Clinical Nutrition 38 (2019) 835–841

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

Overweight in childhood cancer patients at diagnosis and throughout therapy: A multicentre cohort study

Fabiën N. Belle [a, b, 1], Juliane Wenke-Zobler [c, 1], Eva Cignacco [d, e], Ben D. Spycher [a, f], Roland A. Ammann [g], Claudia E. Kuehni [a, g], Karin Zimmermann [d, h, *]

[a] Institute of Social and Preventive Medicine, University of Bern, Switzerland
[b] Institute of Social and Preventive Medicine (IUMSP), Lausanne University Hospital (CHUV), Switzerland
[c] Department of Clinical Nursing Science, Cantonal Hospital Aarau, Switzerland
[d] Pflegewissenschaft - Nursing Science (INS), Department Public Health (DPH), Faculty of Medicine, University of Basel, Switzerland
[e] Department of Health Professions, University of Applied Sciences Bern, Switzerland
[f] Department of Paediatrics, Paediatric Respiratory Medicine, Inselspital, Bern University Hospital, University of Bern, Switzerland
[g] Department of Paediatrics, Inselspital, Bern University Hospital, University of Bern, Switzerland
[h] Children's Research Centre, University Children's Hospital Zurich, University of Zurich, Switzerland

ARTICLE INFO

Article history:
Received 13 October 2017
Accepted 18 February 2018

Keywords:
Childhood cancer patients
Obesity
Overweight
Treatment
Swiss childhood cancer registry
Europe

SUMMARY

Background: Childhood cancer patients (CCP) have been reported to be at increased risk of becoming overweight during treatment. We assessed prevalence of overweight in CCP at diagnosis and at the end of treatment, determined risk factors, and identified weight change during treatment by type of cancer.
Methods: In a multicentre cohort study, we collected height and weight measurements of CCP at diagnosis and repeatedly during treatment. We calculated age- and sex-adjusted BMI Z-scores using references of the International Obesity Taskforce for children. Risk factors were described by multivariable linear regression, and weight change during treatment by multilevel segmented linear regression.
Results: The study included 327 CCP with a median age of 7 years (IQR 3–12) at diagnosis (55% boys), who had been diagnosed with acute lymphoblastic leukaemia (ALL, 29%), lymphoma (16%), central nervous system (CNS) tumours (13%), sarcoma (18%), and other types of cancer (24%). At diagnosis, 27 CCP (8%) were overweight. This increased to 43 (13%) at end of treatment, on average 0.7 years after diagnosis. Being a boy ($p = 0.005$) and having been diagnosed with ALL or lymphoma ($p < 0.001$) were risk factors for weight gain during treatment. During the first half of treatment, BMI Z-scores increased in ALL (regression slope $\beta = 0.4$, 95% CI 0.1–0.7) and lymphoma ($\beta = 1.5$, 95% CI 0.2–2.9) patients, whereas for patients with CNS tumours ($\beta = -1.4$, 95% CI −2.7 to −0.2), sarcoma ($\beta = -1.4$, 95% CI −2.0 to −0.7), or other types of cancer ($\beta = -0.3$, 95% CI −1.5–0.9) BMI Z-scores tended to drop initially. During the second half of treatment BMI Z-scores of all patients tended to increase. Exploratory analyses showed that BMI Z-scores of younger ALL patients (<7 years at diagnosis) increased during induction ($\beta = 3.8$, 95% CI 0.5 −7.0). The inverse was seen for older ALL patients (≥7 years at diagnosis), in whom BMI Z-scores tended to decrease during induction ($\beta = -1.5$, −5.1–2.2), both groups tended to increase afterwards.
Conclusion: CCP diagnosed with ALL or lymphoma are at increased risk of weight gain during treatment, and might particularly benefit from early lifestyle interventions.
© 2018 Elsevier Ltd and European Society for Clinical Nutrition and Metabolism. All rights reserved.

Abbreviations: ALL, acute lymphoblastic leukaemia; BMI, body mass index; CCP, childhood cancer patients; CI, confidence interval; CNS, central nervous system; CRT, cranial radiation therapy; Dx, diagnosis; Gy, gray; ICCC-3, International Classification of Childhood Cancer, 3rd edition; IOTF, International Obesity Taskforce; IQR, interquartile range; OR, odds ratio; SCCR, Swiss Childhood Cancer Registry; SD, standard deviation.

* Corresponding author. Pflegewissenschaft - Nursing Science (INS), University of Basel, Faculty of Medicine, Department Public Health (DPH), Bernoullistr. 28, 4056 Basel, Switzerland. Fax: +41 61 207 09 55.
E-mail addresses: fabien.belle@ispm.unibe.ch (F.N. Belle), juliane.wenke@gmx.de (J. Wenke-Zobler), eva.cignacco@unibas.ch (E. Cignacco), ben.spycher@ispm.unibe.ch (B.D. Spycher), roland.ammann@insel.ch (R.A. Ammann), claudia.kuehni@ispm.unibe.ch (C.E. Kuehni), karin.zimmermann@unibas.ch (K. Zimmermann).
[1] Shared first authorship.

https://doi.org/10.1016/j.clnu.2018.02.022
0261-5614/© 2018 Elsevier Ltd and European Society for Clinical Nutrition and Metabolism. All rights reserved.

1. Introduction

Childhood cancer survival has substantially improved in recent decades, but chronic health problems are common in survivors [1]. Overweight is reported as a frequent late effect, particularly in patients with acute lymphoblastic leukaemia (ALL) and brain tumours [2,3]. Some studies have suggested that patients diagnosed with other cancers such as sarcomas and lymphomas are also affected [2,4]. The consequences of overweight and obesity in childhood cancer patients (CCP) are manifold: reduced health-related quality of life, more comorbidities in later life, and increased risk for relapse, second primary tumours, and mortality [4,5].

