2013; 47: e3.	Abstract
Brauner, R. (2011). Effect of diazoxide on the obesity secondary to hypothalamic-pituitary lesions [WWW document]. URL https://clinicaltrials.gov/show/NCT00306683.	Data unavailable
Breaky BR, Zeraatkar D, Baird B, Timmons B. Improving fitness after childhood cancer: A novel exercise clinic for pediatric oncology patients (Abstract). *J Clin Oncol*. 2015; 33: e21030.	Abstract
Eyal O, Sundararajan S, Inge TH, Rose SR. Obesity in Patients With Craniopharyngioma. *The Endocrinologist*. 2006; 16: 286-93.	Case report
Gagne DJ, Papasavas PK, Maalouf M, Urbandt JE, Caushaj PF. Obesity surgery and malignancy: our experience after 1500 cases. *Surg Obes Relat Dis*. 2009; 5: 160-4.	Not brain tumors
Gatta-Cherifi, B. (2016). Multicentre double-blind randomized clinical trial assessing efficacy and safety of exenatide in the treatment of hypothalamic obesity after craniopharyngioma therapy [WWW document]. URL https://clinicaltrials.gov/ct2/show/NCT02860923.	Ongoing study
Gebhardt U, Wabitsch M, Faldum A, Calaminus G, Mueller H. Analysis of weight/height development and psychosocial situation in long-term survivors of childhood craniopharyngioma in relation to therapeutic interventions for weight regulation (Abstract). *Endocrine Reviews*. 2011: P1-450.	Abstract
Gebhardt U, Wessel V, Schroder S, Kolb R, Wiegand C, Sorensen N, *et al.* Experiences with Laparoscopic Adjustable Gastric banding (LAGB) and Sleeve Gastrectomy in the treatment of patients with childhood craniopharyngioma and morbid obesity (Abstracts). *Neuropediatrics*. 2010; 41: P1355.	Abstract
Haak NV, Osborn M. A retrospective audit of the nutritional status and management of adolescents and young adults (AYAs) with cancer during and after treatment (Abstract). *Asia-Pac J Clin Oncol*. 2013; 9: #294.	Abstract
Hamilton, J. (2016). Evaluation of the SickKids Team Obesity Management Program (STOMP) [WWW document]. URL https://clinicaltrials.gov/show/NCT01515904.	Ongoing study
Holm JC. A chronic care treatment model in a multidisciplinary paediatric clinic: How to keep the family involved? (Abstract). *Obes Facts*. 2012; 5 Suppl 1: 9.	Abstract

Table S1: References of the excluded articles at full-text screening (Contd.)

James EL, Stacey FG, Chapman K, Boyes AW, Burrows T, Girgis A, *et al.* Impact of a nutrition and physical activity intervention (ENRICH: Exercise and Nutrition Routine Improving Cancer Health) on health behaviors of cancer survivors and carers: a pragmatic randomized controlled trial. *BMC cancer*. 2015; 15: 710.	Not brain tumors
Lustig RH, Rose SR, Burghen GA, Velasquez-Mieyer P, Broome DC, Smith K, *et al.* Hypothalamic obesity caused by cranial insult in children: altered glucose and insulin dynamics and reversal by a somatostatin agonist. *J Pediatr*. 1999; 135: 162-8.	Pilot study
McCormack, S. (2016). Intranasal oxytocin in hypothalamic obesity [WWW document]. URL https://clinicaltrials.gov/ct2/show/NCT02849743.	Ongoing study
Mueller HL, Gebhardt U, Wessel V, Sorensen N, Maroske J, Hanisch E. First experiences with bariatric surgery in the treatment of patients with childhood craniopharyngioma and morbid obesity (Abstract). *Pediatr Blood Cancer*. 2011; 57: 831.	Abstract
Novartis Pharmaceuticals (2011). Pediatric hypothalamic obesity [WWW document]. URL https://clinicaltrials.gov/show/NCT00076362.	Data unavailable
Page-Wilson G, Wardlaw SL, Khandji AG, Korner J. Hypothalamic obesity in patients with craniopharyngioma: treatment approaches and the emerging role of gastric bypass surgery. *Pituitary*. 2012; 15: 84-92.	Case report
Philip EJ, Torghabeh MH, Strain GW. Bariatric surgery in cancer survivorship: does a history of cancer affect weight loss outcomes? *Surg Obes Relat Dis*. 2015; 11: 1105-8.	Not brain tumors
Quist M, Rorth M, Zacho M, Andersen C, Moeller T, Midtgaard J, *et al.* High-intensity resistance and cardiovascular training improve physical capacity in cancer patients undergoing chemotherapy. *Scand J Med Sci Sports*. 2006; 16: 349-57.	Not brain tumors
Roth CL, Enriori PJ, Gebhardt U, Hinney A, Muller HL, Hebebrand J, *et al.* Changes of peripheral alpha-melanocyte-stimulating hormone in childhood obesity. *Metabolism*. 2010; 59: 186-94.	Not treating obesity
Schwartz AL, Winters-Stone K. Effects of a 12-month randomized controlled trial of aerobic or resistance exercise during and following cancer treatment in women. *Phys Sportsmed*. 2009; 37: 62-7.	Not brain tumors
Steele CA, Cuthbertson DJ, MacFarlane IA, Javadpour M, Das KS, Gilkes C, *et al.* Hypothalamic obesity: prevalence, associations and longitudinal trends in weight in a specialist adult neuroendocrine clinic. *Eur J Endocrinol*. 2013; 168: 501-7.	Brain tumors diagnosed >18 years old
Sterkenburg AS, Gebhardt U, Hoffmann A, Maroske J, Hanisch E, Muller HL. No long-term weight reduction after gastric banding (LAGB) in obese patients with craniopharyngioma involving hypothalamic structures - Experiences from KRANIOPHARYNGEOM 2000 (Abstract). *Exp Clin Endocrinol Diabetes*. 2012; 120: P16.	Abstract

Table S1: References of the excluded articles at full-text screening (Contd.)

Stern, M. (2016). Targeting caregivers to enhance health behaviors in pediatric cancer survivors (NOURISH-T) [WWW document]. URL https://clinicaltrials.gov/ct2/show/NCT02815982.	Ongoing study
Tessaris D, Tuscano A, Rabbonea I, Lezo A, Fenocchio G, Broglio F, *et al.* Hypothalamic obesity in children and adolescents: A multi-disciplinary approach and novel therapeutic tools (Abstract). *Horm Res Paediatr*. 2014; 82 Suppl 1.	Abstract
Valle CG, Tate DF, Mayer DK, Allicock M, Cai J. A randomized trial of a Facebook-based physical activity intervention for young adult cancer survivors. *J Cancer Surviv.* 2013; 7: 355-68.	Not brain tumors
von der Weid, NX. (2016). SURfit-A physical activity intervention for childhood cancer survivors (SURfit) [WWW document]. URL https://clinicaltrials.gov/ct2/show/NCT02730767.	Ongoing study
Wolf P, Winhofer Y, Smajis S, Kruschitz R, Schindler K, Gessl A, *et al.* Hormone substitution after gastric bypass surgery in patients with hypopituitarism secondary to craniopharyngioma. *Endocr Pract.* 2016; 22: 595-601.	Only one subject was <18 years old
Zafgen, Inc. (2016). An efficacy, safety, and pharmacokinetics study of beloranib in obese subjects with hypothalamic injury [WWW document]. URL https://clinicaltrials.gov/show/NCT02063295.	Data unavailable

Table S2: Evaluation of methodological quality of uncontrolled studies using the UAEPC checklist

Publication (country, year)	Consecutive recruitment	Incomplete outcome addressed	Standardized measurement method
Lifestyle Intervention			
Rakhshani et al. (Canada, 2010)	Yes	Yes	Unclear
Pharmacotherapy			
Ismail et al. (Australia, 2006)	Unclear	Yes	No
Kalina et al. (Poland, 2015)	Yes	Yes	Unclear
Lomenick et al. (USA, 2016)	Yes	No	Unclear
Mason et al. (USA, 2002)	Yes	Yes	Unclear
Bariatric Surgery			
Weismann et al. (Germany, 2013)	Yes	Yes	Unclear
Muller et al. (Germany, 2007 & 2011)	No	Yes	Unclear

Table S3: Evaluation of methodological quality of cohort studies using ROBINS-I

Domain	Sterkenburg et al.	Rationale[1]
Bias due to confounding	Serious risk	Unadjusted confounding
Bias in selection of participants into the study	No information	Unclear whether the start of follow-up coincide with that of intervention
Bias in measurement of interventions	No information	Unclear how and who recorded he intervention status
Bias due to departures from intended interventions	No information	Unclear whether there is departure from the intended intervention
Bias due to missing data	Low risk	No report of missing data
Bias in measurement of outcomes	Low risk	Objective outcome measure (BMI) and errors in measuring unlikely to be related to intervention status
Bias in selection of the reported result	Low risk	All intended results were reported
Overall	Serious risk	At least one domain was judged to be at serious risk, with no critical risk in any domain

[1]The rationale is based on The Risk of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool.

Table S4: Evaluation of methodological quality of RCTs using the Risk of Bias Assessment Tool from the Cochrane Collaboration

Domain	Danielsson et al (Sibutramine)	Lustig et al (Octreotide)
Sequence generation	Low risk	Unclear
Allocation concealment	Low risk	Unclear
Blinding of participants, personnel and outcome assessors	Low risk	Low risk
Incomplete outcome data	Low risk	Low risk
Selective outcome reporting	Low risk	Low risk
Other sources of bias	Low risk	Low risk
Overall	Low risk	Unclear

Table S5: Overall quality of evidence using GRADE for weight-related outcomes

Quality assessment						
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**
Lifestyle Intervention (follow up: range 3 months to >10 years)						
147 (2 observational studies[1,2])	very serious[a,b]	serious[c]	very serious[d]	serious[e]	N/A[f]	⊕◯◯◯ VERY LOW
Pharmacotherapy (follow up: range 20 weeks to 63 months)						
44 (4 observational studies[3-6], 2 RCT[7-8])	serious[a]	serious[c]	very serious[g]	very serious[e]	publication bias strongly suspected [f,h]	⊕◯◯◯ VERY LOW
Bariatric Surgery (follow up: range 1.5 years to 9.1 years)						
12 (2 observational studies[9-11])	serious[a]	serious[i]	very serious[j]	very serious[e]	N/A[f]	⊕◯◯◯ VERY LOW

a. Not consecutive recruitment and/or unclear outcome measurement method in uncontrolled before-and-after studies
b. Uncontrolled confounding factors in the retrospective cohort
c. Different results were reported across studies
d. One study use pharmacological agents when needed
e. Small sample size
f. Publication bias cannot be determined with funnel plot or Eggers test because less than 10 studies were included
g. Use different drugs, dosages, and durations
h. Several trials registered in ClinicalTrials.gov do not have results published and data cannot be retrieved after attempting to contact the principal investigators
i. LAGB was reported useful in one study, but not in the other two
j. Patients in one study were operated at different surgical centers and often received multiple bariatric surgeries

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Chapter 8: Conclusions

Survivors of childhood brain tumors have elevated cardiometabolic risks including type 2 diabetes, cardiovascular disease, and stroke (Gurney et al., 2003; Holmqvist et al., 2014). In the general population, obesity is a main driver of these cardiometabolic diseases (Ng et al., 2014). However, the contribution of obesity to the increased cardiometabolic outcomes in SCBT is unclear. Using a systematic review and meta-analysis, the prevalence of overweight and obesity combined in SCBT excluding craniopharyngioma is 31.7%, compared to 40.4% in non-cancer controls. The results show that SCBT and non-cancer controls have similar overweight and obesity distribution when using BMI as a method of classification. However, craniopharyngioma, a type of brain tumor often involve hypothalamic damage, is particularly vulnerable to obesity development, where the prevalence of overweight and obesity combined is 68.1% in this group.

Higher total and central adiposity are also noted in SCBT compared to non-cancer controls despite the similar overweight and obesity rates between the two groups. Although more longitudinal studies are needed to confirm the impact of adiposity on cardiometabolic outcomes in SCBT, it is possible that adiposity contributes to the elevated cardiometabolic risks in SCBT.

The determinants of the observed adiposity pattern in SCBT are further investigated. Tumors located in the supratentorial region and treated with radiotherapy appear to be associated with higher adiposity in SCBT. It is also important to note that the presence of higher adiposity in SCBT is even when

patients with craniopharyngioma were excluded form the analysis. This means that while patients with craniopharyngioma are vulnerable to obesity, it does not mean that patients with other brain tumor types are at low cardiometabolic risks. It is important to include adiposity as a routine measure to understand the cardiometabolic profile in SCBT.

Although adiposity has been found to be a more robust measure to stratify cardiometabolic risk (Lee et al., 2008; Phillips et al., 2013; Savva et al., 2000), BMI is still the most widely used measured to determine obesity. Therefore, we also aim to explore predictors of BMI in SCBT and one of these possible predictors is birth weight (Qiao et al., 2015; Schellong et al., 2012). A positive relationship between birth weight and BMI is demonstrated in both SCBT and non-cancer controls.

After exploring overweight, obesity, and adiposity profiles and their determinants in SCBT, it is important to understand what interventions are available to mitigate the cardiometabolic risks. Through a systematic review, we summarize the current evidence on the effectiveness of interventions to address obesity and adiposity. Although we intend to abstract adiposity changes as one of the review outcomes, very few studies include this measurement. The results demonstrate a lack of high-quality evidence to conclude the effectiveness of lifestyle interventions, pharmacotherapy, and bariatric surgery on managing obesity in SCBT. Most of the studies eligible for the review have small sample sizes and lack randomization between treatment and control groups. In addition,

the majority of patients included in these studies have craniopharyngioma or hypothalamic tumors while patients with other brain tumors are also at increased adiposity as demonstrated in this thesis.

This highlights the need to conduct more randomized controlled trials with rigorous methodology that include patients with varying brain tumor types beside craniopharyngioma. The outcome measure in these trials should also include adiposity measures in addition to BMI. It is with sufficient high-quality evidence in the field that effective strategies to manage obesity and adiposity can be identified to reduce the cardiometabolic burden and improve the long-term health outcomes in SCBT.

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Systematic Reviews

Appendix 1

PROTOCOL Open Access

Evaluating overweight and obesity prevalence in survivors of childhood brain tumors: a systematic review protocol

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Abstract

Background: Overweight and obesity are well-known risk factors for cardiometabolic diseases including hypertension, myocardial infarction, stroke, and type 2 diabetes in the general population. Survivors of childhood brain tumors (SCBT) are at risk of premature mortality, and recent evidence suggests that these cardiometabolic diseases are potential emerging determinants of survival and quality of life. Therefore, the rates of overweight and obesity in this population need to be examined to assess their impact on outcomes. The objective of this systematic review is to examine the prevalence of overweight and obesity in SCBT. The secondary aim of this review is to evaluate whether SCBT have higher adiposity compared to the general population.

Methods: Searches will be conducted in MEDLINE, CINAHL, EMBASE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, PubMed, and Database of Abstracts of Reviews of Effect. For gray literature, we will search ProQuest Dissertations and Theses A&I and Web of Science. Two reviewers will independently screen all articles against predetermined eligibility criteria and complete data abstraction, risk of bias, and quality assessments. The primary outcome includes the prevalence of overweight or obesity. The secondary outcomes involve waist-to-hip ratio, waist-to-height ratio, body fat percentage, and skinfold thickness. Meta-analysis will be performed when two or more studies with similar design, populations, and outcomes are available.

Discussion: This review will summarize current data on the prevalence of overweight and obesity in SCBT. This will help the development of an understanding of the scale of overweight and obesity in this population and guide the design of interventions that will improve outcomes.

Systematic review registration: PROSPERO CRD42016051035

Keywords: Systematic review protocol, Protocol, Obesity, Childhood brain tumor, Cancer survivorship

Background

Recent advances in the management of pediatric brain tumors have significantly improved survival rates [1, 2]. However, the new record longevity noted in Survivors of Childhood Brain Tumors (SCBT) is being hindered by the emergence of new comorbidities including cardiometabolic diseases like hypertension, myocardial infarction, stroke, and type 2 diabetes [3–13]. The current global overweight and obesity epidemic has been blamed for the rise of these cardiometabolic disorders in the general population, but the scale of overweight and obesity and its role in driving adverse outcomes in survivors is unknown.

Of note, SCBT have several risk factors that predispose them to overweight and obesity. These include impaired satiety signals, lower physical activity, impaired mobility and coordination, pain, disrupted sleep, mental health concerns, pituitary hormonal deficiencies, and medications [14–17]. To further understand the contribution of overweight and obesity to cardiometabolic risk in SCBT, there is a need to determine its scale in SCBT. This will

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inform the design of interventions to target overweight and obesity and their risk factors to improve cardiometabolic outcomes, quality of life, and survival rates in this population.

In this systematic review, the epidemiological data on the prevalence of overweight and obesity in SCBT will be evaluated. The primary aim of this review is to determine whether SCBT have higher rates of overweight or obesity compared to non-cancer counterparts. The secondary aim of this review is to evaluate whether SCBT have higher adiposity compared to the general population.

Methods

This protocol is developed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis-Protocols (PRISMA-P) statement [18, 19] (Additional file 1).

Literature search

Searches will be conducted in MEDLINE, CINAHL, EMBASE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, PubMed, and Database of Abstracts of Reviews of Effect. The following concepts along with their synonyms will be used in the search: pediatric, brain tumors, overweight/obesity, and survivors. A search strategy will be developed in consultation with a senior health sciences librarian with expertise in systematic reviews. We will not set any restrictions on publication date, but will restrict our search to English language publications. A full search strategy for MEDLINE is reported in Table 1.

