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

3

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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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37

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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),  
55 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.<sup>1</sup>  
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.<sup>1, 2</sup> 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.<sup>1, 3</sup> 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.<sup>4</sup> ALL treatment protocols  
74 have not routinely prescribed CRT since the 1980s, and overall cumulative CRT doses have  
75 decreased.<sup>5</sup> In contrast, cumulative glucocorticoid doses have increased in the US, and prednisone  
76 has been partly replaced by the more potent dexamethasone.<sup>6, 7</sup> Many CCS are overweight, especially  
77 in the US, despite decreased doses of CRT.<sup>8</sup>  
78  
79 Glucocorticoids might, therefore, be implicated in excessive weight gain during cancer treatment.<sup>3, 7</sup>  
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 ( $\geq 10,000$  mg/m<sup>2</sup>) compared to the  
84 lowest doses (<7500 mg/m<sup>2</sup>) five years after diagnosis,<sup>9</sup> while another US study found no dose-  
85 response effects  $\geq 10$  years after diagnosis.<sup>10</sup> 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.<sup>11</sup> Previous studies have mainly focused on acute effects of  
88 glucocorticoids during or shortly after treatment,<sup>9, 12-16</sup> have not assessed cumulative glucocorticoid  
89 dose,<sup>11, 13</sup> and often have relatively low numbers of participants (<200).<sup>9, 12-18</sup> 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](http://www.childhoodcancerregistry.ch)) who  
104 have been diagnosed since 1976 and survived  $\geq 5$  years after cancer diagnosis.<sup>19</sup> 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.<sup>20, 21</sup> 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

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

116

#### 117 **Comparison groups**

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

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

124

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

131

## 132 ***Measurements***

### 133 **Body weight and BMI**

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

141

### 142 **Glucocorticoids**

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

149 which represents an average of the factors for persons weighing 20 and 60 kg.<sup>30</sup> Glucocorticoids  
150 administered by intrathecal route and for supportive care or immunosuppression, were not taken into  
151 consideration.<sup>1</sup> 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<sup>2</sup>.<sup>31</sup> 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.<sup>26</sup>

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.<sup>32</sup> 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.<sup>26</sup> 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/m<sup>2</sup> (prednisone and total glucocorticoids)  
185 or 100 mg/m<sup>2</sup> (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***

198 Among 4116 eligible CCS we traced and contacted 3593 of whom 2527 returned the SCCSS  
199 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

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

207 survey. In those responding households, 9591 persons who were aged 15-45 years were included in  
208 the 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  $\geq 20$  Gy CRT (47 of 127,  $p<0.01$ ), and 49% in those treated with both  
227 glucocorticoids and  $\geq 20$  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  
233 with glucocorticoids (**Table 3**). But, CCS and ALL survivors treated with  $\geq 20$  Gy CRT were more likely  
234 to be overweight. Interaction tests did not suggest that the cumulative effect of glucocorticoids differed

235 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 ( $p_{\text{trend no}}$   
241  $\text{CRT}=0.994$ ,  $p_{\text{trend } <20\text{Gy}}=0.510$ , and  $p_{\text{trend } \geq 20\text{Gy}}=0.174$ , **Figure 2**), or when analyzing the entire CCS  
242 group adjusted for cumulative CRT dose ( $p_{\text{trend prednisone}}=0.085$ ,  $p_{\text{trend dexamethasone}}=0.176$ , and  $p_{\text{trend}}$   
243  $\text{glucocorticoids}=0.583$  **Supplementary Figure 4**). CCS who got high prednisone doses ( $\geq 8000$  mg/m<sup>2</sup>)  
244 tended to have higher BMI Z-scores. In ALL survivors we also observed no dose-response relationship  
245 ( $p_{\text{trend prednisone}}=0.223$ ,  $p_{\text{trend dexamethasone}}=0.063$ , and  $p_{\text{trend glucocorticoids}}=0.512$ , **Supplementary Figure 5**).

246

### 247 ***Prednisone versus dexamethasone***

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

254

## 255 **DISCUSSION**

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

262 response relationship between the cumulative glucocorticoid dose and being overweight, except for a  
263 possible effect at the highest doses (prednisone  $\geq 8000$  mg/m<sup>2</sup>).

