

Body Composition and Nuchal Skinfold Thickness in Pediatric Brain Tumor Patients

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Abstract

Background: Obesity, cardiovascular disease (CVD), and relapse/progression have impact on prognosis in pediatric brain tumor (BT) patients.

Methods: In a cross-sectional study, we analyzed nuchal skinfold thickness (NST) on MRI follow-up monitoring as a parameter for body composition (BC) and CVD in 177 BT patients (40 WHO grade 1–2 BT; 31 grade 3–4 BT; 106 craniopharyngioma (CP)), and 53 healthy controls (HC). Furthermore, BMI, waist-to-height ratio (WHtR), caliper-measured skinfold thickness (cSFT), and blood-pressure (BP) were analysed.

Results: CP patients showed higher BMI, WHtR, NST and cSFT when compared with BT and HC. WHO grade 1–2 BT patients were observed with higher BMI, waist circumference and triceps cSFT when compared to WHO grade 3–4 BT patients. NST correlated with BMI, WHtR, and cSFT. NST, BMI and WHtR had predictive value for CVD in terms of increased BP. In multivariate analysis, only BMI was selected for the final model resulting in an odds ratio of 1.25 (1.14–1.379). In CP patients with hypothalamic involvement/lesion or gross-total resection, rate and degree of obesity were increased.

Conclusions: NST could serve as a novel useful parameter for assessment of BC and CVD risk in BT patients.

1. Introduction

Recent reports suggest that survivors of pediatric brain tumors are at increased risk of cardiovascular disease^{1–4}. As obesity is a well-known risk factor for the development of cardiovascular disease in the general population, this might provide a potential explanation of the added cardiometabolic risk in survivors of pediatric brain tumors⁵. However, when obesity rates are analyzed based on body mass index (BMI), pediatric brain tumor patients are observed to have body mass index levels similar to the general population, which is not likely to explain the observed increased risk of cardiovascular disease in pediatric brain tumor survivors^{6,7}.

Childhood-onset craniopharyngiomas are rare malformations of embryonal origin with low-grade histological malignancy (WHO grade 1) located in the sellar/parasellar area and frequently affecting hypothalamus, pituitary gland and optic chiasm^{8–10}. Tumor- and/or treatment-related damage to these anatomical areas result in reduced physical and psychosocial function¹¹, which includes clinically severe neuroendocrine adverse effects, mainly hypothalamic obesity, with adverse influence on quality of survival after craniopharyngioma^{8,12–14}. When compared with the general population, craniopharyngioma patients have a 3–19 fold higher cardiovascular mortality¹⁵. In patients initially presenting with hypothalamic involvement of craniopharyngioma, the 20-years overall survival is reduced¹¹. Regular monitoring by cranial MRI to exclude recurrences and assessment of body composition are important parts of follow-up care¹⁶.

As an important link between cardiovascular disease and obesity, regional distribution of fat in distinct compartments rather than overall obesity has been postulated. In contrast to subcutaneous adipose tissue, visceral adipose tissue is known as a fat depot, conferring metabolic risk of type 2 diabetes and atherosclerosis above and beyond standard auxiological parameters, such as waist circumference and body mass index¹⁷⁻¹⁹. Upper-body subcutaneous fat, as estimated by neck circumference, may confer risk above and beyond visceral abdominal fat. Serum concentrations of free fatty acid are mainly determined by the upper-body subcutaneous fat compartment, indicating that this compartment plays an important role as specific risk factor for cardiovascular disease²⁰. We could previously show that nuchal skinfold thickness (NST) – as assessed in MRI of craniopharyngioma patients – serves as a predictor of metabolic risk above and beyond waist circumference and body mass index in craniopharyngioma patients²¹⁻²⁵.

In the present study, we analyzed NST as a new parameter for assessment of body composition and cardiovascular disease risk in long-term survivors of pediatric brain tumors.

2. Materials And Methods

2.1. Patients

In our single-center, cross-sectional study (University Children's Hospital, Klinikum Oldenburg AöR, Germany), 177 pediatric brain tumor patients (106 craniopharyngiomas, 40 WHO grade 1–2 brain tumors; 31 WHO grade 3–4 brain tumors), recruited and longitudinally evaluated in prospective multicenter trials of the German Pediatric Brain Tumor Network (SIOP low grade glioma study –LGG, SIOP high grade glioma study – HGG; SIOP germ cell tumor study – GCT; SIOP primitive neuroectodermal study – PNET; SIOP choroid plexus tumors study – CPT Registry; KRANIOPHARYNGEOM 2000/2007) were analyzed for body height, body weight, body mass index standard deviation score (SDS), and NST after a median follow-up of 2.4 years (range: 0.1–29.6 years)²⁶. Histological diagnoses of brain tumors were confirmed by neuropathological reference-assessment in all cases. Hypothalamic involvement and hypothalamic surgical lesions of craniopharyngioma were graded based on pre and postoperative MRI as previously described^{27,28}. The control group consisted of 53 pediatric patients with normal MRI findings. In healthy controls, cranial MRIs were performed in order to exclude intracranial pathologies underlying headaches.

In 53 of 106 craniopharyngioma patients (50%), 59 of 71 brain tumor patients (83%) and 42 of 53 healthy controls (79%), associations between NST and body mass index, waist-to-height ratio, caliper-measured skinfold thickness (biceps, triceps, abdominal, subscapular), and blood pressure as risk factors for cardiovascular disease could be analyzed based on complete data for all parameters.

2.2. Assessment of anthropometric parameters

NST was quantified on T1-weighted cranial MRI images of the midline performed on 1.5 T MRI scanners according to a standardized procedure. First, a line was drawn crossing the two anatomically defined points: basion (anterior margin of the foramen magnum) and opisthion (posterior margin of the foramen

magnum). The diameter of subcutaneous nuchal fat was measured over this line to the nearest 0.01 cm using OsiriX® (Pixmeo SARL, Switzerland). Arithmetic mean of NST as measured in triplicate by three independent persons was analyzed (Fig. 1).

