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High Prevalence of Weight Gain in Childhood Brain Tumor Survivors and Its Association With Hypothalamic-Pituitary Dysfunction

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PURPOSE Childhood brain tumor survivors (CBTS) are at risk for developing obesity, which negatively influences cardiometabolic health. The prevalence of obesity in CBTS may have been overestimated in previous cohorts because of inclusion of children with craniopharyngioma. On the contrary, the degree of weight gain may have been underestimated because of exclusion of CBTS who experienced weight gain, but were neither overweight nor obese. Weight gain may be an indicator of underlying hypothalamic-pituitary (HP) dysfunction. We aimed to study prevalence of and risk factors for significant weight gain, overweight, or obesity, and its association with HP dysfunction in a national cohort of noncraniopharyngioma and nonpituitary CBTS.

METHODS Prevalence of and risk factors for significant weight gain (body mass index [BMI] change $\geq +2.0$ standard deviation score [SDS]), overweight, or obesity at follow-up, and its association with HP dysfunction were studied in a nationwide cohort of CBTS, diagnosed in a 10-year period (2002-2012), excluding all craniopharyngioma and pituitary tumors.

RESULTS Of 661 CBTS, with a median age at follow-up of 7.3 years, 33.1% had significant weight gain, overweight, or obesity. Of the CBTS between 4 and 20 years of age, 28.7% were overweight or obese, compared with 13.2% of the general population between 4 and 20 years of age. BMI SDS at diagnosis, diagnosis of low-grade glioma, diabetes insipidus, and central precocious puberty were associated with weight gain, overweight, or obesity. The prevalence of HP dysfunction was higher in overweight and obese CTBS compared with normal-weight CBTS.

CONCLUSION Overweight, obesity, and significant weight gain are prevalent in CBTS. An increase in BMI during follow-up may be a reflection of HP dysfunction, necessitating more intense endocrine surveillance.

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BACKGROUND

Obesity is a common late effect in childhood brain tumor survivors (CBTS), with reported prevalences up to 55%.¹ Obesity during childhood increases the risk for serious morbidity in adulthood, such as diabetes mellitus and cardiovascular disease.²⁻⁶ Not only obesity, but also significant weight gain may affect cardiovascular status in adulthood negatively.^{7,8}

Identifying overweight children early during follow-up may be of great importance for prevention of cardiovascular morbidity. Also, increasing body mass index (BMI) may be a sign of hypothalamic-pituitary dysfunction (HPD) during follow-up.⁹⁻¹¹ Identifying weight gain in CBTS may therefore aid in early diagnosis of HPD.¹² At the other end of the spectrum is underweight, which may be present in CBTS. Underweight survivors may be at risk for adverse health because a proper nutritional state is necessary for motor, cognitive, and social development.^{13,14}

Causes for weight gain in CBTS can be HPD, caused by the tumor or cranial irradiation. However, other

factors such as impaired mobility, visual impairment, disrupted sleep, medication, and poor adherence to dietary and physical activity guidelines are associated with increasing BMI during follow-up.¹⁵⁻²³

In many studies reporting on the prevalence of obesity in CBTS, patients with craniopharyngioma were included.^{15,17,24-26} It is well known that these children are at special risk for HPD, resulting in obesity.^{9,27} Inclusion of craniopharyngioma in CBTS cohorts may, therefore, greatly influence BMI outcome.

In patients with hypopituitarism who are not CBTS, the prevalence of obesity may be increased because of body fat accumulation caused by endocrine deficiencies.²⁸⁻³⁰ Patients with pituitary tumors may be at increased risk for obesity, and inclusion of such patients in a childhood brain tumor cohort might mask the prevalence of weight changes of other patients with brain tumor.

The prevalence and underlying pathophysiology of weight gain, overweight, and obesity in a

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

If craniopharyngioma and pituitary tumors were to be excluded from cohort analyses, are survivors of other childhood brain tumors (CBTS) at risk for weight gain, overweight, or obesity, and if so, what is the association with hypothalamic-pituitary dysfunction?

Knowledge Generated

Not only are the prevalence of overweight (20.3%) and obesity (8.5%) high in CBTS, but also significant ($\geq +2.0$ standard deviation score [SDS]) weight gain is frequent (11.6%). These changes in body mass index (BMI) during follow-up seem to be associated with hypothalamic-pituitary dysfunction. Higher BMI SDS at diagnosis, diabetes insipidus (DI) or central precocious puberty (CPP) during follow-up, and low-grade glioma were associated with overweight and obesity.

Relevance

CBTS with higher BMI SDS at diagnosis, DI or CPP during follow-up, and low-grade glioma may need more intense surveillance of changes in weight and hypothalamic-pituitary function during follow-up, aiming to decrease long-term cardiovascular morbidity.

noncraniopharyngioma and nonpituitary tumor CBTS cohort has been poorly studied. For these reasons, our aim was to study the prevalence of BMI changes in children treated for brain tumors, excluding pituitary tumors and craniopharyngioma. Furthermore, we aimed to study the association between changes in BMI and the prevalence of HPD in these survivors.