Studies of overweight or obesity during treatment have been conducted mainly in ALL and brain tumour patients, and have reported varying results. At diagnosis, 10–36% of ALL patients were reported to be overweight and 2–19% obese [4,6–9]. At the end of treatment, 19–49% were reported as overweight and 9–48% as obese [4,6–9]. In patients with craniopharyngiomas, obesity was reported in 50% of the patients after tumour resection [10,11].

Data on risk factors for overweight in CCP are inconclusive [4,12]. A meta-analysis has concluded that childhood ALL patients have substantial weight gain from diagnosis to start of maintenance treatment and beyond, independent of gender, cranial radiation therapy, and weight status at diagnosis [13]. For brain tumour patients, female gender and younger age were described as risk factors for obesity [10,14]. Yet few studies have covered the whole diagnostic spectrum of childhood cancer. Comparable information on overweight prevalence at diagnosis, during, and at the end of cancer treatment between diagnostic groups in CCP is also lacking, but is crucial for initiating individualised preventive measures at an early stage.

The goals of this multicentre cohort study were to 1) determine overweight prevalence of CCP at diagnosis and at the end of treatment, 2) determine potential risk factors for weight change from diagnosis until the end of treatment, and 3) describe weight change during treatment by type of cancer, with a focus on ALL patients during the different treatment phases.

2. Methods

2.1. Study population

Eligible patients for this retrospective cohort study were CCP aged <18 years at diagnosis who were diagnosed 2003–2006 and treated with chemotherapy and/or percutaneous radiotherapy in three tertiary care centres for paediatric haematology/oncology in Basel, Bern, and Zürich in the German-speaking part of Switzerland. Prospectively collected data on type of cancer, treatment, and demographic information were extracted from the Swiss Childhood Cancer Registry (SCCR, www.childhoodcancerregistry.ch) [15,16]. Height and weight measurements were obtained from a retrospective chart review. Detailed information on our study design was published previously [17]. Ethical approval of the SCCR was granted by the Ethics Committee of the Canton of Bern (KEK-BE: 166/2014).

2.2. Measurements

2.2.1. Body weight and BMI Z-scores

Body mass index (BMI), expressed in kg/m^2 was used to define overweight. BMI Z-scores were calculated according to Cole's LMS method [18] based on the reference values of the International Obesity Taskforce (IOTF). For children under two years of age, we used the standards of the World Health Organization [19]. Underweight (thinness grade I–III), normal weight, and overweight, (including obesity and morbid obesity) was classified according to BMI cut-offs recommended by the IOTF (Supplementary Table 1) [20]. The observation period started with the first measurement at diagnosis and ended with the last measurement before the end of anticancer treatment or when the patient died, relapsed, or was transferred to a nonparticipating hospital for ongoing anticancer treatment [17]. This study used all weight and height measurements available from medical charts.

We obtained birth weights from medical records and by using probabilistic record linkage of the SCCR and birth records from the Swiss Federal Statistical Office, as described previously [21]. Birth weight was classified into three categories: low (<2500 g), normal (2500–4000 g), and high (>4000 g) [22].

2.2.2. Sociodemographic and clinical characteristics

Participants who were not Swiss citizens at birth, not born in Switzerland, or had at least one parent who was not a Swiss citizen were classified as having a migration background. Diagnosis was classified according to the International Classification for Childhood Cancer, 3rd edition (ICCC-3) [23], and grouped into five main categories: ALL, lymphomas, CNS tumours, sarcomas, and other types of cancer. These categories were chosen in accordance with other studies [2,4]. Radiotherapy was classified as cranial radiation therapy (CRT) if the patient had received direct radiation to the brain and/or skull. Cumulative dosage of CRT was obtained from medical records and categorized as <20 Gy or ≥20 Gy. We also extracted information on parenteral and/or enteral nutritional support during treatment.

2.3. Statistical analyses

We first compared the changes in prevalence of overweight and BMI Z-scores between diagnosis and the end of treatment by sociodemographic and clinical characteristics. The time of end of treatment was replaced with time at relapse, death, or end of data collection if these occurred during treatment.

Second, we used linear regression to determine risk factors associated with change in BMI during treatment, from diagnosis till end of treatment. We selected the following potential risk factors a priori based on a literature review: gender, age at diagnosis, ICCC-3 diagnosis, cumulative CRT, parenteral/enteral nutrition support, birthweight, and BMI Z-score at diagnosis. Variables with p-values <0.05 in univariable models were jointly included in a multivariable model. F-tests were used to test the association between the outcome and the covariates. Age at diagnosis and BMI Z-scores at diagnosis were included as continuous variables after testing for linearity of their association with BMI-change using likelihood ratio tests.

Third, to assess whether the slope of BMI change was different between early and late treatment phases we fit multilevel segmented linear regression models with BMI Z-score as dependent variable and therapy duration in years as independent variable. We separated analyses for each diagnostic group. The piecewise linear regression line allowed for a change in trend at a specified breakpoint set to the median treatment duration among patients of the given diagnostic group. For ALL patients, we performed separate analyses with breakpoints at the end of the induction period (33 days, 0.09 years) and the start of the maintenance period (99 days, 0.27 years), based on the cancer protocols used in the study. All regression models included a random effect term on patient level, allowing for intra-individual correlation. The models were adjusted for gender, age at diagnosis, cumulative CRT, parenteral/enteral nutrition support, and BMI Z-score at diagnosis. For these analyses, we included only 311 CCP who had at least five height and weight measurements available.

BMI Z-score curves of individual patients were highly variable, and fitting a single trend by diagnostic group is clearly an oversimplification. In additional exploratory analyses in ALL patients, we therefore fit separate segmented linear regressions with a flexible breakpoint to the BMI Z-score of each patient. We then grouped patients according to whether the initial slope was positive or negative and compared groups according to gender and age (below and above median of 7 years) at diagnosis using chi-square tests. We found that BMI Z-scores tended to initially increase in younger patients, but decreased in older patients ($p = 0.002$). The groups differed little in gender composition ($p = 0.117$). In post hoc analyses we therefore repeated our main analysis for ALL (with specified breakpoints at the end of the induction period and the start of the maintenance period), stratifying patients by these age groups. We used Stata (version 14, Stata Corporation, Austin, Texas) and R (version 3.2.0) for all analyses. The command xtmixed was used for multilevel segmented linear regression analysis.