Measurements of skinfold thickness at defined abdominal, subscapular, biceps and triceps areas were performed by the same person on the right side of the body using a Harpenden caliper and recorded to the nearest 0.1 cm. Waist circumferences were measured at the end of gentle expiration midway between the top of the iliac crest and the lowest rib. Waist circumference was measured over naked skin and noted to the nearest 0.1 cm. Body height was measured in triplicate using a Harpenden stadiometer and the median of three measurements was calculated as height SDS according to the Prader *et al.* references³⁰. Patients and healthy controls wearing underwear only were weighed on calibrated electronic step-scales. Body composition and the degree of obesity were evaluated by calculating the body mass index SDS according to the references of Rolland-Cachera *et al.*²⁹. Systolic and diastolic blood pressure (mm Hg) were measured in seated position after resting for 15 minutes using an automatic sphygmomanometer.

2.3. Statistical analyses

Statistical analyses were performed with SPSS 23® for Windows (IBM Corporation, Somers, NY, USA). Groups were compared using Student's t-test for normally distributed data, the Mann-Whitney U-test for non-normal data and Fisher's exact tests for categorical variables. The normality assumption was verified graphically. Correlation was calculated with the Pearson correlation coefficient and corresponding 95% confidence intervals (CI). Univariate and multivariate logistic regression were applied. A stepwise selection process was used, keeping only variables with $p \leq 0.05$ in the final model. Results of logistic regression are presented as odds ratio (OD) and corresponding 95%CI. All inferential statistics are intended to be exploratory (hypotheses generating), not confirmatory, and are interpreted accordingly. Therefore, no adjustment for multiple testing was applied.

2.4. Ethics approval

All procedures performed in our study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The studies KRANIOPHARYNGEOM 2000 (Clinical trial registration number: NCT00258453) and KRANIOPHARYNGEOM 2007 (Clinical trial registration number: NCT01272622) were approved by the local standing-committee on ethical practice of the Medizinische Fakultät, Julius-Maximilians-Universität Würzburg, Germany (140/99; 94/06, respectively). The current trial was approved by the local ethical committee of the Carl von Ossietzky University Oldenburg, Germany (14. January 2016; 005/2016). Written informed parental (legal guardian) and/or patient consent was obtained in all cases.

3. Results

3.1. Characteristics of patient cohorts and healthy controls

One hundred and six (60 female / 46 male) of 698 childhood-onset craniopharyngioma patients (344 female / 354 male) recruited in the German Childhood-onset Craniopharyngioma Registry with longitudinal follow-up in the prospective trials KRANIOPHARYNGEOM 2000 and KRANIOPHARYNGEOM 2007 were included in our study. 592 craniopharyngioma patients were excluded because one or more of the following inclusion criteria were not fulfilled: sagittal MRI of sufficient technical quality for assessment of NST, and height and weight measured within three months before or after MRI. Forty patients with brain tumor of different histology and reference-confirmed WHO grade 1 or 2 malignancy (26 low-grade glioma, 7 pituitary adenomas, 7 other histologies) and 31 patients with reference-confirmed WHO grade 3 or 4 malignancies (9 supratentorial tumors, 22 infratentorial tumors) including: 2 astrocytoma, 3 germinoma, 2 glioblastoma, 1 plexuscarcinoma, 10 medulloblastoma, 9 ependymoma, 3 diffuse intrinsic pontine glioma, 1 primitive neuroectodermal tumor (PNET) of the meninges were also included in our study. Fifty-three children and adolescents (30 female / 23 male) with normal cranial MRI findings, who fulfilled the above-mentioned inclusion criteria, served as healthy controls.

3.2. Auxiological parameters compared between patient cohorts and healthy controls

Childhood-onset craniopharyngioma patients were older at the time of study and presented with higher body mass index SDS, NST, waist circumference, waist-to-height ratio, and caliper-measured skinfold thickness at the time of study when compared with healthy controls and brain tumor patients. Patients with a brain tumor of WHO grade 1–2 presented with higher body mass index SDS, NST, waist circumference and caliper-measured skinfold thickness triceps at the time of the study when compared with WHO grade 3–4 brain tumor patients (Table 1, 2).

Table 1

Characteristics of the groups of patients (106 childhood-onset craniopharyngioma, 71 childhood brain tumor patients) and 53 healthy controls and the subgroups of patients (53 craniopharyngioma, 59 brain tumor patients) and 42 healthy controls, who could be analyzed for further parameters of body composition (waist circumference, waist-to-height ratio, caliper-measured skinfold thickness) and blood pressure (systolic and diastolic). BMI, body mass index, BT, brain tumor; RR, blood pressure; mm HG, millimeter mercury; SDS, standard deviation score; at study means "at the time of cranial MRI".

Patients characteristics	Craniopharyngioma	Brain tumor	Normal controls	p
Total group (n)	106	71	53	
Gender (female / male)	60 / 46	28 / 43	30 / 23	0.075
Age at BT diagnosis (years)	9.4 (1.3–20.5)	7.8 (0.1–17.2)		0.515
Age at study (years)	16.0 (2.3–39.0)	13.0 (1.5–21.0)	11.0 (3.0–18.0)	< 0.001
BMI at study (SDS)	2.70 (-4.41–11.85)	0.49 (-2.87–14.29)	0.31 (-2.41–12.20)	< 0.001
Height at study (SDS)	-0.41 (-4.9–82)	0.14 (-3.74–3.28)	-0.10 (-3.99–3.67)	0.030
Nuchal skinfold (cm)	1.03 (0.51–2.74)	0.61 (0.25–1.59)	0.64 (0.31–2.17)	< 0.001
Hypertension, n (%)	25 (24)	18 (25)	15 (28)	0.980
Subgroups (n)	53	59	42	
Gender (female / male)	33 / 20	22 / 37	26 / 16	0.017
Age at BT diagnosis (years)	9.5 (1.3–20.5)	7.4 (0.1–17.2)		0.473
Age at study (years)	19.0 (2.3–35.0)	12.9 (1.5–18.0)	11.0 (3.0–17.7)	< 0.001
BMI at study (SDS)	4.86 (-1.57–11.85)	0.44 (-2.14–14.29)	0.45 (-2.41–8.08)	< 0.001
Height at Study (SDS)	-0.10 (-3.37–2.64)	0.22 (-3.74–3.28)	0.06 (-2.93–3.67)	0.103
Waist circumference (cm)	109.0 (51.0–175.0)	84.0 (45.0–115.0)	81.5 (51.0–126.0)	< 0.001
Waist-to-height ratio	0.59 (0.38–0.91)	0.46 (0.37–0.69)	0.45 (0.35–0.70)	< 0.001
Nuchal skinfold (cm)	1.07 (0.51–2.74)	0.62 (0.25–1.59)	0.67 (0.32–1.98)	< 0.001

