Childhood Cancer Survivor Study
Analysis Concept Proposal

Study title:

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

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Background & Rationale

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

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

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

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

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

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

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

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

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

- Using the same analytical approach.

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

Aims & Objectives

We aim

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

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

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

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

Analysis framework

Outcome of interest

We will make use of self-reported height and weight data in both the CCSS as the SCCSS. We will calculate body mass index (BMI), by dividing weight by height in meters squared (kg/m^2). Overweight will be defined as a BMI of 25 to 29.9 kg/m^2 and obesity as a BMI of ≥ 30 kg/m^2 (6). BMI will be used both as a continuous and categorical variable (non-overweight/obese, overweight, obesity).

Study population

Inclusion criteria

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

Matching

The cohorts will be matched on:

- Sex
- Attained age, and
- Calendar year of survey

Potential explanatory factors (Figure 1)

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

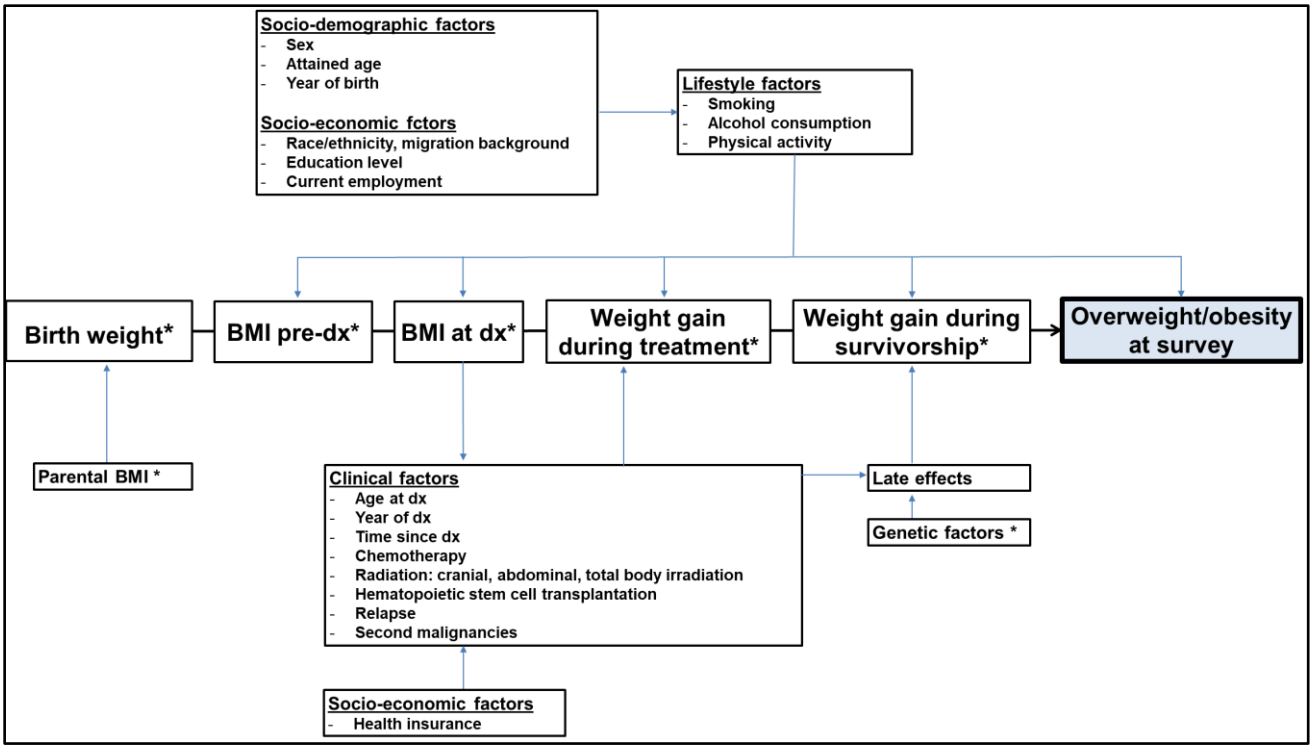

Figure 1. "Lifetime causal diagram" of overweight and obesity at survey

BMI, body mass index; dx, diagnosis

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

Statistical plan

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

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

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

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

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Tables and figures

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

Characteristics	ALL survivors		Siblings	
	North America ***n=….***	**Switzerland** ***n=508***	**North America** ***n=….***	**Switzerland** ***n=678***
Sex, *n (%)*				
Female		252 (50)		402 (59)
Male		256 (50)		276 (42)
Attained age (years), *n (%)*				
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, *n (%)*				
Non-Hispanic White		504 (99)		676 (100)
Non-Hispanic Black		-		
Hispanic		1 (<1)		
Asian		3 (1)		
Other/ Unknown		-		2 (<1)
Living situation, *n (%)*				
Alone		93 (18)		97 (14)
Other		415 (82)		581 (86)
Education level (highest degree), *n (%)*				
Lower than college graduate/ post graduate level		379 (75)		502 (74)
College graduate/post graduate level		129 (25)		176 (26)
Current employment, *n (%)*				
No		90 (18)		236 (35)
Yes		418 (82)		442 (65)
Insurance, *n (%)*				
No		-		-
Yes		508 (100)		678 (100)
Smoking status, *n (%)*				
Never		300 (59)		423 (62)
Former		86 (17)		124 (18)
Current		122 (24)		131 (19)
Alcohol consumption, *n (%)*				
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, *n (%)*				
Inactive		99 (19)		108 (16)
Active[a]		382 (75)		570 (84)
Missing		27 (5)		
BMI, *n (%)*				
Underweight		32 (6)		12 (2)
Normal		318 (63)		477 (70)
Overweight		121 (24)		152 (22)
Obese		37 (7)		37 (5)

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

[a]: ≥150 minutes of moderate intense or ≥75 minutes of vigorous intense or a combination of moderate and vigorous intense physical activity per week.

