

**Childhood Cancer Survivor Study
Analysis Concept Proposal**

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Study title:

Risk factors for overweight and obesity after childhood acute lymphoblastic leukemia in North America and Switzerland: A comparison of two cohort studies

Working group:

Primary: Chronic Disease Working Group
Secondary: Epidemiology/Biostatistics

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67 Background & Rationale

68 Acute lymphoblastic leukemia (ALL) is the most common pediatric cancer accounting for
 69 25% of all cancers in childhood and adolescence (1, 2). Five-year survival exceeds 80%.
 70 This leads to a growing population of long-term survivors of pediatric ALL (1-3). Late effects
 71 after treatment for pediatric ALL are significant and contribute to increased morbidity and
 72 mortality later in life (4, 5). After second malignant neoplasms, chronic diseases, in particular
 73 cardiovascular disease, are predominant.

74 These late effects are partly caused by cancer treatments, such as chemotherapy with
 75 anthracyclines or radiotherapy, which are necessary for cure and thus not avoidable.
 76 However, behavioral risk factors strongly contribute. Excessive caloric intake and sedentary
 77 lifestyle lead to overweight and obesity, which increase the risk for cardiovascular and
 78 metabolic diseases, including hypertension, coronary heart disease, or diabetes (6). These
 79 lead to additional risks for childhood cancer survivors. Behavioral and lifestyle risk factors are
 80 avoidable, and better information on their distribution within CCS and their effects might help
 81 to design preventative strategies.

82 Overweight and obesity (from now on abbreviated as obesity) are typical examples of
 83 avoidable risk factors that are common in pediatric ALL survivors (7-9). Obesity has itself a
 84 multifactorial etiology, and a number of contributing factors have been described:

- 85 • **Sex.** Effects vary between countries: in North American, female CCS were more often
 86 obese than males (10-12); while the opposite was found in Switzerland (13).
- 87 • **Attained age.** Prevalence of obesity varies with age, and this age-dependency differs
 88 between countries. In a meta-analysis including studies from several countries the
 89 strongest evidence for an increased risk of obesity was found for recent children and
 90 adolescent ALL survivors (<5 years off treatment) (9). For long-term survivors (≥10
 91 years), and thus older at study, the association was less clear. In Swiss CCS, obesity
 92 was most common in the age groups 5-14 and 25-29 years (13).
- 93 • **Calendar year of survey.** Prevalence of obesity has increased in healthy people
 94 over the last decades (14). The same can be expected to have happened in CCS.

- 95 • **Socio-economic and cultural factors**, such as race/ethnicity, migration background,
96 educational status and income (15-17).
- 97 • **Lifestyle**, in particular physical activity and diet (18)
- 98 • **Age at diagnosis**. Children diagnosed young (< 5 years) seem to be at particular
99 high risk (8, 9).
- 100 • **Treatments**: Cranial radiation therapy (CRT) has been described as a risk factor for
101 obesity in North America (10-12) and Switzerland (15, 19), although results were not
102 consistent in a meta-analysis (20). Glucocorticoids have been described especially as
103 a risk factor for obesity during or shortly after treatment (18, 21-24), but no long-term
104 associations have yet been confirmed (19).

105 The prevalence of obesity in CCS varies strongly between studies and countries. In a
106 systematic review of long-term (≥ 10 years off treatment) pediatric ALL survivors from North
107 America and Europe the prevalence of obesity ranged from 34% to 46% (9). In a North
108 American study 60% of the long-term pediatric ALL survivors were obese (7), while this
109 proportion was only 6% (26% overweight including obesity) in a national survey of leukemia
110 survivors in Switzerland (15). A small Brazilian study among low socio-economic classes
111 showed even lower numbers; 4% of the ALL survivors were obese (17). These data suggest
112 that the environment, where CCS live, matters and that obesity is not an automatic result of
113 cancer treatment, but can be largely avoided.