3. Results

We included 327 patients in the analysis whose median age at diagnosis of 7 years (interquartile range [IQR] 3–12). ALL was the most common diagnosis among CSS with 95 patients (29%), followed by sarcomas (18%), lymphoma (16%), CNS tumours (13%), other types of cancer (24%) including acute myeloid leukaemia, nephroblastoma, and neuroblastoma (Table 1). The median time from diagnosis until the end of treatment was 0.7 years (IQR 0.4–1.8) for all patients and varied by type of cancer: ALL 2.0 (IQR 2.0–2.3), lymphoma 0.4 (IQR 0.3–0.6), CNS tumours 0.7 (IQR 0.3–1.2), sarcomas 0.7 (IQR 0.5–0.9), and other types of cancer 0.6 (IQR 0.4–0.7) years. Median time interval between successive weight and height measurements was 13 days (IQR 10–19 days), and 267 patients were observed until the end of their anticancer treatment (82%), 23 patients (7%) relapsed during therapy, 12 patients (4%) died, and 25 patients (8%) were lost to follow up. Other patient and clinical characteristics are shown in Table 1.

3.1. Overweight prevalence and BMI Z-scores at diagnosis and at the end of treatment

At diagnosis, 27 patients (8%) were overweight. This proportion increased to 43 (13%) at the end of treatment (Table 1). Mean BMI Z-score was −0.1 (SD 1.1) at diagnosis and −0.1 (SD 1.3) at the end of treatment (Table 2). Prevalence of overweight at diagnosis increased during treatment in boys and girls, all age groups, all types of cancer except "other types," and patients with and without parenteral or enteral nutrition support (Fig. 1). BMI Z-scores tended to increase during treatment in boys, patients below the age of five years, those diagnosed with ALL or lymphoma, with no or <20 Gy CRT, no parenteral or enteral nutrition support, and those who were underweight at diagnosis (Table 2).

3.2. Risk factors for weight change during treatment among childhood cancer patients

In adjusted models, risk factors for weight gain during treatment were being a boy ($\beta = 0.3$; 95%CI: 0.1, 0.5) and being diagnosed with ALL ($\beta = 0.5$; 0.2, 0.8) or lymphoma ($\beta = 0.6$; 0.2, 1.0). Weight loss was associated with older age at diagnosis ($\beta = -0.03$; -0.05, 0.01, per year increase), ≥20 Gy CRT ($\beta = -0.6$; -1.0, 0.1), receiving parenteral/enteral nutrition support ($\beta = -0.3$; -0.5, 0.1), and a higher BMI at diagnosis ($\beta = -0.3$; -0.4, 0.2, per BMI Z-score) (Table 3).

Table 1
General characteristics of the study population (n = 327)

Characteristics	Total	Overweight at diagnosis	Overweight at the end of treatment
	(n = 327)	(n = 27)	(n = 43)
	n (%)	*n* (%)	*n* (%)
Sociodemographic characteristics			
Gender			
Girl	146 (45)	15 (56)	17 (40)
Boy	181 (55)	12 (44)	26 (60)
Age at diagnosis, median years (IQR)	6.8 (2.9, 12.0)	9.2 (1.5, 13.0)	7.0 (3.9, 13.7)
<5	132 (40)	11 (41)	18 (42)
5–9	86 (26)	5 (19)	9 (21)
10–14	71 (22)	6 (22)	8 (19)
≥15	38 (12)	5 (19)	8 (19)
Migration			
No migration background	239 (73)	19 (70)	31 (72)
Migration background	88 (27)	8 (30)	12 (28)
Clinical characteristics			
ICCC-3 diagnosis			
Ia: ALL	95 (29)	7 (26)	17 (40)
II: Lymphoma	53 (16)	2 (7)	7 (16)
III: CNS tumour	42 (13)	5 (19)	6 (14)
VIII-IX: Sarcoma	59 (18)	4 (15)	7 (16)
Other	78 (24)	9 (33)	6 (14)
Treatment centre			
Centre 1	152 (46)	19 (70)	22 (51)
Centre 2	113 (35)	6 (22)	14 (33)
Centre 3	62 (19)	2 (7)	7 (16)
Time from dx until end of treatment, median years (IQR)	0.7 (0.4, 1.8)	–	–
Cranial radiation therapy			
No	284 (87)	20 (74)	38 (88)
<20 Gy	16 (5)	4 (15)	3 (7)
≥20 Gy	27 (8)	3 (11)	2 (5)
Chemotherapy			
No	3 (1)	2 (7)	2 (5)
Yes	324 (99)	25 (93)	41 (95)
Parenteral/ enteral nutrition support			
No	229 (70)	21 (78)	32 (74)
Yes	98 (30)	6 (22)	11 (26)
BMI at diagnosis			
Underweight	63 (19)	–	–
Normal	237 (72)	–	24 (56)
Overweight	20 (6)	20 (74)	13 (30)
Obese	7 (2)	7 (26)	6 (14)
BMI at end of treatment			
Underweight	72 (22)	–	–
Normal	212 (65)	8 (30)	–
Overweight	35 (11)	13 (48)	35 (81)
Obese	8 (2)	6 (22)	8 (19)
Birthweight, gram			
Low: <2500	18 (6)	–	2 (5)
Normal: 2500–4000	239 (73)	18 (67)	31 (72)
High: >4000	29 (9)	2 (7)	3 (7)
Missing	*41 (13)*	*7 (26)*	*7 (16)*

ALL, acute lymphoblastic leukaemia; BMI, body mass index; CNS, central nervous system; Gy, gray; ICCC-3, International Classification of Childhood Cancer, 3rd edition; IQR, interquartile range.