264

265 Overweight and obesity during treatment is frequent in ALL patients who receive high doses of  
266 glucocorticoids,<sup>33</sup> but the long-term 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.<sup>34</sup> 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.<sup>18</sup> 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/m<sup>2</sup>, or more. We also found post hoc evidence  
275 that higher cumulative prednisone doses ( $\geq 8000$  mg/m<sup>2</sup>) 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/m<sup>2</sup>).<sup>9</sup> We found in univariable analyses  
280 that survivors who got the highest cumulative prednisone dose ( $\geq 5824$  mg/m<sup>2</sup>) 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  $\geq 1260$   
285 mg/m<sup>2</sup> 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 dent 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

292 with and without prednisone.<sup>17</sup> The glucocorticoid dose is lower and chemotherapy duration is shorter  
293 in HL compared to ALL survivors. We saw no association between glucocorticoids and overweight in  
294 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.<sup>7</sup>  
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.<sup>35</sup> However, BMI is a practical and inexpensive proxy  
316 measure of overweight that is widely used in population-based studies.

317

318 Treatment of childhood cancer increases survivors' risk of chronic diseases. Overweight can worsen  
319 disease burden, in particular when it involves development of endocrine complications such as type II  
320 diabetes. While our study does not suggest glucocorticoids are associated with long-term overweight,  
321 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 very  
323 high doses of glucocorticoids.

324

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

328

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- 432



**TABLE 1. Clinical characteristics of childhood cancer survivors**

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

<sup>a</sup> 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).

<sup>b</sup> n=3 is missing (3%).

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

° 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)**

Characteristics	CCS (n=1936)		Siblings <sup>a</sup> (n=725)		General population <sup>a</sup> (n=9591)	
	n	(%)	n	(% <sub>std</sub> )	p-value <sup>b</sup>	p-value <sup>b</sup>
<b>Gender</b>						
Male	1034	(53)	301	(54)	<i>n.a.</i>	4645 (54) <i>n.a.</i>
<b>Age at survey, y</b>						
15-19	509	(26)	142	(26)	<i>n.a.</i>	1518 (33) <i>n.a.</i>
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)
<b>Parents' education (highest degree)<sup>c</sup></b>						
Primary	33	(6)	6	(4)	<b>0.243</b>	n.a.
Secondary	302	(59)	77	(54)		
Tertiary	174	(34)	59	(42)		
<b>Personal education<sup>d</sup></b>						
Primary	108	(8)	24	(4)	<b>&lt;0.001</b>	691 (8) <b>&lt;0.001</b>
Secondary	966	(68)	359	(62)		4549 (62)
Tertiary	353	(25)	200	(35)		2833 (30)
<b>Migration background</b>	453	(23)	132	(23)	<i>n.a.</i>	3454 (23) <i>n.a.</i>
<b>Sports<sup>e</sup></b>	1281	(66)	506	(71)	<b>0.041</b>	5598 (64) <b>0.051</b>
<b>BMI at survey</b>						
Underweight	113	(6)	19	(2)	<b>&lt;0.001</b>	349 (3) <b>&lt;0.001</b>
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;

<sup>a</sup> Standardized on gender, age at survey, migration background, and language region according to CCS.

<sup>b</sup> p-value calculated from chi-square statistics comparing comparison group to CCS (2-sided test).

<sup>c</sup> Highest parental education level of participants <20 years at time of survey.

<sup>d</sup> Highest personal education level of participants ≥20 years at time of survey.

<sup>e</sup> Sports participation was classified as sports if respondents reported engaging in a specific gym or sports activity for at least one hour per week.