To identify grey literature, we will search ProQuest Dissertations and Theses A&I and Web of Science. The search in the latter database will be limited to "Conference Proceedings Citation Index-Science-1990-present." We will then search for relevant publications from the first and last authors of the relevant conference abstracts to identify articles originating from the work presented in the abstracts. The reference lists of eligible studies and relevant reviews will also be searched to identify any additional studies. Searches will be updated to capture recent publications by setting publication date restrictions.

The search results will be de-duplicated in EndNote X7 [20] and then exported into an excel file to screen for eligible titles and abstracts. The full texts of relevant records will then be retrieved to screen against the eligibility criteria.

Study selection and eligibility criteria

Two independent reviewers, who will meet after each stage to resolve conflicts and achieve consensus, will screen the title and abstract of each record. A third reviewer will be consulted when disagreements persist. The two reviewers will then independently screen the full text of the relevant studies identified from the title and abstract screening.

This review will include SCBT diagnosed under 18 years of age. The following eligibility criteria will be applied: (1) Primary research articles with observational study design including longitudinal cohort, cross-sectional, or case-control studies. (2) Sample size of ≥10 patients as previously described [21]. (3) Assessment of prevalence of overweight or obesity and/or body composition using measures including Body Mass Index (BMI), BMI z-score, BMI percentile, waist-to-hip ratio, waist-to-height ratio, body fat, and skinfold thickness. The screening process and results will be reported in a PRISMA flow diagram, as previously described [22–24] (Fig. 1).

Data collection

We developed a data abstraction form that will be piloted by two reviewers on two eligible studies. Comments will then be incorporated to finalize the form for this specific systematic review. The abstracted data will include publication information of title, authors' names, journal name, year of publication, as well as the city and country of publication. We will also collect study details including setting, study design, eligibility criteria, sample size, study duration, and funding source. Outcome measures, primary findings, and conclusions will be collected as well.

We will extract survivors' characteristics including age at diagnosis of brain tumor, age at study enrollment, and sex. We will also extract brain tumor details including brain tumor type and location and treatment details such as treatment period, duration since treatment completion, and types of treatments received including radiotherapy, chemotherapy, and surgery or combination therapies with these modalities. If the study has a non-cancer comparison group, we will document the type and source of non-cancer controls used and abstract the same data except for tumor- and treatment-related variables.

Two reviewers will perform data abstraction independently, followed by a discussion to resolve discrepancies. A third reviewer will intervene to resolve persisting differences. In studies that report the data from multiple cancer types as aggregates, data specific to the brain tumor group will be extracted either through published subgroup data or by contacting the research team to acquire the data. We will also contact the corresponding authors of a published work in attempts to obtain any missing data.

The primary outcome for this review is the prevalence of overweight or obesity estimated by BMI, BMI z-score,

Table 1 Search strategy for MEDLINE

#	Searches
1	exp Child/
2	child*.ab,ti,kf.
3	p?ediatric*.ab,ti,kf.
4	exp Adolescent/
5	adolescen*.ab,ti,kf.
6	youth*.ab,ti,kf.
7	teen*.ab,ti,kf.
8	kid*.ab,ti,kf.
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10	exp Brain Neoplasms/
11	exp Neuroectodermal Tumors/
12	exp Glioma/
13	glioma*.ab,ti,kf.
14	astrocytoma*.ab,ti,kf.
15	oligoastrocytoma*.ab,ti,kf.
16	astroglioma*.ab,ti,kf.
17	glioblastoma*.ab,ti,kf.
18	craniopharyngioma*.ab,ti,kf.
19	ependymoma*.ab,ti,kf.
20	subependymoma*.ab,ti,kf.
21	ependymoblastoma*.ab,ti,kf.
22	gangliоglioma*.ab,ti,kf.
23	medulloblastoma*.ab,ti,kf.
24	exp Germinoma/
25	germinoma*.ab,ti,kf.
26	Meningioma/
27	meningioma*.ab,ti,kf.
28	oligodendroglioma*.ab,ti,kf.
29	exp Neurofibromatoses/
30	neurofibromatos*.ab,ti,kf.
31	PNET*.ab,ti,kf.
32	neurocytoma*.ab,ti,kf.
33	choroid plexus papilloma*.ab,ti,kf.
34	((brain or central nervous system or CNS or brainstem or brain stem or cerebel* or cerebr* or hypothalam* or ventric* or intracranial or midline or choroid plexus or infratentorial or supratentorial or neuroectoderm* or germ cell*) adj5 (tumo?r* or neoplasm* or cancer*)).ab,ti,kf.
35	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
36	exp Obesity/
37	obes*.ab,ti,kf.
38	Overweight/
39	over weight.ab,ti,kf.
40	overweight.ab,ti,kf.
41	Body Weight/
42	exp Body Composition/
43	(body adj3 (mass* or size* or composition*)).ab,ti,kf.
44	(fat* adj3 (mass* or body or abdominal* or intra-abdominal* or viscera* or subcutane* or hepatic* or liver* or intramuscular* or intramyocellular*)).ab,ti,kf.
45	BMI*.ab,ti,kf.
46	Weight Gain/
47	exp "Body Weights and Measures"/
48	Anthropometry/
49	anthropometr*.ab,ti,kf.
50	grow*.ab,ti,kf.
51	overnutrition*.ab,ti,kf.
52	over nutrition*.ab,ti,kf.
53	malnutrition*.ab,ti,kf.
54	waist-height ratio*.ab,ti,kf.
55	waist to height ratio*.ab,ti,kf.
56	adipos*.ab,ti,kf.
57	((waist* or hip* or abdominal*) adj3 circumference*).ab,ti,kf.
58	(weight* adj3 (gain* or change* or fluctuat*)).ab,ti,kf.
59	waist-hip ratio*.ab,ti,kf.
60	waist to hip ratio*.ab,ti,kf.
61	skinfold thickness*.ab,ti,kf.
62	36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61
63	Survivors/
64	"Adult Survivors of Child Adverse Events"/
65	Disease-Free Survival/
66	surviv*.ab,ti,kf.
67	remission*.ab,ti,kf.
68	((post or off or after) adj5 (treatment* or therap*)).ab,ti,kf.
69	((treatment* or therap* or cancer* or disease* or event* or progression*) adj5 free).ab,ti,kf.
70	63 or 64 or 65 or 66 or 67 or 68 or 69
71	9 and 35 and 62 and 70
72	limit 71 to english language

or BMI percentile. Secondary outcomes include waist-to-hip ratio, waist-to-height ratio, body fat percentage, and skinfold thickness.

Risk of bias and quality assessment

Two reviewers will independently assess the risk of bias of the eligible studies using the Newcastle-Ottawa Scale (NOS) for observational studies [25]. The NOS will be adapted from its original version by considering a previously used modified version [26], so that the scale is

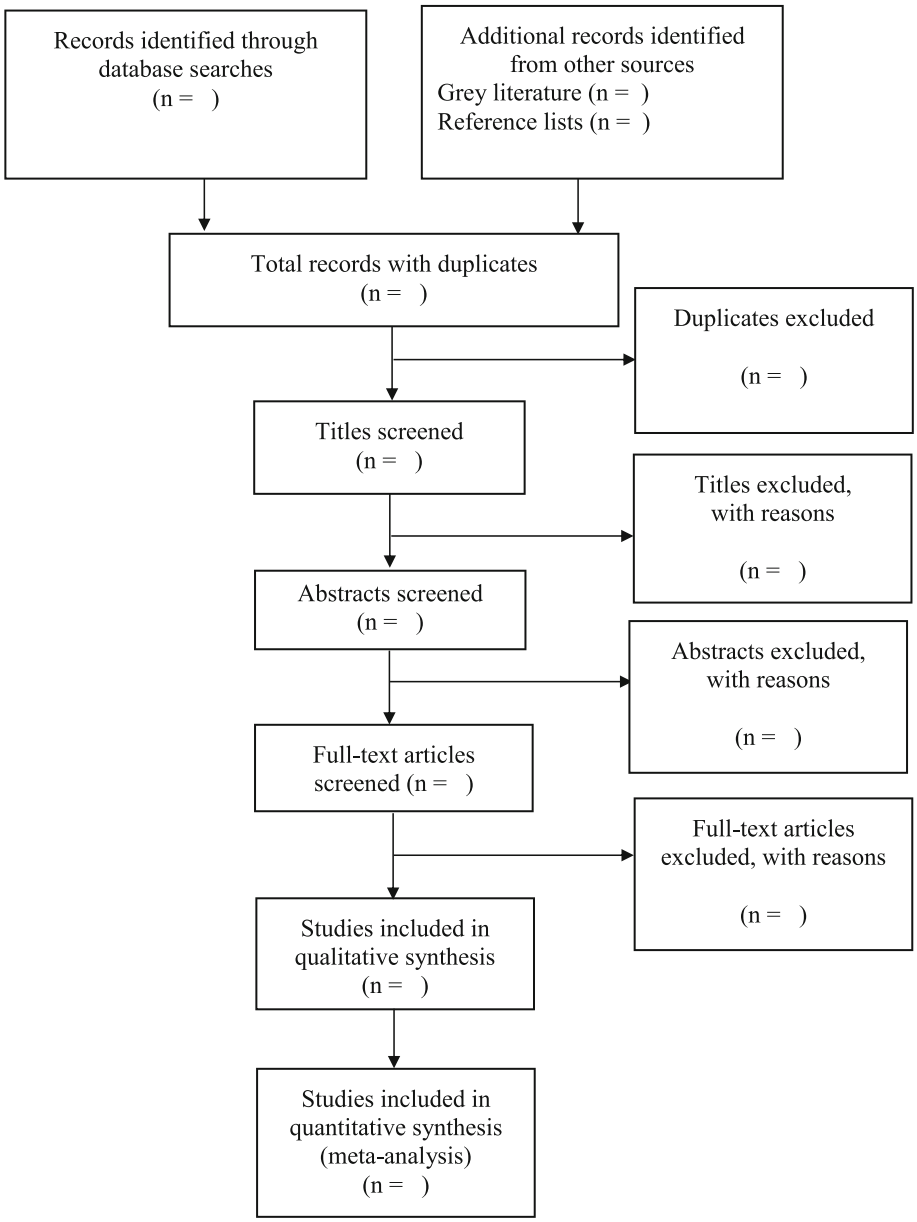

Fig. 1 PRISMA flow diagram

specific to this review. The reviewers will meet and discuss their decisions to include articles and to resolve any disagreement. In the case of persisting conflict, a third reviewer will be consulted.

This adapted NOS evaluates five items pertaining to risk of bias due to sample selection and classification (two items), confounding factors (one item), missing data (one item), and measurement errors (one item). For each item, the risk of bias is rated on a scale of 0 (high risk of bias), 1–2 (moderate risk of bias), and 3 (low risk of bias). The risk of bias is rated as unclear if not enough information is provided. Descriptions with examples for each level of risk of bias are provided (Additional file 2).

The overall risk of bias is rated as low when all five items have low risk of bias or high when one or more items have high risk of bias. The overall risk of bias is considered to be moderate when not all items have low risk of bias, but there are no items with high risk of bias. If one of the items is rated as unclear, the overall risk of bias will be reported as unclear as well.

Furthermore, we will use the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) guideline [27] to evaluate the overall quality of evidence including the risk of bias, inconsistency, indirectness, imprecision, and publication bias to determine the overall quality of evidence for each outcome.

Statistical analysis

We will perform meta-analysis if two or more studies of similar design and population characteristics can be identified for each outcome. We expect high heterogeneity across studies. The possible sources of heterogeneity include age at diagnosis, duration and types of treatment, and brain tumor type and location. Therefore, we will perform meta-analysis using a random effects model if more than ten studies are eligible and will perform both random effects and fixed effects models if less than ten studies are identified [28].

Dichotomous and continuous outcomes will be reported as pooled odds ratio and standardized mean difference with 95% confidence intervals, respectively. In studies where multiple measurements are done, we will include the outcomes measured with the longest follow-up reported.

Both inconsistency index (I^2) and P values from the chi-square test for homogeneity will be considered to determine the level of heterogeneity among the included studies. The threshold set by the Cochrane Collaboration will be used to interpret I^2, with >75% representing considerable heterogeneity. A P value of <0.10 will be used to determine statistical significance [29]. If meta-analysis is not appropriate, heterogeneity will be evaluated by describing and comparing the study samples, methods, and designs across studies. We will perform subgroup meta-analysis by sex and receipt of radiotherapy, chemotherapy, and surgery or combination therapies with these modalities if appropriate, as it has been reported that female SCBT are at higher risk of obesity than males [7, 8, 11]. In addition, to test the impact of outliers and studies with high risk of bias on the results, we will perform sensitivity analysis by excluding these studies if ten or more studies can be identified for an outcome.

To maintain the power of the results, we will not perform sensitivity analyses if less than ten studies are eligible. If ten or more studies are identified, we will use a contour-enhanced funnel plot to investigate publication bias [30]. The plot asymmetry will be determined by Egger's test and visual inspection [30]. Otherwise, we will estimate publication bias based on the number of relevant conference abstracts that did not have published articles originating from the work presented in the abstracts [31].

We will use Review Manager Version 5.3 Software (RevMan 5.3) [32] to conduct the meta-analysis. If Egger's test is appropriate, Comprehensive Meta-Analysis Software Version 3 (CMA 3.0) will be used instead [33]. A comprehensive table for summary of findings with narrative description will be reported when a meta-analysis is not appropriate.

We will report the results of this systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines using the PRISMA checklist [22, 23]. We will also document the date and reasons for any amendments to the protocol.

Discussion

While record numbers of children are surviving the diagnosis of brain tumors, this survival is burdened by the high rate of comorbidities and premature mortality [10, 12, 34]. To improve the quality of the cure, detailed understanding of the factors driving comorbidities in SCBT is likely to provide therapeutic entry points to improve outcomes.

Recent evidence suggests that new emerging risk factors may be contributing to mortality in this population. With increasing longevity, SCBT are at risk of type 2 diabetes and cardiovascular diseases that appear relatively early in life [3–6, 9]. This argues for a premature aging process, whereby diseases of old age are appearing earlier in life in SCBT. This may indicate that similar overweight or obesity levels may have a disproportionately negative impact on SCBT when compared to the general population, and interventions are needed to stem the occurrence of overweight and obesity and reduce their burden in survivors. Notable limitations of this systematic review include the restriction of the search strategy to English language publications only, as this may lead to missing information from non-English literature. In addition, if the heterogeneity of the studies is high, this will preclude the performance of a meta-analysis. Nevertheless, this review will identify gaps in knowledge and inform better clinical practice in identifying overweight and obesity and will help inform the need for specifically designed interventions to tackle overweight and obesity in SCBT and improve outcomes.

Additional files

Additional file 1: PRISMA-P checklist. This checklist includes recommended items to address in a systematic reviews protocol and where they are reported in this protocol. (DOCX 36 kb)

Additional file 2: Adapted version of a modified Newcastle-Ottawa Scale (NOS) to evaluate overweight and obesity in survivors of childhood brain tumors. This form demonstrates the adapted version of the NOS to evaluate risk of bias of the included observational studies in this systematic review. (DOCX 17 kb)

Abbreviations

BMI: Body Mass Index; CINAHL: Cumulative Index to Nursing and Allied Health Literature; CMA 3.0: Comprehensive Meta-Analysis Software Version 3.0; EMBASE: Excerpta Medica dataBASE ; GRADE: Grading of Recommendations, Assessment, Development and Evaluation; MEDLINE: Medical Literature Analysis and Retrieval System Online; NOS: Newcastle-Ottawa Scale; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis-Protocols; RevMan 5.3: Review Manager Version 5.3 Software; SCBT: Survivors of Childhood Brain Tumors

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Availability of data and materials
Not applicable.

Authors' contributions
MCS is the guarantor. Research question was defined by KWW, MCS, AF, SKS, RJdS, and LT. LB, KWW, RJdS, LT, and MCS contributed to the development of search strategy and determination of the eligibility criteria. Data abstraction form was designed by KWW and MCS. RJdS and LT provided the methodological support for this review. KWW and MCS drafted the manuscript, and the final version was reviewed and approved by all authors.

Competing interests
The authors declare that they have no competing interests.

Consent for publication
Not applicable.

Ethics approval and consent to participate
Not applicable.

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Appendix 2

SCIENTIFIC REPORTS

OPEN

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Adiposity in childhood brain tumors: A report from the Canadian Study of Determinants of Endometabolic Health in Children (CanDECIDE Study)

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Children with brain tumors (CBT) are at high risk of cardiovascular diseases and type 2 diabetes compared to the general population. Recently, adiposity has been reported to be more informative for cardiometabolic risk stratification than body mass index (BMI) in the general population. The goal of this study is to describe the adiposity phenotype in CBT, and to establish adiposity determinants. We recruited CBT (n = 56) and non-cancer controls (n = 106). Percent body fat (%FM), waist-to-hip ratio (WHR) and waist-to-height ratio (WHtR) were measured to determine total and central adiposity, respectively. Regression analyses were used to evaluate adiposity determinants. CBT had higher total and central adiposity compared to non-cancer controls despite having similar BMI measurements. Those with tumors at the supratentorial region had increased total and central adiposity, while those who received radiotherapy had increased total adiposity. In conclusion, CBT have increased total and central adiposity in the presence of similar BMI levels when compared to non-cancer controls. Adiposity, especially central adiposity, is a potential cardiometabolic risk factor present relatively early in life in CBT. Defining interventions to target adiposity may improve long-term outcomes by preventing cardiometabolic disorders in CBT.