114 However, data on prevalence and risk factors for obesity are difficult to compare between
115 published studies, because they differ in numerous factors that influence obesity: **sex**
116 **distribution**, **attained** age, **calendar year of survey**, time since diagnosis, race/ethnicity,
117 migration background, educational level, living situation, health insurance, lifestyle (smoking,
118 physical activity, diet), and clinical factors (treatment protocol, frequency and dose of CRT,
119 chemotherapy). Inclusion criteria for study populations and adjustment for risk factors differ
120 so substantially between studies that we cannot compare results based on published data.
121 Only an individual patient data analysis will make it possible to harmonize inclusion criteria
122 and stratify or adjust for the same risk factors. Such an analysis will allow comparison of
123 prevalence and risk factors for obesity between CCS of similar **sex**, attained age, **and**
124 **calendar year** in the two cohorts; to compare the direction and strength of the association
125 with socio-demographic and lifestyle risk factors; and to investigate differences between CCS
126 and siblings. Comparing North America and Switzerland is particularly interesting, because
127 both are developed countries with excellent health care, but they differ in lifestyle habits like
128 diet and physical activity (25, 26). Better understanding on what drives the obesity epidemic
129 in CCS in the two cohorts can help to discover causes and describe pathways, allowing to
130 design interventions on an individual or systemic (societal) level to prevent development of
131 obesity in ALL survivors. This will ultimately reduce development of cardiovascular and
132 metabolic disease in CCS and improve quality of life and reduce premature mortality.

133 We thus propose a de novo individual patient data analysis of the CCSS and SCCSS
134 datasets to enable a direct comparison, by:

- 135 • Applying the same inclusion criteria for the North American and Swiss study
136 population, allowing a maximal overlap between the two populations regarding sex,
137 attained age, and **calendar year of survey**.
- 138 • Evaluating important predictors of obesity

- 139 • Using the same analytical approach.

140 This method will give better insights into the risk factors and allow us to understand if and
141 why prevalence of obesity differs between the two cohorts.

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144 **Aims & Objectives**

145 We aim

- 146 1) **To compare the prevalence of overweight and obesity between pediatric ALL**
147 **survivors and their siblings in North America and Switzerland.**

148 *Hypothesis:* We hypothesize that the absolute prevalence of obesity in ALL survivors
149 and their siblings is higher in North America than in Switzerland, but that the
150 difference between CCS and their siblings is the same.

- 151 2) **To identify risk factors for obesity and compare the direction and strength of**
152 **the associations in North America and Switzerland.** We will investigate
153 demographic (sex, attained age, **calendar year of survey**), socio-economic
154 (race/ethnicity, migration background, living situation, education level, current
155 employment, health insurance), lifestyle (smoking, alcohol consumption, physical
156 activity), and clinical factors (year of diagnosis, age at diagnosis, chemotherapy,
157 radiation, second malignancies).

158 *Hypothesis:* We hypothesize that the effects of treatment are similar in both cohorts,
159 but that effects of socio-demographic, socio-economic, and lifestyle factors differ.

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162 **Analysis framework**

163 ***Outcome of interest***

164 We will make use of self-reported height and weight data in both the CCSS as the SCCSS.
165 We will calculate body mass index (BMI), by dividing weight by height in meters squared
166 (kg/m²). Overweight will be defined as a BMI of 25 to 29.9 kg/m² and obesity as a BMI of ≥ 30
167 kg/m² (6). BMI will be used both as a continuous and categorical variable (non-
168 overweight/obese, overweight, obesity).

169

170 ***Study population***

171 *Inclusion criteria*

- 172 1) All CCSS survivors diagnosed with ALL (diagnosed 1970-1999) and siblings, ≥18
173 years of age at time of survey (baseline; follow-up 1, 2000; follow-up 2, 2003; follow-
174 up 3, 2005; follow-up 4, 2007; follow-up 5, 2014).
- 175 2) All SCCSS survivors diagnosed with ALL (diagnosed 1976-2010) and siblings, ≥18
176 years of age at time of survey (baseline 2007-2013, follow-up 2017).

177 **NOTE: since the cohorts will be matched on attained age and calendar year of survey,**
178 **and analysis will include information on treatment exposures for both cohorts, it is not**
179 **necessary to limit the years of diagnosis to the same time periods (i.e., 1976-1999)**