METHODS

Study Design and Population

The data in this study were derived from a previously reported nationwide retrospective cohort ($n = 718$).¹² Children, diagnosed with a brain tumor between 2002 and 2012, ≤ 18 years of age, and survival of > 2 years after diagnosis were included. Children with craniopharyngioma or a pituitary tumor (secreting or nonsecreting pituitary microadenomas and macroadenomas or Rathke's cleft cysts) were excluded. For this specific study, only CBTS with follow-up data on BMI at least 6 months after diagnosis were included ($n = 661$). In total, 57 CBTS were excluded because of lack of BMI follow-up data ($n = 49$) or BMI follow-up data only being available within 6 months after diagnosis ($n = 8$).

Data Collection

Tumor- and treatment-related characteristics, available follow-up data of anthropometric measurements, and endocrine variables were retrospectively collected through collaboration with seven academic centers in the Netherlands.

Definitions

Weight gain. Significant weight gain was defined as an increase in BMI $\geq +2.0$ standard deviation score (SDS) from diagnosis to most recent moment of follow-up. Significant weight gain was separately assessed in children

with and without underweight at diagnosis, because of the fact that weight gain in these children may have been intended and caused by extra nutritional supplements or nasogastric tube feeding.

Underweight, overweight, and obesity. Underweight, overweight, and obesity in infant CBTS (0-2 years of age) were defined according to the international cutoff points of the WHO using BMI < -2.0 SDS, BMI > 2.0 SDS, and BMI > 3.0 , respectively.³¹

Underweight, overweight, and obesity for CBTS ≥ 2 years of age were defined according to the international cutoff points of Cole et al, using BMI thinness grade 2 (equal to a z-score of -2), and the international cutoff points of BMI by sex and age for overweight and obesity.^{32,33}

Hydrocephalus. Hydrocephalus at diagnosis was defined as being reported as such in the radiologic report of the MRI.

Endocrine disorders. Any endocrine disorder was defined as any disorder of the hypothalamic-pituitary system, including growth hormone deficiency (GHD), thyroid-stimulating hormone deficiency, adrenocorticotrophic hormone deficiency, gonadotropin-releasing hormone deficiency, diabetes insipidus (DI), central precocious puberty (CPP), and disorders of the thyroid or gonads. Any pituitary disorder was defined as any anterior pituitary disorder, DI, or CPP. The diagnostic criteria are attached in Data Supplement, online only.

Statistical Analyses

Data are presented as mean \pm SD or median [IQR] for continuous data, depending on the distribution. Data are presented as percentages for categorical variables. Between-group differences were evaluated by Student's *t* test for continuous data with a normal distribution, Mann-Whitney *U* test for continuous data with a skewed

distribution, and χ^2 test or Fisher's exact test for categorical data. To assess violation of normality distribution, QQ plot of the residuals and the Shapiro-Wilk's test were used. Between-group differences of underweight, normal-weight, overweight, and obese CBTS were evaluated by one-way analysis of variance for continuous data with a normal distribution, Kruskal-Wallis test for continuous data with a skewed distribution (skew variables were not further transformed), and χ^2 test or Fisher's exact test for categorical data. Multivariable logistic regression analysis (if needed, with Firth's bias reduction method^{34,35}) was used to estimate odds ratios (ORs) and 95% CIs for demographic and tumor- and treatment-related risk factors, as well as the occurrence of an adverse hypothalamic-pituitary outcome and specific endocrine disorders. Independent variables to be included in the multivariable logistic regression were selected by estimating the univariate model and by considering the clinical relevance of each variable. Therefore, in the final regression model, not only variables that were significant in the univariate analysis were included, but also factors that were clinically relevant. The logistic regression analyses were estimated by maximum likelihood. For additional analyses, CIs for regression coefficients are computed by penalized profile likelihood. Hypothesis tests, *P*-values, and CIs are presented as two-sided. No adjustments were made for multiplicity of testing. *P* < .05 was considered statistically significant. Analyses were performed by using SPSS version 25.0. Additional analysis to estimate the logistic regression model with Firth correction was performed in R software environment with the package `logistf`.³⁵⁻³⁷

Ethics

Because of the retrospective nature of the study, the local institutional review board decided that the Act on Medical Research Involving Human Subjects did not apply and provided a waiver.

RESULTS

Data upon BMI at follow-up were available for 661 CBTS (Fig 1). Mean follow-up time was 7.3 ± 3.2 years (Table 1). For 634 CBTS, data on BMI at diagnosis were available (Fig 2).

Weight Gain

CBTS without underweight at diagnosis (n = 602). Of 602 CBTS without underweight at diagnosis, 70 (11.6%) developed significant weight gain ($\geq +2.0$ BMI SDS) during follow-up. Significant weight gain was associated with lower BMI SDS at diagnosis (*v* higher BMI SDS) (OR, 0.51; 95% CI, 0.40 to 0.66), longer follow-up time (*v* shorter follow-up time) (OR, 1.12; 95% CI, 1.02 to 1.22), and CPP during follow-up (*v* absence of CPP) (OR, 4.06; 95% CI, 1.58 to 10.42) (Table 2).

