

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

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4 **Fabiën N. Belle, MSc^{a,b}, Rahel Kasteler, MD^a, Christina Schindera, MD^{a, c, d}, Murielle Bochud, Prof.**
5 **MD^b, Roland A. Ammann, Prof. MD^c, Nicolas X. von der Weid, Prof. MD^d, Claudia E. Kuehni, Prof.**
6 **MD^{a, c*} for the Swiss Pediatric Oncology Group (SPOG)****

7
8 ^a SCCR, Institute of Social and Preventive Medicine (ISPM), University of Bern, Bern, Switzerland.

9 ^bDivision of Chronic Diseases, ISPM, Lausanne University Hospital, Lausanne.

10 ^cDepartment of Pediatrics, Inselspital, Bern University Hospital, University of Bern, Bern.

11 ^dUniversity Children's Hospital Basel, Basel.

12
13 *Corresponding author. ISPM, University of Bern, Finkenhubelweg 11, 3012 Bern, Switzerland,

14 claudia.kuehni@ispm.unibe.ch

15
16 ** SPOG Scientific Committee: R. Ammann, Prof. MD, Bern; K. Scheinemann, Prof. MD, Aarau; M.
17 Ansari, Prof. MD, Geneva; M. Beck Popovic, Prof. MD, Lausanne; P. Brazzola, MD, Bellinzona; J.
18 Greiner, MD, St. Gallen; M. Grotzer, Prof. MD, Zurich; H. Hengartner, MD, St. Gallen; T. Kuehne, Prof.
19 MD, Basel; K. Leibundgut, Prof. MD, Bern; F. Niggli, Prof. MD, Zurich; C. Reimann, MD, Lucerne; N.
20 von der Weid, Prof. MD, Basel.

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25 FNB conducted the statistical analyses and wrote the article; RK, CS, MB, RAA, NXvdW, and CEK
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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.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
78
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 ($\geq 10,000$ 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 ≥ 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

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,^{22, 23} with added questions about health behaviors
114 and sociodemographic measures from the Swiss Health Survey (SHS)²⁴ and the Swiss Census.²⁵
115 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
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.¹⁹

124

125 The second comparison group consisted of participants in the SHS questionnaire 2012.²⁴ 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 (kg/m^2). Adult BMI $<18.5 \text{ kg}/\text{m}^2$ was
137 classified as underweight, ≥ 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.²⁷ For adolescents 15-19 years at survey, we standardized BMI into z-scores for age
139 and gender using the latest available Swiss references.²⁸ BMI z-scores lower than -2 were classified
140 as underweight, from -2 to 1 as normal weight, and >1 as overweight including obesity.²⁹

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 (mg/kg) were converted
148 into dose per body surface area (mg/m^2) 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/m².³¹ 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***

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 ≥ 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
233 with glucocorticoids (**Table 3**). But, CCS and ALL survivors treated with ≥ 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_{trend}
243 $\text{glucocorticoids}=0.583$ **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 ($p_{\text{trend prednisone}}=0.223$, $p_{\text{trend dexamethasone}}=0.063$, 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 (≥ 5824
249 mg/m²) tended to be more overweight than those treated with the lowest dose (< 2520 mg/m²). 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 (≥ 1260 mg/m²) were less likely to be
253 overweight than those treated with a lower dose (< 1260 mg/m²).

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 ≥ 20 Gy (37%), and yet higher among CCS treated with both glucocorticoids and cranial
260 radiation ≥ 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 ≥ 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-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.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 (≥ 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 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.¹⁷ 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.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

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,^{9, 12-14, 16} 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 ^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%).

° 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 ^a (n=725)		General population ^a (n=9591)	
	n	(%)	n	(% _{std})	p-value ^b	p-value ^b
Gender						
Male	1034	(53)	301	(54)	<i>n.a.</i>	4645 (54) <i>n.a.</i>
Age at survey, y						
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)
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)	<i>n.a.</i>	3454 (23) <i>n.a.</i>
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)		
	<i>n_{ow}</i> / <i>n_{total}</i>	Crude OR (95% CI)	Adj OR (95% CI) ^a	<i>n_{ow}</i> / <i>n_{total}</i>	Crude OR (95% CI)	Adj OR (95% CI) ^a	<i>n_{ow}</i> / <i>n_{total}</i>	Crude OR (95% CI)	Adj OR (95% CI) ^a	<i>n_{ow}</i> / <i>n_{total}</i>	Crude OR (95% CI)	Adj OR (95% CI) ^a
Cumulative prednisone (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)	34/119	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</i> -value ^b		0.081	0.236		0.276	0.481		0.754	0.351		0.179	0.506
Cumulative dexamethasone (mg/m²)												
<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</i> -value ^b		0.084	0.286		0.022	0.025						
Cumulative glucocorticoids (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)	38/138	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</i> -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	-	-
<i>p</i> -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.

