- No evidence for overweight in long-term childhood cancer survivors after
 glucocorticoid treatment
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- 25 FNB conducted the statistical analyses and wrote the article; RK, CS, MB, RAA, NXvdW, and CEK
- 26 contributed to the concept and the design of the study; CS, NXvdW, and RAA gave support in
- 27 calculating cumulative doses of glucocorticoids, and RK, MB, and CEK gave support in the statistical
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40 ABSTRACT

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

43 METHODS: As part of the Swiss Childhood Cancer Survivor Study, we sent a questionnaire to CCS 44 residing in Switzerland aged <21 years at diagnosis, who survived ≥5 years and were 15-45 years old 45 at survey. We assessed cumulative doses of glucocorticoids from medical records and study protocols 46 and calculated BMI from self-reported height and weight at survey. We compared prevalence of 47 overweight between CCS, their siblings, and the general population (Swiss Health Survey, SHS) and 48 investigated the association of overweight with treatment-related risk factors using multivariable 49 logistic regression.

50 **RESULTS:** The study included 1936 CCS, 546 siblings, and 9591 SHS participants. Median

51 (interquartile range) age of the CCS at survey was 24 (20-31) years and median time since diagnosis

52 was 17 (12-22) years. At survey, 26% of CCS were overweight, a proportion comparable to that

53 among siblings (24%) and the SHS participants (25%). Prevalence of overweight was 24% in CCS

54 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

56 dose-response relationship between cumulative glucocorticoid doses and overweight and no evidence

57 that CRT modified the effect of cumulative glucocorticoid dose treatment on overweight.

58 **CONCLUSION:** This study suggests that glucocorticoids used for the treatment of childhood cancer

59 are not associated with long-term risk of overweight.

60 INTRODUCTION

61 The glucocorticoids prednisone and dexamethasone are currently part of the standard treatment of 62 acute lymphoblastic leukemia (ALL), non-Hodgkin lymphoma (NHL), and Hodgkin lymphoma (HL). 63 Type of glucocorticoid, dose, and duration of treatment can differ by cancer treatment protocol.¹ 64 Cancer treatment with glucocorticoids can lead to weight gain originating in physiological e.g. altered 65 cortisol concentrations and adipose tissue metabolism and psychological changes that among others 66 may influence appetite and lower energy expenditure due to physical inactivity.^{1, 2} An excess of dietary 67 intake and physical inactivity during treatment could be the base for behavioural changes in the long-68 term leading to continues weight gain during survivorship. Prednisone and dexamethasone have 69 similar mechanisms of action, but dexamethasone in the dose range commonly used causes more 70 adverse effects such as acute metabolic side effects, infections, osteopenia, and behavioral 71 abnormalities.^{1, 3} Other treatments for childhood cancer can also affect the development of overweight 72 and obesity in particular cranial radiation therapy (CRT). CRT impairs the hypothalamic-pituitary axis, 73 which in turn can lead to growth hormone deficiency and leptin insensitivity.⁴ ALL treatment protocols 74 have not routinely prescribed CRT since the 1980s, and overall cumulative CRT doses have 75 decreased.⁵ In contrast, cumulative glucocorticoid doses have increased in the US, and prednisone 76 has been partly replaced by the more potent dexamethasone.^{6,7} Many CCS are overweight, especially 77 in the US, despite decreased doses of CRT.8

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79 Glucocorticoids might, therefore, be implicated in excessive weight gain during cancer treatment.^{3, 7} 80 But whether glucocorticoids have a longer-lasting effect on weight is uncertain, and any such effect 81 may depend on the dose and duration of treatment. Research has yielded contradictory results. One 82 small (N=169) study of ALL survivors reported a six-fold increased risk of being overweight or obese in 83 ALL survivors with the highest cumulative doses of glucocorticoids (≥10,000 mg/m²) compared to the 84 lowest doses (<7500 mg/m²) five years after diagnosis,⁹ while another US study found no dose-85 response effects ≥10 years after diagnosis.¹⁰ In an US study glucocorticoid treatment was associated 86 with obesity 25 years after diagnosis in 776 CCS who were treated with CRT, but cumulative dose and 87 type of glucocorticoid were not assessed.¹¹ Previous studies have mainly focused on acute effects of 88 glucocorticoids during or shortly after treatment,^{9, 12-16} have not assessed cumulative glucocorticoid 89 dose,^{11, 13} and often have relatively low numbers of participants (<200).^{9, 12-18} Thus it remains unclear 90 whether glucocorticoids affect overweight in CCS long after treatment.