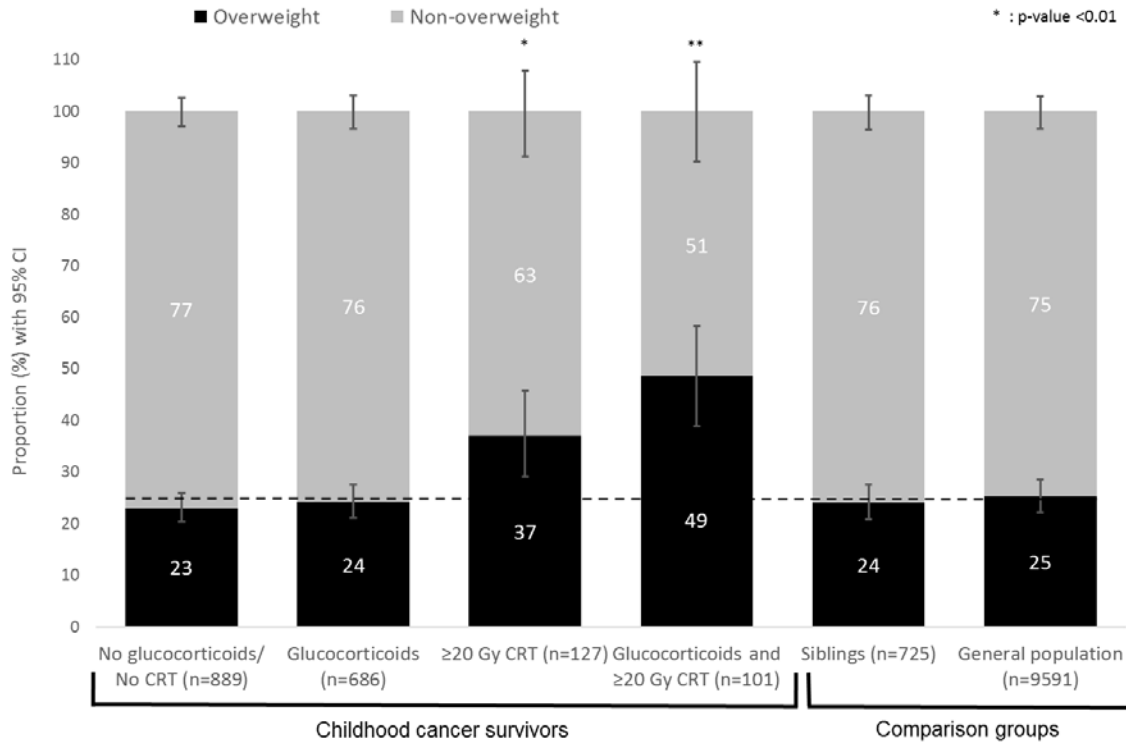
**TABLE 3. Crude and adjusted odds ratios for being overweight in childhood cancer survivors treated with different doses of cumulative glucocorticoid and cranial radiation therapy**

	CCS (n=1936)			ALL survivors (n=546)			NHL survivors (n=114)			HL survivors (n=195)		
	<i>n<sub>ow</sub>/n<sub>total</sub></i>	Crude OR (95% CI)	Adj OR (95% CI) <sup>a</sup>	<i>n<sub>ow</sub>/n<sub>total</sub></i>	Crude OR (95% CI)	Adj OR (95% CI) <sup>a</sup>	<i>n<sub>ow</sub>/n<sub>total</sub></i>	Crude OR (95% CI)	Adj OR (95% CI) <sup>a</sup>	<i>n<sub>ow</sub>/n<sub>total</sub></i>	Crude OR (95% CI)	Adj OR (95% CI) <sup>a</sup>
<b>Cumulative prednisone (mg/m<sup>2</sup>)</b>												
<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)
<i>p-value</i> <sup>b</sup>		<b>0.081</b>	<b>0.236</b>		<b>0.276</b>	<b>0.481</b>		<b>0.754</b>	<b>0.351</b>		<b>0.179</b>	<b>0.506</b>
<b>Cumulative dexamethasone (mg/m<sup>2</sup>)</b>												
<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)	-	-	-	-	-	-
<i>p-value</i> <sup>b</sup>		<b>0.084</b>	<b>0.286</b>		<b>0.022</b>	<b>0.025</b>						
<b>Cumulative glucocorticoids (mg/m<sup>2</sup>)</b>												
<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)
<i>p-value</i> <sup>b</sup>		<b>0.715</b>	<b>0.900</b>		<b>0.438</b>	<b>0.073</b>		<b>0.710</b>	<b>0.940</b>		<b>0.212</b>	<b>0.300</b>
<b>CRT</b>												
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	-	-
<i>p-value</i> <sup>b</sup>		<b>&lt;0.001</b>	<b>&lt;0.001</b>		<b>&lt;0.001</b>	<b>&lt;0.001</b>		<b>0.871</b>	<b>0.963</b>		<b>0.202</b>	<b>0.237</b>

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

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

<sup>b</sup> Global *p*-value calculated from the likelihood ratio test.