BT-Normal Controls: BMI SDS p = 0.750 (total group); BT-Normal Controls: BMI SDS p = 0.962 (Subgroups)

Patients characteristics	Craniopharyngioma	Brain tumor	Normal controls	p
Skinfolds (cm)				
abdominal	4.20 (0.40–6.30)	2.10 (0.30–5.60)	1.50 (0.30–5.80)	< 0.001
subscapular	3.90 (0.90–6.50)	1.40 (0.40–4.80)	1.10 (0.40–5.20)	< 0.001
biceps	2.50 (0.50–6.00)	1.00 (0.20–3.80)	0.90 (0.30–2.80)	< 0.001
triceps	3.10 (0.90–6.00)	1.60 (0.50–4.80)	1.45 (0.60–4.30)	< 0.001
RR systolic (mm HG)	128 (99–176)	118 (80–171)	118 (87–167)	0.014
RR diastolic (mm HG)	82 (54–143)	72 (47–110)	74 (50–104)	0.001
Hypertension, n (%)	20 (38)	16 (27)	13 (31)	0.487
BT-Normal Controls: BMI SDS p = 0.750 (total group); BT-Normal Controls: BMI SDS p = 0.962 (Subgroups)				

Table 2

Patients' characteristics in childhood brain tumor (BT) patients with regard to histological grade of malignancy according to WHO grading system (grade 1 to 4). RR, blood pressure; mm HG, millimeter mercury; BT, brain tumor; SDS, standard deviation score; WHO, World Health Organisation; at study means "at the time of cranial MRI".

Patients characteristics	Grade 1–2 BT	Grade 3–4 BT	p
Total group (n)	40	31	
Gender (female / male)	18 / 22	10 / 21	0.332
Age at BT diagnosis (years)	8.0 (0.5–17.2)	7.7 (0.1–17.0)	0.692
Age at study (years)	13.1 (2.0–21.0)	13.0 (1.5–19.0)	0.719
BMI at study (SDS)	+ 1.04 (-2.87–14.29)	-0.01 (-2.14–4.62)	0.048
Height at study (SDS)	0.60 (-3.74–3.28)	-0.30 (-2.98–2.11)	0.173
Nuchal skinfold (cm)	0.66 (0.34–1.59)	0.58 (0.25–1.10)	0.043
Hypertension, n (%)	13 (33)	5 (16)	0.105
Subgroups (n)	32	27	
Gender (female / male)	14 / 18	8 / 19	0.293
Age at BT diagnosis (years)	7.9 (0.5–17.2)	7.2 (0.1–16.5)	0.585
Age at study (years)	12.7 (4.8–18.0)	13.0 (1.5–18.0)	0.796
BMI at study (SDS)	1.21 (-1.13–14.29)	-0.11 (-2.14–4.62)	0.047
Height at study (SDS)	0.72 (-3.74–3.28)	-0.30 (-2.98–2.11)	0.079
Waist circumference (cm)	87.0 (55.0–115.0)	75.5 (45.0–107.0)	0.048
Waist-to-height ratio	0.47 (0.37–0.69)	0.44 (0.37–0.60)	0.639
Nuchal skinfold (cm)	0.65 (0.34–1.59)	0.52 (0.25–1.10)	0.169
Skinfolds-caliper (cm)			
abdominal	1.60 (0.30–5.50)	1.30 (0.60–5.60)	0.090
subscapular	1.60 (0.40–4.80)	1.30 (0.50–4.00)	0.242
biceps	1.25 (0.20–3.40)	0.90 (0.40–3.80)	0.220
triceps	2.10 (0.60–3.80)	1.30 (0.50–4.80)	0.016
RR systolic (mm HG)	121 (96–171)	114 (80–141)	0.065
RR diastolic (mm HG)	74 (47–97)	70 (52–110)	0.135
Hypertension, n (%)	11 (34)	5 (18)	0.242

High positive correlations were observed between NST and body mass index SDS and NST and waist-to-height ratio: NST vs. waist-to-height ratio: $r = 0.804$, 95%CI (0.744–0.852); body mass index SDS vs. waist-to-height ratio: $r = 0.878$, 95%CI (0.839–0.909); NST vs. body mass index SDS: $r = 0.716$, 95%CI (0.645–0.774). The results in all patient subgroups and healthy controls are shown in Fig. 2.

The different ranges of body mass index SDS, waist-to-height ratio and NST values lead to differences in correlation coefficients between the subgroups that do not necessarily reflect different underlying associations.