91

92 We analyzed data from the Swiss Childhood Cancer Survivor Study (SCCSS) to investigate whether 93 1) overweight in long-term CCS (on average 17 years after diagnosis) is associated with the 94 cumulative glucocorticoid dose received, 2) there is a dose-response relationship between cumulative 95 glucocorticoid dose and BMI, and 3) the respective effects of prednisone and dexamethasone differ. 96 We studied the entire group of CCS, and separately the three cancer types treated most frequently 97 with glucocorticoids (ALL, NHL, and HL). 98 99 METHODS 100 Sampling 101 The Swiss Childhood Cancer Survivor Study 102 The Swiss Childhood Cancer Survivor Study (SCCSS) is a long-term follow-up study of patients 103 registered in the Swiss Childhood Cancer Registry (SCCR, www.childhoodcancerregistry.ch) who

104 have been diagnosed since 1976 and survived \geq 5 years after cancer diagnosis.¹⁹ The SCCR is a

105 population-based registry that includes all children and adolescents under age 21 in Switzerland who

106 are diagnosed with leukemia, lymphoma, central nervous system (CNS) tumors, malignant solid

107 tumors, or Langerhans cell histiocytosis.^{20, 21} Ethical approval of the SCCR and the SCCSS has been

108 given by the Ethics Committee of the Canton of Bern to (KEK-BE: 166/2014).

109

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}

116

117 Comparison groups

118 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

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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.

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132 Measurements

133 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/m²). Adult BMI <18.5 kg/m² was classified as underweight, \geq 18.5 to <25 kg/m² as normal weight, and \geq 25 kg/m² 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

141

142 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/m²) by multiplying the dose in mg/kg by a conversion factor of 30,

149 which represents an average of the factors for persons weighing 20 and 60 kg.³⁰ Glucocorticoids 150 administered by intrathecal route and for supportive care or immunosuppression, were not taken into 151 consideration.¹ Treatment protocols that were included came from the Swiss Pediatric Oncology 152 Group (31%), Pediatric Oncology Group (29%), Berlin/Frankfurt/Muenster study group (24%), German 153 Society of Pediatric Oncology and Hematology (7%), and others (9%) (Supplementary Table 1). In 67 154 cases in which the study arm was unknown, survivors were assigned to the protocol arm with the 155 lowest glucocorticoid dosage. We calculated the total cumulative glucocorticoid dose in equivalent of 156 prednisone for each patient using the formula cumulative glucocorticoid dose = cumulative prednisone 157 dose + (cumulative dexamethasone dose x 6.67) in mg/m^{2,31} The recommended cumulative 158 glucocorticoid doses dropped over time when all cancer types were combined, and specifically for 159 each type of cancer with the exception of ALL protocols, in which doses increased (Supplementary 160 Figure 1). We assessed other clinical and sociodemographic variables as described previously.²⁶

161

162 Statistical analysis

163 We included all SCCSS survivors and their siblings, and the SHS participants in the general 164 population, who were aged 15-45 years at time of survey and provided self-reported height and weight 165 (Supplementary Figure 2). We excluded CCS with hematopoietic stem cell transplantation (HSCT); 166 this specific group is at substantial risk of underweight due to chronic graft-versus-host disease and 167 long-term immunosuppression with recurrent infections.³² For better comparison between CCS and 168 peers, we standardized comparison groups for gender, age at survey, migration background, and 169 language region as described previously.²⁶ First, we assessed whether overweight at survey was 170 associated with the cumulative glucocorticoid dose during treatment. We determined these 171 associations using multivariable logistic regression within all CCS, and within patients with the three 172 cancer types frequently treated with glucocorticoids. We divided BMI into two categories: overweight 173 (overweight and obesity) versus non-overweight (underweight and normal) because the group of 174 obese people was small and the glucocorticoids and CRT risk estimates for the two categories 175 overweight and obesity had the same direction and comparable magnitude. Cumulative prednisone 176 and glucocorticoid usage was divided into three categories: lower than the median intake of all CCS, 177 median to third quartile, and equal to or higher than the third quartile. Cumulative dexamethasone was 178 divided into two categories: lower than the median intake of all CCS, and equal to or higher than the

