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No evidence for overweight in long-term childhood cancer survivors after glucocorticoid treatment

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AUTHOR CONTRIBUTIONS

FNB conducted the statistical analyses and wrote the article; RK, CS, MB, RAA, NXvdW, and CEK contributed to the concept and the design of the study; CS, NXvdW, and RAA gave support in calculating cumulative doses of glucocorticoids, and RK, MB, and CEK gave support in the statistical analyses. All authors have revised earlier drafts and approved the final article.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

ABSTRACT

BACKGROUND: Glucocorticoids can lead to weight gain during cancer treatment, but we know little about their long-term effects in childhood cancer survivors (CCS).

METHODS: As part of the Swiss Childhood Cancer Survivor Study, we sent a questionnaire to CCS residing in Switzerland aged <21 years at diagnosis, who survived ≥5 years and were 15-45 years old at survey. We assessed cumulative doses of glucocorticoids from medical records and study protocols and calculated BMI from self-reported height and weight at survey. We compared prevalence of overweight between CCS, their siblings, and the general population (Swiss Health Survey, SHS) and investigated the association of overweight with treatment-related risk factors using multivariable logistic regression.

RESULTS: The study included 1936 CCS, 546 siblings, and 9591 SHS participants. Median (interquartile range) age of the CCS at survey was 24 (20-31) years and median time since diagnosis was 17 (12-22) years. At survey, 26% of CCS were overweight, a proportion comparable to that among siblings (24%) and the SHS participants (25%). Prevalence of overweight was 24% in CCS treated with glucocorticoids only (n=686), 37% in those with cranial radiation therapy (CRT) (n=127), and 49% in those with both glucocorticoids and CRT (n=101), p<0.001. We found no evidence for a dose-response relationship between cumulative glucocorticoid doses and overweight and no evidence that CRT modified the effect of cumulative glucocorticoid dose treatment on overweight.

CONCLUSION: This study suggests that glucocorticoids used for the treatment of childhood cancer are not associated with long-term risk of overweight.

INTRODUCTION

The glucocorticoids prednisone and dexamethasone are currently part of the standard treatment of acute lymphoblastic leukemia (ALL), non-Hodgkin lymphoma (NHL), and Hodgkin lymphoma (HL). Type of glucocorticoid, dose, and duration of treatment can differ by cancer treatment protocol.[1] Cancer treatment with glucocorticoids can lead to weight gain originating in physiological e.g. altered cortisol concentrations and adipose tissue metabolism and psychological changes that among others may influence appetite and lower energy expenditure due to physical inactivity.[1, 2] An excess of dietary intake and physical inactivity during treatment could be the base for behavioural changes in the long-term leading to continues weight gain during survivorship. Prednisone and dexamethasone have similar mechanisms of action, but dexamethasone in the dose range commonly used causes more adverse effects such as acute metabolic side effects, infections, osteopenia, and behavioral abnormalities.[1, 3] Other treatments for childhood cancer can also affect the development of overweight and obesity in particular cranial radiation therapy (CRT). CRT impairs the hypothalamic-pituitary axis, which in turn can lead to growth hormone deficiency and leptin insensitivity.[4] ALL treatment protocols have not routinely prescribed CRT since the 1980s, and overall cumulative CRT doses have decreased.[5] In contrast, cumulative glucocorticoid doses have increased in the US, and prednisone has been partly replaced by the more potent dexamethasone.[6, 7] Many CCS are overweight, especially in the US, despite decreased doses of CRT.[8]

Glucocorticoids might, therefore, be implicated in excessive weight gain during cancer treatment.[3, 7] But whether glucocorticoids have a longer-lasting effect on weight is uncertain, and any such effect may depend on the dose and duration of treatment. Research has yielded contradictory results. One small (N=169) study of ALL survivors reported a six-fold increased risk of being overweight or obese in ALL survivors with the highest cumulative doses of glucocorticoids (≥10,000 mg/m^2) compared to the lowest doses (<7500 mg/m^2) five years after diagnosis,[9] while another US study found no dose-response effects ≥10 years after diagnosis.[10] In an US study glucocorticoid treatment was associated with obesity 25 years after diagnosis in 776 CCS who were treated with CRT, but cumulative dose and type of glucocorticoid were not assessed.[11] Previous studies have mainly focused on acute effects of glucocorticoids during or shortly after treatment,[9, 12-16] have not assessed cumulative glucocorticoid dose,[11, 13] and often have relatively low numbers of participants (<200).[9, 12-18] Thus it remains unclear whether glucocorticoids affect overweight in CCS long after treatment.

We analyzed data from the Swiss Childhood Cancer Survivor Study (SCCSS) to investigate whether 1) overweight in long-term CCS (on average 17 years after diagnosis) is associated with the cumulative glucocorticoid dose received, 2) there is a dose-response relationship between cumulative glucocorticoid dose and BMI, and 3) the respective effects of prednisone and dexamethasone differ. We studied the entire group of CCS, and separately the three cancer types treated most frequently with glucocorticoids (ALL, NHL, and HL).