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

Characteristics		ALL survivors	
		North America ***n=***	**Switzerland** ***n=508***
Age at diagnosis (years), *n (%)*			
	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, *n (%)*			
	<1980		60 (12)
	1980-1989		214 (42)
	1990-1999		182 (36)
	2001-2010	N/A	52 (10)
Time since diagnosis, *n (%)*			
	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, *n (%)*			
	Any		485 (95)
	Prednisone		482 (95)
	Dexamethasone		169 (33)
	Prednisone and dexamethasone		166 (33)
	Missing		***4 (1)****
Cranial radiation therapy (gray), *n (%)*			
	None		386 (76)
	<18		48 (9)
	≥18		74 (15)
Abdominal radiation therapy (gray), *n (%)*			
	None		508 (100)
	<10		-
	≥10 to <20		-
	≥20		-
Total body radiation, *n (%)*			
	No		498 (98)
	Yes		10 (2)
Hematopoietic stem cell transplantation, *n (%)*			
	No		485 (95)
	Yes		23 (5)
Relapse, *n (%)*			
	No		440 (87)
	Yes		68 (13)
Second malignancies			
	No		*
	Yes		

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

344 * still needs to be checked

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						

ALL: acute lymphoblastic leukemia
a: Standardized on sex, attained age… according to ALL survivors
b: adjusted for….

Table IV. Predictors for overweight and obesity in ALL survivors by cohort (retrieved from 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						
…						

CI: confidence interval; OR: odds ratio; ALL: acute lymphoblastic leukemia
a: Column percentages are given;
b: Adjusted for: 1) socio-demographic/-economic variables: sex, attained age, education … and 2) lifestyle factors: smoking, physical activity, …;
c: global p-value for an association between overweight/obesity and the variable as a whole (Wald test comparing models with and without the variable).

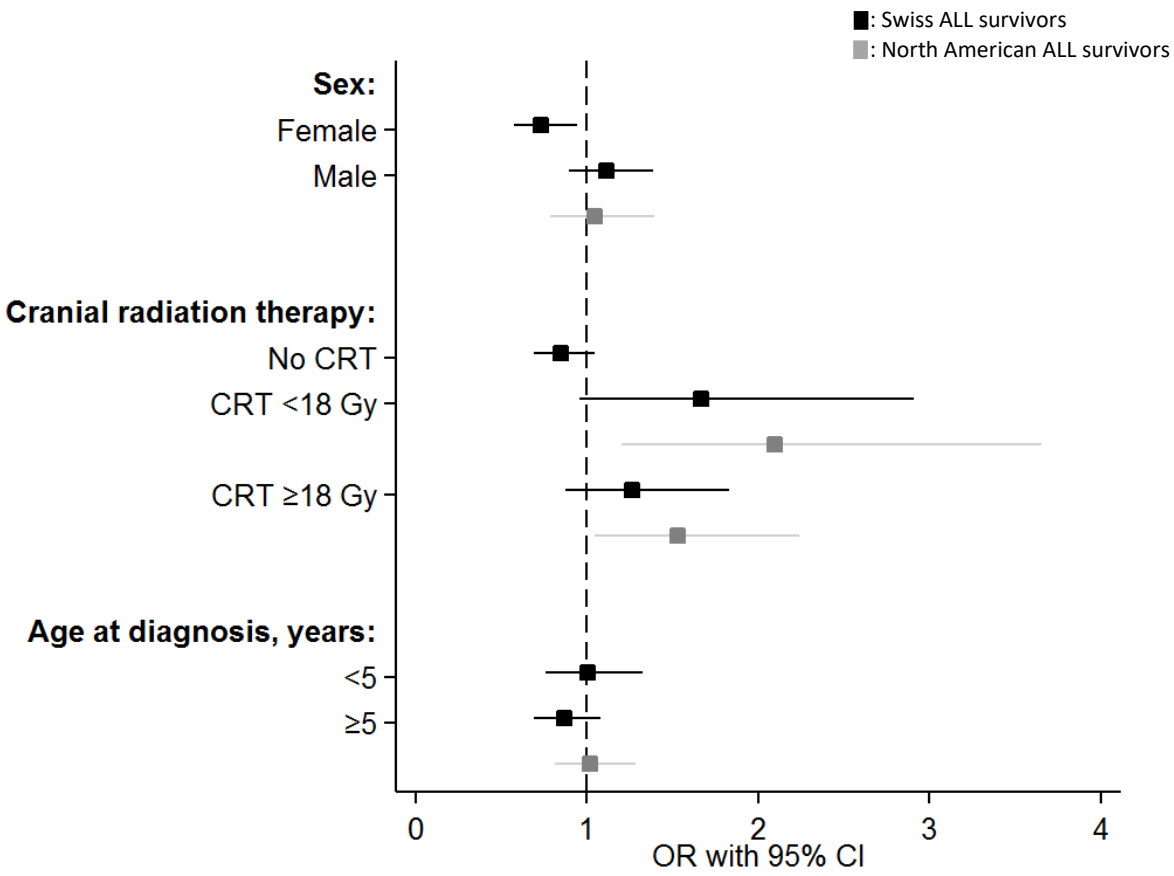

Figure 1 (EXAMPLE). Risk factor specific OR and 95%CI for overweight in North American and Swiss pediatric ALL survivors (from multivariable logistic regression[1])
Squares, OR for overweight; whiskers, the respective 95% CI
Abbreviations: CI, confidence interval; CRT, cranial radiation therapy; Gy,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