Brain tumors are the most common pediatric solid tumors[1]. Groundbreaking discoveries in tumor biology and advances in diagnosis and therapy have significantly improved the survival of many of these children[2]. As the number of survivors has risen, it has become evident that this group is at risk of developing chronic morbidities[3,4] and premature mortality[5,6].

Recent evidence suggests that adult survivors of childhood brain tumors are at risk of cardiovascular diseases, including stroke, cardiac events, and type 2 diabetes[7–10]. As obesity is an independent risk factor for

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Variables	Non-cancer controls (n = 106)			CBT (n = 56)		
	Total Mean (SD)	Male Mean (SD)	Female Mean (SD)	Total Mean (SD)	Male Mean (SD)	Female Mean (SD)
Age (years)	14.00 (2.80)	14.00 (2.60)	14.00 (3.00)	14.70 (7.10)	14.80 (5.50)	14.50 (9.00)
Sex, No. (%)						
Female	51.00 (48.10)	—	—	23.00 (41.10)	—	—
Male	55.00 (51.90)	—	—	33.00 (58.90)	—	—
Height (cm)	161.70 (15.30)	166.00 (16.80)	157.20 (11.90)	150.60 (25.20)	155.90 (26.10)	143.00 (22.30)
Weight (kg)	59.00 (20.80)	64.30 (25.00)	53.50 (13.30)	52.40 (24.10)	55.20 (23.00)	48.50 (25.50)
BMI (kg/m2)	22.10 (5.60)	22.80 (6.60)	21.40 (4.10)	21.60 (5.50)	21.40 (4.40)	21.80 (6.80)
BMI z-score	0.49 (1.16)	0.58 (1.27)	0.41 (1.02)	0.41 (1.15)	0.32 (1.26)	0.55 (0.96)
BMI category, No. (%)						
BMI%ile < 85	69.00 (65.10)	34.00 (61.80)	35.00 (68.60)	36.00 (64.30)	22.00 (66.70)	14.00 (60.90)
BMI%ile ≥ 85	37.00 (34.90)	21.00 (38.10)	16.00 (31.40)	20.00 (35.70)	11.00 (33.30)	9.00 (39.10)
%FM	22.20 (9.00)	19.10 (9.00)	25.60 (7.80)	25.80 (9.60)	23.00 (9.40)	29.90 (8.60)
WHR	0.82 (0.09)	0.84 (0.08)	0.80 (0.10)	0.87 (0.07)	0.86 (0.07)	0.88 (0.08)
WHtR	0.45 (0.08)	0.45 (0.09)	0.44 (0.07)	0.47 (0.06)	0.47 (0.06)	0.48 (0.07)
Sys BP (mmHg)	107.20 (10.60)	110.40 (10.60)	103.70 (9.60)	104.00 (11.50)	104.10 (11.60)	103.90 (11.80)
Dia BP (mmHg)	67.60 (9.60)	67.10 (10.00)	68.10 (9.10)	66.30 (8.50)	66.20 (8.50)	66.40 (8.80)
Physical activity, No. (%)						
Active	97.00 (91.50)	48.00 (87.30)	49.00 (96.10)	43.00 (76.80)	25.00 (75.80)	18.00 (78.30)
Inactive	9.00 (8.50)	7.00 (12.70)	2.00 (3.90)	13.00 (23.20)	8.00 (24.20)	5.00 (21.70)
Screen time (hours/day)	4.30 (2.60)	4.80 (2.70)	3.80 (2.50)	4.50 (2.70)	4.80 (2.60)	3.90 (2.70)
Sleep duration (hours/day)	9.50 (1.40)	9.70 (1.70)	9.40 (1.10)	9.60 (1.20)	9.40 (1.20)	9.70 (1.10)

Table 1. Characteristics of study population. Abbreviations: SD, Standard Deviation; BMI, Body Mass Index; %tile, percentile; %FM, fat mass percentage; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio; Sys BP, systolic blood pressure; Dia BP, diastolic blood pressure; mmHg, millimeter Mercury.

cardiometabolic disorders in the general population, it may provide an explanation of the added cardiometabolic risk in survivors[11]. However, when obesity rates are measured by using Body Mass Index (BMI), children with brain tumors (CBT) are reported to have BMI levels that are either close to or slightly higher than rates in the general population, which does not seem to explain this increased cardiometabolic risk in survivors[12,13].

While BMI is the most widely used clinical measure of obesity, it does not distinguish the relative contribution of fat, muscle, or bone to body mass, which are considerably variable in growing children[14].

On the other hand, adiposity may be a better measurement to determine cardiometabolic risk in CBT. Adiposity is defined as the presence of fat in and outside the adipose tissue, including muscle and hepatic fat depots. The adipose depot is composed of a subcutaneous compartment, which is considered protective against cardiometabolic risk[15,16]. On the other hand, the visceral adipose compartment secretes inflammatory cytokines which can lead to insulin resistance, and is linked to adverse cardiometabolic outcomes[17].

Measures of total adiposity (fat mass percentage; %FM) and central adiposity, including waist-to-hip ratio (WHR) and waist-to-height ratio (WHtR), have been shown to be more robust predictors of cardiometabolic health and risk compared to BMI[18–24], with WHtR emerging as a strong indicator of intra-abdominal fat[25].

However, adiposity is not routinely measured in children, including pediatric cancer patients. While brain tumors are a heterogeneous group, a common tumor classically reported to be associated with obesity is craniopharyngioma[26]. There have been very few reports on the evaluation of obesity in other brain tumor subtypes and beyond hypothalamic obesity[27,28]. As BMI-based obesity rates are similar between CBT and controls yet CBT have high risk of cardiometabolic disorders, we hypothesized that CBT, excluding craniopharyngioma, have higher adiposity when compared to non-cancer controls. This excess adiposity may contribute to adverse cardiometabolic outcomes and premature mortality. A secondary aim of this study was to investigate the determinants of adiposity in CBT.

Results

We included 56 CBT (n = 23 female) and 106 non-cancer controls (n = 51 female) in this study. The characteristics of the study population are reported in Table 1.

The two groups were similar in terms of age (CBT: 5.20–42.70 years; controls: 5.40–18.80 years; p-value 0.59) and sex distribution (p-value 0.39). The CBT group had more participants in prepubertal stage (n = 19, 33.90%) versus controls (n = 16, 15.10%). Age of diagnosis of brain tumor was 9.10 ± 4.90 years, and average time since diagnosis was 5.60 ± 5.10 years.

As reported previously[29], CBT were shorter (150.60 ± 25.20 versus 161.70 ± 15.30 cm, p-value = 0.002) and weighed less (52.40 ± 24.10 versus 59.00 ± 20.80 kg, p-value = 0.02) than the control group.

The %FM correlated with central adiposity (Spearman's rho test WHR 0.31, p-value < 0.001; WHtR 0.73, p-value < 0.001). Central adiposity measures were highly correlated with each other as well (Spearman's rho test 0.67, p-value < 0.001).

Variables	No. (%)
Brain tumor type	
CNS germ cell tumors	5 (8.90)
PNET/Medulloblastoma	11 (19.60)
Ependymoma	2 (3.60)
Subependymal giant cell astrocytoma	3 (5.40)
Meningioma	1 (1.80)
NF-1, low grade glioma	10 (17.85)
Non-NF-1, low grade glioma	24 (42.85)
Brain tumor location	
Supratentorial	26 (46.40)
Infratentorial	30 (53.60)
Brain tumor treatments	
Surgery	41 (73.20)
Radiotherapy	22 (39.30)
Chemotherapy	27 (48.20)
No treatment	8 (14.30)
Steroids	27 (48.20)

Table 2. Brain tumor type, location, and treatments. Abbreviations: PNET, Primitive Neuroectodermal Tumor; NF-1, Neurofibromatosis Type 1.

The total screen time and sleep duration were similar between the two groups (Table 1). The most common tumor subtypes in participants included gliomas (n = 34, 60.70%) and Primitive Neuroectodermal tumors (PNET)/medulloblastoma (n = 11, 19.60%) (Table 2). The tumors were distributed between supratentorial (n = 26, 46.40%) and infratentorial regions (n = 30, 53.60%) (Table 2), with only 7 patients (12.50%) having tumors involving the hypothalamus. The therapeutic modalities were used in the management of brain tumors are shown in Table 2. Surgery alone was the most common treatment modality (n = 18, 32.10%), followed by a combination of surgery, chemotherapy and radiotherapy (n = 15, 26.80%). Chemotherapy alone was noted in five cases (8.90%), and radiotherapy alone was implemented in one patient (1.80%). Four patients (7.10%) received surgery and chemotherapy, and four (7.10%) received surgery and radiotherapy; one received radiotherapy and chemotherapy (1.80%).

In the 22 participants who received radiotherapy, the radiotherapy dosage was 47.10 ± 12.40 Gy. Sixteen participants received craniospinal irradiation (72.70%), and six received cranial irradiation (27.30%). Eight patients were being managed with watch-and-wait strategy (14.30%).

Post-therapy endocrinopathies were observed in 14 (26.80%) CBT participants. Among this group, a single diagnosis was made in seven patients including hypothyroidism (n = 3, 21.40%), growth hormone deficiency (n = 2, 14.30%), hypogonadism (n = 1, 7.10%), and precocious puberty (n = 1, 7.10%). The other seven patients had multiple hormonal deficiencies including hypothyroidism (n = 5, 35.70%), growth hormone deficiency (n = 6, 42.90%), hypogonadism (n = 4, 28.60%), adrenocorticotropic hormone deficiency (n = 4, 28.60%), diabetes insipidus (n = 3, 21.40%), and precocious puberty (n = 1, 7.10%). All endocrinopathies were treated appropriately.

Adiposity patterns in CBT and controls. To determine if CBT have enhanced adiposity compared to non-cancer controls, we used logistic regression analysis.

CBT had higher total adiposity compared to controls (%FM $25.50 \pm 9.60\%$ versus $22.40 \pm 9.30\%$; $\beta = 1.51$, 95% CI = 1.08, 2.10, p-value = 0.016). CBT also had higher central adiposity compared to controls including higher WHR (0.87 ± 0.07 versus 0.82 ± 0.09; $\beta = 7.53$, 95% CI = 2.30, 24.64, p-value = 0.001) and a trend of higher WHtR (0.47 ± 0.06 versus 0.45 ± 0.08; $\beta = 0.34$, 95% CI = 0.12, 1.02, p-value = 0.053).

Importantly, there were no differences in BMI and overweight/obesity rates between CBT and non-cancer controls (Table 1). BMI correlated with total adiposity (%FM) in CBT and controls (Spearman's rho test CBT 0.50, p-value < 0.001; controls 0.76, p-value < 0.001). BMI also correlated with WHR in controls but not in CBT (Spearman's rho test CBT 0.41, p-value 0.12; controls 0.17, p-value 0.038). Furthermore, BMI correlated with WHtR in CBT and controls (Spearman's rho test CBT 0.51, p-value < 0.001; controls 0.73, p-value < 0.001). These results demonstrate that CBT have higher total and central adiposity compared to non-cancer controls, in the presence of similar obesity rates based on BMI measurements.

Determinants of adiposity in survivors and controls. To define the determinants of adiposity, we conducted separate exploratory subgroup analyses using multivariate linear regression for CBT and controls (Table 3 for CBT; Supplementary Table S1 for controls). Dietary data are included in Table 4.

Females in the control group had higher total adiposity, while males had increased WHR, and puberty was associated with all measures of adiposity. These trends were not noted in CBT.

Variables	%FM		WHR		WHtR	
	β (SE)	P-value	β (SE)	P-value	β (SE)	P-value
Age	−0.12 (0.10)	0.23	−0.28 (0.03)	0.29	−0.02 (0.03)	0.50
Sex	0.55 (0.52)	0.30	−0.13 (0.14)	0.36	−0.13 (0.18)	0.46
Puberty	1.11 (0.99)	0.28	0.28 (0.26)	0.29	0.35 (0.34)	0.32
Brain tumor type	−0.33 (0.44)	0.46	−0.06 (0.11)	0.58	0.08 (0.15)	0.61
Brain tumor location	−1.83 (0.80)	0.028	−0.37 (0.21)	0.08	−0.53 (0.27)	0.06
Surgery	0.91 (0.81)	0.27	0.08 (0.21)	0.69	0.20 (0.28)	0.47
Radiotherapy	1.65 (0.79)	0.046	0.08 (0.21)	0.69	0.22 (0.27)	0.43
Chemotherapy	−0.86 (0.74)	0.25	0.06 (0.19)	0.77	−0.02 (0.25)	0.93
Steroids	0.68 (0.62)	0.28	0.04 (0.16)	0.81	0.21 (0.21)	0.32
Prudent diet	0.13 (0.33)	0.68	0.06 (0.08)	0.44	0.06 (0.11)	0.62
Western diet	0.15 (0.33)	0.64	0.04 (0.09)	0.64	0.17 (0.11)	0.13
High-protein diet	−0.19 (0.27)	0.48	−0.02 (0.07)	0.76	−0.09 (0.09)	0.33
Refined carbohydrate diet	0.38 (0.29)	0.20	0.06 (0.08)	0.43	0.07 (0.10)	0.45
Physical inactivity	−0.89 (0.57)	0.12	−0.12 (0.15)	0.42	−0.26 (0.19)	0.19
Screen time	1.08 (1.33)	0.42	0.14 (0.34)	0.68	0.42 (0.46)	0.37
Sleep duration	6.41 (7.24)	0.38	1.77 (1.87)	0.35	1.44 (2.49)	0.57

Table 3. The determinants of adiposity in participants with brain tumors. Abbreviations: %FM, Percent Fat Mass; WHR, Waist-to-Hip Ratio; WHtR, Waist-to-Height Ratio; SE, standard error.

Items	Factor loadings			
	Prudent	Western	High-protein	Refined carbohydrate
Fruits	**0.73**	—	—	—
Vegetables	**0.70**	—	—	—
Water	**0.57**	—	—	—
Crackers	**0.52**	—	—	—
Grain	0.49	—	—	—
Juice	—	−0.18	—	—
Fried Foods	—	**0.68**	—	—
Desserts	—	**0.61**	—	—
Baked Goods	—	**0.56**	—	—
Chips	—	**0.53**	—	—
Snacks	—	**0.53**	—	—
Candies	—	**0.51**	—	—
Poultry	−0.31	—	**0.67**	—
Red Meat	—	—	**0.63**	—
Eggs	—	—	**0.57**	—
Soft Drinks	−0.39	—	0.40	—
Peanut/other nuts	0.30	−0.31	0.38	—
White Bread	—	0.30	—	**0.71**
Dark Bread	0.35	—	0.34	**−0.67**
Gelatin	—	—	—	**0.66**
Fish	—	—	—	0.37
Dairy	—	—	—	0.35
Total variance explained (%)	15.7	10.1	8.4	7.1

Table 4. Factor loading matrix for dietary patterns in participants. Absolute values < 0.30 were not listed in the table, except for juice whose highest value of factor loading is shown. Absolute values > 0.50 were bolded to emphasize strength of association and determination of dietary patterns.

CBT with Supratentorial tumors had increased total adiposity (β −1.83, SE 0.80, p-value 0.028), with trended association with central adiposity (WHR β −0.37, SE 0.21, p-value 0.08; WHtR β −0.53, SE 0.27, p-value 0.06) (Table 3).

CBT who received radiotherapy had higher %FM (β = 1.65, SE 0.79, p-value = 0.046). However, radiotherapy type (craniospinal versus cranial irradiation) and radiation dose did not correlate with %FM (Spearman's rho test radiotherapy type r 0.13, p-value 0.57; Dose r 0.24, p-value 0.36), WHR (Spearman's rho test radiotherapy type

r 0.18, p-value 0.43; Dose r 0.33, p-value 0.17), or WHtR (Spearman's rho test radiotherapy type r 0.10, p-value 0.67; Dose r 0.24, p-value 0.3)'.

While 27 (48.2%) CBT were treated with corticosteroids, there was no association between steroid use and %FM ($\beta = 0.68$, SE 0.62, p-value = 0.28), WHR ($\beta = 0.04$, SE 0.19, p-value = 0.81), or WHtR ($\beta = 0.21$, SE 0.21, p-value = 0.32) (Table 3).

When examining the contribution of lifestyle factors (diet, physical activity, screen time, sleep duration) to adiposity in controls, physical inactivity trended with WHR, while screen time was associated with WHtR. Diet and sleep duration were not associated with adiposity measures. None of the lifestyle factors were associated with total or central adiposity measures in CBT (Table 3 for CBT; Supplementary Table S1 for controls; Diet data Table 4).

Discussion

The improved survival rates of children with brain tumors have been hindered by premature mortality and the development of morbidities. Of particular importance, recent evidence confirms that survivors are at risk of type 2 diabetes and cardiovascular diseases[7–10]. In this study, we demonstrate that adiposity, one of the most important determinants of cardiometabolic risk, is enhanced in CBT when compared to non-cancer controls.

Importantly, the adipose phenotype noted in CBT is evident with equivalent overweight/obesity rates to controls based on BMI measurements.