METHODS

Sampling

The Swiss Childhood Cancer Survivor Study

The Swiss Childhood Cancer Survivor Study (SCCSS) is a long-term follow-up study of patients registered in the Swiss Childhood Cancer Registry (SCCR, www.childhoodcancerregistry.ch) who have been diagnosed since 1976 and survived ≥5 years after cancer diagnosis.[19] The SCCR is a population-based registry that includes all children and adolescents under age 21 in Switzerland who are diagnosed with leukemia, lymphoma, central nervous system (CNS) tumors, malignant solid tumors, or Langerhans cell histiocytosis.[20, 21] Ethical approval of the SCCR and the SCCSS has been given by the Ethics Committee of the Canton of Bern to (KEK-BE: 166/2014).

As part of the SCCSS, we traced addresses of all CCS diagnosed between 1976-2005, who we sent questionnaires between 2007-2013. A second questionnaire was sent to nonresponders four to six weeks later. If they again did not respond, we contacted them by phone. Our questionnaire included core questions from the US and UK CCS studies,[22, 23] with added questions about health behaviors and sociodemographic measures from the Swiss Health Survey (SHS)[24] and the Swiss Census.[25] Detailed information on our study design has been published previously.[19, 26]

Comparison groups

We used two comparison groups in this study: siblings of the CCS and a random sample of the general Swiss population represented by data from the Swiss Health Survey (SHS). The sibling survey

was conducted from 2009 to 2012. We asked CCS for consent to contact siblings and for contact information. We sent siblings the same questionnaire as CCS, omitting questions about cancer history. Siblings who did not respond received another copy of the questionnaire four to six weeks later, but were not contacted by phone.[19]

The second comparison group consisted of participants in the SHS questionnaire 2012.[24] This is a nationally representative telephone survey repeated every five years. The SHS compiled a randomly selected sample of Swiss households with telephone landlines and attempted to contact someone in each household. Sampling was stratified by region and in the selected households the survey was administered to the consenting household member, age 15 years or older, who first answered the phone.

Measurements

Body weight and BMI

Body weight and height at the time of survey were collected from the questionnaires. We instructed all study participants and control groups to record height without shoes and weight without clothes. We calculated BMI by dividing weight by height in meters squared (kg/m^2). Adult BMI <18.5 kg/m^2 was classified as underweight, ≥18.5 to <25 kg/m^2 as normal weight, and ≥25 kg/m^2 as overweight including obesity.[27] For adolescents 15-19 years at survey, we standardized BMI into z-scores for age and gender using the latest available Swiss references.[28] BMI z-scores lower than -2 were classified as underweight, from -2 to 1 as normal weight, and >1 as overweight including obesity.[29]

Glucocorticoids

We calculated prednisone and/or dexamethasone doses based on the intended doses in the cancer treatment protocol and, if applicable, the treatment arm. Glucocorticoid tapering was taken into account if protocols indicated this. In the event tapering information on duration and dosage was missing, we assumed that the dosage decreased by 50% of the prior dose in three steps over three days. The few protocols (3%) that prescribed glucocorticoids by body weight (mg/kg) were converted into dose per body surface area (mg/m^2) by multiplying the dose in mg/kg by a conversion factor of 30,

which represents an average of the factors for persons weighing 20 and 60 kg.[30] Glucocorticoids administered by intrathecal route and for supportive care or immunosuppression, were not taken into consideration.[1] Treatment protocols that were included came from the Swiss Pediatric Oncology Group (31%), Pediatric Oncology Group (29%), Berlin/Frankfurt/Muenster study group (24%), German Society of Pediatric Oncology and Hematology (7%), and others (9%) (**Supplementary Table 1**). In 67 cases in which the study arm was unknown, survivors were assigned to the protocol arm with the lowest glucocorticoid dosage. We calculated the total cumulative glucocorticoid dose in equivalent of prednisone for each patient using the formula cumulative glucocorticoid dose = cumulative prednisone dose + (cumulative dexamethasone dose x 6.67) in mg/m^2.[31] The recommended cumulative glucocorticoid doses dropped over time when all cancer types were combined, and specifically for each type of cancer with the exception of ALL protocols, in which doses increased (**Supplementary Figure 1**). We assessed other clinical and sociodemographic variables as described previously.[26]