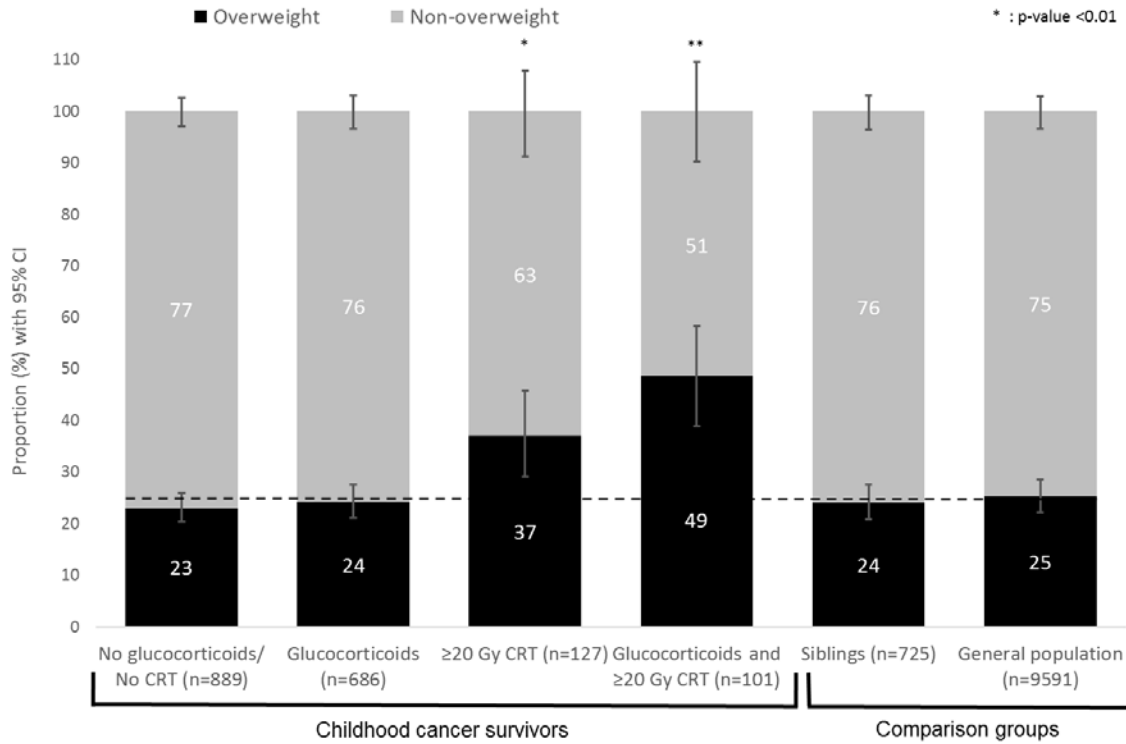


FIGURE 1. Prevalence of overweight in long-term childhood cancer survivors, by treatment with glucocorticoids and ≥20 Gray cranial radiation.

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.