It has been reported that BMI can underestimate the prevalence of obesity in childhood cancer survivors, including survivors of brain tumors[18]. Until further knowledge is generated of the potential role of early excess adiposity in programming future cardiometabolic risk in CBT, there is a need to measure both BMI and adipose depots, and to continue to attempt to define their determinants. Our data are consistent with studies that used dual X-ray absorptiometry (DXA) scans[30], and reported the presence of higher total adiposity in cancer survivors who were treated with cranial irradiation[30]. The first study identified impaired mobility as an association of adiposity; the second study recruited patients with different cancers including brain tumors, and used siblings as a control group. The latter study identified male sex and screen time as risk factors of adiposity[30]. Our study population included CBT exclusively, with non-cancer controls as a comparison group. This may explain why the previously identified risk factors were not associated with adiposity in our study.

An important contribution of our study is that it provides evidence for the use of clinically feasible measures to determine adiposity in CBT. This has important implications for settings where access to DXA is not practical or possible, allowing clinicians to estimate the adiposity patterns in their survivor populations.

Our data also demonstrate that tumor location and radiotherapy have important associations with adiposity. Supratentorial tumors were associated with enhanced total and central adiposity, while radiotherapy was associated with excess total adiposity.

While tumors and their treatment can lead to anatomical or functional hypothalamic-pituitary damage with pituitary hormonal deficiencies[31], disruption of hypothalamic satiety signaling and reduced basal metabolic rate that can drive obesity[26], these factors may also contribute to excess adiposity.

Our results did not corroborate previous evidence of the association of higher doses of radiotherapy with obesity in childhood cancers, including brain tumors[32,33]. While these studies used BMI to measure obesity, our results suggest that adiposity may be associated with radiotherapy regardless of dosage. Clarifying the effect of radiotherapy type, dosing and fractionation on adiposity is an important question to address in CBT.

Endocrinopathies have been reported to increase the risk of higher BMI, but their effect on adiposity patterns in CBT early on requires further study, as these effects may become more apparent as CBT age. Given that radiation dosage is associated with hormonal abnormalities in cancer survivors, the effect of radiation dosage on adiposity may have been masked in our population who were treated for existing endocrinopathies[34].

It has been reported that certain tumors including craniopharyngiomas, pilocytic astrocytomas, and medulloblastomas are associated with elevated BMI[33]. We purposefully excluded craniopharyngiomas, to determine the contribution of other tumors to the adipose phenotype in CBT. A larger sample size is needed to clarify whether adiposity is driven by specific tumor types.

Several lifestyle factors are associated with obesity in the general pediatric population, Including excess caloric intake from sugar-sweetened beverages, prolonged screen time, and short sleep duration. Physical inactivity has been a controversial determinant of obesity in children[35–39].

While biological (sex), hormonal (puberty) and lifestyle factors were associated with adiposity in controls, none emerged as an explanation of the enhanced adiposity profile in CBT, which was associated with tumor location and radiotherapy.

The lack of association of diet with adiposity in our study is consistent with a study in craniopharyngioma patients, which revealed that physical inactivity, and not nutritional factors, were associated with higher adiposity[40]. As our study is cross-sectional, one caveat is that the dietary patterns may have changed from the time of diagnosis onwards. Longitudinal studies are needed to clarify the link between diet and adiposity in CBT.

The association of physical inactivity with childhood obesity and its use as a treatment for obesity has yielded inconsistent results[41–44]. In CBT, physical inactivity can be driven by treatment-related pulmonary and cardiac dysfunction[45,46], reduced muscle strength and fitness[47], fatigue, sleep disturbance[48], mental health issues, visual impairment, imbalance and pain[49,50]. Further studies on the association of physical inactivity with adiposity, and fat mass modification by targeted interventions in CBT are needed.

Our data suggest that within few years from having a brain tumor, CBT are following the secular lifestyle trends noted in the general population. However, the effect of adopting these trends on adiposity and cardiometabolic risk in CBT can be disproportionate, due to the added burden of the tumor and its treatment. Multipronged,

personalized, and sustained interventions are needed in CBT, as adiposity is only one of many risk factors that may respond to lifestyle alteration.

There are several limitations to our study. While the WHR and WHtR demonstrated the presence of excess central adiposity in CBT, it is not clear if this is due to subcutaneous or visceral fat depot expansion. It is also unclear yet if these adiposity patterns will be sustained as CBT age. In addition, due to the cost and logistics involved we did not measure other fat depots including hepatic and intermyocellular fat. Larger sample size and longitudinal studies of the fat depots are needed starting at diagnosis, to elucidate the evolution of the adiposity patterns in CBT.

As the questionnaires were self-administered, the presence of recall bias is possible. However, this is less likely, as the data collected were related to recent lifestyle factors, and the clinical data related to the tumor and its treatment were collected from the medical records.

Conclusions

In summary, our study reveals that excess total and central adiposity are present in non-craniopharyngioma population of CBT compared to controls. Adiposity, especially central adiposity, is an important cardiometabolic risk marker that appears in CBT within few years of their diagnosis. Tumor location and radiotherapy are important determinants of the noted adipose phenotype in these patients.

There is a need to understand the determinants of adiposity so that new therapies and prevention strategies can be developed to mitigate premature cardiovascular diseases and type 2 diabetes and improve outcomes in CBT.

Methods

Participants. The participants in this study were recruited into the Canadian Study of Determinants of Endometabolic Health in Children (CanDECIDE Study). This is a cohort study based at McMaster Children's Hospital, a tertiary pediatric academic center in Hamilton, Ontario, Canada. The study protocol and feasibility have been published[51,52]. The data reported are cross-sectional data collected at recruitment into the study.

We consecutively recruited CBT from the neurooncology clinics, and non-cancer controls were recruited from orthopedic clinics at the hospital and from the community. The orthopedic clinic controls included healthy children who suffered fractures or sprains and were seen for evaluation. Importantly, all study measures were performed after the fractures or sprains have healed, and participants had returned to their usual lifestyle before the injury. The recruitment period lasted from November 2012-March 2016.

We recruited boys and girls, 5 years and older, who were free of infection for 15 days prior to participation in the study, with no history of autoimmune diseases and not receiving immunosuppressive therapy for 15 days prior to inclusion. The exclusion criteria included active infection, autoimmune diseases, pregnancy or inability to provide informed consent.

Consent. The Hamilton Integrated Research Ethics Board approved this study. Consent forms were signed by parents if the participants were less than 16 years old, or by the participants if they were 16 years or older[53]. Children 7–15 years of age also signed an additional assent form. Informed consent was obtained from all participants. The study was conducted in accordance with appropriate clinical practice guidelines and national legal requirements.

Sociodemographic and clinical data. Data collected during the initial encounter with potential participants included self-reported age and sex, and this was confirmed from the medical records. Additional data collected from the medical records included age at diagnosis, tumor type, location, details of treatments received, and associated endocrinopathies and their treatment. Pubertal staging was assessed by pictorial Tanner pubertal staging in girls (>8 year old) and boys (>9 year old)[54].

Height and weight were measured to the nearest one tenth of a centimeter and one tenth of a kilogram using a stadiometer and an electronic weighing scale (Seca, USA), respectively. Body mass index (BMI) was calculated as kg/m^2. BMI percentile was obtained using the Children's BMI Tool for Schools[55] and BMI z-score were determined from the Centers for Disease Control and Prevention (CDC) growth chart[56]. Sitting systolic and diastolic blood pressures were measured twice using the right arm with an automated blood pressure monitor (Welch Allyn, Inc., USA) and the average values of these two measurements are reported.

The two commonly used methods to measure body fat include Dual-energy X-ray absorptiometry (DXA) scan and bioelectrical impedance analysis (BIA)[57]. The latter is less expensive, easier to access and perform than DXA. In this study, we used BIA to measure %FM to determine total adiposity. This method has been validated against DXA scans, and the two measures are highly correlated[57]. While the Tanita body fat monitor (Tanita Corporation, Illinois, USA) is portable, it cannot be used on those 18 years and older. In this case, the InBody520 body composition analyzer (Biospace Co., Ltd, Korea) was used to measure %FM. High correlations were established between the Tanita body fat monitor and the InBody520 body composition analyzer when tested on 5–17 year old children ($r = 0.87$; p-value $= 0.001$).

Waist and hip circumferences were measured to the nearest one tenth of a centimeter, using a spring-loaded measuring tape (OHAUS Corporation, Canada)[58]. Central adiposity was determined by calculating the WHR and WHtR[21].

Diet. Dietary intake was assessed as we previously reported[52]. Briefly, we used items from the Youth and Adolescent Food Frequency Questionnaire[52,59,60]. This is a questionnaire developed in a US pediatric cohort, and includes questions about food intake based on average portion sizes of different dietary constituents. The number of servings per day was calculated from the questionnaire by multiplying the frequency of consumption by portion size.

Principal component analysis was used to analyze the dietary patterns in participants. This analysis revealed four dietary patterns including prudent, western, high-protein and refined carbohydrate diets (Table 4). The prudent diet included high intake of fruits and vegetables. The western diet included high intake of fried foods, desserts, baked goods, and refined foods (e.g., chips, snacks, candies). The high-protein diet included high intake of meat and eggs. The refined carbohydrate diet included high intake of white bread and low intake of dark (whole grain) bread.

Physical activity. Physical activity was measured using the Habitual Activity Estimation Scale (HAES)[61]. The participants were asked to indicate their overall physical activity level as very inactive, inactive, somewhat inactive, somewhat active, active, or very active. This data were used to report physical activity levels. The levels were dichotomized into active and inactive for statistical analyses.

Sleep. Sleep duration (hours/day) was calculated from the difference between the self-reported time the participant went to bed and woke up the next morning. Sleep duration calculated with this method has been shown to correlate well with objective sleep quantification methods[62].

Screen time. Total screen time (hours/day) was calculated from the sum of self-reported time spent watching television, using cell phone, computer, computer games, and tablets.

Statistical analysis. All analyses were performed with SPSS version 20 software[63]. Kolmogorov-Smirnov test was used to test for normality, and variables with non-normal distribution were log-transformed. Age log-transformation revealed no outliers.

We used variance inflation factor to test for collinearity of variables, and found none that were collinear. Multiple imputations were used to handle missing data.

Continuous variables are reported as mean $\pm$ SD, and categorical variables are reported as counts (%). Chi-square tests and independent sample t-tests were used to compare brain tumor survivors and controls for categorical and continuous variables, respectively. We used Spearman's test to assess the correlation of adiposity measures with BMI and with each other in this study.

To assess the association of adiposity with brain tumor status, we used binary logistic regression. The dependent variable (event) was the cancer case status, with 56 events included in the analysis and 106 controls (non-events). Age, sex, %FM, WHR, and WHtR were included as the predictor variables in the analysis. We rescaled the WHR and WHtR coefficients by multiplying the log-transformed data by 10[64,65]. Logistic regression was conducted based on the assumption that ten events per predictor variable are needed for the analysis. As there are five predictor variables included in the analysis, our study is sufficiently powered to answer the main study question.

To explore the determinants of the adiposity patterns in CBT and controls, we performed exploratory subgroup analyses of the cancer cases and controls separately with multivariate linear regression analysis. The dependent variables included %FM, WHR, and WHtR.

The predictor variables of interest in CBT included age, sex, puberty, brain tumor histopathology, tumor location, and treatments including surgery, radiotherapy, chemotherapy, and steroids. In addition, we included lifestyle factors encompassing diet, physical activity, screen time, and sleep duration in the analysis. For controls, we included age, sex, puberty, diet, physical activity, screen time, and sleep duration in the analysis. The sample size of 56 events and 106 non-events provide adequate power for this analysis, as two events per variable are required in linear regression analyses to address the question of adiposity determinants in CBT and controls[66]. To analyze the dietary patterns in participants, we used principal component analysis. Twenty-two food items were included in the factor analysis. The number of dietary patterns retained was determined by visual inspection of scree plots in conjunction with eigenvalues (>1.0) and principal component interpretability. The factors were orthogonally transformed by using the varimax rotation to ensure the independence of factors in the structure. Dietary patterns were characterized based on dietary items with their factor loadings $\geq|0.30|$. The PCA scores for each pattern obtained for each individual represented how closely their food choices reflected one of the empirically-derived dietary patterns, with higher scores reflecting a greater degree of adherence to that dietary pattern[67].

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Author Contributions

M.C.S. is the guarantor. Study conception and design determined by M.C.S., K.W.W., R.J.d.S., A.F., S.K.S., D.L.J., S.M.Z., S.R.R., S.B., K.S. and L.T. Subjects recruitment and data collection was done by K.W.W., with the support from M.C.S, A.F., S.K.S., S.B., and K.S. Dietary data interpretation and analysis was completed by K.W.W., R.J.d.S., and M.C.S. Other statistical analyses and data interpretation was completed by K.W.W., M.C.S., R.J.d.S., A.F., S.K.S., D.L.J., S.M.Z., S.R.R., S.B., K.S., and L.T. K.W.W. and M.C.S. drafted the manuscript. All authors provided critical revisions of the manuscript and approved the final submitted version.

Additional Information

Supplementary information accompanies this paper at http://www.nature.com/srep

Competing Interests: In the last five years, Dr. de Souza has served as an external resource person to the World Health Organization's Nutrition Guidelines Advisory Group on trans fats and saturated fats. The WHO paid for his travel and accommodation to attend meetings from 2012–2015 to present and discuss this work. He has also done contract research for the Canadian Institutes of Health Research's Institute of Nutrition, Metabolism, and Diabetes, Health Canada, and the World Health Organization for which he received remuneration. He has held a grant from the Canadian Foundation for Dietetic Research as a principal investigator, and is a co-investigator on several funded team grants from Canadian Institutes of Health Research. The other authors declare no conflict of interest.

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Systematic Reviews

Appendix 3

PROTOCOL Open Access

The effectiveness of interventions to treat obesity in survivors of childhood brain tumors: a systematic review protocol

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Abstract

Background: Pediatric brain tumors are the most common solid tumors in children. Advances in understanding the hallmarks of cancer biology and novel therapies have led to an increasing number of survivors of childhood brain tumors (SCBT). However, these survivors are at an increased risk of obesity and cardiometabolic disorders that affect their quality of life and lifespan. It is important to define effective strategies to treat and prevent obesity in this population. This systematic review aims to investigate the effectiveness of lifestyle interventions, pharmacotherapy, and bariatric surgery on treating obesity in SCBT.

Methods: Searches will be conducted in PubMed, MEDLINE, EMBASE, PsycINFO, SPORTDiscus, CINAHL, Cochrane Database of Systematic Review, Cochrane Central Register of Controlled Trials (CENTRAL), and Database of Abstracts of Reviews of Effect (DARE). In addition, ClinicalTrials.gov and ProQuest Dissertations and Theses A&I will be searched to identify relevant gray literature. The reference lists of eligible articles will be searched for additional studies. All screening, quality assessment, and data abstraction will be done independently by two reviewers. We will perform meta-analysis if there are sufficient studies.

Discussion: This review will summarize evidence for the effectiveness of interventions used to reduce obesity risk in SCBT. This has significant implications for SCBT, as it can identify gaps in knowledge and provide insights into the development of new interventions to manage obesity in survivors, which may improve their outcomes.

Systematic review registration: PROSPERO CRD42015025909

Keywords: Systematic review, Protocol, Obesity, Intervention, Children, Brain tumor, Brain tumor survivors, Cancer survivorship

Introduction

Brain tumors are the most common solid tumors in children and constitute up to 20 % of childhood cancers [1]. Significant breakthroughs in understanding the hallmarks of cancer biology, coupled with advances in diagnostic imaging and improved therapies, have enhanced the survival rates of these children [2, 3].

As the number of survivors of childhood brain tumors (SCBT) increased, it has become apparent that survivors remain at risk of premature mortality [4–6] and the development of multiple comorbidities [7, 8]. Many SCBT develop chronic health conditions within years of their initial diagnosis [9], and one such morbidity is obesity [10–13]. In one study, obesity was reported in 36.5 % of SCBT, compared to 29 % in the general population [14, 15]. In the general population, the annual healthcare expenditures of obese individuals are about US$1360 higher than for their non-obese counterparts [16], and this is likely to be replicated in SCBT.

Addressing obesity in SCBT is crucial, as it increases the risk of cardiometabolic disorders in a similar fashion to the general population, and may contribute to premature mortality [17, 18]. Obesity is an independent risk

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factor for decreased survival in some children with brain tumors [19]. Understanding the drivers of obesity in SCBT will allow the development of precision-based strategies for reducing the risk of obesity and its cardiometabolic comorbidities, which in turn may improve the quality of life and lifespan of SCBT.

Obesity in SCBT is multifactorial and can be related to altered energy intake [20, 21], reduced mobility and physical activity [22–25], hypothalamic-pituitary damage [11], pituitary hormone deficiencies [26], sleep problems [27], vision problems, imbalance and pain [8, 28], mental health issues, and medications, e.g., antidepressants [29].

As obese children are likely to become obese adults [30–34], it is important to develop effective interventions to manage obesity from an early age. The purpose of this systematic review is to evaluate current evidence of effectiveness of interventions to manage obesity in SCBT.

Research question

In survivors of childhood brain tumors, are the current interventions including lifestyle intervention, pharmacotherapy, and bariatric surgery effective in managing obesity?

Study objectives

1) Measure the effectiveness of lifestyle interventions, pharmacotherapy, and bariatric surgery in the treatment of obesity in SCBT
2) Conduct a meta-analysis of primary studies, if appropriate, to gain a more precise estimate of the effectiveness of different strategies in managing obesity
3) Critically appraise existing evidence and identify gaps in the literature to provide future research directions

Methods

The protocol for this systematic review is developed and reported with guidance from the Preferred Reporting Items for Systematic Review and Meta-Analysis-Protocols (PRISMA-P) statement (Additional file 1) [35].