Statistical analysis

We included all SCCSS survivors and their siblings, and the SHS participants in the general population, who were aged 15-45 years at time of survey and provided self-reported height and weight (**Supplementary Figure 2**). We excluded CCS with hematopoietic stem cell transplantation (HSCT); this specific group is at substantial risk of underweight due to chronic graft-versus-host disease and long-term immunosuppression with recurrent infections.[32] For better comparison between CCS and peers, we standardized comparison groups for gender, age at survey, migration background, and language region as described previously.[26] First, we assessed whether overweight at survey was associated with the cumulative glucocorticoid dose during treatment. We determined these associations using multivariable logistic regression within all CCS, and within patients with the three cancer types frequently treated with glucocorticoids. We divided BMI into two categories: overweight (overweight and obesity) versus non-overweight (underweight and normal) because the group of obese people was small and the glucocorticoids and CRT risk estimates for the two categories overweight and obesity had the same direction and comparable magnitude. Cumulative prednisone and glucocorticoid usage was divided into three categories: lower than the median intake of all CCS, median to third quartile, and equal to or higher than the third quartile. Cumulative dexamethasone was divided into two categories: lower than the median intake of all CCS, and equal to or higher than the

median. We adjusted the models for gender, age at diagnosis, time since diagnosis, and cumulative CRT and/or glucocorticoid dose. We used interaction terms to test whether age, gender, and the clinical variables e.g. age at diagnosis, year of diagnosis, time since diagnosis, and CRT modified the effect of cumulative glucocorticoid dose treatment on overweight since these variables are related to the total dose. Second, we illustrated the dose-response relationship by comparing the distribution of BMI by cumulative glucocorticoid dose in steps of 1000 mg/m^2 (prednisone and total glucocorticoids) or 100 mg/m^2 (dexamethasone) with boxplots. Because 26% of CCS were 15-19 years at survey, we used BMI Z-scores for all CCS. We used trend tests to test for an ordered relationship between cumulative glucocorticoid dose categories and BMI Z-scores. Third, we examined whether effects differed between dexamethasone and prednisone treatment again using multivariable logistic regression models. Finally, we performed sensitivity analyses to compare standardized data for gender, age, migration background, and language region in all comparison groups according to the distribution in CCS to non-standardized data. For the 67 survivors for whom the study arm was unknown we performed sensitivity analyses in which they were excluded or were assigned to the protocol arm with the highest glucocorticoid dose instead of the lowest. We used Stata (version 14, Stata Corporation, Austin, Texas) for all statistical analyses.

RESULTS

Response rate and characteristics of the study populations

Among 4116 eligible CCS we traced and contacted 3593 of whom 2527 returned the SCCSS questionnaire. We excluded 119 participants who did not report height and weight, 355 who were younger than 15 or older than 45 years, and a further 117 who had received HSCT. We thus included 1936 CCS in this study, of whom 546 had been treated for ALL, 114 NHL, 195 HL, and 1081 for other types of cancer (**Supplementary Figure 2**).

We received consent to contact 1530 siblings, of whom 866 returned the questionnaire; 300 were outside the age range, and 20 did not report height and weight, thus 546 siblings were finally included in the analyses. Of 41,008 households surveyed in the general population (SHS), 21,597 replied to the

survey. In those responding households, 9591 persons who were aged 15-45 years were included in the analysis.

Among CCS, median age at diagnosis was 8 (IQR 4–13) years overall, 5 (3–9) years for ALL, 11 (8–14) for NHL, and 14 (12–16) for HL survivors **(Table 1)**. The median time from diagnosis to survey was 17 (IQR 12–22) years for CCS overall, 18 (13–23) for ALL, 17 (12-22) for NHL, and 15 (10-21) for HL survivors. Most ALL survivors had received glucocorticoids (96% prednisone, and 34% dexamethasone). NHL and HL were less often treated with glucocorticoids (86% NHL, and 59% HL). Sociodemographic characteristics were mostly identical between CCS and the comparison groups after standardization, except that fewer CCS than both siblings and the general population completed tertiary education **(Table 2).** CCS engaged in less sports than siblings, but were comparable to the general population.

Overweight and glucocorticoid therapy

The prevalence of overweight among all CCS was 26% at survey. This was similar to the overweight prevalence in the comparison groups after standardization according to CCS: 24% in siblings (p=0.34) and 25% in the general population (p=0.48) **(Table 2, Supplementary Figure 3).** When we stratified CCS by the treatment, we found that the prevalence of overweight was 23% in CCS treated with no glucocorticoids and no CRT (205 of 889), 24% in those treated with glucocorticoids alone (166 of 686), 37% in CCS treated with ≥20 Gy CRT (47 of 127, p<0.01), and 49% in those treated with both glucocorticoids and ≥20 Gy CRT (49 of 101, p<0.001) **(Figure 1)**. There was a weak trend (p=0.08), suggesting an interaction that the effect of CRT tended to be higher in CCS also treated with glucocorticoids.

In multivariable logistic regression models we found that overweight was not associated with cumulative glucocorticoid dose either in CCS overall or in the three cancer types treated frequently with glucocorticoids (**Table 3**). But, CCS and ALL survivors treated with ≥20 Gy CRT were more likely to be overweight. Interaction tests did not suggest that the cumulative effect of glucocorticoids differed

by gender, age, year of diagnosis, time since diagnosis, chemotherapy, CRT, or history of relapse (**Supplemental Table 2**).