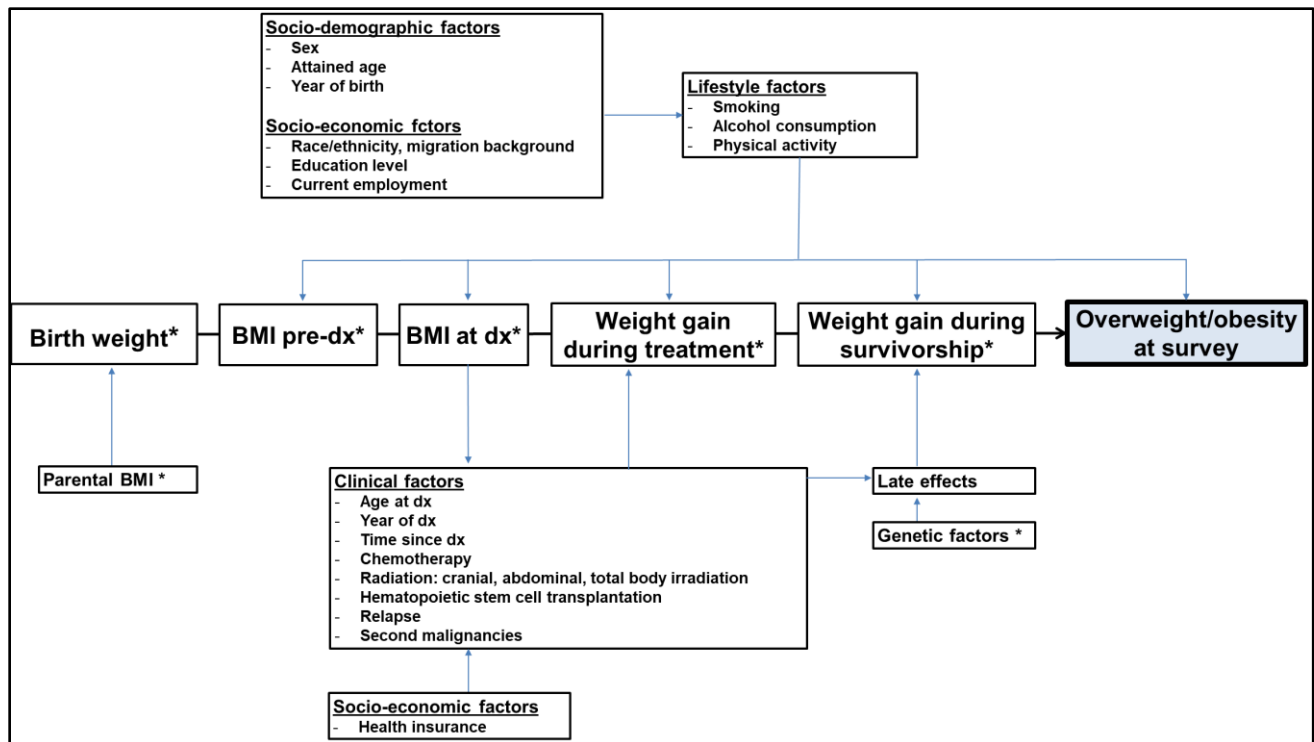
180 **Matching**181 **The cohorts will be matched on:**

- 182 • Sex
- 183 • Attained age, and
- 184 • Calendar year of survey

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186 **Potential explanatory factors (Figure 1)**

- 187 • Socio-demographic factors:
 - 188 ▪ Sex (contradicting findings) (7, 8, 12, 13, 20)
 - 189 ▪ Attained age (13, 20)
 - 190 ▪ Calendar year of survey (14)
 - 191 ▪ Year of birth
- 192 • Socio-economic factors:
 - 193 ▪ Race/ethnicity (Non-Hispanic White/ Non-Hispanic Black/ Hispanic/ Asian/ Other/
 - 194 Unknown) (15, 16)
 - 195 ▪ Living situation (Living alone/ With others)
 - 196 ▪ Education level (Lower than college graduate/post graduate level – college
 - 197 graduate/post graduate level) (13)
 - 198 ▪ Current employment (Yes/ No)
 - 199 ▪ Health insurance (Yes/ No)
- 200 • Lifestyle factors
 - 201 ▪ Smoking (Never/ Former/ Current)
 - 202 ▪ Alcohol consumption (Yes/ No/ Average drinks per week/day)
 - 203 ▪ Physical activity (Inactive/ Active; according to CDC recommendations. Active is
 - 204 defined as ≥ 150 minutes of moderate intense or ≥ 75 minutes of vigorous intense
 - 205 or a combination of moderate and vigorous intense physical activity per week)
 - 206 (13, 25)
- 207 • Clinical factors
 - 208 ▪ Age at diagnosis (8, 9, 27, 28)
 - 209 ▪ Year of diagnosis
 - 210 ▪ Time since diagnosis
 - 211 ▪ Chemotherapy (Yes / No/ Glucocorticoids: prednisone, dexamethasone [yes/no]):
 - 212 no long-term association (19), short-term (18, 21-24)
 - 213 ▪ Radiation
 - 214 - Cranial (Yes/ No/ Cumulative dose) (7-9, 13, 19, 29)
 - 215 - Abdominal (Yes/ No/ Cumulative dose) (12)
 - 216 - Total body irradiation; proxy for more severe disease, involvement of cranial
 - 217 field (Yes/ No/ Cumulative dose) (30)
 - 218 ▪ Hematopoietic stem cell transplantation (Yes/ No)
 - 219 ▪ Relapse (Yes/ No)
 - 220 ▪ Second malignancies; proxy for more intensive treatment (Yes/ No)