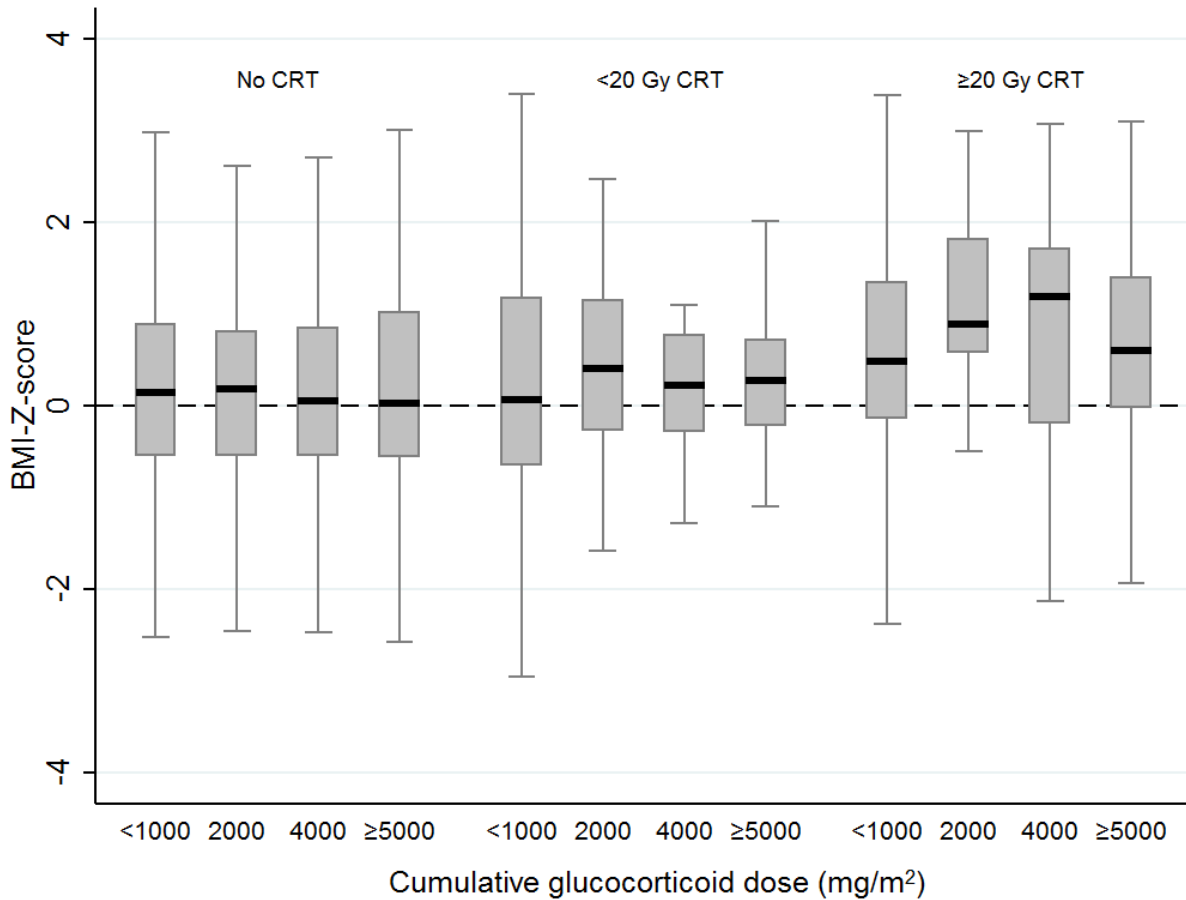


FIGURE 2. Box-plot of the dose-response relationship between BMI Z-score and cumulative glucocorticoid dose stratified by cranial radiation therapy in childhood cancer survivors (N=1936)

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

SUPPORTING INFORMATION

Supplementary TABLE 1. Protocols of clinical trials included

Protocol	CCS, n (%)	Dexamethasone	Prednisone ^a
BFM	234 (24%)		
ALL-BFM 83	1	X	X
ALL-BFM 86	2	X	X
ALL-BFM 90	56	X	X
ALL-BFM 95	64	X	X
ALL-BFM 99 MRD Pilot	4	X	X
ALL-BFM 2000	23	X	X
ALL/NHL-BFM 86	2	X	X
ALL-REZ-BFM 87	1	X	X
ALL-REZ-BFM 90	8	X	X
ALL-REZ-BFM P95/96	8	X	X
ALL-REZ-BFM 2002	2	X	X
AML-BFM 87	1		X
AML-BFM 93	7		X
AML-BFM 98	4		X
B-NHL-BFM 04	3	X	
NHL-BFM 83	3	X	X
NHL-BFM 90	18	X	X
NHL-BFM 95	27	X	X
GPOH	64 (7%)		
ALCL99 (GPOH)	1	X	
GPOH HD 95	47		X
GPOH HD 2002	16		X
POG	279 (29%)		
POG-7376	2		X
POG-7837	3		X
POG-7909	4		X
POG-8036	27		X
POG-8101	5	X	X
POG-8304	5		X
POG-8314	4		X
POG-8426	1		X
POG-8602	34		X
POG-8616	6		X
POG 8618	1		X
POG-8691	2		X
POG-8704	18		X
POG-8710	1		X
POG-8719	11		X
POG-9005	27		X
POG-9006	12		X
POG-9061	1	X	
POG-9201	11		X
POG-9219	14		X
POG-9310	1		X
POG-9315	5		X
POG-9398	2		X
POG-9404	4		X
POG-9405	6		X
POG-9406	7		X
POG-9411	3	X	X
POG-9412	4	X	
POG-9425	2		X
POG-9605	16		X
POG 9900	12	X	X