Dose-response relationship between overweight and glucocorticoids

We found no evidence supporting a dose-response relationship between cumulative prednisone, dexamethasone, or both combined and BMI Z-scores, either when stratifying for CRT ($p_{trend\ no\ CRT}$=0.994, $p_{trend\ <20Gy}$=0.510, and $p_{trend\ ≥20Gy}$= 0.174, **Figure 2**), or when analyzing the entire CCS group adjusted for cumulative CRT dose ($p_{trend\ prednisone}$=0.085, $p_{trend\ dexamethasone}$=0.176, and $p_{trend\ glucocorticoids}$ =0.583 **Supplementary Figure 4**). CCS who got high prednisone doses (≥8000 mg/m^2) tended to have higher BMI Z-scores. In ALL survivors we also observed no dose-response relationship ($p_{trend\ prednisone}$=0.223, $p_{trend\ dexamethasone}$=0.063, and $p_{trend\ glucocorticoids}$ =0.512, **Supplementary Figure 5).**

Prednisone versus dexamethasone

In unadjusted analyses, CCS who were treated with the highest cumulative dose of prednisone (≥5824 mg/m^2) tended to be more overweight than those treated with the lowest dose (<2520 mg/m^2). This was not significant after adjustment for time since diagnosis. We made further adjustments for gender, age at diagnosis, cumulative cranial radiation therapy, and dexamethasone **(Table 3)**. In contrast, ALL survivors who were treated with at a higher dexamethasone dose (≥1260 mg/m^2) were less likely to be overweight than those treated with a lower dose (<1260 mg/m^2).

DISCUSSION

At a median 17 years after cancer diagnosis, 26% of CCS in Switzerland were overweight. This prevalence is comparable to that in siblings and healthy peers in the general population. Prevalence of overweight was 23% in those CCS treated with glucocorticoids, but higher for CCS treated with cranial radiation ≥20 Gy (37%), and yet higher among CCS treated with both glucocorticoids and cranial radiation ≥20 Gy (49%). The effect of CRT on overweight tended to be higher if CCS were also treated with glucocorticoids, but power for interaction tests was low. There was no evidence for a dose-

response relationship between the cumulative glucocorticoid dose and being overweight, except for a possible effect at the highest doses (prednisone ≥8000 mg/m^2).

Overweight and obesity during treatment is frequent in ALL patients who receive high doses of glucocorticoids,[33] but the long-tern impact of glucocorticoids on overweight has not been well studied. An US study of 784 ALL survivors followed over 26 years found an association of obesity with CRT, but not cumulative glucocorticoid dose. That finding is similar to ours, but ALL survivors with low glucocorticoid doses in the US study received high CRT doses. This could have masked an association between glucocorticoids and obesity.[34] A Dutch study of 113 ALL survivors 10 years after treatment found that higher cumulative prednisone doses led to higher BMI Z-scores at end of treatment and shortly thereafter, but not in the long-term.[18] The cumulative prednisone doses in the study were much higher than ours; of the 65 survivors who received only prednisone 60 (92%) survivors had received a cumulative dose of 9800 mg/m^2, or more. We also found post hoc evidence that higher cumulative prednisone doses (≥8000 mg/m^2) lead to more overweight, but after multivariable adjustment this effect disappeared. A dose-response association between cumulative glucocorticoid dose and BMI was also seen in a longitudinal single-center study in the US of 165 ALL survivors. BMI was assessed five years after diagnosis and again, cumulative glucocorticoid doses were higher (around 50% had a cumulative dose of >9000 mg/m^2).[9] We found in univariable analyses that survivors who got the highest cumulative prednisone dose (≥5824 mg/m^2) were more likely to be overweight. After adjustment, the association was similar in magnitude and direction, but was no longer significant. We did not find an association between cumulative dexamethasone and overweight in CCS. However, follow-up time was longer in CCS treated with prednisone because dexamethasone was introduced more recently. ALL survivors who got a cumulative dexamethasone dose of ≥1260 mg/m^2 were even less likely to be overweight than those who were treated with a lower dosage. The dose-response relationship between cumulative dexamethasone and BMI Z-scores showed a dent with higher doses of dexamethasone. Given the wide confidence intervals this finding is most likely due to chance. The dint could also be a surrogate for more severe disease and more intense treatment, leading to less weight gain over time. Studies that look at the association between glucocorticoids and overweight in survivors of tumors other than ALL are limited. In 88 HL survivors in complete continuous remission for 16 years, no difference in BMI was found between those treated

with and without prednisone.[17] The glucocorticoid dose is lower and chemotherapy duration is shorter in HL compared to ALL survivors. We saw no association between glucocorticoids and overweight in either survivor group.