179 median. We adjusted the models for gender, age at diagnosis, time since diagnosis, and cumulative 180 CRT and/or glucocorticoid dose. We used interaction terms to test whether age, gender, and the 181 clinical variables e.g. age at diagnosis, year of diagnosis, time since diagnosis, and CRT modified the 182 effect of cumulative glucocorticoid dose treatment on overweight since these variables are related to 183 the total dose. Second, we illustrated the dose-response relationship by comparing the distribution of 184 BMI by cumulative glucocorticoid dose in steps of 1000 mg/m² (prednisone and total glucocorticoids) 185 or 100 mg/m² (dexamethasone) with boxplots. Because 26% of CCS were 15-19 years at survey, we 186 used BMI Z-scores for all CCS. We used trend tests to test for an ordered relationship between 187 cumulative glucocorticoid dose categories and BMI Z-scores. Third, we examined whether effects 188 differed between dexamethasone and prednisone treatment again using multivariable logistic 189 regression models. Finally, we performed sensitivity analyses to compare standardized data for 190 gender, age, migration background, and language region in all comparison groups according to the 191 distribution in CCS to non-standardized data. For the 67 survivors for whom the study arm was 192 unknown we performed sensitivity analyses in which they were excluded or were assigned to the 193 protocol arm with the highest glucocorticoid dose instead of the lowest. We used Stata (version 14, 194 Stata Corporation, Austin, Texas) for all statistical analyses.

195

196 **RESULTS**

197 **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

- 200 younger than 15 or older than 45 years, and a further 117 who had received HSCT. We thus included
- 201 $\,$ 1936 CCS in this study, of whom 546 had been treated for ALL, 114 NHL, 195 HL, and 1081 for other $\,$
- 202 types of cancer (**Supplementary Figure 2**).

203

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 inthe analysis.

209

210 Among CCS, median age at diagnosis was 8 (IQR 4-13) years overall, 5 (3-9) years for ALL, 11 (8-211 14) for NHL, and 14 (12–16) for HL survivors (Table 1). The median time from diagnosis to survey was 212 17 (IQR 12-22) years for CCS overall, 18 (13-23) for ALL, 17 (12-22) for NHL, and 15 (10-21) for HL 213 survivors. Most ALL survivors had received glucocorticoids (96% prednisone, and 34% 214 dexamethasone). NHL and HL were less often treated with glucocorticoids (86% NHL, and 59% HL). 215 Sociodemographic characteristics were mostly identical between CCS and the comparison groups 216 after standardization, except that fewer CCS than both siblings and the general population completed 217 tertiary education (Table 2). CCS engaged in less sports than siblings, but were comparable to the 218 general population. 219

220 **Overweight and glucocorticoid therapy**

221 The prevalence of overweight among all CCS was 26% at survey. This was similar to the overweight 222 prevalence in the comparison groups after standardization according to CCS: 24% in siblings (p=0.34) 223 and 25% in the general population (p=0.48) (Table 2, Supplementary Figure 3). When we stratified 224 CCS by the treatment, we found that the prevalence of overweight was 23% in CCS treated with no 225 glucocorticoids and no CRT (205 of 889), 24% in those treated with glucocorticoids alone (166 of 686), 226 37% in CCS treated with ≥20 Gy CRT (47 of 127, p<0.01), and 49% in those treated with both 227 glucocorticoids and ≥ 20 Gy CRT (49 of 101, p<0.001) (Figure 1). There was a weak trend (p=0.08), 228 suggesting an interaction that the effect of CRT tended to be higher in CCS also treated with 229 glucocorticoids.

230

231 In multivariable logistic regression models we found that overweight was not associated with

232 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

236 (Supplemental Table 2).