Of the 634 CBTS with data on BMI at diagnosis and follow-up, 104 CBTS (without underweight at diagnosis) had \geq

+1.5 SDS weight gain (prevalence 16.4%) and 174 CBTS (without underweight at diagnosis) had $\geq +1.0$ SDS weight gain (prevalence 27.4%).

CBTS being underweight at diagnosis. Of 32 CBTS being underweight at diagnosis, 22 (68.8%) showed significant weight gain. After a median period of 8.4 ± 3.7 years, one (3.1%) remained underweight, 12 (37.5%) were normal weight, seven (21.9%) overweight, and two (6.3%) progressed to obesity.

Of the CBTS being underweight at diagnosis with progression to overweight or obesity at follow-up (n = 9), seven (77.8%) had low-grade glioma, one (11.1%) medulloblastoma, and one (11.1%) a germ cell tumor. In five patients, the tumor was localized in the suprasellar region. In six of the nine (66.7%) CBTS being underweight and progressing into overweight or obesity at follow-up, an anterior pituitary deficiency was diagnosed compared with 39.1% of the underweight CBTS without progression to overweight or obesity. Seven (77.8%) of the nine CBTS developed DI and/or CPP, compared with two of the 23 (8.7%) other underweight CBTS.

Overweight and Obesity at Follow-Up

Of the 661 CBTS, 190 (28.7%) were classified as overweight (n = 134, 20.3%) or obese (n = 56, 8.5%) at most recent follow-up, with a mean BMI SDS of 2.6 ± 1.0 , after a mean follow-up time of 7.8 ± 3.3 years. Of the obese CBTS (n = 56), mean BMI SDS was 3.5 ± 1.1 , after a mean follow-up time of 7.9 ± 3.6 years.

Of the 578 CBTS, between 4 and 20 years of age at follow-up, 20.3% classified as overweight and 8.5% as obese compared with 10.5% and 2.7%, respectively, in the general Dutch population between 4 and 20 years of age. Of the 78 CBTS, between 20 and 30 years of age, 21.8% was found overweight and 7.7% obese, compared with reported prevalence of BMI by questionnaire in the general Dutch population between 20 and 30 years of age of 20.8% and 5.9%, respectively.³⁸

Higher BMI SDS at diagnosis (*v* lower BMI SDS) (OR, 2.00; 95% CI, 1.70 to 2.34), low-grade glioma (LGG) (*v* other brain tumors) (OR, 1.68; 95% CI, 1.05 to 2.67), presence of DI during follow-up (*v* absence of DI) (OR, 6.41; 95% CI, 1.35 to 30.41), and CPP during follow-up (*v* absence of CPP) (OR, 3.12; 95% CI, 1.38 to 7.04) were associated with overweight or obesity at follow-up (Table 3). Of the CBTS with LGG and overweight or obesity, the glioma of 26.5% was located suprasellar and 35.3% supratentorial, compared with 12.9% and 31.8% of the normal-weight LGG-CBTS, respectively (*P* = .003). Within the suprasellar and supratentorial LGG, pituitary disorders were significantly more prevalent in the overweight and obese survivors (33.3% *v* 14.4%, *P* = .005), CPP (25.4% *v* 10.3%, *P* = .011), or DI (9.5% *v* 1.0%, *P* = .010).

Obesity at follow-up was associated with higher BMI SDS at diagnosis (*v* lower BMI SDS) (OR, 1.94; 95% CI, 1.57 to