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222 **Figure 1.** “Lifetime causal diagram” of overweight and obesity at survey

223 BMI, body mass index; dx, diagnosis

224 *: information is not available in both cohorts: CCSS and SCCSS

225

226 **Statistical plan**

227 We will describe characteristics of survivors (socio-demographic, socio-economic, lifestyle,
 228 and clinical) and siblings (socio-demographic, socio-economic, and lifestyle) using means
 229 (SD) and medians (IQR) in both cohorts.

230 For comparisons between survivors and siblings (**aim 1**), we will use weighted analyses.
 231 Siblings will be weighted such that they become representative of survivors regarding the
 232 distribution of key socio-demographic variables (sex, attained age, calendar year,
 233 race/ethnicity, and migration background). For this, we will first fit a logistic regression with
 234 survivorship status as the outcome and the key demographic variables as predictors.
 235 Analysis weights for siblings will then be calculated as the inverse probability of being a
 236 survivor estimated from this regression. To evaluate the difference in obesity prevalence
 237 between ALL survivors and siblings, we will perform univariable and multivariable logistic
 238 regressions. We will adjust for socio-demographic, socio-economic, and lifestyle factors and
 239 include survivorship as an exposure. Variables with p-values <0.01 in univariable models will
 240 be jointly included in a multivariable model.

241 We will use multinomial logistic regressions (BMI categories based on self-reported height
 242 and weight data) to determine risk factors associated with obesity at survey in pediatric ALL
 243 survivors and use interaction tests to see if effects of risk factors differ between e.g. cohorts
 244 (**aim 2**). The SCCSS questionnaire has used the questions from the CCSS questionnaire
 245 with the same answer categories. This enables pooling of both cohort datasets and allows
 246 direct comparison of effects of risk factors. We will match Swiss with North American ALL
 247 survivors based on sex, attained age, and calendar year of survey on a 1:3 ratio or with
 248 frequency matching. We will select potential risk factors a priori based on a literature review,

249 e.g. sex, age at diagnosis, attained age, calendar year of survey, year of birth, physical
250 activity, cumulative CRT, steroid usage. Variables with p-values <0.01 in univariable models
251 will be jointly included in a multivariable model.

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338 **Tables and figures**

339

340 **Table I. Socio-demographic, socio-economic, and lifestyle characteristics by cohort**