Eligibility criteria

This review will include studies involving boys and girls who are overweight or obese (BMI z-score ≥85th percentile) [36], with a diagnosis of brain tumor made under the age of 18 years. Randomized controlled trials (RCTs), quasi-RCTs, prospective or retrospective cohort studies, case-control studies, cross-sectional studies, and controlled or uncontrolled studies with before-and-after comparisons will be included [37].

There will be no restriction to the language or timing of publication. Conference proceedings, congress reports, and editorials will be hand searched for suggested relevant studies. We will exclude interim analyses, case reports, and pilot studies.

In studies where SCBT are included in an intervention with other cancer types, we will extract data for the brain tumor subgroup. If the data from subgroups are not published or pooled with data from survivors of other cancers, we will attempt to contact the authors to obtain the subgroup data.

The interventions included in the study are

- Lifestyle intervention: any form of modifications in subjects' daily life including their dietary patterns, physical activity, and eating behaviors
- Pharmacotherapy: any administration of medications
- Bariatric surgery: any surgical approach performed with the intention of treating obesity, including adjustable gastric banding, sleeve gastrectomy, biliopancreatic diversion with duodenal switch, and gastric bypass

Studies that are entered into the databases up to February 1, 2016, will be screened for eligibility. The search will be updated to capture recently published literature.

Outcome measures

Primary outcome

The primary outcome in this review is BMI z-score change from baseline to the end of the intervention and/or at follow-up.

Secondary outcomes

Secondary outcomes include changes in waist and hip circumference, waist-to-hip ratio, waist-to-height ratio, body fat percentage, and blood pressure as reported. We will also report changes in diabetes status, insulin resistance, and non-alcoholic fatty liver disease, if available. In addition, we will document changes in lipid levels including high-density lipoprotein, low-density lipoprotein, cholesterol, and triglycerides, if reported.

We will also abstract any adverse events observed during the study. Adverse events directly related to lifestyle interventions include back and shoulder pain, musculoskeletal injuries, and others [38, 39]. Adverse events for the pharmacological agents include insomnia, headaches, hypertension, and others [40]. Adverse outcomes for bariatric surgery include surgical complications, perioperative outcomes, and mortality as defined previously [41]. Additional adverse events will be included as reported.

Table 1 Search strategy for MEDLINE

1	exp Child/
2	child*.mp.
3	p?ediatric*.mp.
4	exp Adolescent/
5	adolescen*.mp.
6	youth*.mp.
7	exp Adult/
8	adult*.mp.
9	Young Adult/
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11	exp Brain Neoplasms/
12	exp Cranial Nerve Neoplasms/
13	exp Neuroectodermal Tumors/
14	cerebroma*.mp.
15	exp Glioma/
16	glioma*.mp.
17	astrocytoma*.mp.
18	oligoastrocytoma*.mp.
19	astroglioma*.mp.
20	glioblastoma*.mp.
21	retinoblastoma*.mp.
22	pinealoma*.mp.
23	pineoblastoma*.mp.
24	pinealoblastoma*.mp.
25	pinealblastoma*.mp.
26	pineal blastoma*.mp.
27	pineocytoma*.mp.
28	pinealocytoma*.mp.
29	craniopharyngioma*.mp.
30	ependymoma*.mp.
31	subependymoma*.mp.
32	ependymoblastoma*.mp.
33	ganglioglioma*.mp.
34	gliosarcoma*.mp.
35	medulloblastoma*.mp.
36	exp Germinoma/
37	germinoma*.mp.
38	Meningioma/
39	meningioma*.mp.
40	oligodendroglioma*.mp.
41	exp Neurofibromatoses/
42	neurofibromatos*.mp.
43	PNET*.mp.
44	neurocytoma*.mp.
45	choroid plexus papilloma*.mp.

Table 1 Search strategy for MEDLINE *(Continued)*

46	exp Neoplasms/
47	cancer*.mp.
48	tumo?r*.mp.
49	neoplasm*.mp.
50	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49
51	exp Obesity/
52	obes*.mp.
53	Overweight/
54	over weight.mp.
55	overweight.mp.
56	51 or 52 or 53 or 54 or 55
57	life style*.mp.
58	lifestyle*.mp.
59	exp Diet/
60	diet*.mp.
61	exp Nutrition Therapy/
62	nutrition.mp.
63	behavi*.mp.
64	exp Exercise Therapy/
65	kinesiotherap*.mp.
66	physical activ*.mp.
67	exp Exercise/
68	exercis*.mp.
69	walk*.mp.
70	jog*.mp.
71	run*.mp.
72	swim*.mp.
73	exp Bariatrics/
74	bariatric*.mp.
75	bariatric surger*.mp.
76	gastrojejunostomy.mp.
77	gastric bypass.mp.
78	stomach bypass.mp.
79	jejunoileal bypass.mp.
80	lipectomy.mp.
81	gastroplasty.mp.
82	stomach stapling.mp.
83	drug*.mp.
84	pharm*.mp.
85	exp Weight Reduction Programs/
86	((weight reduc* or weight los*) adj5 surger*).mp.
87	((weight reduc* or weight los*) adj5 program*).mp.

Table 1 Search strategy for MEDLINE *(Continued)*

88	57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87
89	Body Weight/
90	body mass*.mp.
91	BMI.mp.
92	exp Body Weight Changes/
93	exp Body Weights and Measures/
94	body fat.mp.
95	waist-height ratio*.mp.
96	waist to height ratio*.mp.
97	adipos*.mp.
98	body size*.mp.
99	waist circumference*.mp.
100	hip circumference*.mp.
101	weight*.mp.
102	height*.mp.
103	waist-hip ratio*.mp.
104	waist to hip ratio*.mp.
105	skinfold thickness*.mp.
106	89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105
107	10 and 50 and 56 and 88 and 106

Search strategy

We will consult a Health Sciences librarian with expertise in systematic reviews when designing the search strategy. A proposed search strategy for MEDLINE is described in Table 1. Searches will be conducted in PubMed, MEDLINE, EMBASE, PsycINFO, SPORTDiscus, CINAHL, Cochrane Database of Systematic Review, Cochrane Central Register of Controlled Trials (CENTRAL), and Database of Abstracts of Reviews of Effect (DARE). We will search ClinicalTrials.gov and ProQuest Dissertations and Theses A&I to identify relevant gray literature. We will also search the reference lists of articles deemed eligible for inclusion in the analysis for relevant studies.

Data management

Two independent reviewers will perform data abstraction and quality assessment. Disagreement between the two reviewers will be resolved by discussion, with subsequent involvement of a third reviewer to arbitrate disagreements. Excel spreadsheets will be used to manage study records during the screening process. We will use the Grading of Recommendations Assessment, Development and Evaluation Profiler (GRADEpro) software to create tables for summary of findings and quality assessment [42].

Data screening

Duplicates will be removed, followed by screening of titles and abstracts. Full-text articles that meet the inclusion criteria will be retrieved and screened. Screening at all steps will be conducted independently by two reviewers, who will meet after each step to ensure consistency and to resolve conflicts. In the case of persisting disagreement, a third reviewer will be consulted. A flow diagram will be included to report the screening process (Fig. 1) [43, 44].

Data abstraction

Data will be extracted independently by two reviewers, using a data abstraction form specifically designed for this systematic review. Details to be collected include title, authors, publication date, journal name, setting, country, funding source, study design, study duration, eligibility criteria, sample size, and methods used for brain tumor diagnosis including imaging, histology, and clinical assessment.

Participants' characteristics include age at diagnosis of brain tumor and at study enrollment, sex, ethnicity, and brain tumor location and laterality. Treatment details include radiotherapy type (fractionated or non-fractionated) and dose, chemotherapy type, dose and duration, and surgery details (total resection, partial resection, shunting, ventriculostomy, others).

Detailed description of the obesity interventions will be recorded including study design, components, duration, and adverse events. We will document primary and secondary outcomes of the studies. Adjustment for confounders and details of the statistical analyses performed will be extracted as well as study results. We will attempt to retrieve incomplete data by contacting the corresponding authors of published work.

Quality assessment

The Risk of Bias Assessment Tool from the Cochrane Collaboration will be used to assess RCT [45]. This tool includes six domains: sequence generation, allocation concealment, blinding, incomplete data, selective reporting outcomes, and other sources of bias. Each RCT will be rated as having either a high, low, or unclear risk of bias.

The Risk of Bias In Non-randomized Studies—of Interventions (ROBINS-I) assessment tool will be used for non-randomized studies such as cohort studies [46]. This tool includes three domains: pre-intervention, at-intervention, and post-intervention.

In the pre-intervention domain, bias due to confounding and participant selection are evaluated. Possible confounding factors include brain tumor location, type, treatments, years of survival, age, sex, pubertal stage, baseline body composition, and presence of comorbidities such as metabolic syndrome and hormonal

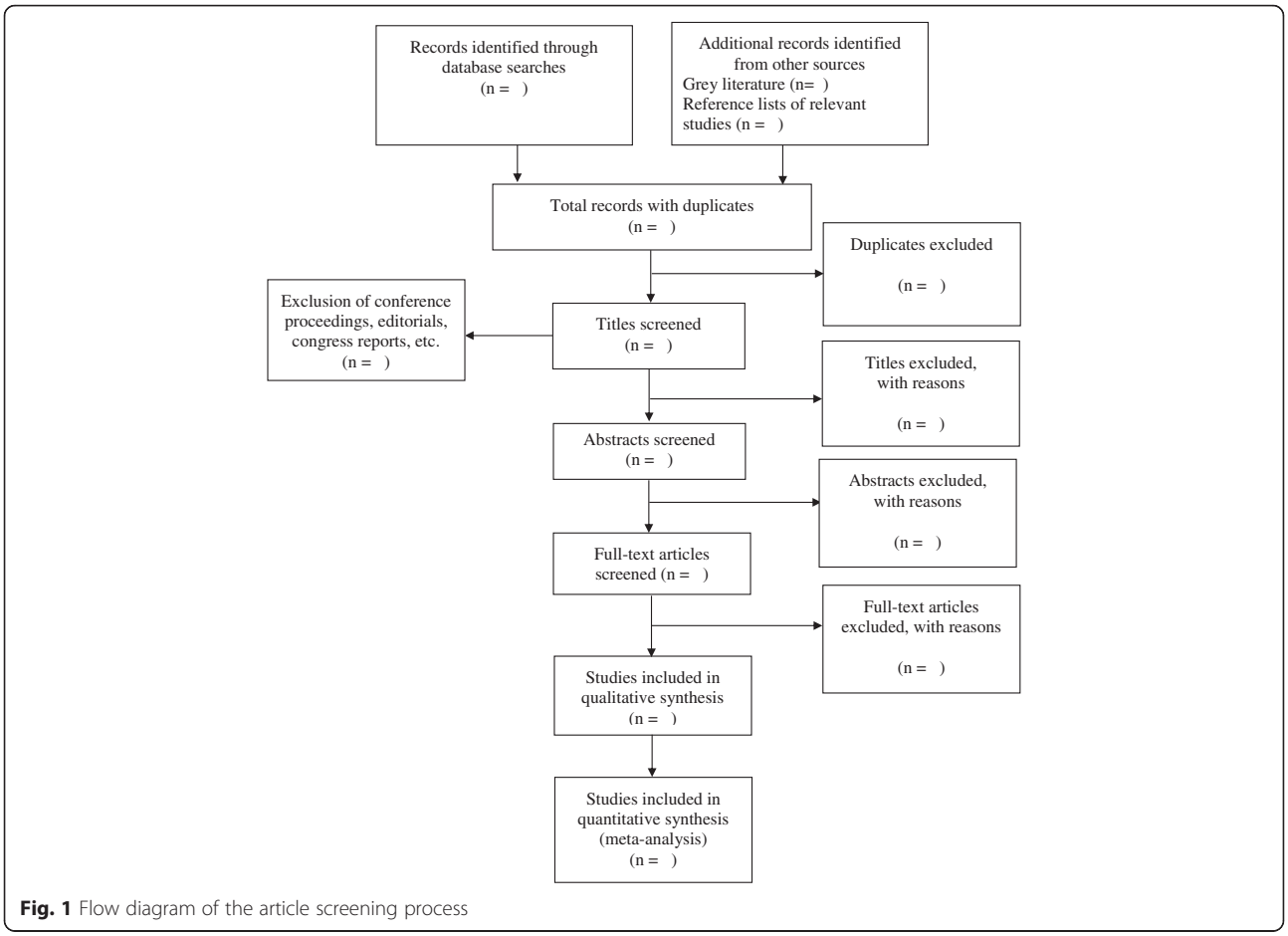

Fig. 1 Flow diagram of the article screening process

deficiency. Bias due to misclassification of the intervention status is assessed in the at-intervention domain. The post-intervention domain includes bias due to departures from the intended interventions, missing data, methods of outcome measurements, and selective reporting outcomes. In particular, co-interventions between lifestyle interventions, pharmacotherapy, and bariatric surgery can contribute to bias during the post-intervention domain. For example, participants may take antiobesity agents while they are on diet restriction. Each non-randomized study will be rated as having either a low, moderate, serious, critical, or unclear risk of bias.

The quality of uncontrolled studies will be assessed with a checklist developed by the University of Alberta Evidence-based Practice Center (UAEPC) [47]. This checklist evaluates selection bias, incomplete data, and the methods of outcome assessments. We will tabulate risk of bias for all included studies and discuss its impact on the meta-analysis.

The quality of evidence will be assessed using the Grading quality of evidence and strength of recommendations (GRADE) guidelines [48]. The GRADE guideline covers risk of bias, inconsistency, indirectness, imprecision, and publication bias. The overall quality of evidence is reported by each outcome measure as high, moderate, low, or very low.

Data analysis

Detailed characteristics of the included studies will be provided, in addition to a meta-analysis if applicable. We will analyze each intervention separately, and outcomes will be analyzed separately based on study designs. We will perform a meta-analysis if two or more studies are identified per intervention.

Dichotomous outcomes will be reported as odds ratio, while continuous outcomes will be reported as standardized mean differences and 95 % confidence intervals. Expecting high levels of heterogeneity, our primary approach will emphasize the random effects estimate if more than ten studies can be identified [49]. Otherwise, both random effect and fixed effect models will be presented.

Inconsistency index (I^2) and P values will be used to quantify heterogeneity. The interpretation of the I^2 will be based on the threshold set by the Cochrane

Collaboration [50]. If appropriate, a stratified analysis by sex will be pursued to identify a source of heterogeneity, as female SCBT are more at risk of developing obesity than males [8, 10].

If sufficient studies are identified for an outcome (≥10), we will perform sensitivity analysis by excluding outlier, small-sized, or highly biased studies to determine the impact of these studies on the meta-analysis result. To investigate publication bias, we will create a contour-enhanced funnel plot and use Egger's test and visual inspection to determine plot asymmetry, if there are ten or more studies for an outcome [51].

All meta-analyses will be conducted using Review Manager software version 5.3 (RevMan 5.3) [52] while Comprehensive Meta-Analysis software version 3 (CMA 3.0) will be used for Egger's test [53]. When meta-analysis is not appropriate, a table for summary of findings will be created using GRADEpro software and a narrative summary will be reported. The results of this systematic review will be presented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [43, 44]. When amendments of the protocol are needed, we will document the date and the rationale for these changes.

Discussion

As the number of SCBT increased over time, it has become apparent that the burden of surviving a brain tumor is significant [4, 6, 12, 13]. Obesity is a critical comorbidity to address in survivors, as it drives the risk of cardiovascular diseases, type 2 diabetes, metabolic syndrome, and hypertension [7, 8, 17–19]. This reduces the quality of life and lifespan of the survivors and increases healthcare system utilization.

In order to improve health outcomes in SCBT, it is important to develop evidence-based interventions to treat and prevent obesity and its cardiometabolic comorbidities.

The findings from this systematic review will have important implications for SCBT, as it will provide insights into the current best form of obesity intervention for these patients. The review will also define gaps in knowledge and help improve the quality of life and lifespan of SCBT by guiding the design of new interventions to target obesity and its cardiometabolic comorbidities.

Additional file

Additional file 1: PRISMA-P checklist. This checklist includes recommended items to address in a systematic reviews protocol and their location in this protocol. (DOCX 40 kb)

Abbreviations

BMI, body mass index; CENTRAL, Cochrane Central Register of Controlled Trials; CINAHL, Cumulative Index to Nursing and Allied Health Literature; CMA 3.0, Comprehensive Meta-Analysis version 3; DARE, Database of Abstracts of Reviews of Effect; EMBASE, Excerpta Medica Database; GRADE, Grading of Recommendations Assessment, Development and Evaluation; PRISMA, Preferred Reporting Items for Systematic Review and Meta-Analyses; RCT, randomized controlled trial; RevMan 5.3, Review Manager software version 5.3; ROBINS-I, Risk Of Bias in Non-randomized Studies—of Interventions; SCBT, survivors of childhood brain tumors; UAEPC, University of Alberta Evidence-based Practice Center

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Authors' contributions

MCS is the guarantor. Research question was defined by MCS, AF, SKS, SB, and LT. Search strategy and eligibility criteria were developed by KWW, MV, RC, LB, and MCS. Data abstraction form was designed by KWW, MV, RC, and MCS. Quality and risk of bias assessments were conducted by KWW and RC. Methodological support was provided by RJdeS and LT. KWW, RC, AF, SKS, SB, LT, LB, and MCS drafted the manuscript. All authors reviewed, edited, and approved the final version of the manuscript.