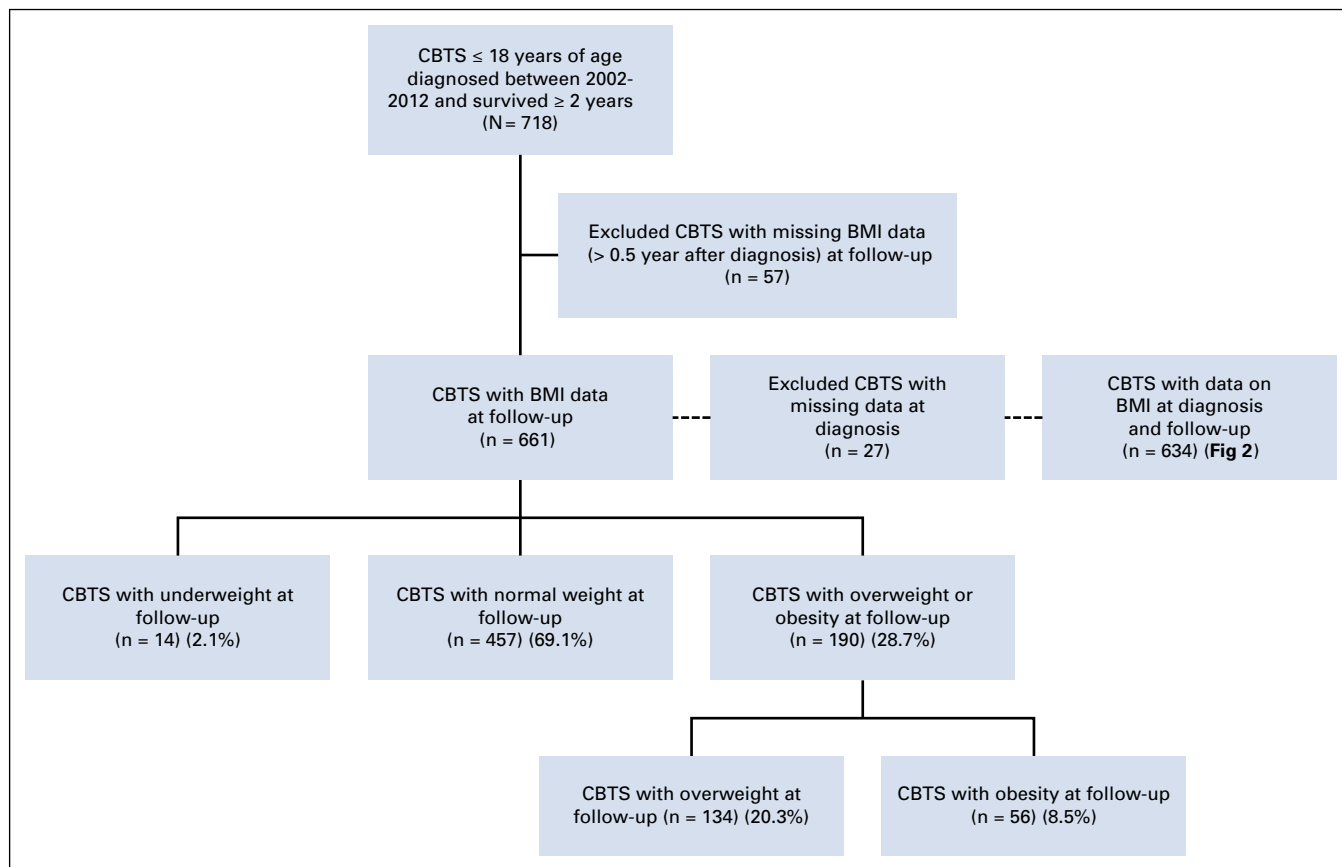


FIG 1. Patient inclusion of childhood brain tumor survivors for analyses of BMI at follow-up. BMI, body mass index; CBTS, childhood brain tumor survivors.

2.45), metastases at diagnosis (*v* absence of metastases) (OR, 3.00; 95% CI, 1.00 to 8.12), and the presence of DI during follow-up (*v* absence of DI) (OR, 6.81; 95% CI, 2.00 to 22.14).

Underweight at Follow-Up

Fourteen (2.1%) CBTS were underweight at follow-up, with a mean BMI-SDS of -2.3 ± 1.0 . None had a tumor in the suprasellar region, and six developed GHD. Underweight CBTS received chemotherapy and/or radiotherapy more frequently when compared with the normal-weight, overweight, or obese CBTS (chemotherapy: 71.4% *v* 33.9%, 40.3%, and 41.4%, respectively [$P = .019$] and radiotherapy: 92.9% *v* 35.9%, 38.1%, and 46.4%, respectively [$P < .001$]).

Hypothalamic-Pituitary Disorders at Follow-Up

Of the 661 CBTS, 151 (22.8%) had one or more HP disorders at follow-up. Of them, 75 (11.3%) was diagnosed with one, 35 (5.3%) with two, 17 (2.6%) with three, 13 (2.0%) with four, and 11 (1.7%) with five HP disorders.

In 491 (74.3%) of the 661 CBTS, endocrine testing after oncologic treatment was performed. Of the 170 CBTS (25.7% of $n = 661$), in whom no endocrine testing was performed, 149 CBTS (87.6%) were defined as low risk for the development of endocrine disorders (no suprasellar

tumor, no neurosurgery in the [supra]sellar region, and no radiotherapy). Of the 491 CBTS with endocrine testing, 151 CBTS (30.8%) were diagnosed with one or more HP disorders at follow-up.

The mean time of onset of diagnosis of the first pituitary disorder was 3.0 ± 2.0 years after brain tumor diagnosis. Of the CBTS with a normal BMI, overweight, or obesity, 14.7%, 24.6%, and 23.2%, respectively, were diagnosed with an anterior pituitary disorder. Diagnosis of DI was made in 1.5% of normal-weight CBTS, in 5.2% of the overweight, and in 10.7% of the obese CBTS. CPP occurred in 4.6%, 18.7%, and 10.7%, respectively (Fig 3). A significant difference in prevalence of HP disorders between the normal-weight versus the overweight or obese CBTS was found for all pituitary deficiencies, except for GHD (Fig 3).