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

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.

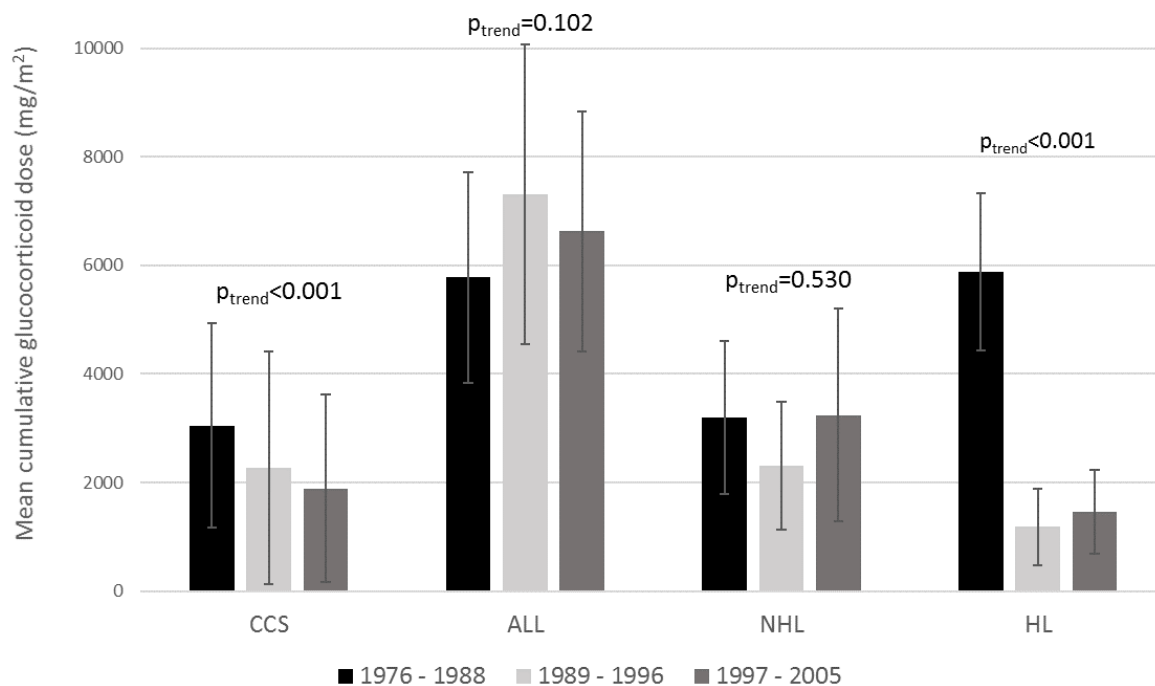
Supplementary TABLE 2. P-values for interaction of glucocorticoid use in childhood cancer survivors with sociodemographic and clinical characteristics (retrieved from multivariable logistic regressions^a)

	p-values for interactions ^b			
	CCS (n=1936)	ALL (n=546)	NHL (n=114)	HL (n=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 lymphoma

^a adjusted for gender, age at diagnosis, and time since diagnosis.