237

238 **Dose-response relationship between overweight and glucocorticoids**

239 We found no evidence supporting a dose-response relationship between cumulative prednisone,

240 dexamethasone, or both combined and BMI Z-scores, either when stratifying for CRT (ptrend no

241 CRT=0.994, ptrend <20Gy=0.510, and ptrend ≥20Gy= 0.174, Figure 2), or when analyzing the entire CCS

group adjusted for cumulative CRT dose (ptrend prednisone=0.085, ptrend dexamethasone=0.176, and ptrend

243 glucocorticoids =0.583 Supplementary Figure 4). CCS who got high prednisone doses (≥8000 mg/m²)

244 tended to have higher BMI Z-scores. In ALL survivors we also observed no dose-response relationship

245 (ptrend prednisone=0.223, ptrend dexamethasone=0.063, and ptrend glucocorticoids =0.512, Supplementary Figure 5).

246

247 **Prednisone versus dexamethasone**

In unadjusted analyses, CCS who were treated with the highest cumulative dose of prednisone (\geq 5824 mg/m²) tended to be more overweight than those treated with the lowest dose (<2520 mg/m²). 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 (\geq 1260 mg/m²) were less likely to be overweight than those treated with a lower dose (<1260 mg/m²).

254

255 **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 \geq 20 Gy (37%), and yet higher among CCS treated with both glucocorticoids and cranial radiation \geq 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 \geq 8000 mg/m²).

264

265 Overweight and obesity during treatment is frequent in ALL patients who receive high doses of 266 glucocorticoids,³³ but the long-tern impact of glucocorticoids on overweight has not been well studied. 267 An US study of 784 ALL survivors followed over 26 years found an association of obesity with CRT, 268 but not cumulative glucocorticoid dose. That finding is similar to ours, but ALL survivors with low 269 glucocorticoid doses in the US study received high CRT doses. This could have masked an 270 association between glucocorticoids and obesity.³⁴ A Dutch study of 113 ALL survivors 10 years after 271 treatment found that higher cumulative prednisone doses led to higher BMI Z-scores at end of 272 treatment and shortly thereafter, but not in the long-term.¹⁸ The cumulative prednisone doses in the 273 study were much higher than ours; of the 65 survivors who received only prednisone 60 (92%) 274 survivors had received a cumulative dose of 9800 mg/m², or more. We also found post hoc evidence 275 that higher cumulative prednisone doses (≥8000 mg/m²) lead to more overweight, but after 276 multivariable adjustment this effect disappeared. A dose-response association between cumulative 277 glucocorticoid dose and BMI was also seen in a longitudinal single-center study in the US of 165 ALL 278 survivors. BMI was assessed five years after diagnosis and again, cumulative glucocorticoid doses 279 were higher (around 50% had a cumulative dose of >9000 mg/m²).⁹ We found in univariable analyses 280 that survivors who got the highest cumulative prednisone dose (\geq 5824 mg/m²) were more likely to be 281 overweight. After adjustment, the association was similar in magnitude and direction, but was no 282 longer significant. We did not find an association between cumulative dexamethasone and overweight 283 in CCS. However, follow-up time was longer in CCS treated with prednisone because dexamethasone 284 was introduced more recently. ALL survivors who got a cumulative dexamethasone dose of ≥1260 285 mg/m² were even less likely to be overweight than those who were treated with a lower dosage. The 286 dose-response relationship between cumulative dexamethasone and BMI Z-scores showed a dent 287 with higher doses of dexamethasone. Given the wide confidence intervals this finding is most likely 288 due to chance. The dint could also be a surrogate for more severe disease and more intense 289 treatment, leading to less weight gain over time. Studies that look at the association between 290 glucocorticoids and overweight in survivors of tumors other than ALL are limited. In 88 HL survivors in 291 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.