DISCUSSION

The results of this unique heterogeneous nationwide cohort of CBTS with long follow-up time demonstrate that not only the prevalence of overweight and obesity is high when compared with the general population, especially 4-20 years of age, but also weight gain occurs frequently. In our cohort, 33.1% CBTS developed overweight, obesity, or significant weight gain during follow-up. Because of the

TABLE 1. Patient Characteristics of Underweight, Normal-Weight, Overweight, and Obese CBTS at Follow-Up

Weight at Most Recent Follow-Up Patient Characteristics	Total (N = 661) 100%	UW (n = 14) 2.1%	NW (n = 457) 6.9%	OW (n = 134) 20.3%	O (n = 56) 8.5%	P
Sex (female/male)	305/356 (46.1/53.9)	7/7 (50.0/50.0)	203/254 (44.4/55.6)	68/66 (50.7/49.3)	27/29 (48.2/51.8)	.600
Median age at diagnosis, years	7.4 [4.2-11.2]	10.7 [6.7-14.5]	7.3 [4.1-11.2]	8.0 [4.2-11.4]	8.2 [4.2-11.0]	.164
Mean age at follow-up, years	15.1 ± 4.4	17.7 ± 3.1	14.9 ± 4.4	15.6 ± 4.5	15.8 ± 4.6	.047 ^c
Mean follow-up time	7.3 ± 3.1	7.2 ± 3.9	7.2 ± 3.1	7.7 ± 3.2	7.9 ± 3.6	.150
Tumor histology at primary diagnosis						.011 ^c
LGG	319 (48.3)	2 (14.3)	215 (47.0)	73 (54.5)	29 (51.8)	
DNET	13 (2.0)	0 (0.0)	12 (2.6)	1 (0.7)	0 (0.0)	
High-grade glioma	18 (2.7)	1 (7.1)	12 (2.6)	4 (3.0)	1 (1.8)	
Medulloblastoma	96 (14.5)	7 (50.0)	68 (14.9)	15 (11.2)	6 (10.7)	
SET	13 (2.0)	1 (7.1)	8 (1.8)	2 (1.5)	2 (3.6)	
Ependymoma	48 (7.3)	1 (7.1)	36 (7.9)	7 (5.2)	4 (7.1)	
Choroid plexus tumors	16 (2.4)	0 (0.0)	14 (3.1)	1 (0.7)	1 (1.8)	
Germ cell tumor	26 (3.9)	0 (0.0)	12 (2.6)	8 (6.0)	6 (10.7)	
ATRT	7 (1.1)	1 (7.1)	3 (0.7)	2 (1.5)	1 (1.8)	
Other ^a	21 (3.2)	0 (0.0)	18 (3.9)	3 (2.2)	0 (0.0)	
No histology	84 (12.7)	1 (7.1)	59 (12.9)	18 (13.4)	6 (10.7)	
Tumor location						.002 ^c
Infratentorial	307 (46.4)	11 (78.6)	225 (49.2)	53 (39.6)	18 (32.1)	
Supratentorial	243 (36.8)	3 (21.4)	167 (36.5)	47 (35.1)	26 (46.4)	
Suprasellar	111 (16.8)	0 (0.0)	65 (14.2)	34 (25.4)	12 (21.4)	
Tumor treatment						
Surgery	578 (87.4)	13 (92.9)	399 (87.3)	116 (86.6)	50 (89.3)	.885
Chemotherapy	242 (36.6)	10 (71.4)	155 (33.9)	54 (40.3)	23 (41.1)	.019 ^c
Radiotherapy	254 (38.4)	13 (92.9)	164 (35.9)	51 (38.1)	26 (46.4)	< .001 ^c
Median dosage (Gy)	54.0 [54.0-55.8]	54.0 [54.0-55.4]	54.0 [54.0-55.8]	54.0 [50.4-55.8]	54.0 [54.0-55.8]	.760
Radiotherapy > 50 Gy	220 (33.3)	12 (85.7)	144 (31.5)	43 (32.1)	21 (37.5)	< .001 ^c
Hydrocephalus at diagnosis ^b	374 (56.6)	10 (71.4)	261 (57.1)	72 (53.7)	31 (55.4)	.354
Metastases at diagnosis	39 (5.9)	1 (7.1)	23 (5.0)	8 (6.0)	7 (12.5)	.168
Mean BMI SDS at diagnosis	0.26 ± 1.4	-1.1 ± 1.5	-0.0 ± 1.2	0.9 ± 1.5	1.4 ± 1.9	< .001 ^c
Mean BMI SDS at follow-up	0.80 ± 1.5	-2.3 ± 1.0	0.2 ± 0.9	2.2 ± 0.5	3.5 ± 1.1	< .001 ^c

NOTE. Numbers are displayed as n (%), mean ± SDS or median [IQR]. Between-group differences were evaluated by one-way ANOVA for continuous data with a normal distribution, Kruskal-Wallis test for continuous data with a skewed distribution, and χ^2 test or Fisher's exact test for categorical data.