Characteristics	ALL survivors		Siblings	
	North America <i>n</i> =....	Switzerland <i>n</i> =508	North America <i>n</i> =....	Switzerland <i>n</i> =678
Sex, <i>n</i> (%)				
Female		252 (50)		402 (59)
Male		256 (50)		276 (42)
Attained age (years), <i>n</i> (%)				
Mean (SD)		30.3 ± 8.2		29.4 ± 8.0
Median (IQR)		28.6 (23.7-36.0)		28.1 (23.0-34.8)
18-24		161 (32)		234 (35)
25-34		201 (40)		281 (41)
35-44		119 (23)		136 (20)
≥45		27 (5)		27 (4)
Race/ethnicity, <i>n</i> (%)				
Non-Hispanic White		504 (99)		676 (100)
Non-Hispanic Black		-		
Hispanic		1 (<1)		
Asian		3 (1)		
Other/ Unknown		-		2 (<1)
Living situation, <i>n</i> (%)				
Alone		93 (18)		97 (14)
Other		415 (82)		581 (86)
Education level (highest degree), <i>n</i> (%)				
Lower than college graduate/ post graduate level		379 (75)		502 (74)
College graduate/post graduate level		129 (25)		176 (26)
Current employment, <i>n</i> (%)				
No		90 (18)		236 (35)
Yes		418 (82)		442 (65)
Insurance, <i>n</i> (%)				
No		-		-
Yes		508 (100)		678 (100)
Smoking status, <i>n</i> (%)				
Never		300 (59)		423 (62)
Former		86 (17)		124 (18)
Current		122 (24)		131 (19)
Alcohol consumption, <i>n</i> (%)				
Never/rarely		251 (49)		358 (53)
Weekly, ≥1 std drink/week		235 (46)		290 (43)
Daily, 1 std drink/day		9 (2)		18 (3)
Frequently, >1 std drink/day		13 (3)		12 (2)
Physical activity, <i>n</i> (%)				
Inactive		99 (19)		108 (16)
Active ^a		382 (75)		570 (84)
Missing		27 (5)		
BMI, <i>n</i> (%)				
Underweight		32 (6)		12 (2)
Normal		318 (63)		477 (70)
Overweight		121 (24)		152 (22)
Obese		37 (7)		37 (5)

341 IQR: interquartile range, SD: standard deviation, BMI: body mass index

342 ^a: ≥150 minutes of moderate intense or ≥75 minutes of vigorous intense or a combination of moderate and vigorous intense physical

343 activity per week.

344

345 **Table II.** Clinical characteristics of ALL survivors by cohort

Characteristics	ALL survivors	
	North America <i>n</i> =	Switzerland <i>n</i> =508
Age at diagnosis (years), <i>n</i> (%)		
Mean (SD)		7.0 ± 4.4
Median (IQR)		5.7 (3.4-10.5)
<5		224 (44)
6-9		147 (29)
10-14		112 (22)
≥15		25 (5)
Year of diagnosis, <i>n</i> (%)		
<1980		60 (12)
1980-1989		214 (42)
1990-1999		182 (36)
2001-2010	N/A	52 (10)
Time since diagnosis, <i>n</i> (%)		
Mean (SD)		23.3 ± 8.7
Median (IQR)		22.8 (17.1-29.5)
<10		35 (7)
11-14		56 (11)
15-19		102 (20)
≥20		315 (62)
Chemotherapy, <i>n</i> (%)		
Any		485 (95)
Prednisone		482 (95)
Dexamethasone		169 (33)
Prednisone and dexamethasone		166 (33)
Missing		4 (1)*
Cranial radiation therapy (gray), <i>n</i> (%)		
None		386 (76)
<18		48 (9)
≥18		74 (15)
Abdominal radiation therapy (gray), <i>n</i> (%)		
None		508 (100)
<10		-
≥10 to <20		-
≥20		-
Total body radiation, <i>n</i> (%)		
No		498 (98)
Yes		10 (2)
Hematopoietic stem cell transplantation, <i>n</i> (%)		
No		485 (95)
Yes		23 (5)
Relapse, <i>n</i> (%)		
No		440 (87)
Yes		68 (13)
Second malignancies		
No		*
Yes		

346 IQR: interquartile range, SD: standard deviation, ALL: acute lymphoblastic leukemia

347 * still needs to be checked

348 **Table III.** Overweight and obesity in ALL survivors compared to siblings by cohort

	Non overweight/obese OR (95%CI)		Overweight OR (95%CI)		Obese OR (95%CI)	
	Univariable	Multivariable ^b	Univariable	Multivariable ^b	Univariable	Multivariable ^b
North America						
Siblings ^a	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
ALL survivors						
Switzerland						
Siblings ^a	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
ALL survivors						

349 ALL: acute lymphoblastic leukemia

350 a: Standardized on sex, attained age... according to ALL survivors

351 b: adjusted for....

352

353

354 **Table IV.** Predictors for overweight and obesity in ALL survivors by cohort (retrieved from
355 multinomial logistic regressions)

	Overweight ALL survivors		Obese ALL survivors		
	% ^a OR (95%CI) ^b	p-value ^c	% ^a	OR (95%CI) ^b	p-value ^c
Cohort					
North American	1.00 (ref)			1.00 (ref)	
Swiss					
Sex					
Female	1.00 (ref)			1.00 (ref)	
Male					
Attained age, y					
18-24	1.00 (ref)			1.00 (ref)	
25-34					
35-44					
≥45					
...					