3.3. Weight change during treatment by type of cancer

Using multilevel segmented linear regressions, we found that BMI Z-scores tended to increase throughout treatment in ALL patients ($\beta_{0-0.6\ yrs}$: 0.4; 95%CI: 0.1, 0.7; $\beta_{\geq 0.6\ yrs}$: 0.3; 0.2, 0.5) (Table 4), especially during early treatment from diagnosis until end of the induction phase ($\beta_{0-0.1\ yrs}$: 2.3; 95%CI: −0.2, 4.8) (Fig. 2, Supplementary Table 2). BMI Z-score also tended to increase throughout the whole treatment period in lymphoma patients

Table 2
BMI Z-scores at diagnosis and at the end of treatment.

	BMI Z-score mean (SD)		
	Diagnosis (n = 327)	End of treatment (n = 327)	Difference between diagnosis and end of treatment
All CCS	−0.10 (1.1)	−0.08 (1.3)	0.02 (1.1)
Gender			
Girl	−0.13 (1.2)	−0.30 (1.3)	−0.17 (1.1)
Boy	−0.08 (1.1)	0.10 (1.3)	0.18 (1.0)
Age at diagnosis			
<5	−0.19 (1.2)	0.02 (1.3)	0.21 (1.2)
5-9	−0.18 (1.0)	−0.19 (1.4)	−0.01 (1.1)
10-14	−0.05 (1.0)	−0.18 (1.2)	−0.14 (0.9)
≥15	0.26 (1.1)	0.03 (1.4)	−0.23 (0.9)
ICCC-3 diagnosis			
Ia: ALL	−0.14 (1.2)	0.28 (1.1)	0.42 (1.0)
II: Lymphoma	−0.07 (1.0)	0.22 (1.1)	0.29 (0.9)
III: CNS tumour	−0.25 (1.4)	−0.60 (1.6)	−0.35 (1.3)
VIII-IX: Sarcoma	−0.08 (0.9)	−0.32 (1.2)	−0.24 (0.8)
Other	−0.02 (1.1)	−0.26 (1.3)	−0.24 (1.2)
Cranial radiation therapy			
No	−0.14 (1.1)	−0.04 (1.3)	0.10 (1.1)
<20 Gy	0.41 (1.6)	0.55 (1.4)	0.14 (0.9)
≥20 Gy	−0.05 (1.1)	−0.84 (1.3)	−0.79 (1.0)
Parenteral/enteral nutrition support			
No	−0.04 (1.1)	0.06 (1.2)	0.11 (1.0)
Yes	−0.24 (1.1)	−0.41 (1.4)	−0.17 (1.3)
BMI at diagnosis			
Underweight	−1.64 (0.6)	−0.98 (1.1)	0.66 (1.0)
Normal	0.07 (0.6)	−0.04 (1.1)	−0.11 (1.1)
Overweight	1.98 (0.7)	1.70 (1.3)	−0.29 (0.9)

ALL, acute lymphoblastic leukaemia; BMI, body mass index; CCS, childhood cancer survivors; CNS, central nervous system; Dx, diagnosis; Gy, gray; ICCC-3, International Classification of Childhood Cancer, 3rd edition; OW, overweight; SD, standard deviation.

($\beta_{0-0.2\ yrs}$: 1.5; 0.2, 2.9; $\beta_{\geq 0.2\ yrs}$: 0.6; 0.2, 1.1). In patients with CNS tumours, sarcoma, and other types of cancer BMI Z-scores tended to drop during the first half of the treatment period (β_{CNS}: -1.4; -2.7, -0.2; $\beta_{sarcoma}$: -1.4; -2.0, -0.7; β_{other}: -0.3; -1.5, 0.9), but tended to increase thereafter ($coef_{CNS}$: 0.2; -0.5, 0.9; $coef_{sarcoma}$: 1.2; 0.7, 1.7, $coef_{other}$: 0.6; 0.1, 1.1) (Table 4).

In post hoc analyses of ALL patients, BMI Z-scores of ALL patients who were <7 years at diagnosis tended to increase during treatment ($\beta_{0-33\ days}$: 3.8; 0.5, 7.0; $\beta_{34-99\ days}$: -0.4; -1.9, 1.0; $\beta_{\geq 100\ days}$: 0.2; 0.1, 0.3) (Supplementary Table 2, Supplementary Fig. 1A). BMI Z-scores of older ALL patients tended to drop during the induction phase of their cancer treatment protocol ($\beta_{0-33\ days}$: -1.5; -5.1, 2.2), and increase thereafter ($\beta_{34-99\ days}$: 0.5; -1.3, 2.2; $\beta_{\geq 100\ days}$: 0.3; 0.2, 0.4) (Supplementary Table 2, Supplementary Fig. 1B).

4. Discussion

The prevalence of overweight at diagnosis of Swiss CCP increased from 8% at diagnosis to 13% at the end of treatment. Being a boy and being diagnosed with ALL or lymphoma were risk factors for weight gain during treatment. Patients with ALL and lymphoma showed a continuously increasing trend in BMI Z-scores over the treatment period. The increase was particularly steep during early treatment in ALL patients, from diagnosis until end of induction. However, in older ALL patients (≥7 years at diagnosis) BMI initially tended to drop and increase later.