Abbreviations: ANOVA, analysis of variance; ATRT, atypical teratoid rhabdoid tumor; BMI, body mass index; CBTS, childhood brain tumor survivors; CT, chemotherapy; DNET, dysembryoplastic neuroepithelial tumor; LGG, low-grade glioma; NW, normal weight; O, obesity; OW, overweight; RT, radiotherapy; SDS, standard deviation score; SET, supratentorial embryonal tumor; UW, underweight.

^aMeningioma, pineoblastoma (not treated with chemotherapy or radiotherapy), schwannoma, and desmoplastic small-round cell tumor.

^bHydrocephalus defined as increased width of ventricles on MRI.

^cStatistically significant.

exclusion of craniopharyngioma and pituitary tumors, the effects on BMI in the general CBTS group is better reflected than in previous studies. By using a cutoff point for weight gain of BMI $\geq +2.0$ SDS, our results may even underestimate the prevalence of weight gain, and it is important for oncologists and endocrinologists to be aware of these

metabolic changes during follow-up. The changes in BMI appear to be associated with HPD, suggesting that increasing BMI may be an indicator of underlying HPD. Weight changes in time may have a major impact on the cardiovascular health of the cancer survivors. The results of this study may be used to develop new follow-up programs

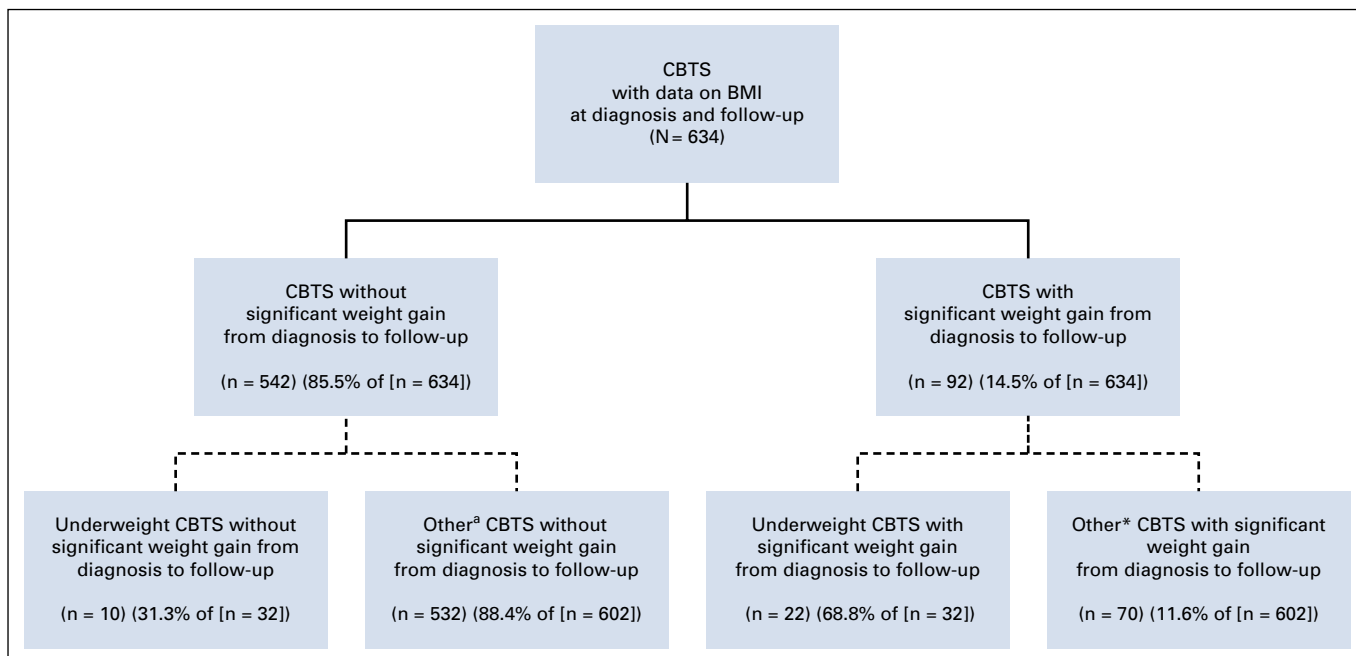


FIG 2. Weight gain in CBTS. For this analysis, only CBTS of whom BMI at diagnosis and follow-up was available were included ($n = 634$). In 14.5% of CBTS, significant weight gain was found. In children with underweight at diagnosis, a high percentage of significant weight gain was seen (68.8%).^aCBTS with normal, overweight, or obesity at diagnosis. BMI, body mass index; CBTS, childhood brain tumor survivors.

aiming to counsel and aid survivors with weight gain and increase surveillance for HPD in those survivors at risk.