This study is the largest of its kind to have looked at cumulative glucocorticoid dose and overweight in CCS long after end of treatment. It also had a specific focus on ALL, NHL, and HL survivors who usually receive high doses of glucocorticoids. Other strengths include its national coverage and high response rate, which increase confidence that the results are representative, as does its access to both socioeconomic factors and detailed treatment data. We also compared CCS with two other groups from whom contemporaneous data were collected: CCS siblings, and the general population in Switzerland. Among the study's limitations was the unavailability of patient dose levels, which necessitated deriving cumulative glucocorticoid doses from cancer protocol information. This could have led to either under- or over estimation of the cumulative glucocorticoid dose when the protocol arm was unknown. But for only 67 survivors was the study arm unknown. Sensitivity analyses where we excluded those with unknown study arms or were we assigned them to the highest dose instead of the lowest dose found the same results. Only 239 CCS were treated with dexamethasone because, though we included CCS diagnosed since 1976, dexamethasone use has increased only recently.[7] Height and weight at survey were self-reported; both under- and over-reporting could have occurred. However, since height and weight were self-reported in all study populations we expected the degree of nondifferential errors of BMI assessment to be similar across all CCS, the comparison groups, and across CCS treated with different glucocorticoid doses. Finally, we used BMI as a measure of overweight. BMI measures neither the ratio of lean to fat mass nor fat distribution. Since glucocorticoids have a catabolic effect on muscle, CCS could have less lean mass and more fat mass than the general population with a similar BMI.[35] However, BMI is a practical and inexpensive proxy measure of overweight that is widely used in population-based studies.

Treatment of childhood cancer increases survivors' risk of chronic diseases. Overweight can worsen disease burden, in particular when it involves development of endocrine complications such as type II diabetes. While our study does not suggest glucocorticoids are associated with long-term overweight, advice on weight control, a healthy lifestyle, and physical activity should always be part of survivorship

care, with a special focus on patients who received CRT as well as potentially those who received very high doses of glucocorticoids.

Essentially, however, the findings of our study are comforting: treatment with glucocorticoids leads to overweight at the time of treatment,[9, 12-14, 16] but our results suggests that glucocorticoid treatment is not a reason for concern for long term overweight in CSS.

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TABLE 1. Clinical characteristics of childhood cancer survivors

	CCS (*n*=1936)		ALL survivors (*n*=546)			NHL survivors (*n*=114)			HL survivors (*n*=195)		
Characteristics	*n*	(%)	*n*	(%)	***p-value***[a]	*n*	(%)	***p-value***[a]	*n*	(%)	***p-value***[a]
Age at diagnosis, median (IQR)	7.8	(3.7-13.1)	5.1	(3.1-9.1)	***<0.001***	11.1	(7.7-14.0)	***<0.001***	14.2	(11.6-15.9)	***<0.001***
Time since diagnosis, median (IQR)	16.5	(11.8-22.1)	18.1	(13.3-23.3)	***<0.001***	16.8	(11.6-22.0)	***0.918***	14.7	(9.5-21.4)	***<0.001***
Year of diagnosis											
1976-1988	667	(34)	242	(44)	***<0.001***	41	(36)	***0.653***	50	(26)	***<0.001***
1989-1996	703	(36)	187	(34)		44	(39)		58	(30)	
1997-2005	566	(29)	117	(21)		29	(25)		87	(45)	
History of relapse	194	(10)	58	(11)	***0.580***	8	(7)	***0.271***	13	(7)	***0.100***
Chemotherapy	1494	(77)	546	(100)	***<0.001***	111	(97)[b]	***<0.001***	171	(88)	***<0.001***
Prednisone exposure[c]	852	(44)	524	(96)	***<0.001***	84	(74)	***<0.001***	116	(59)	***<0.001***
Dose, median (IQR), mg/m^2	2520	(1680-5824)	2880	(1680-5824)		1836	(1836-3880)		3060	(2340-4824)	
Dexamethasone exposure[c]	239	(12)	183	(34)	***<0.001***	34	(30)	***<0.001***	-		***<0.001***
Dose, median (IQR), mg/m^2	1260	(250-1260)	1260	(770-1260)		236	(200-240)		n.a.		
Glucocorticoids[c]	882	(46)	528	(97)[d]	***<0.001***	98	(86)	***<0.001***	116	(59)	***<0.001***
Dose, median (IQR), mg/m^2	3470	(1960-8100)	5824	(3360-10084)		2520	(1836-3516)		3060	(2340-4824)	
CRT											
Yes, <20 Gy	133	(7)	71	(13)	***<0.001***	4	(4)	***0.234***	17	(9)	***<0.001***
Yes, ≥20 Gy	228	(12)	65	(12)		11	(10)		4	(2)	
Glucocorticoids and CRT											
No glucocorticoids and No CRT	889	(46)	17	(3)	***<0.001***	16	(14)	***<0.001***	72	(37)	***<0.001***
Glucocorticoids only	686	(35)	393	(72)		83	(73)		102	(52)	
<20 Gy CRT only	38	(2)	1	(<1)		-			7	(4)	
≥20 Gy CRT only	127	(7)	-			-			-		
Glucocorticoids and <20 Gy CRT	95	(5)	70	(13)		4	(4)		10	(5)	
Glucocorticoids and ≥20 Gy CRT	101	(5)	65	(12)		11	(10)		4	(2)	

ALL, acute lymphoblastic leukemia; CCS, childhood cancer survivors; CRT, cranial radiation therapy; HL, Hodgkin lymphoma; IQR, interquartile range; NHL, non-Hodgkin lymphoma

[a] p-value calculated from two-sample mean comparison test (t test) or chi-square statistics comparing separate diagnostic groups with remaining CCS (2-sided test).