4.1. Prevalence of overweight and BMI Z-scores in comparison with other studies

Direct comparison with other studies is limited due to the lack of studies including all types of cancers and different overweight definitions that were used. A Dutch prospective study in 133 CCP with a median age of 8 years, found that 5% of the children were

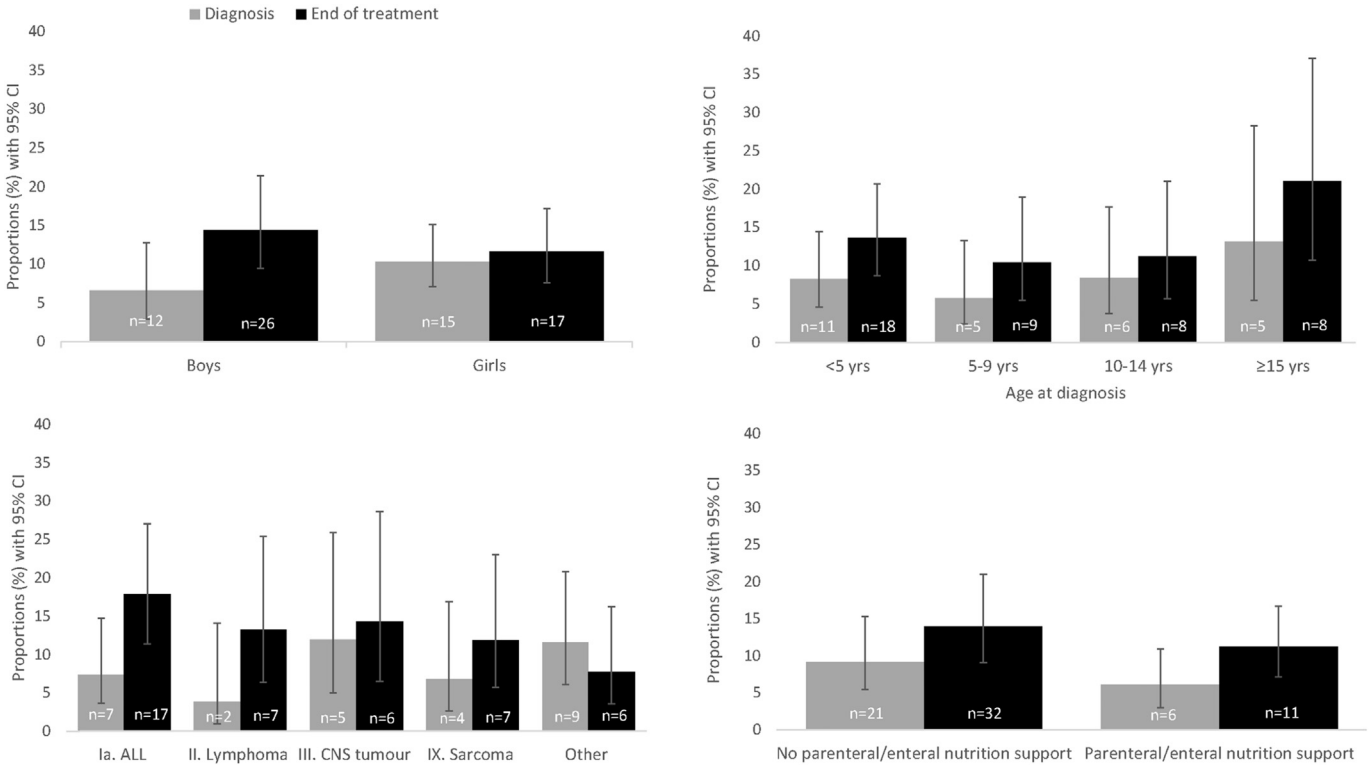

Fig. 1. Prevalence of overweight at diagnosis and end of treatment for childhood cancer patients by gender, age at diagnosis, type of cancer, and nutritional support. CI, confidence interval; ALL, acute lymphoblastic leukaemia; CNS, central nervous system.

Table 3
Risk factors for change in BMI per Z-score from diagnosis until end of treatment (retrieved from univariable and multivariable linear regression models).

	β (95% CI) for change in BMI per Z-score from diagnosis until end of treatment			
	Univariable		Multivariable[a]	
	β (95% CI)	p-value[b]	β (95% CI)	p-value[b]
Gender				
Girl	Ref		Ref	
Boy	0.35 (0.12–0.59)	0.003	0.30 (0.09–0.51)	0.005
Age at diagnosis, years	−0.03 (−0.05 to 0.01)	0.007	−0.03 (−0.05 to 0.01)	0.010
ICCC-3 diagnosis				
Other	Ref		Ref	
Ia: ALL	0.66 (0.35–0.98)		0.54 (0.24–0.84)	
II: Lymphoma	0.53 (0.17–0.90)		0.57 (0.20–0.95)	
III: CNS tumour	−0.11 (−0.50 to 0.28)		0.10 (−0.30 to 0.50)	
VIII-IX: Sarcoma	0.01 (−0.35 to 0.36)	<0.001	0.11 (−0.24 to 0.46)	<0.001
Cranial radiotherapy				
No	Ref		Ref	
<20 Gy	0.05 (−0.49 to 0.58)		0.30 (−0.20 to 0.80)	
≥20 Gy	−0.88 (−1.30 to 0.46)	<0.001	−0.58 (−1.02 to 0.14)	0.015
Parenteral/enteral nutrition support				
No	Ref		Ref	
Yes	−0.28 (−0.53 to 0.02)	0.035	−0.29 (−0.53 to 0.06)	0.016
Birthweight				
Low: <2500	0.03 (−0.50 to 0.55)		–	–
Normal: 2500-4000	Ref			
High: >4000	0.06 (−0.36 to 0.49)	0.992		
BMI at diagnosis (BMI Z-scores)	−0.29 (−0.40 to 0.19)	<0.001	−0.29 (−0.39 to 0.20)	<0.001

ALL, acute lymphoblastic leukaemia; BMI, body mass index; CI, confidence interval; CNS, central nervous system; Gy, gray; ICCC3, International Classification of Childhood Cancer, 3rd edition; OR, odds ratio.
[a] Adjusted for gender, age at diagnosis, ICCC-3, CRT, parenteral/enteral nutrition support, and weight at diagnosis.
[b] p-value calculated from F-test.

Table 4
Slopes of change in BMI Z-score from multilevel segmented linear regression models[a] for childhood cancer patients by cancer type.