295

296 This study is the largest of its kind to have looked at cumulative glucocorticoid dose and overweight in 297 CCS long after end of treatment. It also had a specific focus on ALL, NHL, and HL survivors who 298 usually receive high doses of glucocorticoids. Other strengths include its national coverage and high 299 response rate, which increase confidence that the results are representative, as does its access to 300 both socioeconomic factors and detailed treatment data. We also compared CCS with two other 301 groups from whom contemporaneous data were collected: CCS siblings, and the general population in 302 Switzerland. Among the study's limitations was the unavailability of patient dose levels, which 303 necessitated deriving cumulative glucocorticoid doses from cancer protocol information. This could 304 have led to either under- or over estimation of the cumulative glucocorticoid dose when the protocol 305 arm was unknown. But for only 67 survivors was the study arm unknown. Sensitivity analyses where 306 we excluded those with unknown study arms or were we assigned them to the highest dose instead of 307 the lowest dose found the same results. Only 239 CCS were treated with dexamethasone because, 308 though we included CCS diagnosed since 1976, dexamethasone use has increased only recently.⁷ 309 Height and weight at survey were self-reported; both under- and over-reporting could have occurred. 310 However, since height and weight were self-reported in all study populations we expected the degree 311 of nondifferential errors of BMI assessment to be similar across all CCS, the comparison groups, and 312 across CCS treated with different glucocorticoid doses. Finally, we used BMI as a measure of 313 overweight. BMI measures neither the ratio of lean to fat mass nor fat distribution. Since 314 glucocorticoids have a catabolic effect on muscle, CCS could have less lean mass and more fat mass 315 than the general population with a similar BMI.³⁵ However, BMI is a practical and inexpensive proxy 316 measure of overweight that is widely used in population-based studies.

317

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

322 care, with a special focus on patients who received CRT as well as potentially those who received very323 high doses of glucocorticoids.

324

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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	CCS	ALL survivors	NHL survivo	rs	HL survivors		
	(<i>n</i> =1936)	(<i>n</i> =546)	(<i>n</i> =114)		(<i>n</i> =195)		
Characteristics	n (%)	n (%) p-v	ie ª n (%)	p-value ^a n	(%) <i>p-value</i> ^a		
Age at diagnosis, median (IQR)	7.8 (3.7-13.1)	5.1 (3.1-9.1) < 0.	1 11.1 (7.7-14.0)	<0.001 14	I.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.	1 16.8 (11.6-22.0)	0.918 14	4.7 (9.5-21.4) <0.001		
Year of diagnosis							
1976-1988	667 (34)	242 (44) <0.0	1 41 (36)	0.653 50) (26) <0.001		
1989-1996	703 (36)	187 (34)	44 (39)	58	3 (30)		
1997-2005	566 (29)	117 (21)	29 (25)	87	7 (45)		
History of relapse	194 (10)	58 (11) 0.58	8 (7)	0.271 13	3 (7) 0.100		
Chemotherapy	1494 (77)	546 (100) <0.0	1 111 (97) ^b	<0.001 17	′1 (88) <0.001		
Prednisone exposure ^c	852 (44)	524 (96) <0.0	1 84 (74)	<0.001 11	6 (59) <0.001		
Dose, median (IQR), mg/m ²	2520 (1680-5824)	2880 (1680-5824)	1836 (1836-3880)	30)60 (2340-4824)		
Dexamethasone exposure ^c	239 (12)	183 (34) <0.	1 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 <0.0	1 98 (86)	<0.001 11	6 (59) <0.001		
Dose, median (IQR), mg/m ²	3470 (1960-8100)	5824 (3360-10084)	2520 (1836-3516)	30)60 (2340-4824)		
CRT							
Yes, <20 Gy	133 (7)	71 (13) <0.	1 4 (4)	0.234 17	7 (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.	1 16 (14)	<0.001 72	2 (37) <0.001		
Glucocorticoids only	686 (35)	393 (72)	83 (73)	10)2 (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)		

TABLE 1. Clinical characteristics of childhood cancer survivors

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.

	CCS Siblings ^a		ngs ^a	General population ^a				
	(<i>n</i> =1936)		(<i>n</i> =725)		(<i>n</i> =9591)		91)	
Characteristics	n	(%)	n	$(%_{std})$	p-value ^b	n	(%std)	<i>p-value</i> ^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)	

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

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			ALL surviv	/ors		NHL survi	vors	Н	L survi	vors
		(<i>n</i> =1936)			(<i>n</i> =546))		(<i>n</i> =114	l)		(<i>n</i> =19	5)
	n _{ow} /n _{total}	Crude OR	Adj OR	n _{ow} /n _{tota}	Crude OR	Adj OR	n _{ow} /n _{tota}	Crude OR	Adj OR	now/ntota Crude	e OR	Adj OR
		(95% CI)	(95% CI) ª	1	(95% CI)	(95% CI) ª	I	(95% CI)	(95% CI) ª	ı (95%	6 CI)	(95% CI) ª
Cumulative	prednison	ne (mg/m²)										
<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)	34/1191.00 (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	1	0.754	0.351		0.179	0.506
Cumulative	dexameth	asone (mg/m²)										
<1260	478/1813	1.00 (ref)	1.00 (ref)	123/424	1.00 (ref)	1.00 (ref)	34/1141	.00 (ref)	1.00 (ref)	53/1951.00 (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	5					
Cumulative	glucocort	icoids (mg/m²)										
<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)	38/1381.00 (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		0.43	8 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)	46/1741.00 (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	1	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.