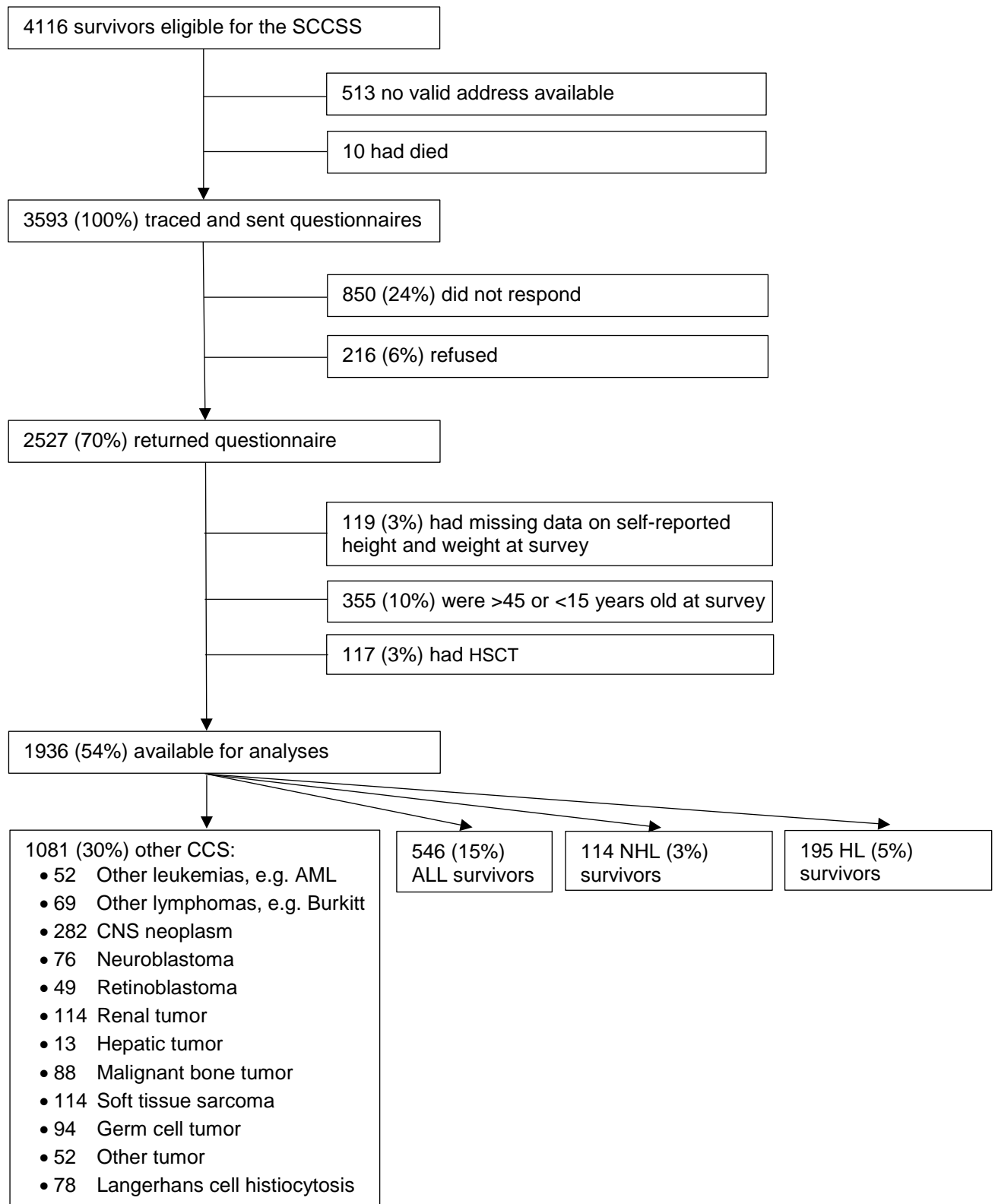
^b p-value for interaction was calculated with the likelihood ratio test.