ICCC-3 diagnosis	slope 1 β (95%CI)	slope 2 β (95%CI)	Break point, years[b]
ALL	0.38 (0.08–0.69)	0.32 (0.19–0.45)	0.61
Lymphoma	1.53 (0.18–2.87)	0.62 (0.17–1.07)	0.22
CNS	−1.44 (−2.73 to 0.16)	0.22 (−0.46 to 0.89)	0.37
Sarcoma	−1.39 (−2.04 to 0.74)	1.18 (0.72–1.65)	0.34
Other	−0.28 (−1.50 to 0.89)	0.61 (0.09–1.14)	0.27

ALL, acute lymphoblastic leukaemia; BMI, body mass index; CI, confidence interval; CNS, central nervous system; ICCC-3, International Classification of Childhood Cancer, 3rd ed.
[a] Adjusted for gender, age, cumulative cranial radiation therapy, parenteral/enteral nutrition support, and BMI at diagnosis with a random effect on patient level.
[b] Breakpoint defined at the median treatment duration within each diagnostic group.

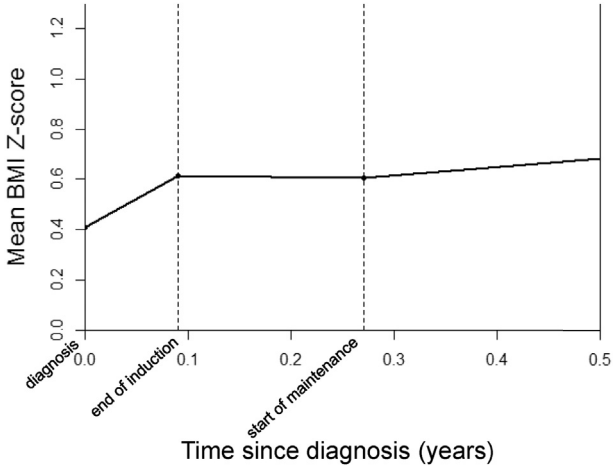

Fig. 2. Slope of change in BMI Z-score from a multilevel segmented linear regression model[a] for childhood acute lymphoblastic leukaemia patients (n = 95). [a] Adjusted for gender, age at diagnosis, cranial radiation therapy, parenteral/enteral nutrition support, and BMI at diagnosis with a random effect on patient level. Breakpoints defined at the end of the induction period (33 days, 0.09 years) and the start of the maintenance period (99 days, 0.27 years).

overweight at diagnosis, and 10% one year later [12]. They used higher cut-offs to define overweight than we did, which might explain the lower prevalence. We found similar overweight prevalence in the general Swiss population; 12% in the general population versus 8% in CCP at diagnosis to 13% at the end of treatment [24]. In a study in the US, 55% of 183 patients were overweight at diagnosis and 69% at the end of treatment [6] while in another US-based study 21% of 83 ALL patients were overweight and this rose to almost 40% at the end of treatment [8]. The BMI Z-scores of these respective ALL patients increased between diagnosis and end of treatment from 0.2 to 0.8 and 0.6 to 1.1 respectively [6,8]. These studies are in accord with the higher prevalence of overweight seen in the general US population, with around 33% of the children being overweight [25]. We observed a lower prevalence of overweight, 7%, at diagnosis, and 18% at the end of treatment. In our study mean BMI Z-score in ALL patients increased from −0.1 to 0.3 during the observation period, with an accentuated weight increase during early treatment potentially due to the high doses of glucocorticoids given during this treatment period in all patients with ALL. Glucocorticoids may also effect linear growth suppression which could be associated with a BMI increase [26,27]. The overall increase in BMI we observed in ALL patients is in line with previous literature [6–8,13,28,29].

Patients with CNS tumours, especially those diagnosed with craniopharyngioma, astrocytoma, or ependymoma have been reported to be at increased risk of overweight after treatment [2,4]. We could not confirm this. We found that the BMI Z-score of CNS patients dropped during the first four months of treatment, but tended to increase afterwards. These results are in contrast to 36 CNS patients in the Dutch study mentioned above in whom a rapid

increase in BMI Z-scores was observed after diagnosis [12]. The differences in these results might be due to the higher proportion of medulloblastoma patients in our study who are often undernourished [17], whereas the opposite is seen for patients diagnosed with astrocytoma and craniopharyngioma.

4.2. Risk factors for weight gain during treatment in relation to other studies

Mixed results are reported in literature. Female gender [4,7,10,14], and male gender have been associated with becoming overweight during treatment [9,30,31], while no gender association has also been observed [13]. We found that boys were more likely to gain weight than girls, which is in line with the gender differences found in the general Swiss child population [32]. Furthermore, we found that ALL patients who were older at diagnosis (≥7 years) tended to show a decline in BMI during the induction treatment phase, after which BMI tended to increase. This initial drop may reflect the physiological and psychosocial burden of a cancer diagnosis among children who are old enough to fully understand its consequences and hazards. We observed the same tendency for all cancer diagnosis groups combined. Weight at diagnosis was associated with overweight at the end of treatment in other studies [8,9,33]. This has not been seen, however, in meta-analysis: weight gain during treatment was independent of weight at diagnosis, but patients who were underweight at diagnosis showed a greater BMI increase than normal and overweight patients [13]. We saw an inverse association between BMI at diagnosis and change of BMI during treatment with an overall increase in BMI Z-scores in underweight patients and a decrease in overweight patients; however, the majority of overweight patients at diagnosis stayed overweight at end of treatment (70%).

4.3. Limitations and strengths of the study

Our study is limited by its retrospective study design. Weight and height measurements were based on routine, clinically indicated measurements, documented in charts, and were not taken at specific times during patients' treatments. Second, BMI Z-scores do not measure the ratio of lean to fat mass or the fat distribution. Although BMI Z-scores are an easy, low cost, and appropriate method to assess overweight, they correlate less with body fat than other methods such as skinfold measurements, underwater weighing, dual energy X-ray, or magnetic resonance imaging [34], and are not recommended as a sole overweight indicator in childhood cancer patients [35]. Third, we did not collect data on lifestyle and social factors like diet, physical activity, and parenting style that could potentially affect weight gain during treatment. Finally, the multilevel segmented linear regression models were a poor fit to the highly variable BMI Z-score curves of individual patients. More complex analyses are required to take this heterogeneity into account among patients.