Competing interests

The authors declare that they have no competing interests.

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Appendix 4

Obesity Treatment

The effectiveness of interventions to treat hypothalamic obesity in survivors of childhood brain tumours: a systematic review

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Summary

Background: Survivors of childhood brain tumours (SCBT) are at risk of type 2 diabetes and cardiovascular diseases. Obesity is a major driver of cardiometabolic diseases in the general population, and interventions that tackle obesity may lower the risk of these chronic diseases. The goal of this systematic review was to summarize current evidence for the presence of interventions to manage obesity, including hypothalamic obesity, in SCBT.

Methods: The primary outcome of this review was the body mass index *z*-score change from baseline to the end of the intervention and/or follow-up. Literature searches were conducted in PsycINFO, CINAHL, the Cochrane Library, Medline, SPORTDiscus, EMBASE and PubMed. Two reviewers completed study evaluations independently.

Results: Eleven publications were included in this systematic review (lifestyle intervention $n = 2$, pharmacotherapy $n = 6$ and bariatric surgery $n = 3$). While some studies demonstrated effectiveness of interventions to manage obesity in SCBT and alter markers of obesity and cardiometabolic risk, the evidence base was limited and of low quality, and studies focused on hypothalamic obesity. We conclude that there is urgent need to conduct adequately powered trials of sufficient duration, using existing and novel therapies to manage obesity, reduce the burden of cardiometabolic disorders and improve outcomes in SCBT.

Keywords: Obesity, paediatric brain tumour, survivorship, interventions.

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Introduction

Brain tumours account for up to 20% of all childhood cancers and are the most common solid tumours in children. While survival rates of children with brain tumours have improved over the past three decades, these tumours remain a leading cause of childhood mortality after accidents (1–4). In addition, it has become clear that these children are at an increased risk of significant comorbidities and premature mortality (5–9).

Traditionally, the most common causes of death in survivors were the recurrence of the primary tumour, and the development of secondary tumours. However, emerging adverse cardiometabolic outcomes may contribute to the risk of premature mortality in survivors. Recent evidence suggests that survivors of childhood brain tumours (SCBT) have approximately a two-fold higher risk of developing type 2 diabetes compared to the general population (10). In addition, cardiovascular diseases including hypertension, cardiac events and stroke are also more frequent in survivors (11–13).

While type 2 diabetes and cardiovascular diseases are driven by the global obesity epidemic in the general population (14–17), it is unclear if obesity contributes to the elevated cardiometabolic burden and outcomes in survivors.

The most commonly reported obesity phenotype in SCBT is noted with lesions in the hypothalamus, e.g. craniopharyngioma (18). These tumours and their treatment cause hypothalamic damage and disruption of satiety signalling, decreased basal metabolic rate and pituitary hormonal deficiencies (19–21). As hypothalamic injury is multifactorial, treating patients with hypothalamic obesity is challenging, as they often do not respond to conventional lifestyle modifications (18).

Intriguingly, recent data suggest that SCBT have comparable rates of obesity to population-based controls (9,12). There is currently no complete explanation for the excess cardiometabolic risk in survivors compared with the general population at equivalent body mass index (BMI), and further studies to define the determinants of cardiometabolic risk and their contribution to outcomes are needed.

While there is limited understanding of the pathogenesis of cardiometabolic diseases in SCBT, managing obesity, including hypothalamic obesity, is a prudent strategy to improve the quality of life and lifespan of survivors (22,23). In this systematic review, our goal was to determine the current evidence base for interventions designed to manage obesity, including hypothalamic obesity, in SCBT.

Research question

In SCBT, are lifestyle interventions, pharmacotherapy or bariatric surgery effective in treating obesity, including hypothalamic obesity?

Methods

The protocol for this systematic review was previously published (24) and registered with the International Prospective Register of Systematic Reviews (PROSPERO; CRD42015025909).

Eligibility criteria

This systematic review included studies of overweight (BMI *z*-score ≥85th to <95th percentile) and obese (BMI *z*-score ≥ 95th percentile) SCBT (25), whose brain tumour diagnosis was made before 18 years of age. Randomized controlled trials (RCTs), quasi-RCTs, prospective and retrospective cohort studies, case–control studies, cross-sectional studies and uncontrolled studies with before-and-after comparisons were all eligible for inclusion. Case reports, interim analyses and pilot/feasibility studies were excluded. We included a comprehensive list of interventions in the search strategy including lifestyle-based interventions, pharmacotherapy and bariatric surgery. Lifestyle interventions involved any form of modification to the subjects' daily life such as diet and physical activity. Pharmacotherapy and bariatric surgery referred to the use of medications and surgical approaches with the intention of treating obesity, respectively. For bariatric surgery, surgical approaches incorporated laparoscopic adjustable gastric banding (LAGB), gastric bypass, sleeve gastrectomy and biliopancreatic diversion with duodenal switch (26).

Search strategy

Searches were conducted in PsycINFO, CINAHL, Cochrane Central Registry of Controlled Trials, Cochrane Database of Systematic Review, Database of Abstracts and Reviews of Effect, Medline, SPORTDiscus, EMBASE and PubMed. The grey literature was searched in ClinicalTrials.gov and ProQuest Dissertations and Theses A&I. The searches included all publications in these databases up to September 1st, 2016. The reference lists of eligible articles were scanned for potentially eligible records. Publications from the first and last authors of the relevant articles were also reviewed. A finalized search strategy for Medline was reported in the protocol paper (24).

Study selection

Article screening was conducted by two reviewers independently at all steps including titles, abstracts and full texts. The reviewers met after each step to compare the results and resolve conflicts through discussion. A third reviewer arbitrated persistent disagreements.

Quality assessment

Two reviewers independently assessed the study's risk of bias. The risk of bias in RCTs was assessed using the Risk of Bias Assessment Tool from the Cochrane Collaboration (27). Non-randomized studies were assessed using the Risk of Bias In Non-randomized Studies – of Interventions assessment tool (ROBINS-I) (28). Uncontrolled studies were evaluated using a checklist developed by the University of Alberta Evidence-based Practice Center (29). The overall quality of evidence was determined using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) guidelines (30). Discrepancies in assessments were resolved by discussion, and if no agreement could be reached, a third reviewer helped the reviewers resolve disagreements.

Data abstraction and synthesis

Two reviewers using a pre-established data abstraction form extracted data independently. The primary outcome for this review was BMI *z*-score (reported at times as BMI SDS) change from baseline to the end of the intervention and/or follow-up if available. Secondary outcomes included changes in adiposity measures including waist-to-hip ratio, waist-to-height ratio and fat mass percentage. We also aimed to examine changes in blood pressure, diabetes status, insulin resistance, non-alcoholic fatty liver disease and lipid profiles, when available. We documented the adverse events reported during the studies. Data were analysed separately on the basis of intervention types and study designs.

For any intervention type, a meta-analysis was deemed appropriate if two or more eligible studies with similar study design and patient populations were identified. If such conditions were satisfied, odds ratios would be used as the summary measure for dichotomous outcomes, and standardized mean differences with 95% confidence intervals for continuous outcomes.

Heterogeneity was quantified by using the inconsistency index (I^2) and interpreted using the threshold set by the Cochrane Collaboration (31). Publication bias would be assessed by visual inspection of a contour-enhanced funnel plot and by Egger's test, if more than 10 studies were available for an outcome (32).

Results

Search results

The literature screening process is reported in Fig. 1. The literature search identified 17,854 unique records from all databases, including grey literature and reference lists of relevant studies. After evaluating the titles, 16,205 records (16,003 records of title review and 202 conference proceedings, editorials and congress reports) were excluded with an agreement rate of 96.9%. The most common reason for exclusion was that the paper was not relevant to obesity interventions. Out of the 1,649 abstracts screened, 1,609 were excluded mostly because the participants were not brain tumour survivors. The agreement rate for abstract screening was 95.7%.

Following title and abstract screening, 40 articles were retrieved for full-text screening, and 21 were excluded owing to the non-inclusion of brain tumour populations (n = 6), brain tumours diagnosed >18 years (n = 1), only one subject was <18 years old (n = 1), case reports (n = 2), pilot studies (n = 1), interventions not related to obesity management (n = 1) and conference abstracts (n = 9). In addition, five trials identified from ClinicalTrials.gov were in the recruitment stage and were not included in this systematic review. Three completed trials identified from ClinicalTrials.gov did not have published results, and their data could not be retrieved after contacting the principal investigators.

One study was reported as a pilot study in the title, yet it was included in this systematic review, as on reviewing the paper, the report was more consistent with a trial design and not a pilot study (33). Another RCT included two subjects with acute lymphoblastic leukaemia in addition to SCBT and was included in this review (34).

In total, 11 records were included in this review, and the references of the excluded articles at full-text screening are listed in Table S1. No meta-analysis was performed owing to high heterogeneity and risk of bias across published studies.

Table 1 includes data describing the interventions reported, while Table 2 reports on the change in obesity measures with the different interventions. Table 3 reports on effects of interventions on diabetes, insulin resistance status and lipid profiles in studies that report these variables.

Lifestyle interventions (Tables 1–3)

Two studies examined lifestyle interventions, (35,36). The first study included 39 subjects (n = 23 female) with the majority of patients having a diagnosis of craniopharyngioma (n = 33), and including participants with other types of brain tumours including germinoma (n = 3), lipoma (n = 1), hamartoma (n = 1) and glioma (n = 1) (35). The intervention was delivered in a hospital clinic setting and involved goal setting for healthy dietary intake and physical activity. Nine subjects also received pharmacological agents including metformin. Subjects attended the clinic every 1–6 months, with a mean follow-up duration of 0.97 ± 0.92 years. Thirty-one subjects were

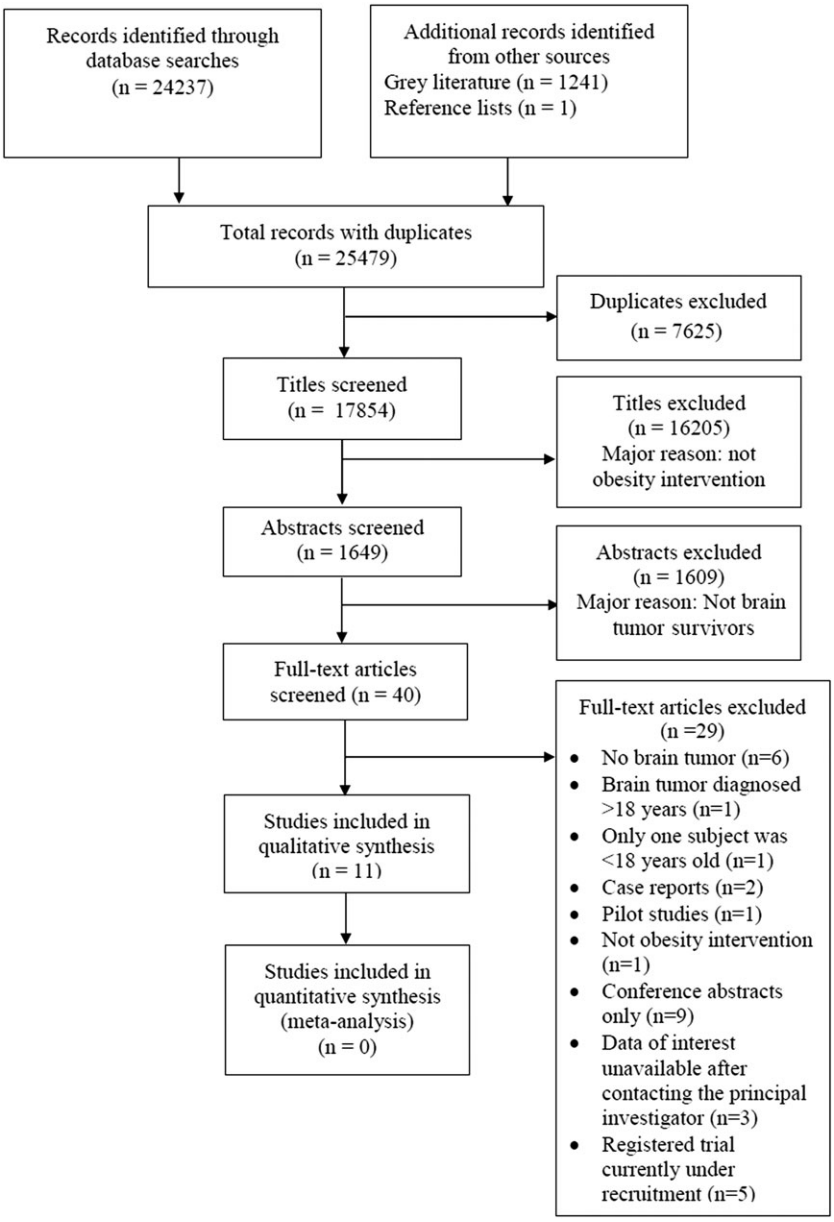

Figure 1 Flow diagram of article screening process.

already managed at the endocrine clinic in the hospital before starting the programme. In the absence of a control group, before-and-after comparisons were performed for weight and metabolic variables.

The study reported significant reduction in BMI and weight changes post-intervention, with increased high-density lipoprotein (HDL; 1.09 ± 0.33 vs 1.24 ± 0.04 mmol L^{-1}, p = 0.03), but no significant changes in BMI z-score, low-density lipoprotein (LDL), triglycerides (TG) or fasting glucose (35).

The German study was a retrospective cohort study, with 108 craniopharyngioma patients. Thirty-one were treated with rehabilitation programme and 77 were non-treated controls (36). The participants were involved in a rehabilitation programme promoting healthy lifestyle and psychological well-being.

The median duration of the programme was 39 days (range, 20–135 days), with varying numbers of visits. The subjects were monitored from the initial brain tumour diagnosis with a broad range of follow-up duration (9.8–36.4 years). The results revealed higher BMI z-score in the intervention group at follow-up, which may be explained by its significantly higher baseline BMI z-score when compared with that of the control group. Neither study reported on adverse events during the conduct of the interventions.

Table 1 Characteristics of included studies

Author (country, year, study design)	Population	Intervention	Outcomes	Duration	Notes
		Lifestyle intervention			
Rakhshani *et al.* (Canada, 2010, uncontrolled before–after)	• Brain tumours (n = 39, 23 female) • CP (n = 33), germinoma (n = 3), lipoma (n = 1), hamartoma (n = 1), glioma (n = 1) • Median age 7.6 (range, 2.2–15.9) years at brain tumour diagnosis • 71.8% surgery, 20.5% radiation, 20.5% chemotherapy • Pituitary hormone dysfunction (n = 34) • 24 growth hormone deficiency (20 treated)	Comprehensive care clinic • Modification on diet and physical activity • Pharmacological agents such as metformin in certain cases	Change in %BMI per year, BMI z-score, % ideal body weight per year, % weight gain, blood pressure, fasting glucose, HDL, LDL, triglycerides from baseline to follow-up	• Frequency of once per month up to every 6 months at patients' choices • Patients attended mean of 3.3 ± 2.2 visits • Duration of follow-up mean 0.97 ± 0.92 years (range, 3–41 months)	31 patients were already treated at the endocrine clinic before attending the programme
Sterkenburg *et al.* (Germany, 2014, retrospective cohort)	• CP (n = 108, 58 female) Intervention group (n = 31,1 9 female) • Median age 9.2 (range, 1.9–17.4) years at brain tumour diagnosis • 55% had complete resection Control group (n = 77, 39 female) • Median age 7.8 (range, 0.05–18.8) years at brain tumour diagnosis • 35% had complete resection	Rehabilitation programme Training eating habits, promoting physical activity and improve psychological well-being	Change in BMI z-score, from diagnosis to follow-up and comparison between intervention and control groups	• Duration of each programme median 39 d (range, 20–135 d), with varying frequency of attendance • Follow-up period median 16.3 years (range, 9.8–36.4) from diagnosis to last evaluation	21 patients from the intervention group had life-threatening comorbidities associated with a metabolic syndrome, hyperphagia and conduct disorders
		Pharmacotherapy			
Danielsson *et al.* (Sweden, 2007, RCT)	• Brain tumours (n = 5, 3 female) • CP (n = 4), astrocytoma (n = 3), optic glioma (n = 1), Prolactinoma (n = 1), Histiocytosis X (n = 1) • Median age 5 (range, 2–11) years at brain tumour diagnosis • All undergone surgical resection	Sibutramine (10 mg d^{-1}) • The daily dose was increased to 15 mg if weight reduction of at least 4 kg was not observed within 8 weeks	Change in BMI z-score, total body fat percentage, fasting glucose and insulin levels, and non-fasting cholesterol and triglyceride levels from baseline to end of trial	20 weeks each for intervention phase and placebo phase	The sibutramine-placebo group received sibutramine at baseline and crossed over to placebo at week 20
Ismail *et al.* (Australia, 2006, uncontrolled before–after)	• Invasive hypothalamic lesions (n = 12, 7 female) • CP (n = 9), astrocytoma (n = 2), glioma (n = 1) • Median age 9.4 (range, 4.4–13.1) years at brain tumour diagnosis • Total resection (n = 6), partial resection (n = 4), drainage (n = 2), adjuvant	Dexamphetamine (5 mg twice daily)	Change in weight and BMI z-score, from baseline to follow-up	• Duration of treatment median 13 months (range, 7–63) in men and 15 months (range, 6–48) in female	

(*Continues*)

Table 1 (Continued)