The association of DI and CPP with weight gain, overweight, and obesity suggests an HP origin for the increase in weight. The significant increase in the prevalence of HP disorders (except for GHD) found between the normal-weight versus the overweight or obese CBTS confirms this positive association. The fact that GHD was not more prevalent in the overweight and obese may be explained by the fact that 88% of the 96 CBTS with GHD at follow-up

received growth hormone supplementation. Therefore, a possible effect of weight gain because of GHD may have been minimized by GH treatment.

In contrast to our expectations, suprasellar tumor location could not be associated with overweight or obesity in our cohort.^{15,39-42} Children with LGG were found to be at increased risk for overweight or obesity. After performing a subanalysis in children with LGG only, significantly more suprasellar and supratentorial located gliomas were found in the overweight and obese group. Also, as expected, the

TABLE 2. Risk Factors for Weight Gain in CBTS

Variable	OR	95% CI		P
		Lower	Upper	
BMI SDS at diagnosis	0.52	0.40	0.66	< .001 ^b
Follow-up time (years)	1.12	1.02	1.22	.016 ^b
Hydrocephalus at diagnosis	1.72	0.92	3.22	.093
Suprasellar v others ^a	1.08	0.46	2.57	.855
Chemotherapy	1.20	0.65	2.21	.555
Radiotherapy dosage above 50 Gy	0.77	0.41	1.4	.411
CPP during follow-up	3.86	1.50	9.94	.005 ^b

NOTE. Multivariable logistic regression for risk factors of CBTS with significant weight gain (increase of BMI $\geq +2$ SDS) from diagnosis to follow-up ($n = 70$) compared with CBTS without significant weight gain from diagnosis to follow-up ($n = 532$). CBTS with underweight at diagnosis were excluded.

Abbreviations: BMI, body mass index; CBTS, childhood brain tumor survivors; CPP, central precocious puberty; OR, odds ratio; SDS, standard deviation score.

^aSuprasellar brain tumors v other brain tumors.

^bStatistically significant.

TABLE 3. Risk Factors to Develop Overweight or Obesity in CBTS

Variable	OR	95% CI		P
		Lower	Upper	
BMI SDS at diagnosis	2.00	1.70	2.34	< .001 ^c
Follow-up time, years	1.05	0.98	1.16	.187
Suprasellar v others ^a	1.08	0.58	1.99	.811
LGG v others ^b	1.68	1.05	2.67	.029 ^c
Hydrocephalus at diagnosis	1.05	0.69	1.61	.813
Chemotherapy	1.34	0.80	2.26	.266
Radiotherapy dosage above 50 Gy	1.15	0.68	1.93	.601
Endocrine disorder before treatment	1.03	0.25	4.26	.973
Anterior pituitary deficiency	1.49	0.78	2.83	.229
DI during follow-up	6.41	1.35	30.41	.019 ^c
CPP during follow-up	3.12	1.38	7.04	.006 ^c

NOTE. Multivariable logistic regression for risk factors of CBTS with overweight or obesity at follow-up (n = 190) compared with CBTS without overweight or obesity at follow-up (n = 471).

Abbreviations: BMI, body mass index; CBTS, childhood brain tumor survivors; CPP, central precocious puberty; DI, diabetes insipidus; LGG, low-grade glioma; OR, odds ratio; SDS, standard deviation score.

^aSuprasellar brain tumors v other brain tumors.

^bLGG v other brain tumors (high-grade glioma, medulloblastoma, ependymoma, choroid plexus tumors, germ cell tumor, atypical teratoid rhabdoid tumor, dysembryoplastic neuroepithelial tumor, supratentorial embryonal tumor, meningioma, pineoblastoma [not treated with chemotherapy or radiotherapy], schwannoma and desmoplastic small-round cell tumor and tumors without histology).

^cStatistically significant.

prevalence of HPD was significantly more frequent in the overweight and obese survivors with LGG located in the suprasellar or supratentorial region.

We could not associate weight gain to radiation dose in our cohort in contrast to other studies,¹⁵ perhaps because of the inclusion of the overall cranial radiation doses. Future studies should include more exact dosimetry.

BMI at diagnosis was found to be significantly correlated with overweight or obesity, which confirms previous results and may point toward a genetic or environmental origin of weight gain.^{17,25} It must also be considered that BMI at diagnosis in children with a brain tumor can be a reflection of HP damage already present at diagnosis. Future studies should correlate BMI of CBTS with BMI data of siblings and their parents.

When compared to the general population, percentages for overweight and obesity in CBTS, 4-20 years of age, were significantly increased compared with the general Dutch population. The percentage of overweight of CBTS between 20-30 years of age, however, did not differ from the general population (21.8% v 20.8%), but the percentage of obesity did (7.7% v 5.8%). We hypothesize that the lack of difference for overweight in this age group and the smaller difference for obesity may be caused by the relative low numbers of CBTS > 20 years of age in our cohort. The prevalence of underweight at follow-up (2.1%) was not increased compared with the general Dutch population,

with a reported prevalence of 5.3% in children (4-20 years of age) and 4.1% in adults (20-30 years of age).³⁸ Underweight thus seems to be less of a problem in CBTS.