Cumulative glucocorticoid dose (mg/m²)

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

SUPPORTING INFORMATION

		Devenue there are	S Included
Protocol	CCS, n (%)	Dexamethasone	Prednisonea
BFM	234 (24%)		
ALL-BFM 83	1	Х	Х
ALL-BFM 86	2	Х	Х
ALL-BFM 90	56	Х	Х
ALL-BFM 95	64	Х	Х
ALL-BFM 99 MRD Pilot	4	Х	Х
ALL-BEM 2000	23	Х	х
ALL/NHL-BEM 86	2	X	x
ALL-REZ-BEM 87	1	X	X
	8	X	X
ALL DEZ DEM DOS/06	0	A V	×
ALL-REZ-DFIM F93/90	0	A V	A V
	2	X	X
	1		X
AML-BFM 93	1		X
AML-BFM 98	4		Х
B-NHL-BFM 04	3	Х	
NHL-BFM 83	3	Х	Х
NHL-BFM 90	18	Х	Х
NHL-BFM 95	27	Х	Х
GPOH	64 (7%)		
ALCL99 (GPOH)	1	Х	
GPOH HD 95	47		Х
GPOH HD 2002	16		X
POG	279 (29%)		~
POG-7376	213 (2370)		Y
POC 7827	2		X
POG 7000	3		×
POG-7909	4		×
POG-6036	21	V	X
POG-0101	5	Λ	A V
POG-8304	5		X
POG-8314	4		X
POG-8426	1		X
POG-8602	34		Х
POG-8616	6		Х
POG 8618	1		Х
POG-8691	2		Х
POG-8704	18		Х
POG-8710	1		Х
POG-8719	11		Х
POG-9005	27		Х
POG-9006	12		Х
POG-9061	1	Х	
POG-9201	11		Х
POG-9219	14		Х
POG-9310	1		X
POG-9315	5		x
POG-9398	2		x
POG-9404	2		X
	т 6		X
	7		A V
	י כ	V	
POG-9411	С 4	л У	^
POG-9412	4	X	N/
POG-9425	2		X
POG-9605	16		X
POG 9900	12	Х	Х

Supplementary TABLE 1. Protocols of clinical trials included

POG-9904	2	Х	Х
POG-9905	7	Х	Х
POG-9906	10	Х	Х
POG-9917	7	Х	
POG-A5971	2	Х	Х
SPOG	299 (31%)		
SPOG ALL 79/84	129		Х
SPOG ALL LR 76	35		Х
SPOG ALL HR 76	5		Х
SPOG ALL HR 79	11		Х
SPOG ALL REZ LR 77	1		Х
SPOG ALL REZ HR 77	2		Х
SPOG NHL (1977)	32		Х
SPOG H77	26		Х
SPOG H87	13		Х
SPOG Hodgkin 1985	10		Х
SPOG HT(Hirntumor) A76	7		Х
SPOG HX	28		Х
Other	91 (9%)		
CALGB 7111	9	Х	Х
CALGB 7411	12		Х
CALGB 7611	16		Х
CALGB 7721	4		Х
CCG-2961	1	Х	
COG-AALL0433	2	Х	Х
DAL HD 90	4		Х
DAL HX 90	6		Х
EORTC 58881	1	Х	Х
EURO LB 02	1	Х	Х
HD 5	1		Х
HD 9	1		Х
LALA 94	1	Х	Х
LCH II	17		Х
LCH III	5		Х
LMB 84	3		Х
LMB 89	2		Х
R-CHOP	1		Х
SAKK NHL	1		Х
SIOP HD IV 87	3		Х

CCS could have received several protocols based on the cancer type, relapse etc.