[b] n=3 is missing (3%).

[c] Protocols with an unknown glucocorticoid dose were not taken into account. Survivors who were treated with unknown dose: 1st protocol: prednisone N=31 (2%), dexamethasone N=19 (<1%); 2nd protocol: prednisone N=7 (<1%), dexamethasone N=6 (<1%); and 3rd protocol: prednisone N=2 (<1%), dexamethasone N=2 (<1%).

[e] Of the 18 survivors who did not receive glucocorticoids during their treatment, N=13 (72%) had no protocol information in their medical records, N=5 (28%) got a classification protocol, after which no protocol information was given in their medical record, N=9 (50%) survivors were diagnosed before 1990.

TABLE 2. General characteristics of childhood cancer survivors, their siblings, and the general population (Swiss Health Survey)

	CCS (*n*=1936)		Siblings[a] (*n*=725)			General population[a] (*n*=9591)		
Characteristics	*n*	(%)	*n*	($\%_{std}$)	***p-value***[b]	*n*	($\%_{std}$)	***p-value***[b]
Gender								
Male	1034	(53)	301	(54)	***n.a.***	4645	(54)	***n.a.***
Age at survey, y								
15-19	509	(26)	142	(26)	***n.a.***	1518	(33)	***n.a.***
20-24	504	(26)	162	(24)		1440	(23)	
25-29	388	(20)	168	(23)		1174	(13)	
30-34	259	(13)	115	(13)		1424	(11)	
35-45	276	(14)	138	(14)		4035	(19)	
Parents' education (highest degree)[c]								
Primary	33	(6)	6	(4)	***0.243***	n.a.		
Secondary	302	(59)	77	(54)				
Tertiary	174	(34)	59	(42)				
Personal education[d]								
Primary	108	(8)	24	(4)	***<0.001***	691	(8)	***<0.001***
Secondary	966	(68)	359	(62)		4549	(62)	
Tertiary	353	(25)	200	(35)		2833	(30)	
Migration background	453	(23)	132	(23)	***n.a.***	3454	(23)	***n.a.***
Sports[e]	1281	(66)	506	(71)	***0.041***	5598	(64)	***0.051***
BMI at survey								
Underweight	113	(6)	19	(2)	***<0.001***	349	(3)	***<0.001***
Normal	1321	(68)	523	(74)		6354	(72)	
Overweight	372	(19)	149	(20)		2285	(24)	
Obese	130	(7)	34	(4)		603	(6)	

BMI, body mass index; CCS, childhood cancer survivors; n.a., not applicable;
[a] Standardized on gender, age at survey, migration background, and language region according to CCS.
[b] p-value calculated from chi-square statistics comparing comparison group to CCS (2-sided test).
[c] Highest parental education level of participants <20 years at time of survey.
[d] Highest personal education level of participants ≥20 years at time of survey.
[e] Sports participation was classified as sports if respondents reported engaging in a specific gym or sports activity for at least one hour per week.

TABLE 3. Crude and adjusted odds ratios for being overweight in childhood cancer survivors treated with different doses of cumulative glucocorticoid and cranial radiation therapy