Author (country, year, study design)	Population	Intervention	Outcomes	Duration	Notes
	radiotherapy >51 Gy (n = 7) • Pituitary hormone deficiency (treated)			• Followed up every 3–6 months	
Kalina *et al.* (Poland, 2015, uncontrolled before–after)	• CP (n = 22, 12 female) • Median age 10.5 (range, 0.2–16.8) years at brain tumour diagnosis • Gross total resection (n = 8), subtotal/partial resection (n = 14), radiotherapy (n = 18) for tumour residue or progression • Short stature, lack of pubertal progression, hypothyroidism, adrenal insufficiency (treated)	Metformin with micronized fenofibrate (n = 10) • Metformin hydrochloride: 500–1500 mg d^{-1} • Micronized fenofibrate: 160 mg d^{-1}	Change in BMI z-score, total cholesterol, triglycerides, HOMA-IR from baseline to follow-up	• Duration of treatment 6 months • Evaluation at baseline and at 6 months	Ten out of 22 patients received pharmacotherapy to treat obesity, after unsuccessful lifestyle intervention
Lomenick *et al.* (USA, 2016, uncontrolled before–after)	• Brain tumours (n = 5, 4 female) • CP (n = 3), astrocytoma (n = 1), hypothalamic tumour of unknown origin (n = 1) • Median age 8 (range, 5–14) years at brain tumour diagnosis • All received surgical resection, one of them also received radiation and chemotherapy • Multiple pituitary hormone deficiency (treated)	Exenatide • Subcutaneously twice a day • Dosage started at 5 μg per dose and increased to 10 μg per dose after 8 weeks, unless an adverse reaction occurred	Change in weight, glucose and insulin levels from baseline to follow-up	• Duration of treatment: 50 weeks • Followed up at 0–2 weeks (baseline) and 50–52 weeks (during treatment)	• Out of the 10 subjects enrolled in the study, only 5 had a brain tumour diagnosed under 18 years of age. • Among the five subjects eligible for this review, 2 withdrew owing to adverse events including mood swing and kidney stones
Lustig *et al.* (USA, 2003, RCT)	Treatment group (n = 10, 4 female) • CP (n = 6), hypothalamic astrocytoma (n = 2), acute lymphoblastic leukaemia (n = 2) • Mean age 13.8 ± 1.2 years at start of the study protocol • Surgery (n = 8), radiotherapy (n = 10), chemotherapy (n = 2) • Pituitary hormone deficiency (treated) Placebo group (n = 10, 5 female) • CP (n = 7), hypothalamic astrocytoma (n = 1),	Octreotide • Dosage started with 5 μg (kg d)$^{-1}$ and increased bimonthly by 5 μg (kg d)$^{-1}$ to a maximum of 15 μg (kg d)$^{-1}$ • Each dosage was divided into 3 daily doses	Change in weight, BMI, fasting glucose and insulin, and leptin from baseline to follow-up	• Duration of treatment: 6 months • Followed up bimonthly	Two subjects, 1 from each group, withdrew from the study owing to tumour recurrence or the development of diabetes hyperosmolar nonketotic coma

(*Continues*)

Table 1 (Continued)

Author (country, year, study design)	Population	Intervention	Outcomes	Duration	Notes
	germinoma (n = 1), optic pathway glioma (n = 1) • Mean age 14.2 ± 0.9 years at start of the study protocol • Surgery (n = 8), radiotherapy (n = 10), chemotherapy (n = 2) • Pituitary hormone deficiency (treated)				
Mason *et al.* (USA, 2002, uncontrolled before–after)	• CP (n = 5, 2 female) • Median age 8.5 (range, 6–9.8) years at start of the study protocol • All had surgical resection • Multiple pituitary hormone deficiency (treated)	Dexamphetamine • Dosage started at 5 mg d^{-1} and was increased by 2.5 mg weekly until either an outcome or an adverse reaction occurred • Maximal daily dosage was mean 16 ± 2 mg, divided into 3 doses	Change in weight, BMI, insulin, IGF-1, and IGFBP-3 from baseline to follow-up	• Duration of treatment: 24 months • Followed up at 1, 3, 6, 9, 12, 18 and 24 months of therapy	
		Bariatric surgery			
Muller *et al.* (Germany, 2007 and 2011, uncontrolled before–after)	• CP (n = 3, 2 female) • Brain tumour diagnosed at 2, 11 and 12 years • Age 14, 17.5 and 21 at the time of LAGB • All received surgical resection, one of them also had radiation	Adjustable LAGB	Change in BMI z-score, from baseline to follow-up	2007: Follow-up period 4.5, 1.5, 3 years 2011: Follow-up period 9.1, 5.3 and 7.1 years	The subjects previously had unsuccessful treatment efforts in weight control and insisted on receiving LAGB
Weismann *et al.* (Germany, 2013, uncontrolled before–after)	Hypopituitarism (treated) • CP (n = 9, 7 female) • Non-cancer control (n = 143) • Median age 10 (range, 1–21) years at brain tumour diagnosis • Median age 17 (range, 12–30) years at bariatric surgery • Hypopituitarism (treated)	• LAGB (n = 6) • SG (n = 4) • GB (n = 2)	Difference of % weight change between obese CP and non-cancer control at baseline and at follow-up	Median follow-up (CP, control) years • LAGB (5.5, 3) • SG (2, 1) • GB (3, 2)	Patients received different surgeries at different centres and often receive multiple times of bariatric surgeries

BMI, body mass index (kg m^{-2}); CCC, comprehensive care clinic; CP, craniopharyngioma; GB, gastric bypass; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment insulin resistance index (fasting insulin (μU L^{-1}) × fasting glucose (nmol L^{-1}))/22.5; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor binding protein; LAGB, laparoscopic gastric banding; LDL, low-density lipoprotein; RCT, randomized controlled trials; SG, sleeve gastrectomy.

Pharmacotherapy (Tables 1–3)

Six studies using pharmacotherapies to manage obesity in patients with brain tumours were identified (33,34,37–40). All were small (n = 5–12), with the majority of pooled participants having hypothalamic obesity. The participants included 32 patients with craniopharyngioma, eight patients with astrocytoma and two patients with glioma.

Only two studies were RCTs and reported the use of the appetite suppressant sibutramine (10–15 mg d^{-1}, 20 weeks) (37) and somatostatin analogue octreotide (5–15 μg kg^{-1} d^{-1}, 6 months) (34). In the Subutramine

Table 2 Effects of interventions on BMI, BMI *z*-score or weight change and adverse events

Publication (country, year)	BMI, BMI SDS, weight		*p*-value*	Adverse events
	Baseline	Follow-up		
	Lifestyle interventions			
Rakhshani *et al.* (Canada, 2010)	Median (range) Change from brain tumour diagnosis to first visit	Median (range) Change from first to last visit		Not reported
	• % BMI change per year 8.4 (−3.1 to 28.1)	• % BMI change per year 4.5 (−17.8 to 8.4)	$p < 0.01$	
	• BMI *z*-score change 0.4 (−2.1 to 2.2)	• BMI *z*-score change 0.0 (−5.2 to 0.5)	ns	
	• % IBW change per year 19.9 (−18.7 to 149.2)	• % IBW change per year −4 (−141.7 to 34)	$p = 0.003$	
	• % weight gain per year before clinic entry 21.4 (15.8–32.0)	• % weight gain per year during CCC 8.5 (3.4–14.0)	$p < 0.05$	
Sterkenburg *et al.* (Germany, 2014)	Intervention Median BMI *z*-score +1.3 (−1.1 to +7.0) Control Median BMI *z*-score +0.2 (−2.7 to +7.0) $p = 0.000^{\dagger}$	Intervention Median BMI *z*-score +4.9 (−0.2 to +13.13) Control Median BMI *z*-score +2.1 (−1.5 to +10.2) $p = 0.039^{\dagger}$	Not reported	Not reported
	Pharmacotherapy			
Danielsson *et al.* (Sweden, 2007)	Sibutramine-placebo group ($n = 3$) Mean BMI *z*-score 4.8 ± 1.3	Sibutramine-placebo group ($n = 3$) Mean BMI *z*-score (sibutramine, placebo) 4.4 ± 1.3, 4.4 ± 1.2	Not reported	Fluctuation in mood ($n = 2$), constipation ($n = 1$), fatigue ($n = 1$), insomnia ($n = 1$), depression ($n = 1$)
	Placebo-sibutramine group ($n = 2$) Mean BMI *z*-score 4.9 ± 2.8	Placebo-sibutramine group ($n = 2$) Mean BMI *z*-score (placebo, sibutramine) 5.1 ± 2.7, 4.7 ± 2.7	Not reported	
Ismail *et al.* (Australia, 2006)	Mean weight 106.2 kg	Mean weight 101.4 kg Median BMI *z*-score reduction 0.7 in men ($n = 5$); 0.4 in female ($n = 5$)	Not reported	Insomnia ($n = 1$), tumour recurrence ($n = 1$)
Kalina *et al.* (Poland, 2015)	Median BMI *z*-score 1.91 (1.2 to 2.7)	Median BMI *z*-score 1.87 (1.3 to 2.6)	ns	None
Lomenick *et al.* (USA, 2016)	Mean weight ($n = 3$) 158.1 ± 59.01 kg	Mean weight ($n = 3$) 155.6 ± 57.6 kg	Not reported	Among all ten subjects: nausea/vomiting ($n = 7$), joint pain ($n = 3$), injection site reaction ($n = 3$), mood swing ($n = 1$), nephrolithiasis ($n = 1$)
Lustig *et al.* (USA, 2003)	Octreotide group ($n = 9$) Mean weight 98.5 ± 9.2 Mean BMI 37.4 ± 2.5 Placebo group ($n = 9$) Mean weight 102.7 ± 6.8 Mean BMI 36.8 ± 1.2	Octreotide group ($n = 9$) Mean weight 100.0 ± 9.5 Mean BMI 37.2 ± 2.5 Placebo group ($n = 9$) Mean weight 111.9 ± 7.5 Mean BMI 39.0 ± 1.4	$p < 0.001^{\ddagger}$	Abdominal discomfort and diarrhoea ($n = 9$), cholelithiasis ($n = 4$), mild glucose intolerance ($n = 2$), diabetes ($n = 1$)
Mason *et al.* (USA, 2002)	Mean BMI 32 ± 2.8 Mean monthly weight gain (from brain tumour diagnosis to the start of protocol) 2 ± 0.3 kg month^{-1}	Mean BMI 31 ± 3.3 Mean monthly weight gain (from start to the end of protocol) 0.4 ± 0.2 kg month^{-1}	ns $p = 0.009$	Headache ($n = 1$), cyst enlargement ($n = 1$)
	Bariatric surgery			
Muller *et al.* (Germany, 2007)	BMI *z*-score at diagnosis: +0.9, +4.45, +4.7 BMI *z*-score at LAGB: +13.9, +10.3, +11.4	BMI *z*-score at latest visit: +9.9, +9.7, +9.5	Not reported	None

(*Continues*)

Table 2 (Continued)

Publication (country, year)	BMI, BMI SDS, weight		*p*-value*	Adverse events
	Baseline	Follow-up		
Muller *et al.* (Germany, 2011)	BMI *z*-score at diagnosis: −0.9, +4.45, +4.7 BMI *z*-score at LAGB: +10.9, +10.4, +11.4	Lowest BMI *z*-score after LAGB: +6.9, +9.4, +7.5 BMI *z*-score at latest visit: +10.2, +13.9, +10.2	Not reported	
	Brain tumour group	Non-cancer control group	*p*-value§	Adverse events
Weismann *et al.* (Germany, 2013)	Estimated % weight change¶: • LAGB (n = 6) ~ +5% • SG (n = 4) ~ +3% • GB (n = 2) ~ −28%	Estimated % weight change¶: • LAGB (n = 40) ~ −17% • SG (n = 49) ~ −32% • GB (n = 54) ~ −31%	$p < 0.01$ $p < 0.05$ ns	Suspected acute adrenal insufficiency (n = 1), transient increased of hydrocortisone (n = 2)

BMI, body mass index (kg m^{-2}); GB, gastric bypass; IBW, ideal body weight; LAGB, laparoscopic gastric banding; SG, sleeve gastrectomy.
*Comparison between baseline and last evaluation.
†Comparison between treated and untreated groups.
‡Comparison of changes from month 0 to month 6 for weight and BMI between octreotide and placebo groups with two-sided *t*-test.
§Comparison between non-cancer controls and brain tumours.
¶Values were estimated from graphs where exact values were not reported.

Table 3 Effects of interventions on diabetes, insulin resistance status and lipid profiles

Publication (country, year)	Diabetes or insulin resistance status			Lipid profiles		
	Baseline	Follow-up	*p*-value	Baseline	Follow-up	*p*-value
			Lifestyle interventions			
Rakhshani *et al.* (Canada, 2010)	Mean ± SD Fasting glucose 4.8 ± 0.8 mmol L^{-1}	Mean ± SD Fasting glucose 4.4 ± 0.6 mmol L^{-1}	0.06	Mean ± SD • HDL: 1.1 ± 0.3 mmol L^{-1} • LDL: 2.8 ± 0.9 mmol L^{-1} • Triglyceride: 1.5 ± 0.6	Mean ± SD • HDL: 1.2 ± 0.04 mmol L^{-1} • LDL: 2.9 ± 0.2 mmol L^{-1} • Triglyceride: 1.5 ± 0.7	0.03 ns 0.9
			Pharmacotherapy			
Danielsson *et al.* (Sweden, 2007)	Sibutramine-placebo group (n = 3) Mean ± SD • Fasting glucose 4.6 ± 0.06 mmol L^{-1} • Fasting insulin 87.7 ± 51.7 pmol L^{-1}	Sibutramine-placebo group (n = 3) Mean ± SD (sibutramine, placebo) • Fasting glucose 4.6 ± 0.3, 4.4 ± 0.3 mmol L^{-1} • Fasting insulin 77 ± 45.0, 92.7 ± 61.4 pmol L^{-1}	Not reported	Sibutramine-placebo group (n = 3) Mean ± SD • Cholesterol 5.5 ± 0.1 mmol L^{-1} • Triglyceride 1.5 ± 0.75 mmol L^{-1}	Sibutramine-placebo group (n = 3) Mean ± SD (sibutramine, placebo) • Cholesterol 5.5 ± 0.1, 5.6 ± 0.1 mmol L^{-1} • Triglyceride 1.5 ± 0.2, 1.5 ± 0.6 mmol L^{-1}	Not reported
	Placebo-sibutramine group (n = 2) Mean ± SD • Fasting glucose 4.7 ± 0.3 mmol L^{-1} • Fasting insulin 116 ± 28.3 pmol L^{-1}	Placebo-sibutramine group (n = 2) Mean ± SD (placebo, sibutramine) • Fasting glucose 5.1 ± 0.5, 5.8 ± 1.1 mmol L^{-1} • Fasting insulin 172.5 ± 116.7, 331 pmol L^{-1}	Not reported	Placebo-sibutramine group (n = 2) Mean ± SD • Cholesterol 4.3 ± 0.1 mmol L^{-1} • Triglyceride 1.8 ± 0.4 mmol L^{-1}	Placebo-sibutramine group (n = 2) Mean ± SD (placebo, sibutramine) • Cholesterol 4.1 ± 0.5, 3.6 ± 0.1 mmol L^{-1} • Triglyceride 2.6 ± 0.8, 2.7 mmol L^{-1}	Not reported

(*Continues*)

Table 3 (Continued)

Publication (country, year)	Diabetes or insulin resistance status			Lipid profiles		
	Baseline	Follow-up	*p*-value	Baseline	Follow-up	*p*-value
Kalina *et al.* (Poland, 2015)	Median HOMA-IR 8.6 (5.1 to 12.7)	Median HOMA-IR 4.7 (0.7 to 7.9)	<0.05	• Median cholesterol 230 (199 to 274) mg dL^{-1} • Median triglyceride 263.5 (171–362) mg dL^{-1}	• Median cholesterol Not reported • Median triglyceride 154 (102–183) mg dL^{-1}	ns <0.05
Lustig *et al.* (USA, 2003)	Octreotide group (n = 9) Mean ± SD • Fasting insulin 29.2 ± 4.9 μU mL^{-1} • Fasting glucose 78.7 ± 4.5 mg dL^{-1}	Octreotide group (n = 9) Mean ± SD • Fasting insulin 27.7 ± 11.8 μU mL^{-1} • Fasting glucose 94.0 ± 6.7 mg dL^{-1}	ns* 0.076*	Octreotide group (n = 9) Mean ± SD • Leptin 45.3 ± 8.2 ng mL^{-1}	Octreotide group (n = 9) Mean ± SD • Leptin 32.8 ± 5.1 ng mL^{-1}	ns*
	Placebo group (n = 9) Mean ± SD • Fasting insulin 36.9 ± 6.8 μU mL^{-1} • Fasting glucose 70.4 ± 7.7 mg dL^{-1}	Placebo group (n = 9) Mean ± SD • Fasting insulin 27.9 ± 4.6 μU mL^{-1} • Fasting glucose 71.6 ± 4.1 mg dL^{-1}		Placebo group (n = 9) Mean ± SD • Leptin 34.7 ± 4.7 ng mL^{-1}	Placebo group (n = 9) Mean ± SD • Leptin 29.1 ± 4.4 ng mL^{-1}	
Mason *et al.* (USA, 2002)	Mean ± SD • Fasting insulin 43.8 ± 4.6 μU mL^{-1} • IGF-1 99.8 ± 43.5 ng mL^{-1} • IGFBP-3 1.8 ± 0.3 mg L^{-1} • Fasting glucose Not reported	Mean ± SD • Fasting insulin 49.4 ± 11.8 μU mL^{-1} • IGF-1 49.8 ± 38.4 ng mL^{-1} • IGFBP-3 1.7 ± 0.4 mg L^{-1} • Fasting glucose Not reported	0.32 0.005 0.91 ns	Cholesterol Not reported	Cholesterol Not reported	ns

HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment insulin resistance index (fasting insulin (μU L^{-1}) × fasting glucose (nmol L^{-1}))/22.5; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor binding protein; LDL, low-density lipoprotein; ns, non-significant (exact value not reported); SD, standard deviation.