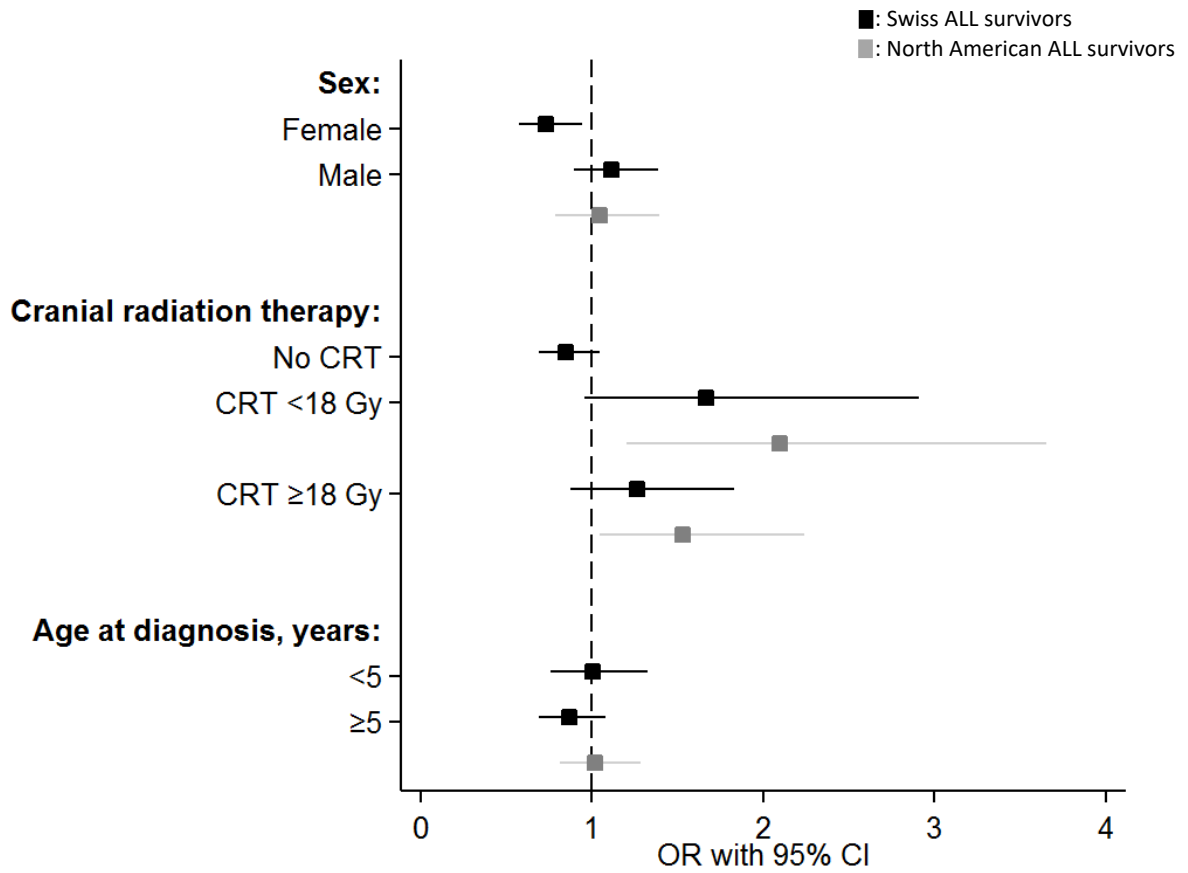
376 CI: confidence interval; OR: odds ratio; ALL: acute lymphoblastic leukemia

377 a: Column percentages are given;

378 b: Adjusted for: 1) socio-demographic/-economic variables: sex, attained age, education ... and 2) lifestyle factors: smoking,
379 physical activity, ...;380 c: global p-value for an association between overweight/obesity and the variable as a whole (Wald test comparing models with
381 and without the variable).

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Figure 1 (EXAMPLE). Risk factor specific OR and 95%CI for overweight in North American and Swiss pediatric ALL survivors (from multivariable logistic regression¹)
Squares, OR for overweight; whiskers, the respective 95% CI
Abbreviations: CI, confidence interval; CRT, cranial radiation therapy; Gy, gray; ALL: acute lymphoblastic leukemia
¹ Adjusted for sex, attained age ...