	CCS (*n*=1936)			ALL survivors (*n*=546)			NHL survivors (*n*=114)			HL survivors (*n*=195)		
	n_{ow}/n_{total}	Crude OR (95% CI)	Adj OR (95% CI)[a]	n_{ow}/n_{total}	Crude OR (95% CI)	Adj OR (95% CI)[a]	n_{ow}/n_{total}	Crude OR (95% CI)	Adj OR (95% CI)[a]	n_{ow}/n_{total}	Crude OR (95% CI)	Adj OR (95% CI)[a]
Cumulative prednisone (mg/m^2)												
<2520	375/1489	1.00 (ref)	1.00 (ref)	60/255	1.00 (ref)	1.00 (ref)	23/74	1.00 (ref)	1.00 (ref)	34/119	1.00 (ref)	1.00 (ref)
2520-5823	54/220	0.97 (0.70-1.34)	0.87 (0.62-1.22)	32/111	1.32 (0.80-2.18)	0.69 (0.37-1.28)	6/25	0.70 (0.25-1.98)	0.45 (0.13-1.56)	9/49	0.56 (0.25-1.28)	0.61 (0.25-1.48)
≥5824	73/227	1.41 (1.04-1.90)	1.24 (0.90-1.70)	54/180	1.39 (0.91-2.14)	0.78 (0.45-1.34)	5/15	1.11 (0.34-3.61)	0.51 (0.14-1.87)	10/27	1.47 (0.61-3.53)	1.02 (0.37-2.84)
p-value[b]		**0.081**	**0.236**		***0.276***	***0.481***		***0.754***	***0.351***		***0.179***	***0.506***
Cumulative dexamethasone (mg/m^2)												
<1260	478/1813	1.00 (ref)	1.00 (ref)	123/424	1.00 (ref)	1.00 (ref)	34/114	1.00 (ref)	1.00 (ref)	53/195	1.00 (ref)	1.00 (ref)
≥1260	24/123	0.68 (0.43-1.07)	0.78 (0.49-1.24)	23/122	0.57 (0.34-0.94)	0.54 (0.31-0.93)	-	-	-	-	-	-
p-value[b]		**0.084**	**0.286**		***0.022***	***0.025***						
Cumulative glucocorticoids (mg/m^2)												
<3470	381/1495	1.00 (ref)	1.00 (ref)	60/214	1.00 (ref)	1.00 (ref)	25/89	1.00 (ref)	1.00 (ref)	38/138	1.00 (ref)	1.00 (ref)
3470-8099	60/219	1.10 (0.80-1.52)	1.04 (0.75-1.45)	44/152	1.05 (0.66-1.66)	1.15 (0.70-1.87)	5/15	1.28 (0.40-4.12)	1.28 (0.33-5.04)	5/30	0.53 (0.19-1.47)	0.44 (0.15-1.34)
≥8100	61/222	1.11 (0.81-1.52)	1.07 (0.78-1.49)	42/180	0.78 (0.49-1.23)	0.63 (0.39-1.03)	4/10	1.71 (0.44-6.56)	1.01 (0.24-4.24)	10/27	1.55 (0.65-3.68)	0.96 (0.34-2.68)
p-value[b]		**0.715**	**0.900**		***0.438***	***0.073***		***0.710***	***0.940***		***0.212***	***0.300***
CRT												
No CRT	371/1575	1.00 (ref)	1.00 (ref)	97/410	1.00 (ref)	1.00 (ref)	29/99	1.00 (ref)	1.00 (ref)	46/174	1.00 (ref)	1.00 (ref)
<20 Gy	35/133	1.16 (0.77-1.73)	1.16 (0.76-1.77)	11/71	0.59 (0.30-1.17)	0.63 (0.31-1.28)	1/4	-	-	7/17	1.95 (0.70-5.42)	1.93 (0.65-5.74)
≥20 Gy	96/228	2.36 (1.77-3.15)	2.28 (1.70-3.06)	38/65	4.54 (2.64-7.82)	4.40 (2.45-7.89)	4/11	1.38 (0.37-5.07)	0.84 (0.20-3.46)	-/4	-	-
p-value[b]		***<0.001***	***<0.001***		***<0.001***	***<0.001***		***0.871***	***0.963***		***0.202***	***0.237***

ALL, acute lymphoblastic leukemia; CCS, childhood cancer survivors; CI, confidence interval; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; OR, odd ratio

[a] Adjusted for gender, age at diagnosis, time since diagnosis, cumulative cranial radiation therapy, and glucocorticoid dose (prednisone only, dexamethasone only, or both).

[b] Global p-value calculated from the likelihood ratio test.

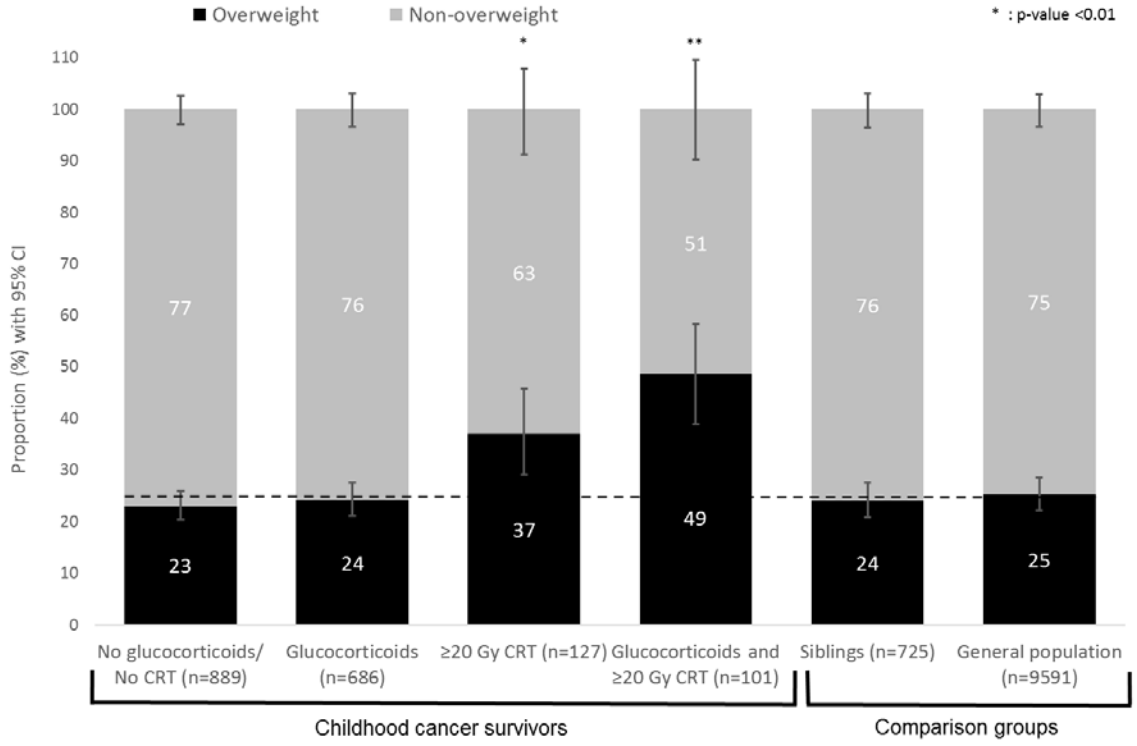

FIGURE 1. Prevalence of overweight in long-term childhood cancer survivors, by treatment with glucocorticoids and ≥20 Gray cranial radiation.