ALL, acute lymphoblastic leukemia; ALCL, anaplastic large cell; AML, acute myelogenous leukemia lymphoma; BFM, Berlin/Frankfurt/Muenster study group; CALGB, Cancer and Leukemia Group B; CCG, Children's Cancer Group; R-CHOP, rituximab cyclophosphamide hydroxyl-doxorubicin vincristine prednisone; COG, Children's Oncology Group; DAL, German-Austrian multicentre trial; EORTC, European Organisation for Research and Treatment of Cancer; EURO, European; GPOH, German Society of Pediatric Oncology and Hematology; HD, high dose / Hodgkin's disease; HR, high risk; LB, lymphoblastic; LCH, Langerhans cell histiocytosis; LMB, B-cell non-Hodgkin's lymphoma and B-ALL; LR, low risk; MRD, minimal residual disease; NHL, non-Hodgkin lymphoma; POG, Pediatric Oncology Group; REZ, relapse; SAKK, Swiss Group for Clinical Cancer Research; SIOP, International Society of Pediatric Oncology; SPOG, Swiss Pediatric Oncology Group ^a Intrathecal prednisone is not taken into account. Supplementary TABLE 2. P-values for interaction of glucocorticoid use in childhood cancer survivors with sociodemographic and clinical characteristics (retrieved from multivariable logistic regressions^a)

	p-values for interactions ^b				
	CCS	ALL	NHL	HL	
	(<i>n</i> =1936)	(<i>n</i> =546)	(<i>n</i> =114)	(<i>n</i> =195)	
Sociodemographic					
Gender	0.869	0.283	0.381	0.084	
Age at survey	0.943	0.207	0.466	0.834	
Clinical					
Age at diagnosis, years	0.633	0.800	0.670	0.756	
Year of diagnosis	0.462	0.433	0.700	0.293	
Time since diagnosis, years	0.343	0.502	0.5627	0.580	
Chemotherapy (No, Yes)	0.818	n.a.	0.707	0.434	
Cranial radiation therapy (No, Yes)	0.261	n.a.	n.a.	0.422	
History of relapse (No, Yes)	0.138	n.a.	n.a.	n.a.	

ALL, acute lymphoblastic leukemia; CCS, childhood cancer survivors; HL, Hodgkin lymphoma; NHL, non-Hodgkin ^a adjusted for gender, age at diagnosis, and time since diagnosis.
 ^b p-value for interaction was calculated with the likelihood ratio test.



Supplementary FIGURE 1. Time trends in exposure to glucocorticoids (cumulative dose) during treatment in CCS, ALL, NHL, and HL survivors

ALL, acute lymphoblastic leukemia; CCS, childhood cancer survivors; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma

p-values for testing trend of cumulative glucocorticoid dose across year of diagnosis by childhood cancer type.



Supplementary FIGURE 2. Response rates and study populations in the Swiss Childhood Cancer Survivor Study

ALL, acute lymphoblastic leukemia; AML; acute myeloid leukemia; CCS, childhood cancer survivors; CNS, central nervous system; HL, Hodgkin lymphoma; HSCT, hematopoietic stem cell transplantation; NHL, non-Hodgkin lymphoma; SCCSS, Swiss Childhood Cancer Survivor Study



Comparison groups

Supplementary FIGURE 3. Prevalence of overweight in childhood cancer survivors, their siblings, and the general population

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

Comparison groups were standardized on gender, age at survey, migration background, and language region according to CCS.

The dotted line reflects the overweight prevalence in the general population.



Supplementary FIGURE 4. Dose-response relationship between cumulative A. Prednisone, B. Dexamethasone, C. Glucocorticoids combined (prednisone and dexamethasone) and BMI Z-score in childhood cancer survivors (N=1936), adjusted for cumulative dose of cranial radiation therapy

BMI, body mass index; CI, confidence interval; No, number

p-values for testing trend of BMI Z-score across cumulative glucocorticoid dose.



Supplementary FIGURE 5. Dose-response relationship between cumulative A. Prednisone, B. Dexamethasone, C. Glucocorticoids combined (prednisone and dexamethasone) and BMI Z-score in ALL survivors (N=546), adjusted for cumulative dose of cranial radiation therapy ALL, acute lymphoblastic leukemia; BMI, body mass index; CI, confidence interval; No, number p-values for testing trend of BMI Z-score across cumulative glucocorticoid dose.