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

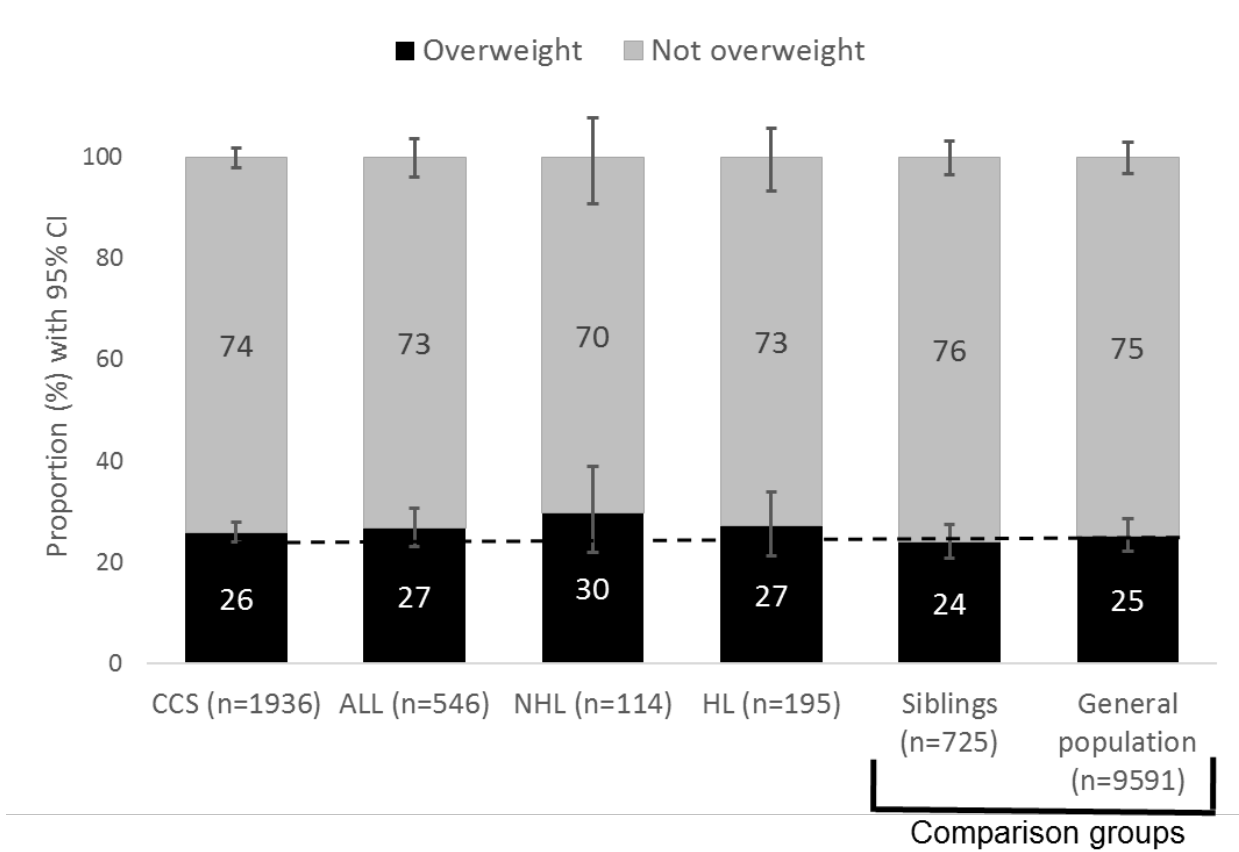
ALL, acute lymphoblastic leukemia; CCS, childhood cancer survivors; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma

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

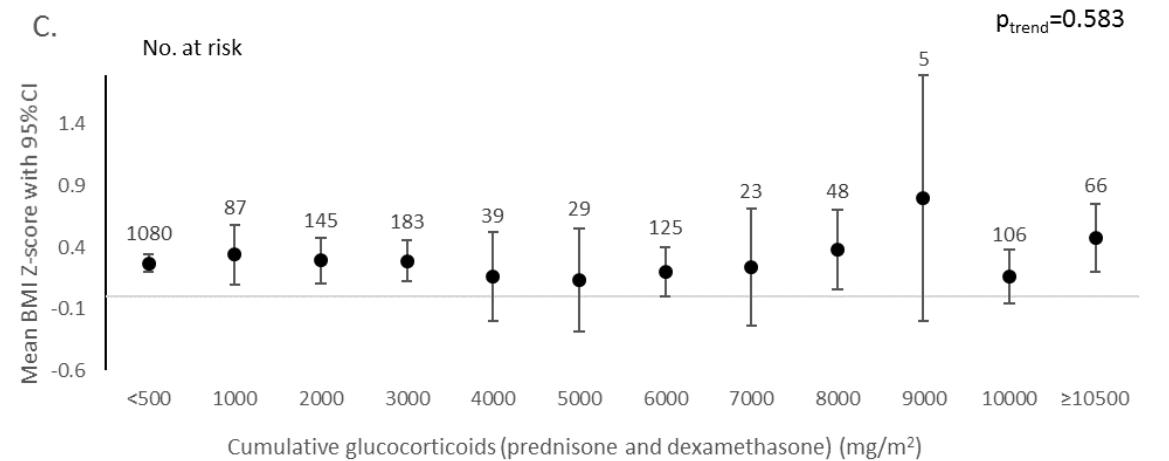
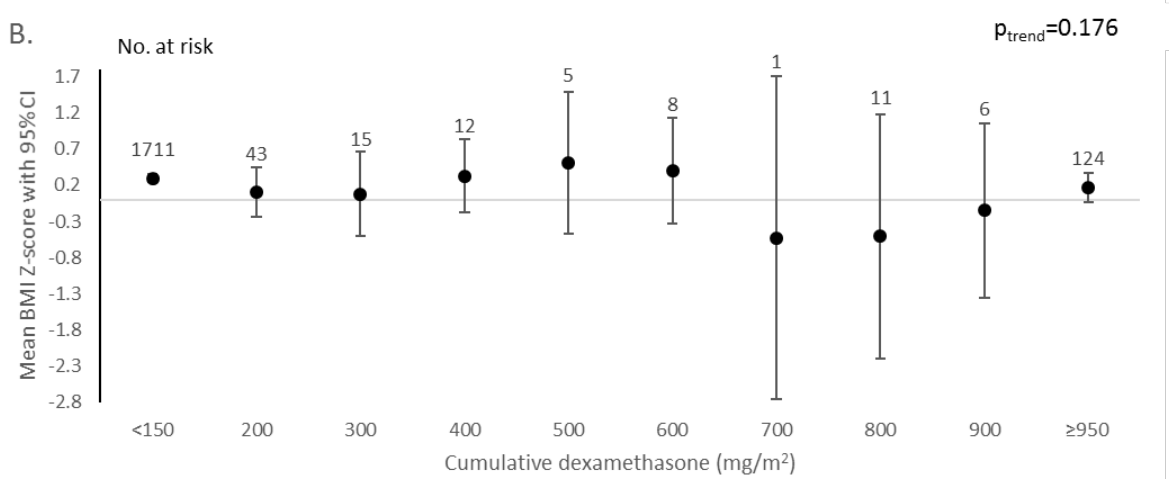
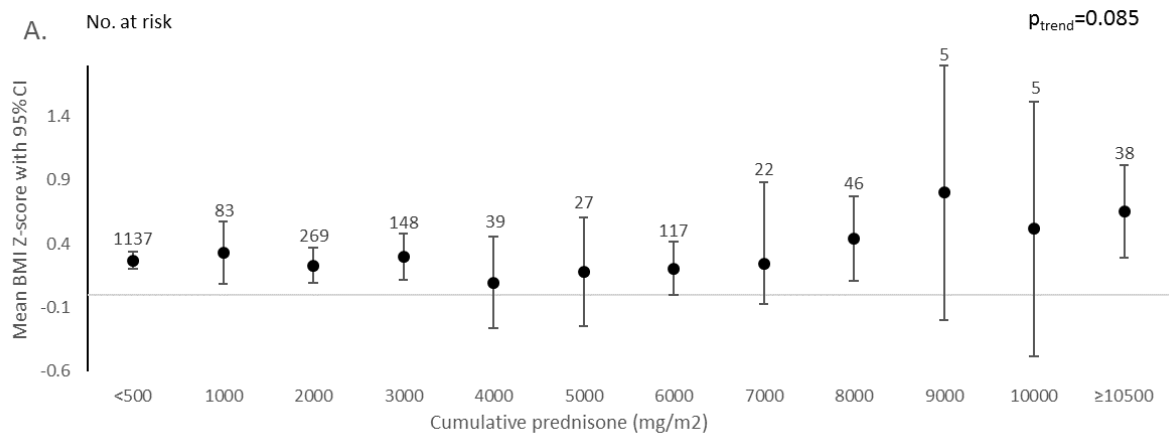


Supplementary FIGURE 3. Prevalence of overweight in childhood cancer survivors, their siblings, and the general population