CI, confidence interval; CRT, cranial radiation therapy; Gy, gray.
Comparison groups were standardized on gender, age at survey, migration background, and language region according to CCS.
All p-values were calculated from chi-square statistics comparing CCS who got no glucocorticoids and no CRT to other CCS and comparison groups.
The dotted line reflects the overweight prevalence of the general population.

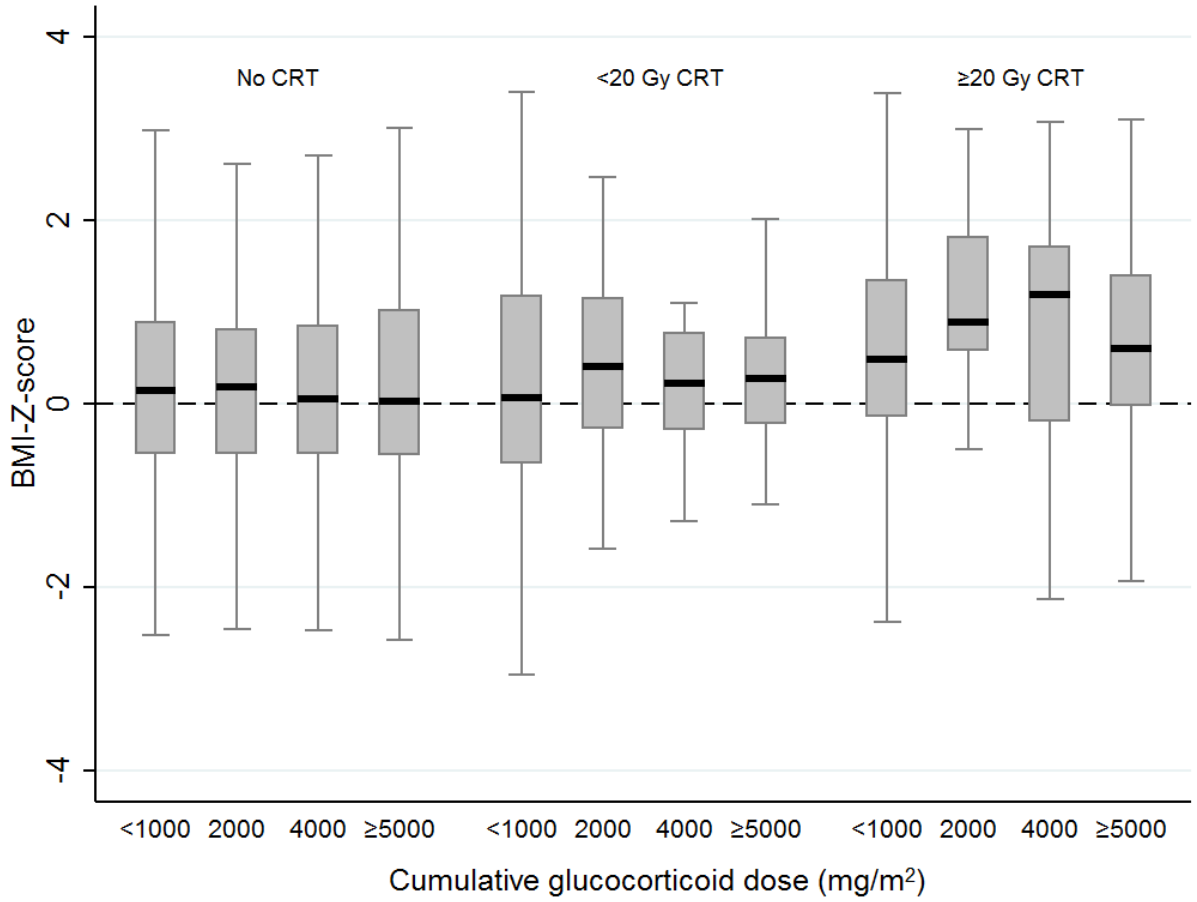

FIGURE 2. Box-plot of the dose-response relationship between BMI Z-score and cumulative glucocorticoid dose stratified by cranial radiation therapy in childhood cancer survivors (N=1936)

BMI, body mass index; CRT, cranial radiation therapy; Gy, gray
p-values for trend for no CRT 0.658, <20Gy CRT 0.937, and ≥20Gy CRT 0.309