3.3. Caliper-measured skinfold thickness

In the subgroups of 53 craniopharyngioma patients, 32 patients with WHO grade 1–2 brain tumor, 27 patients with WHO grade 3–4 brain tumor, and 42 healthy controls, associations between NST, waist-to-height ratio, caliper-measured skinfold thickness (abdominal, subscapular, biceps, triceps), body mass index, and blood pressure could be analyzed (Table 1). Also in these subgroups, NST correlated with body mass index SDS and waist-to-height ratio: body mass index SDS vs. NST: $r = 0.743$ 95%CI (0.663–0.807); body mass index SDS vs. waist-to-height ratio: $r = 0.885$, 95%CI (0.846–0.915); waist-to-height ratio vs. NST: $r = 0.793$, 95%CI (0.726–0.845). Comparing NST with caliper-measured skinfold thickness, high correlations between NST and all assessed caliper-measured skinfold thicknesses were observed: NST vs. caliper-measured abdominal skinfold thickness: $r = 0.705$, 95%CI (0.617–0.776); NST vs. caliper-measured biceps skinfold thickness: $r = 0.677$, 95%CI (0.583–0.753); NST vs. caliper-measured triceps skinfold thickness: $r = 0.733$, 95%CI (0.653–0.798); NST vs. caliper-measured subscapular skinfold thickness: $r = 0.783$, 95%CI (0.715–0.837) (Fig. 3).

The analyses depicted in Fig. 3 were calculated for all pairwise non-missing observations, therefore the sample sizes may differ between Table 1 and 2.

Systolic blood pressure correlated with NST ($r = 0.327$, 95%CI 0.198–0.444), body mass index SDS ($r = 0.387$; 95%CI 0.263–0.497), and waist-to-height ratio ($r = 0.266$; 95%CI 0.119–0.400). Similar results were observed for diastolic blood pressure, showing that also diastolic blood pressure correlated with NST ($r = 0.400$, 95%CI 0.278–0.510), body mass index SDS ($r = 0.417$, 95%CI 0.297–0.524), and waist-to-height ratio ($r = 0.352$; 95%CI 0.212–0.478) (Fig. 4).

3.4. Multivariate analysis of risk factors for hypertension

In multivariate analyses including 53 craniopharyngioma patients, 59 brain tumor patients and 42 healthy controls, we analyzed which of the anthropometric parameters NST, body mass index SDS, waist-to-height ratio, caliper-measured skinfold thickness had potential impact on blood pressure as a risk factor for cardiovascular disease. In all patients and healthy controls, systolic and diastolic blood pressure values were adjusted for age, gender and height and classified as normotensive or hypertensive blood pressure according to a study on waist-to-height ratio and elevated blood pressure³¹. When analyzing the total group of 154 participating patients/healthy controls, several parameters such as

waist-to-height ratio, caliper-measured skinfold thickness, NST, waist and hip circumferences and body mass index SDS could be identified as potential risk factors for hypertension in univariable analysis (data not shown). When entering all anthropometric parameters in a multivariate logistic regression analysis and performing stepwise selection, only body mass index SDS was selected for the final model resulting in an odds ratio of 1.25, 95%CI (1.14–1.37). Of course, this analysis was strongly limited by the small cohort size and also the high correlation of the anthropometric measures.

3.5. Hypothalamic involvement

Seventy-four of 85 craniopharyngioma patients (87%) with available data presented with hypothalamic involvement of craniopharyngioma at the time of diagnosis, which was associated with obesity. Patients with hypothalamic involvement presented with higher body mass index SDS (median body mass index: +2.15 SDS, range: -4.41 to + 11.85 SDS, $p = 0.001$), higher NST (median NST: 1.02 cm, range: 0.51–2.74 cm, $p = 0.017$), and higher waist-to-height ratio (median waist-to-height ratio: 0.58, range: 0.38–0.87, $p = 0.004$), when compared to craniopharyngioma patients without hypothalamic involvement (median body mass index: -0.31 SDS, range: -1.57 to + 3.30 SDS; median NST: 0.77 cm, range: 0.51–1.13 cm; median waist-to-height ratio: 0.42, range: 0.39–0.44).

3.6. Degree of surgical resection

Twenty-one of 96 craniopharyngioma patients (22%) were treated by gross-total resection achieving reference-confirmed complete tumor removal. After gross-total resection, patients presented with higher body mass index SDS (median body mass index: +4.86 SDS, range: -1.57 to + 10.54 SDS, $p = 0.008$), NST (median: 1.12 cm, range: 0.51–2.74 cm, $p = 0.305$) and waist-to-height ratio (median: 0.65, range: 0.39–0.91, $p = 0.385$) at time of study when compared with patients after incomplete resection (median body mass index: +1.79 SDS, range: -4.41 to + 11.85 SDS; median NST: 1.00 cm, range: 0.54–2.39 cm; median waist-to-height ratio: 0.59, range: 0.38–0.86).

3.7. Surgical hypothalamic lesions

Fourty-eight of 87 craniopharyngioma patients (55%) with available data for surgical hypothalamic lesions presented with post-surgical hypothalamic lesions. Patients with hypothalamic lesions presented with higher body mass index SDS (median: +3.16 SDS, range: -4.41 to + 11.85 SDS, $p < 0.001$), higher NST (median: 1.11 cm, range: 0.54–2.74 cm, $p < 0.001$), and waist-to-height ratio (median: 0.64, range: 0.42–0.87, $p = 0.001$) when compared to the subgroup of craniopharyngioma patients without hypothalamic lesions (body mass index SDS median: +0.87 SDS, range: -2.63 to + 11.68 SDS; NST median: 0.91 cm, range: 0.51–1.95 cm; waist-to-height ratio median: 0.55, range: 0.38–0.86).

4. Discussion

Metabolic syndrome consisting of insulin resistance and a minimum of two other risk factors from increased body mass index, elevated blood pressure, hypertriglyceridemia, low serum HDL-cholesterol, and microalbuminuria, can result in cardiovascular disease. Obese children have an increased risk of

metabolic syndrome, due to their large compartment of fat tissue when compared with normal-weight children^{32–35}. Two fat tissue compartments (subcutaneous adipose tissue and visceral adipose tissue) are known with different metabolic characteristics³⁶. Visceral adipose tissue is a known risk factor for metabolic syndrome and has a stronger association with the risk of cardiovascular disease than subcutaneous adipose tissue and total adipose tissue.