Despite these limitations, our study is among the few to have captured weight at diagnosis and end of treatment in childhood cancer patients of all diagnoses. We chose the IOTF cut-off values [20], which are stricter than national cut-offs [6–8], to define overweight for international comparability. Finally, we had access to detailed clinical information of patients from the SCCR.

4.4. Implications for future recommendations

Overweight plays a significant role in childhood cancer treatment [3,4,33] and has been reported to affect treatment-related toxicity, relapse rates, and (event-free) survival rates [3,4,36]. Weight gain during treatment tends to persist in ALL patients beyond treatment completion [13]. Early weight management should therefore be emphasized. Furthermore, in overweight CCP lower emotional, cognitive, and social functioning has been reported compared to children with a normal weight [5]. This can reveal new target areas for overweight interventions because awareness of influential factors can help to proactively introduce and specifically review current methods. Since early overweight is a risk factor for overweight later in life, weight management interventions should be individually tailored and provided especially to patients who have a high risk of developing overweight during treatment. Overweight later in life is associated with development of chronic cardiac disorders and type II diabetes [37]. As CCP already have an increased risk of developing these disorders, early overweight management could prevent long-term consequences [1]. Purposeful prevention and treatment measures should be developed and implemented with regard to encouraging a balanced diet and sufficient physical exercise. Focus should lie on the prevention of overweight and underweight as 19% of the patients were underweight at diagnosis and 22% at end of treatment. Both overweight and underweight CCP have a reduced health-related quality of life compared to normal weight CCP [5]. Therefore, future research needs to focus on testing interventions that aim to improve the nutritional status of children with cancer and behavioural interventions should be well grounded in theory and empirical evidence as they are complex.

5. Conclusion

This multicentre cohort study found that overall prevalence of overweight markedly increased in CCP within an average treatment duration of less than one year. Lifestyle interventions to prevent overweight development should start early during treatment, particularly for patients diagnosed with ALL or lymphoma.

Statement of authorship

FB conducted the statistical analyses and wrote the final article, JWZ performed initial statistical analyses and wrote the first draft of the article, KZ designed the study and collected the complementary registry data, and BS, KZ, and CK gave support in the statistical analyses. All authors have participated in the data interpretation, and have revised and approved the final article.

Funding sources

The work of the Swiss Childhood Cancer Registry is supported by the Swiss Paediatric Oncology Group (www.spog.ch), Schweizerische Konferenz der kantonalen Gesundheitsdirektorinnen und −direktoren (www.gdk-cds.ch), Swiss Cancer Research (www.krebsforschung.ch), Kinderkrebshilfe Schweiz (www.kinderkrebshilfe.ch), the Federal Office of Public Health (FOPH) and the National Institute of Cancer Epidemiology and Registration (www.nicer.org). FNB is supported by a research grant from the Swiss Cancer League (KLS-3412-02-2014 and KLS-3644-02-2015) and Foundation Force, CHUV, Lausanne, Switzerland. BDS is supported by a Swiss National Science Foundation fellowship (PZ00P3_147987).

Conflicts of interest

None of the authors report any conflict of interest related to the study.

Acknowledgements

The authors express their gratitude to all childhood cancer patients who supported this study. Additionally, we would like to

thank Christopher Ritter for editorial assistance. A previous abstract on this study was submitted to the 39th Annual Congress of the European Society for Clinical Nutrition and Metabolism (ESPEN) and was a ESPEN 2017 Annual Congress paper of excellence.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.clnu.2018.02.022.