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

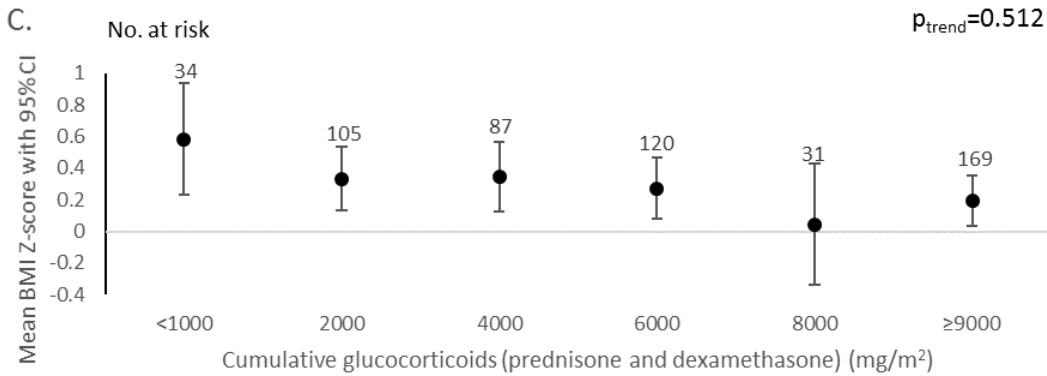
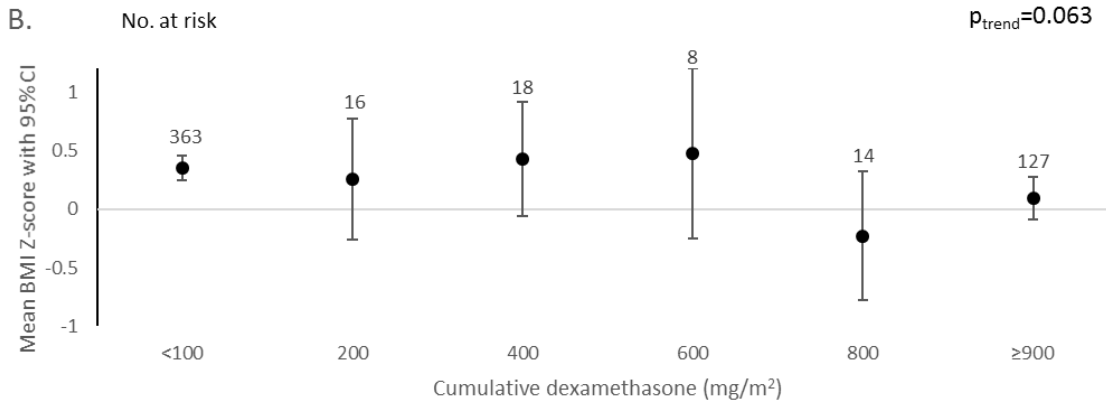
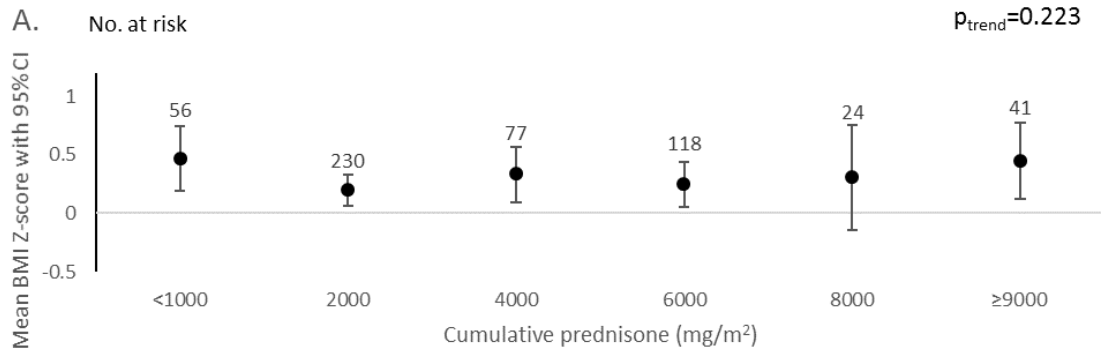
Comparison groups were standardized on gender, age at survey, migration background, and language region according to CCS.

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.