MRI is the golden standard to quantify compartments of different adipose tissue. However, MRI is an expensive method to be performed for this purpose alone. The value and feasibility of auxiological parameters for risk prediction of metabolic syndrome and cardiovascular disease have been analysed by several studies. In a study of adults, where the visceral adipose tissue on MRI was used as reference, waist circumference correlated better with visceral adipose tissue than body mass index, which seemed to be more associated with total adipose tissue^{37,38}. A study of Koren *et al.*³⁹ showed that in adolescents the sagittal abdominal diameter, which represents abdominal thickness at waist level in supine position, was a better predictor of visceral adipose tissue than waist-to-hip ratio, waist circumference, and body mass index. Although in adults the waist-to-hip ratio is associated with cardiovascular disease and type 2 diabetes, this association is less clear in the pediatric age group, most likely due to changes in distribution of body fat during growth^{40,41}. Several studies could show that the ratio of waist circumference to height (waist-to-height ratio) is superior to body mass index and waist circumference to predict risks of cardiovascular disease^{42–45}. In a study of adolescents, waist-to-height ratio was associated with body mass index SDS and both waist-to-height ratio and body mass index had predictive value for arterial hypertension³¹. An advantage of waist-to-height ratio measurement is that waist-to-height ratio does not need adjustment for age: a cut-off value of 0.5 can be used in every age group. This makes waist-to-height ratio usable for comparison in pediatric patients of different age^{31,46}.

Preis *et al.*²¹ and Da Silva *et al.*⁴⁷ reported on neck circumference as a new parameter for prediction of cardiovascular disease risk. Preis *et al.*²¹ could show that neck circumference was correlated with both body mass index and visceral adipose tissue. After adjustment for visceral adipose tissue, the authors observed that neck circumference was positively correlated with blood pressure and risk factors for cardiovascular disease²¹.

Long-term prognosis after pediatric brain tumor disease is frequently impaired by cardiovascular disease¹. Craniopharyngioma patients have a 3–19 fold higher cardiovascular mortality when compared with the general population¹⁵ due to hypothalamic obesity caused¹⁵ by tumor and/or treatment related hypothalamic lesions^{8,11–14}. Incidence of cardiovascular disease is also increased in patients with pediatric brain tumors of other histology. However, when obesity rates of patients with brain tumors different from craniopharyngioma are measured by using body mass index, pediatric brain tumor patients were observed to present with body mass index levels that were either close to or slightly higher than body mass index in the general population^{6,7}. In accordance with previous reports^{6,7}, we also observed no body mass index differences between brain tumor patients and healthy controls in our study. However, patients with WHO grade 1–2 brain tumors presented with higher body mass index when

compared with WHO grade 3–4 brain tumor patients, indicating that low histological grade of malignancy and different treatment might have impact on body composition.

In our previous study ²⁵, analyzing NST on cranial MRIs of craniopharyngioma patients performed during follow-up monitoring, we reported on NST as a new parameter for body composition assessment. We observed that NST was associated with other parameters of body composition such as body mass index, caliper-measured skinfold thickness, and waist-to-height ratio. Furthermore, NST had predictive value for cardiovascular disease risk in craniopharyngioma patients and healthy controls.

In this study, we analyzed NST and the above mentioned diagnostic parameters of body composition not only in larger cohorts of craniopharyngioma and healthy controls, but also in pediatric patients with brain tumors of different histological diagnoses and grades of malignancy. In cross-sectional analyses, NST correlated with all analyzed parameters of body composition (body mass index, caliper-measured skinfold thickness) and was associated with waist-to-height ratio as a known parameter of visceral adipose tissue in all patient groups and in healthy controls. Craniopharyngioma patients with hypothalamic involvement presented with the highest NST. The high predictive value of NST for body composition and blood pressure as cardiovascular disease risk factor was also confirmed in healthy controls.

Increased levels of upper-body visceral fat, indicating central obesity, are associated with higher rates of adverse metabolic outcome, when compared with lower-body obesity ⁴⁸. Our observations support the hypothesis that NST could be a standardized and easily measurable proxy of body composition and presumably upper-body subcutaneous fat. Furthermore, our observations support previous reports ^{11,12} that hypothalamic involvement and hypothalamic lesions are associated with severe obesity in long-term survivors of childhood-onset craniopharyngioma.

The results of our study add to the literature on body composition and obesity in brain tumor patients by reporting on the novel observation that NST is correlating with body composition (body mass index SDS, waist-to-height ratio) not only in craniopharyngioma patients but also in patients with brain tumors of different histology and grade of malignancy. Assessment of NST is easy to perform based on a standardized procedure with high reliability. Limitations of our pilot study are differences with regard to older age of CP patients at the time of study/MRI and the small cohort size of patients with pediatric brain tumors other than craniopharyngioma, which warrants further analyses of larger age-matched cohorts. A further limitation relates to the fact, that due to the high rate of eating disorders in craniopharyngioma patients fasting blood samples for assessment of other risk factors for cardiovascular disease such as glycemic control or lipid status were not available. HOMA-IR and other measures of visceral adiposity (i.e. impedance analyses, abdominal MRI, dual-energy X-ray absorptiometry) could not be evaluated in this study but will be part of future prospective studies in context of the German Craniopharyngioma Registry.

5. Conclusions

MRI-based assessment of NST is not recommended as a routine clinical procedure for general assessment of body composition in obese patients. However, as cranial MRI plays an important role in follow-up monitoring for early detection of recurrent brain tumour disease, measurement of NST could serve as a reliable, standardized and easily determinable parameter for body composition analysis during follow-up after brain tumour. Based on the high association with visceral adipose tissue, NST might have high value for risk prediction of hypertension and cardiovascular disease especially in pediatric patients with brain tumors of low histological malignancy (WHO grade 1 or 2) and craniopharyngioma patients with hypothalamic involvement.