References

[1] Hudson MM, Ness KK, Gurney JG, Mulrooney DA, Chemaitilly W, Krull KR, et al. Clinical ascertainment of health outcomes among adults treated for childhood cancer: a report from the St. Jude lifetime cohort study. JAMA. J Am Med Assoc 2013;309:2371–81.
[2] Siviero-Miachon AA, Spinola-Castro AM, Guerra-Junior G. Adiposity in childhood cancer survivors: insights into obesity physiopathology. Arquivos Brasileiros Endocrinol Metabol 2009;53:190–200.
[3] Reilly JJ. Obesity during and after treatment for childhood cancer. In: Endocrinopathy After Childhood Cancer Treatment. Karger Publishers; 2009. p. 40–58.
[4] Co-Reyes E, Li R, Huh W, Chandra J. Malnutrition and obesity in pediatric oncology patients: causes, consequences, and interventions. Pediatr Blood Canc 2012;59:1160–7.
[5] Brinksma A, Sanderman R, Roodbol PF, Sulkers E, Burgerhof JGM, de Bont ESJM, et al. Malnutrition is associated with worse health-related quality of life in children with cancer. Support Care Canc 2015;23:3043–52.
[6] Esbenshade AJ, Simmons JH, Koyama T, Koehler E, Whitlock JA, Friedman DL. Body mass index and blood pressure changes over the course of treatment of pediatric acute lymphoblastic leukemia. Pediatr Blood Canc 2011;56:372–8.
[7] Iughetti L, Bruzzi P, Predieri B, Paolucci P. Obesity in patients with acute lymphoblastic leukemia in childhood. Ital J Pediatr 2012;38. 4-.
[8] Zhang FF, Rodday AM, Kelly MJ, Must A, MacPherson C, Roberts SB, et al. Predictors of being overweight or obese in survivors of pediatric acute lymphoblastic leukemia (ALL). Pediatr Blood Canc 2014;61:1263–9.
[9] Love E, Schneiderman JE, Stephens D, Lee S, Barron M, Tsangaris E, et al. A cross-sectional study of overweight in pediatric survivors of acute lymphoblastic leukemia (ALL). Pediatr Blood Canc 2011;57:1204–9.
[10] Iughetti L, Bruzzi P. Obesity and craniopharyngioma. Ital J Pediatr 2011;37:38.
[11] Bereket A, Kiess W, Lustig RH, Muller HL, Goldstone AP, Weiss R, et al. Hypothalamic obesity in children. Obes Rev 2012;13:780–98.
[12] Brinksma A, Roodbol PF, Sulkers E, Kamps WA, de Bont ESJM, Boot AM, et al. Changes in nutritional status in childhood cancer patients: a prospective cohort study. Clin Nutr 2015;34:66–73.
[13] Zhang FF, Liu S, Chung M, Kelly MJ. Growth patterns during and after treatment in patients with pediatric ALL: a meta-analysis. Pediatr Blood Canc 2015;62:1452–60.
[14] Brouwer CAJ, Gietema JA, Kamps WA, de Vries EGE, Postma A. Changes in body composition after childhood cancer treatment: impact on future health status - a review. Crit Rev Oncol Hematol 2007;63:32–46.
[15] Michel G, von der Weid NX, Zwahlen M, Adam M, Rebholz C, Kühni C. The Swiss Childhood Cancer Registry: rationale, organisation and results for the years 2001-2005. Swiss Med Wkly 2007;137:502–9.
[16] Michel G, von der Weid NX, Zwahlen M, Redmond S, Strippoli MPF, Kuehni CE. Incidence of childhood cancer in Switzerland: the Swiss childhood cancer registry. Pediatr Blood Canc 2008;50:46–51.
[17] Zimmermann K, Ammann RA, Kuehni CE, De Geest S, Cignacco E. Malnutrition in pediatric patients with cancer at diagnosis and throughout therapy: a multicenter cohort study. Pediatr Blood Canc 2013;60:642–9.
[18] Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. BMJ. Br Med J 2000;320:1240–3.
[19] World Health Organization. WHO child growth standards: methods and development: length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age. Geneva: World Health Organization; 2006.
[20] Cole TJ, Lobstein T. Extended international (IOTF) body mass index cut-offs for thinness, overweight and obesity. Pediatric Obesity 2012;7:284–94.
[21] Belle FN, Weiss A, Schindler M, Goutaki M, Bochud M, Zimmermann K, et al. Overweight in childhood cancer survivors: the Swiss childhood cancer survivor study. Am J Clin Nutr 2018;107(1):3–11.
[22] International statistical classification of diseases and related health problems 10th revision (ICD-10). Chapter XVI, certain conditions originating in the perinatal period (P00-P96), disorders related to length of gestation and fetal growth (P05-P08). 2010.
[23] Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P. International classification of childhood cancer, third edition. Cancer 2005;103:1457–67.
[24] Stamm H, Gebert A, Guggenbühl L, Lamprecht M. Excess weight among children and adolescents in Switzerland-prevalence and correlates for the early 2010s. Swiss Med Wkly 2014;144, w13956.
[25] Skinner AC, Perrin EM, Skelton JA. Prevalence of obesity and severe obesity in US children, 1999-2014. Obesity 2016;24:1116–23.
[26] Ahmed SF, Tucker P, Mushtaq T, Wallace AM, Williams DM, Hughes IA. Short-term effects on linear growth and bone turnover in children randomized to receive prednisolone or dexamethasone. Clin Endocrinol 2002;57:185–91.
[27] Touyz LM, Cohen J, Neville KA, Wakefield CE, Garnett SP, Mallitt K-A, et al. Changes in body mass index in long-term survivors of childhood acute lymphoblastic leukemia treated without cranial radiation and with reduced glucocorticoid therapy. Pediatric Blood & Cancer 2017;64. https://doi.org/10.1002/pbc.26344.
[28] Esbenshade AJ, Simmons JH, Koyama T, Lindell RB, Friedman DL. Obesity and insulin resistance in pediatric acute lymphoblastic leukemia worsens during maintenance therapy. Pediatr Blood Canc 2013;60. https://doi.org/10.1002/pbc.24489.
[29] Ness KK, Armenian SH, Kadan-Lottick N, Gurney JG. Adverse effects of treatment in childhood acute lymphoblastic leukemia: general overview and implications for long-term cardiac health. Expet Rev Hematol 2011;4:185–97.
[30] Razzouk BI, Rose SR, Hongeng S, Wallace D, Smeltzer MP, Zacher M, et al. Obesity in survivors of childhood acute lymphoblastic leukemia and lymphoma. J Clin Oncol 2007;25:1183–9.
[31] Nathan PC, Jovcevska V, Ness KK, Mammone D'Agostino N, Staneland P, Urbach SL, et al. The prevalence of overweight and obesity in pediatric survivors of cancer. J Pediatr 2006;149. 518–525.e2.
[32] Murer SB, Saarsalu S, Zimmermann MB, Aeberli I. Pediatric adiposity stabilized in Switzerland between 1999 and 2012. Eur J Nutr 2014;53:865–75.
[33] Withycombe JS, Smith LM, Meza JL, Merkle C, Faulkner MS, Ritter L, et al. Weight change during childhood acute lymphoblastic leukemia induction therapy predicts obesity: a report from the Children's oncology group. Pediatr Blood Canc 2015;62:434–9.
[34] Cole TJ, Rolland-Cachera MF. Measurement and definition. Child and adolescent obesity: causes, consequences, prevention, and management. 2002. p. 3–27.
[35] Nething J, Ringwald-Smith K, Williams R, Hancock ML, Hale GA. Establishing the use of body mass index as an indicator of nutrition risk in children with cancer. J Parenter Enteral Nutr 2007;31:53–7.
[36] Orgel E, Sposto R, Malvar J, Seibel NL, Ladas E, Gaynon PS, et al. Impact on survival and toxicity by duration of weight extremes during treatment for pediatric acute lymphoblastic leukemia: a report from the Children's oncology group. J Clin Oncol 2014;32:1331–7.
[37] National Institutes of Health. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: the evidence report. Obes Res 1998;6:51S–209S.