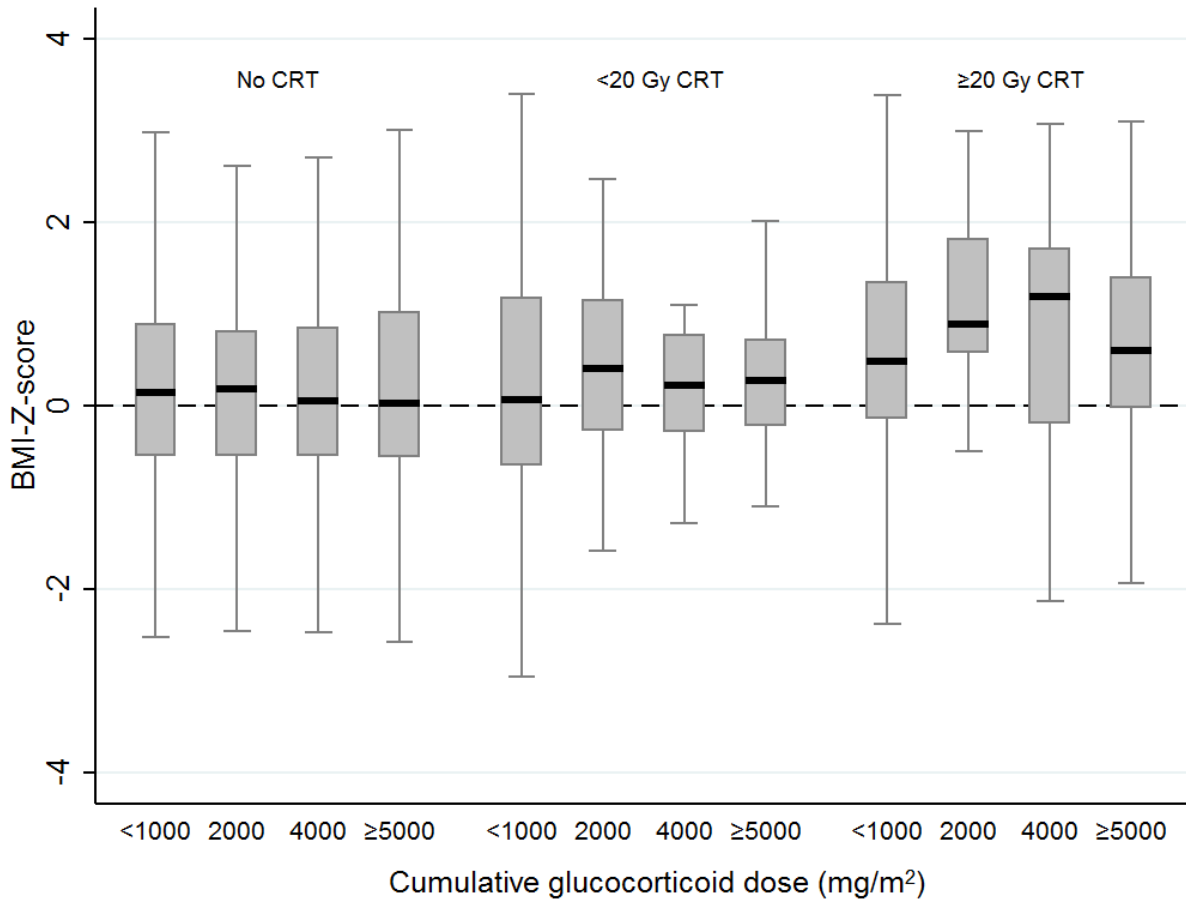
**FIGURE 1. Prevalence of overweight in long-term childhood cancer survivors, by treatment with glucocorticoids and ≥20 Gray cranial radiation.**

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