Declarations

Data availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

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Author Contributions

J.P. researched the data and wrote the manuscript. S.B. collected the data and prepared statistical analyses, contributed to the analytical plan and discussion and reviewed/edited the manuscript. M.E. performed all statistical analyses, contributed to the analytical plan and discussion and reviewed/edited the manuscript. B.B. did neuroradiological assessment of all imaging. B.B. is the neuroradiologist, who performs reference-assessment of imaging in all patients recruited in KRANIOPHARYNGEOM 2000/2007. She prepared the imaging data and their presentation and reviewed/edited the manuscript. P.S. contributed to the analytical plan and discussion and reviewed/edited the manuscript. H.L.M. initiated and conducted the multicenter trials KRANIOPHARYNGEOM 2000 and KRANIOPHARYNGEOM 2007, contributed to the analytical plan and discussion and reviewed/edited the manuscript. Assessments of NST were performed in triplicate (by J.P., S.B., and H.L.M.) for each patient.

Conflicts of Interest

H.L.M. has received reimbursement of participation fees for scientific meetings and continuing medical education events from the following companies: Ferring, Lilly, Pfizer, Sandoz/Hexal, Novo Nordisk, IPSEN, and Merck Serono. He has received reimbursement of travel expenses from IPSEN and lecture honoraria from Pfizer. The other authors declare that they have no conflict of interest.

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Figures

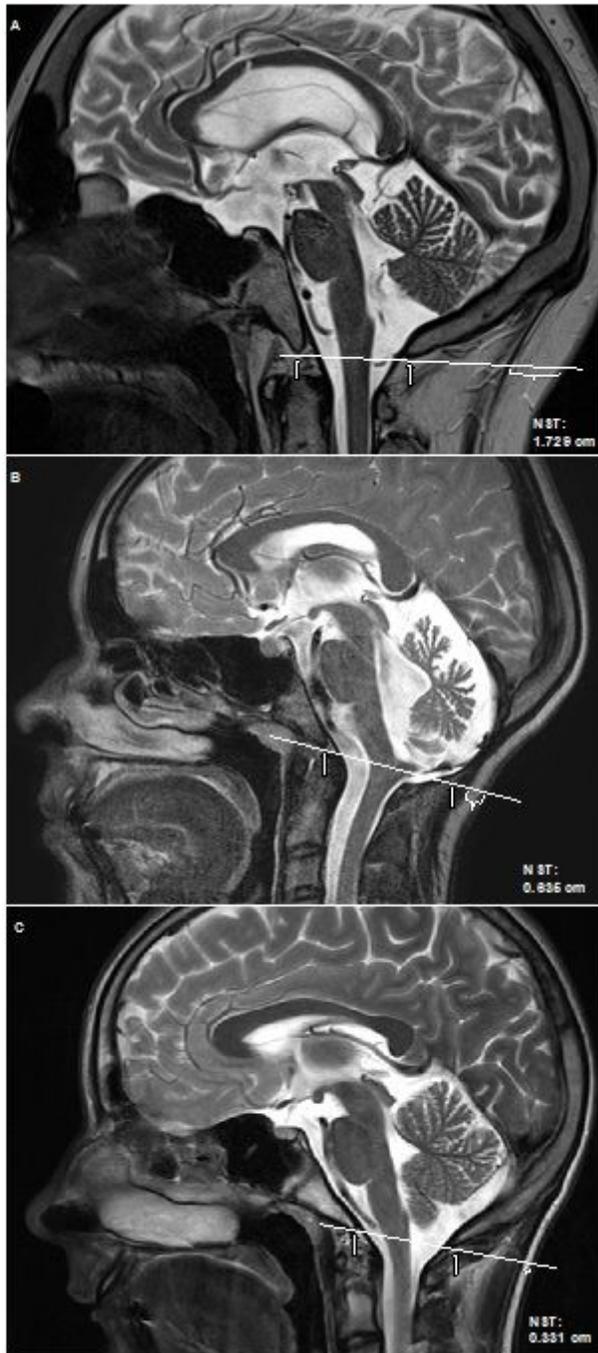


Figure 1

Figure 1

Nuchal skinfold thickness (NST) is shown on T2-weighted sagittal cranial magnetic resonance imaging (MRI) of the midline. NST was quantified according to the following standardized assessment: First a line was drawn crossing the two anatomically defined points: basion (anterior margin of the foramen magnum, indicated by arrow) and opisthion (posterior margin of the foramen magnum, indicated by arrow). The diameter of subcutaneous nuchal fat was measured over this line to the nearest 0.01 cm using OsiriX® (Pixmeo SARL, Switzerland). Figure 1 A shows NST in a childhood-onset craniopharyngioma patient with severe obesity due to hypothalamic involvement (hypothalamic

involvement grade II 11, BMI: +4.86 SDS 29). Figure 1 B shows NST in a patient with low-grade glioma of the brain stem, BMI: +0.48 SDS 29). Figure 1 C shows NST in a healthy, normal-weight control (BMI: +0.41 SDS 29). SDS, standard deviation score. The inter-rater reliability of the used arithmetic mean of NST was 0.982.