A high percentage of children with underweight at diagnosis (5.0% of the total cohort) developed significant weight gain (68.0%), overweight (21.9%), or obesity (6.3%) at follow-up. Some of these children will have had high caloric feeding. Future studies should look into the most optimal diet for such children. This increase in weight may, however, also be a consequence of hypothalamic dysfunction, as most of them had been diagnosed with a suprasellar LGG and were known with pituitary deficiencies. The phenomenon of (extreme) underweight in children diagnosed with a tumor located in the hypothalamic-optic chiasmatic region is known as the diencephalic syndrome, which is an uncommon cause of failure to thrive in early childhood. The development of obesity in children who presented with underweight at diagnosis in combination with the occurrence of endocrine disorders may thus be seen as a reflection of damage in different hypothalamic areas.^{43,44}

This study has several limitations. The data for these analyses came from a retrospective chart evaluation collected in different academic hospitals. At the time of data collection, there was no standardized national protocol for surveillance of BMI and HP function in CBTS. Laboratory investigations and measurement of BMI may only have been done in the most affected children, possibly resulting in an underestimation of the prevalence of endocrine

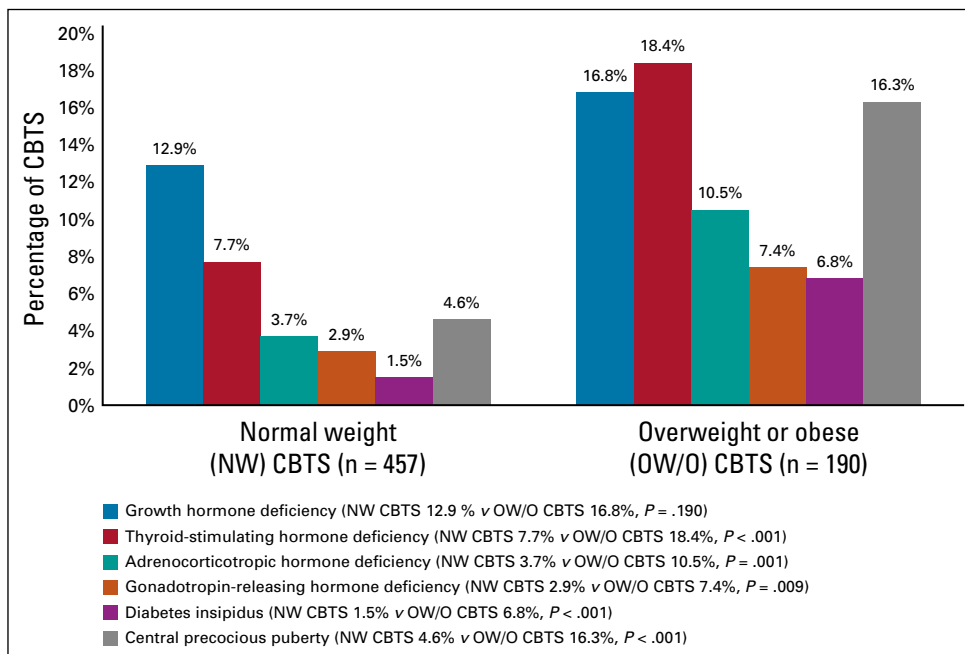


FIG 3. Prevalence of hypothalamic-pituitary disorders in CBTS with normal weight, overweight, or obesity at follow-up. Endocrine disorders: GHD, TSHD, ACTHD, GnRHD, DI, and CPP. *Percentage of CBTS with GHD, TSHD, ACTHD, GnRHD, DI, or CPP in normal-weight CBTS (n = 457) v overweight or obese CBTS (n = 190) (χ^2 test). ACTHD, adrenocorticotropic hormone deficiency; CBRS, childhood brain tumor survivors; CPP, central precocious puberty; DI, diabetes insipidus; GnRHD, gonadotropin-releasing hormone deficiency; GHD, growth hormone deficiency; TSHD, thyroid-stimulating hormone deficiency.

disorders and BMI changes at follow-up. To overcome these limitations, future prospective studies should include systemic endocrine testing and BMI measurements in all CBTS. Second, our main outcome was BMI, which is calculated by weight and height. BMI does not differentiate between the amount of fat mass, fat-free mass, and muscle mass. New research, taking bioimpedance measurement data into account, may be more specific to classify CBTS being at risk for cardiometabolic morbidity.

In conclusion, this retrospective analysis of a nationwide cohort of noncraniopharyngioma and nonpituitary tumor CBTS shows a high prevalence of significant weight gain, overweight, and obesity during follow-up. Changes in BMI may reflect HPD. Physicians should be aware of the fact that CBTS with underweight at diagnosis, DI, or CPP during follow-up are at risk for weight gain resulting in obesity. These CBTS should receive endocrine surveillance and early support regarding weight control as they are at serious risk for adverse metabolic health.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

High Prevalence of Weight Gain in Childhood Brain Tumor Survivors and Its Association With Hypothalamic-Pituitary Dysfunction

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