*Comparison of changes from month 0 to month 6 between octreotide and placebo groups with a two-sided *t*-test.

study, while 10 recruited patients were classified as having central nervous system damage, two were excluded as one had Prolactinoma, while the second participant had Histiocytosis X. Of the remaining eight subjects, three did not complete the study due to craniopharyngioma recurrence. The data reported in Table 1 are based on data provided by the author to our team having contacted the author directly. Of the five eligible participants remaining in the study, sibutramine did not significantly lower BMI *z*-score. Octreotide was shown to stabilize weight and BMI gain in SCBT.

Two uncontrolled studies reported using another appetite suppressant, dexamphetamine (5 mg twice daily, 6–63 months (38); 5 mg d^{-1} starting dose, and titrated up to a mean dose of 16 ± 2 mg d^{-1}, with a total treatment duration of 24 months) (40). The first study revealed that using dexamphetamine reduced BMI *z*-score (0.7 in male and 0.4 in female) (38), while the second study revealed no alteration in BMI with the treatment but reduced the rate of weight gain (before 2.0 ± 0.3 kg $month^{-1}$ versus after 0.4 ± 0.2 kg $month^{-1}$, p = 0.009) (40).

Another uncontrolled study used exenatide, a glucagon-like peptide-1 receptor agonist, at 5 μg per dose for 8 weeks and then 10 μg per dose twice daily, for a total duration of 50 weeks of treatment. Exenatide therapy resulted in weight reduction in SCBT (before 158.1 ± 59.01 kg versus after 155.6 ± 57.6 kg, n = 3 from data provided by the author upon contact by our team for eligible participants, no reported *p*-value due to small sample size) (33).

One study adopted a combination therapy of the insulin sensitizer metformin (500–1,500 mg d^{-1}, 6 months) with micronized fenofibrate (160 mg d^{-1}, 6 months) as a lipid-modulating therapy (39). Metformin with micronized fenofibrate treatment did not alter BMI *z*-score (39).

In evaluating glucose homeostasis and lipid profiles with these therapies, the impact of sibutramine could not be

evaluated owing to small sample size (Table 3) (37). Neither octreotide nor dexamphetamine had a significant impact on fasting glucose, insulin or lipid profiles (34,40). No significant changes in metabolic parameters were reported with the use of exenatide (33).

As expected with combination therapy, metformin lowered insulin resistance measured by the homeostatic model assessment insulin resistance index (HOMA-IR) from a median of 8.64 (range, 5.08–12.65) to a median of 4.68 (range, 0.7–7.9), with three out of six participants having a HOMA-IR below the insulin resistance cut-off levels (39). Furthermore, fenofibrate lowered triglycerides (median 263.5 vs 154 mg dL^{-1}) (39). Both dexamphetamine and combination therapy of metformin and micronized fenofibrate did not alter total cholesterol (39,40). Adverse events attributed to pharmacotherapy included nausea/vomiting, joint pain, injection site reaction, nephrolithiasis (33), diarrhoea, cholelithiasis, mild glucose intolerance, diabetes (34), insomnia (37,38), fluctuation in mood (33,37), constipation, fatigue, depression (37) and headache (40) (Table 2).

Bariatric surgery (Tables 1 and 2)

Two studies reported the use of bariatric surgery to treat hypothalamic obesity in craniopharyngioma (41–43), and survivors of other brain tumour types were not included in the study. In one study, the short-term and long-term surgical outcomes were reported in separate papers (41,42). A total of nine women and three men were included in the two studies. Weismann *et al*. also included a group of obese non-cancer subjects (n = 143) treated with the same type of bariatric surgery, and comparisons were made between the survivors and the non-cancer participants (43).

The most commonly implemented surgical procedure was LAGB. Muller *et al*. reported weight reduction with LAGB in obese patients with craniopharyngioma with short-term follow-up (<5 years) (41), but that effect disappeared with long-term follow-up (>5 years) (42). Weismann *et al*. reported that LAGB was effective in non-cancer controls but not in craniopharyngioma-related obesity (43). Sleeve gastrectomy was not effective in patients with craniopharyngioma, while gastric bypass achieved similar weight reductions in both craniopharyngioma patients and controls (43).

Risk of bias assessments

The risk of bias for the seven uncontrolled studies that included different interventions (33,35,38–43) was evaluated using the University of Alberta Evidence-based Practice Center checklist (Table S2) (29). Of these, five had consecutive recruitment (33,35,39,40,43), one did not have consecutive recruitment (41,42) and one did not clearly report this parameter (38). Although six studies addressed incomplete outcome reporting adequately (35,38–43), one study had 40% dropout rate among SCBT and may be biased by incomplete outcome reporting (33). Six studies did not clearly describe who collected the outcome measures (33,35,39–43), and one had the treatment provider collecting the outcomes (38).

One retrospective cohort study compared a lifestyle intervention group with a non-intervention group (36), and ROBINS-I tool was used to evaluate risk of bias of this study (Table S3) (28). Sample selection, outcome measurements and missing data were rated to have low risk of bias for this study. It was classified as having a high risk of bias as potential confounders were not accounted for in the design or analysis. Insufficient data were available to assess risk of bias owing to participant selection, intervention measurement or treatment infidelity. Overall, this study was assessed as having serious risk of bias.

The Risk of Bias Assessment Tool from the Cochrane Collaboration (27) was used to evaluate the two RCTs identified in this review (Table S4) (34,37). The RCT using sibutramine had appropriate sequence generation, allocation concealment and blinding. The risk of bias due to incomplete outcome data and selective outcome reporting were also low. Therefore, the overall risk of bias for this RCT is low. The RCT using octreotide did not provide sufficient information on how the randomization sequence was generated, or how the allocation was concealed. The overall risk of bias for this RCT was determined to be unclear.

Overall quality of evidence assessment

We used the GRADE guidelines to evaluate the overall quality of evidence (30). The studies produced a low quality evidence (44), and the risk of bias, inconsistency, indirectness, and imprecision were all rated as serious or very serious. This eventually led to downgrading the overall quality of evidence to very low (Table S5).

The risk of bias was considered serious because of the lack of consecutive recruitment (38,41,42), unclear or inappropriate outcome measurement method in all of the uncontrolled studies (33,35,38–43), or very serious owing to the unadjusted confounding factors in the cohort study of the population in a rehabilitation program (36). Inconsistency was also serious across studies as opposite results were reported.

Indirectness was rated as very serious owing to differences across studies even within the same intervention type. Although the interventions can be generally categorized into lifestyle interventions, pharmacotherapy and bariatric surgery, some involved combined approaches to therapy, with one study implementing lifestyle intervention and the use of metformin (35). Studies on pharmacotherapy used

different drugs, and even when the drugs were similar (e.g. dexamphetamine), the doses and durations of treatment were different (33,34,37–40). In the bariatric surgery group, the number of surgeries in survivors was small, with some patients receiving multiple bariatric surgery procedures (43), while others had only one procedure performed (41,42).

Imprecision was quantified to be mostly very serious owing to small sample size in the studies. The presence of publication bias could not be determined with funnel plot or Egger's test, as there were less than 10 eligible studies in each intervention type.

Importantly, several trials using pharmacologic agents registered in ClinicalTrials.gov were unpublished after the completion of the studies. Although attempts were made to contact the study investigators, data from these trials could not be retrieved. Therefore, we suspect that publication bias is present at least for the pharmacologic interventions. One of the completed trials from ClinicalTrials.gov reported an adverse event of venous thromboembolism with beloranib, while another study using octreotide depot was discontinued owing to low efficacy (45,46). Selective reporting was also noted in studies on exenatide, dexamphetamine and combined metformin plus micronized fenofibrate therapy, where certain outcomes were reported as insignificant, without actual data (33,39,40).

Discussion

Although a substantial evidence base for effective obesity management has been developed from adult cancer survivorship studies (47–49), there is a dearth of evidence for the paediatric population. When paediatric data are available, much of the evidence on obesity management is focused on survivors of leukaemia (50,51).

In addition, while obesity interventions have short-term benefits in obese non-cancer children (52–54), the short-term and long-term benefits of these interventions in brain tumour survivors are unclear. This systematic review has focused on synthesizing current evidence for managing obesity in brain tumour survivors. Although the goal of the review was to summarize the evidence for managing hypothalamic and non-hypothalamic obesity in this population, almost all participants included in these studies had craniopharyngioma or hypothalamic involvement of their tumour. Therefore, the current evidence of managing obesity in SCBT included in this review is concentrated on managing hypothalamic obesity.

There was a small number of studies identified and a high level of heterogeneity across the studies. Lifestyle interventions differed in the composition of diet and the exercise or activity regimens recommended to the participants (35,36), while studies on pharmacotherapy used different drugs with different dosages, frequencies and durations (33,34,37–40). In the two bariatric surgery studies identified, the type and number of surgical procedures were different among participants (41–43).

In addition, there was a wide variation in the obesity-related outcomes measured including absolute weight lost (33,34,36–42), weight gain per year or month (35,40) or weight change percentage (35,43). Another source of heterogeneity was the broad range of the follow-up period, which ranged from weeks to years (35–37,42).

Lifestyle interventions

Obesity in SCBT can be partly attributed to lifestyle changes including sedentary behaviours coupled with increased caloric intake (55–57). The goal of lifestyle intervention is to trigger behavioural change in diet and physical activity to manage obesity, but the long-term effect of these interventions is unknown. In addition, patients with hypothalamic obesity are not likely to respond to lifestyle interventions because of the multiple pathways through which hypothalamic injury contributes to obesity in SCBT (18).

Studies on lifestyle intervention identified in this review have reported different results, with some studies reporting less weight gain per year over months to years of follow-up (35), while other studies failed to show an effect (36). In addition, studies have not reported on adverse events in the study populations.

Paediatric bariatric programmes report short-term benefits related to lifestyle interventions for up to 1 year (58). However, long-term efficacy data are lacking, and young children seem to benefit more than adolescents (59). This argues for the need for further research to understand the determinants of hypothalamic and non-hypothalamic obesity in survivors, and to re-think the approaches used in lifestyle-based obesity intervention programmes. There may be a need to pursue combination therapies, with lifestyle being one component of the intervention. In addition, renewed focus on the development of sustainable methods of delivery of long-term interventions is needed, to improve obesity management and cardiometabolic outcomes in survivors.

Pharmacotherapy

The mechanisms of action of anti-obesity drugs are centred on hunger and satiety signalling (60). The drugs used in these studies target obesity mainly by appetite suppression (e.g. sibutramine (37) and dexamphetamine (38,40)). One alternative and interesting approach involved the combined use of insulin sensitization and lipid-lowering therapy to mitigate the adverse effects of obesity on glucose and lipid metabolism rather than targeting obesity *per se* (39).

Dexamphetamine lowered BMI *z*-score and had favourable effects on body composition in one study (38) and slowed weight gain in another study (40). A dual-pronged approach using metformin and micronized fenofibrate had favourable metabolic effects on glucose homeostasis and the lipid profile but did not affect BMI *z*-score (39). One of the RCTs in this field used sibutramine, and this appetite suppressant had no effect on BMI *z*-score in the subgroup of participants eligible for this review (37). In addition, sibutramine was recently withdrawn from the market owing to serious side effects of increased risk of stroke and myocardial infarction (61).

We also included another RCT that used octreotide to manage hypothalamic obesity. (34) This study included two survivors of leukaemia, and having contacted the authors, we could not obtain the brain tumour subgroup data to analyse them separately. This RCT demonstrated beneficial effects of octreotide on lowering insulin and stabilizing weight and BMI gain in paediatric hypothalamic obesity, although the results were not exclusive to SCBT.

In addition, a recent study on exenatide showed no significant weight loss in patients with hypothalamic obesity, but stabilization of weight gain (33). Exenatide may be a promising therapeutic option for hypothalamic obesity in SCBT, but it requires further validation especially if used in combination with additional modalities including lifestyle intervention.

Adverse events in all pharmacotherapy-based studies were reported to be mild and tolerable (33,34,37–40). However, these studies were of short duration, and may fail to detect long-term adverse events or benefits of these interventions. Therefore, it is still unclear whether anti-obesity agents will be well tolerated with long-term use in SCBT, which is an area for further research.

Bariatric surgery

The potential mechanisms by which bariatric surgery induces weight loss may involve the induction of satiety, gut–brain axis effects, reduction of gastric volume, changes in gastrointestinal hormones, the microbiome and reduced nutrient absorption (62–64). The efficacy of bariatric surgery also varies by procedure and tumour type, with gastric bypass having a greater effect in craniopharyngioma, but not in other brain tumour types (63).

The most common procedure used in SCBT is LAGB. Although LAGB has low mortality risk and few metabolic complications, it has the highest (>50%) long-term failure rate among bariatric procedures, and re-intervention is very common (65).

The small sample size and high risk of selection bias (41–43) preclude a definite conclusion on the utility of surgery in survivors as a therapeutic modality for obesity.

Strengths and limitations

One of the strengths of this review is the comprehensive search strategy, with inclusion of papers published in languages other than English. This allowed the inclusion of an eligible study published in German (36). Furthermore, the rigour of the search strategy was standardized through a three-step development process (24). An initial limited search in Medline was conducted, followed by examination of the index terms used to describe the articles. The search strategy was then finalized including all the identified keywords and index terms (24). Lastly, the reference lists of the relevant articles were examined, and publications from the first and last authors of the relevant articles were sought. Another strength of this review is the use of an inclusive search strategy of brain tumour survivors with and without craniopharyngioma, whereby hypothalamic obesity in the latter diagnosis is commonplace, and for which interventions are usually geared. This inclusive approach highlights the limited current evidence in managing non-hypothalamic obesity in SCBT. Finally, this review used the GRADE approach to assess the confidence in the findings, which provides a comprehensive interpretation of the overall quality of evidence.

Some of the limitations of this review include our inability to perform meta-analysis owing to lack of studies with low risk of bias and high levels of heterogeneity across studies. In addition, when we separated data for patients with brain tumours from other cancer types, the sample size was reduced substantially, and the results may be insignificant owing to insufficient study power to detect meaningful differences. Furthermore, almost all the studies included in this systematic review were uncontrolled studies with before-and-after comparisons. The lack of randomization and absence of control groups downgraded the quality of the evidence. In addition, most studies did not report long-term follow-up data. Therefore, the long-term outcomes of these interventions in survivors remain unclear.

Conclusions

This systematic review demonstrates that the interpretation of intervention effectiveness in SCBT is limited by small sample size, uncontrolled study design, absent long-term follow-up data, lack of randomization and the absence of control groups.

This highlights the limited evidence base to derive effective management strategies of hypothalamic obesity in SCBT, which has a direct impact on outcomes. The *a priori* design of RCT will allow sample size calculation to create studies that are sufficiently powered to measure meaningful differences in obesity management outcomes in SCBT.

In addition, as few centres will have sufficient power to conduct single centre studies, and creating multicentre

studies appears to be an appropriate recommendation. Recently, there has been considerable advocacy for the performance of well-designed trials on children (66,67). We believe that this is an opportunity to create collaborations to improve cardiometabolic outcomes in survivors. These interventions may include already available interventions, e.g. exenatide, and utilize novel or combined therapeutic strategies.

For many rare paediatric conditions (e.g. cancer and intensive care patients), multicentre RCT is the norm in creating high-quality evidence, and this approach is applicable to the study of interventions aimed at improving cardiometabolic outcomes in the brain tumour population.

Authors' contributions

M. C. S. is the guarantor. The research question was defined by M. C. S., K-W. W., A. F., S. K. S., S. B., R. J. d. S. and L. T. The search strategy and eligibility criteria were developed by K-W. W., R. C., L. B., M. V., R. J. d. S., D. L. J., S. M. Z., S. R. R., L. T. and M. C. S. Title, abstract and full-text screening was performed by K-W. W., R. C. and M. V. Data abstraction was completed by K-W. W., R. C. and M. V. Quality and risk of bias assessments were conducted by K-W. W. and R. C. Methodological and statistical support was provided by M. C. S., R. J. d. S. and L. T. K-W. W. and M. C. S. drafted the manuscript, and all authors reviewed, edited and approved the final version of the manuscript.

Conflict of interest statement

K-W. W. received student scholarships from Ontario Graduate Scholarship Program and Canadian Institutes of Health Research. M. C. S. received a grant from Pediatric Oncology Group of Ontario Research Unit.

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Supporting information

Additional Supporting Information may be found online in the supporting information tab for this article. http://dx.doi.org/10.1111/obr.12534

Table S1. References of the excluded articles at full-text screening.
Table S2. Evaluation of methodological quality of uncontrolled studies using the UAEPC checklist.
Table S3. Evaluation of methodological quality of cohort studies using ROBINS-I tool.
Table S4. Evaluation of methodological quality of RCTs using the Risk of Bias Assessment Tool from the Cochrane Collaboration.
Table S5. Overall quality of evidence using GRADE for weight-related outcomes.

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