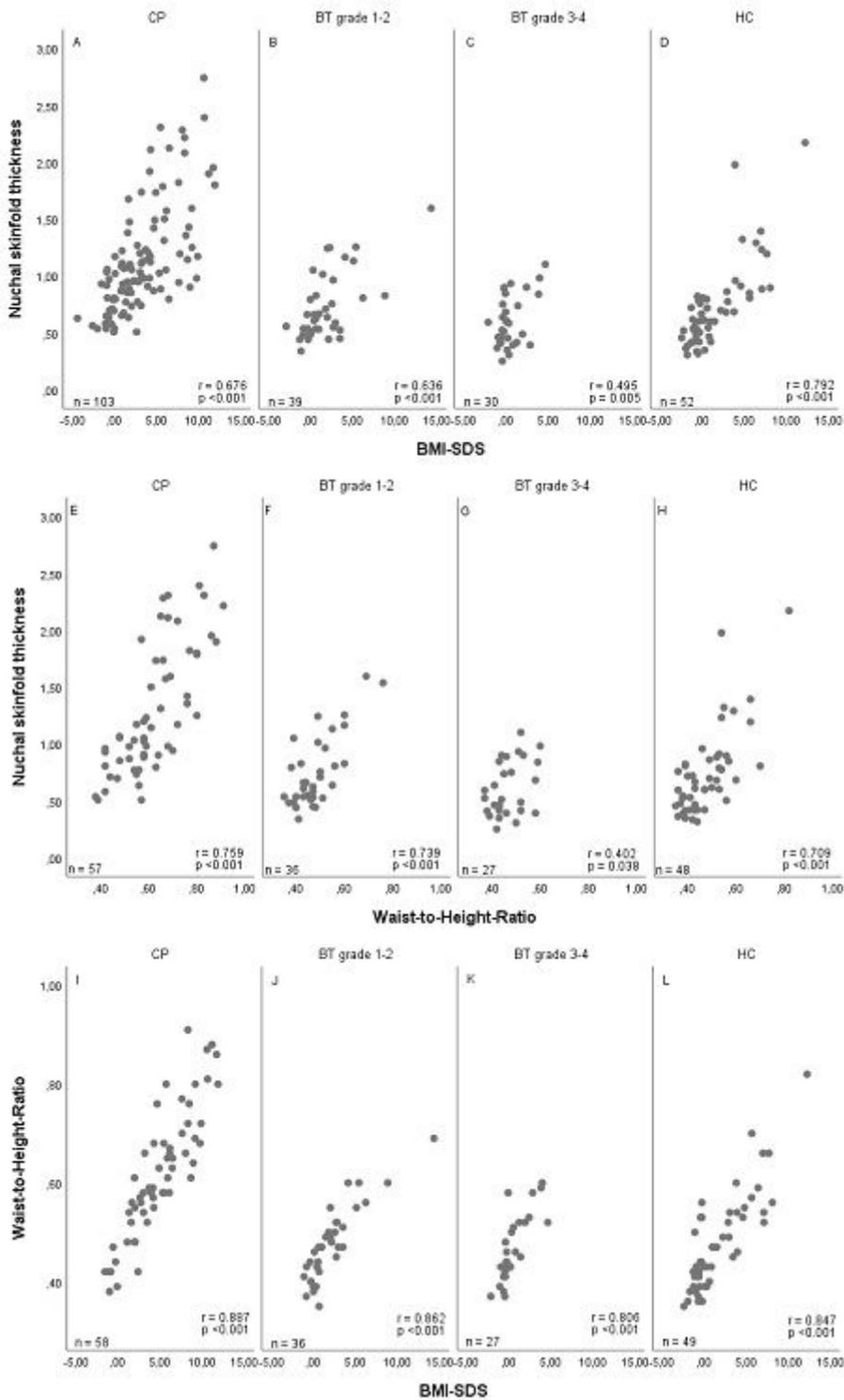


Figure 2

Correlations between nuchal skinfold thickness (NST) as measured on cranial magnetic resonance (MRI) imaging and body mass index (BMI) SDS 29 (Figure 2 A–D), between NST and waist-to-height ratio (Figure 2 E–H), and between BMI SDS and waist-to-height ratio (Figure 2 I–L) in patients with childhood-onset craniopharyngioma (CP) recruited in HIT Endo and KRANIOPHARYNGEOM 2000/2007 (Figure 2 A, E, I), WHO grade 1–2 brain tumor (BT) patients (Figure 2 B, F, J), WHO grade 3–4 BT patients (Figure 2 C, G, K), and healthy controls (HC) (Figure 2 D, H, L). r = Pearson correlation coefficient; SDS, standard deviation score.

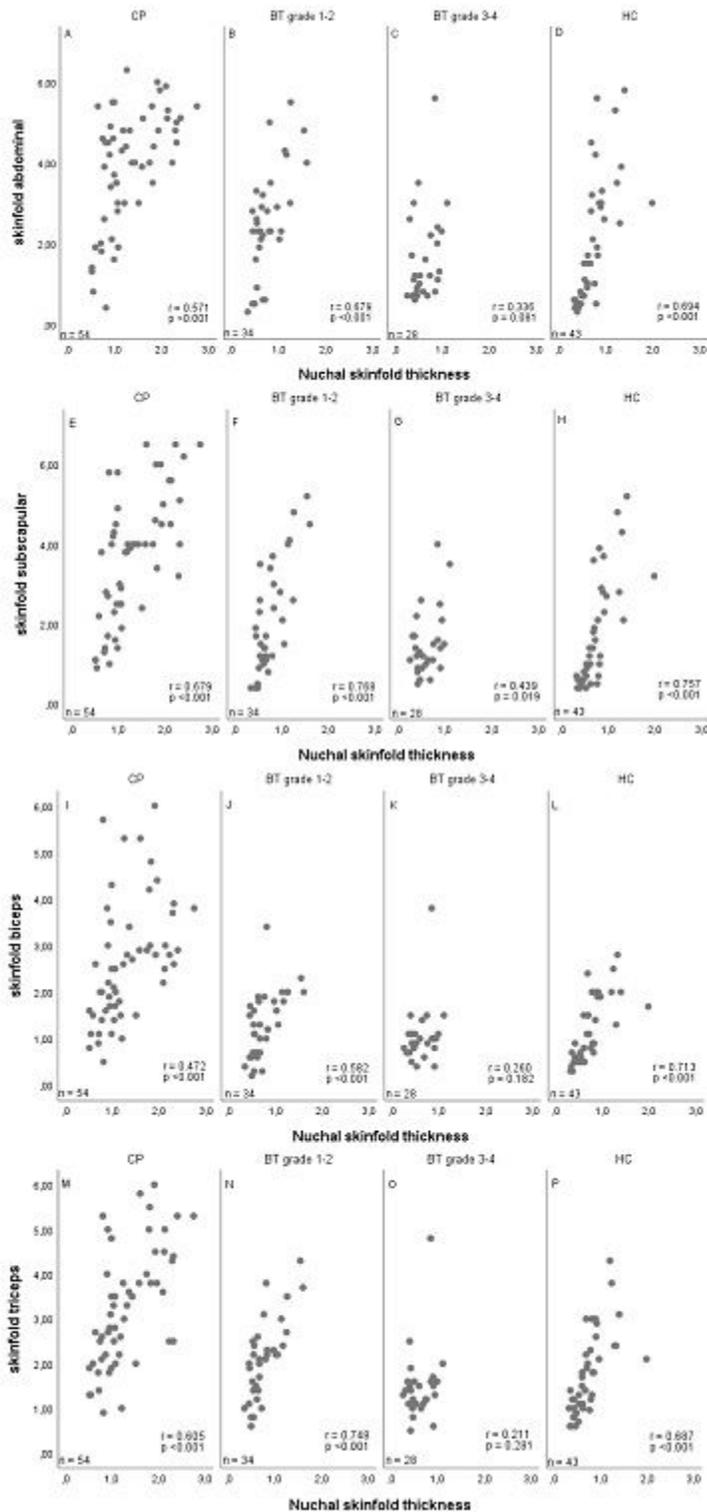


Figure 3

Correlations between nuchal skinfold thickness (NST) as measured on cranial magnetic resonance imaging (MRI) and caliper-measured skinfold thickness for abdominal (Figure 3 A–D), subscapular (Figure 3 E–H), biceps (Figure 3 I–L) and triceps (Figure 3 M–P) skinfold thickness in patients with childhood-onset craniopharyngioma (CP) (Figure 3 A, E, I, M), WHO grade 1–2 brain tumor (BT) patients (Figure 3 B, F, J, N), WHO grade 3–4 BT patients (Figure 3 C, G, K, O), and healthy controls (HC) (Figure 3 D, H, L, P). r = Pearson correlation coefficient.

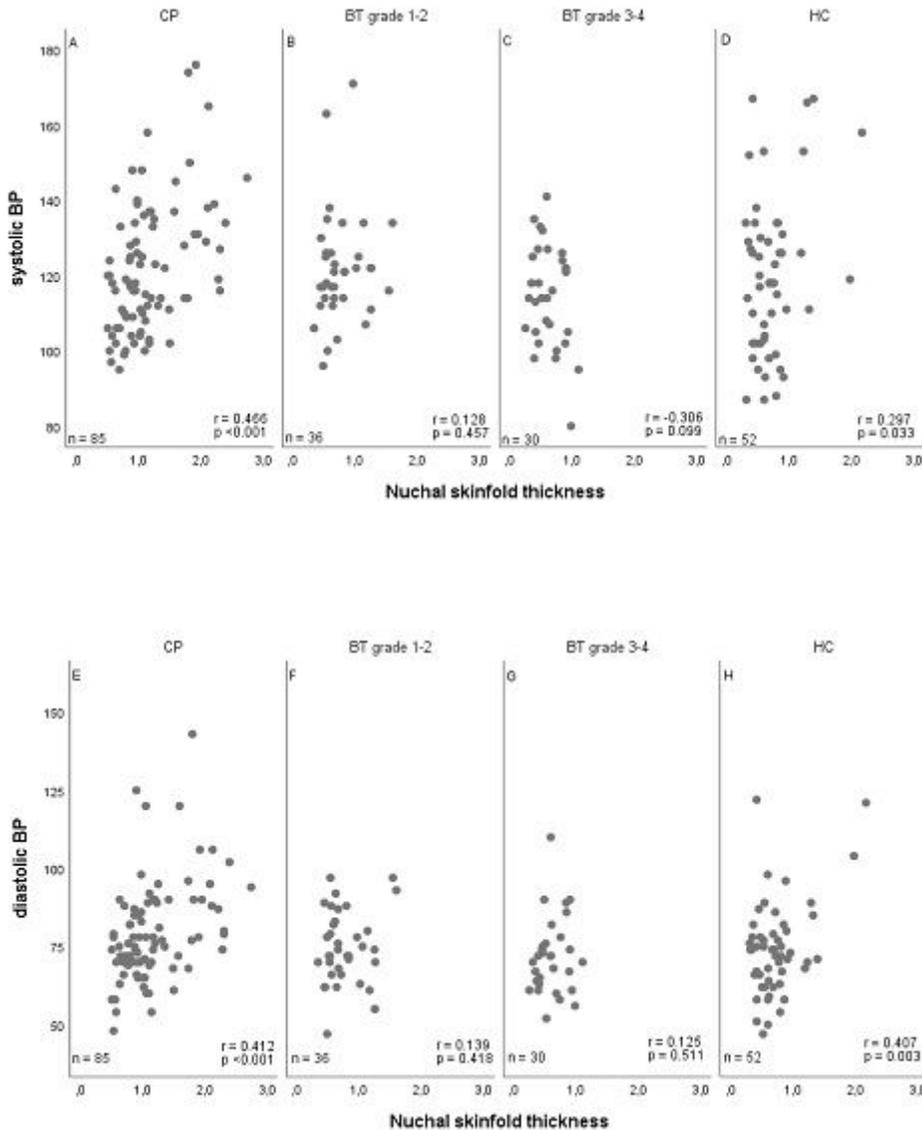


Figure 4

Correlations between nuchal skinfold thickness (NST) as measured on cranial magnetic resonance imaging (MRI) and systolic (Figure 3 A–D) and diastolic (Figure 3 E–H) blood pressure (mm Hg) in patients with childhood-onset craniopharyngioma (CP) (Figure 3 A, E), WHO grade 1–2 brain tumor (BT) patients (Figure 3 B, F), WHO grade 3–4 BT patients (Figure 3 C, G), and 43 healthy controls (HC) (Figure 3 D, H). r = Pearson correlation coefficient; mm HG, millimeter mercury.