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Dietary intake and overweight in childhood cancer during treatment and survivorship

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par

Fabiën BELLE-VAN SPRUNDEL

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Jury

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Dietary intake and overweight in childhood cancer during treatment and survivorship

Lausanne, le 9 août 2018

pour le Doyen
de la Faculté de biologie et de médecine

Prof. Luc Tappy

For Laurence

SUMMARY

Unhealthy nutrition and overweight may increase the risk for chronic health problems after childhood cancer treatment. It is therefore important to get a better understanding of the dietary intake of survivors and the personal and clinical characteristics related to adherence to dietary recommendations. Additionally, it is key to determine risk factors related to weight gain during and after treatment, e.g. type of cancer, treatment, age, gender etc.

Our research is based on several sources of information. As part of the “Swiss Childhood Cancer Survivor Study” project, we sent two questionnaires. Childhood cancer survivors who survived at least 5 years filled in the first questionnaire. This questionnaire assessed adherence to dietary recommendations, and height and weight to calculate body mass index. The second questionnaire was a newly developed follow-up questionnaire completed by 1578 survivors, which assessed dietary intake in detail. Next, we measured several times height and weight of childhood cancer patients during treatment. Finally, we collected urine spot samples from 125 survivors and patients to compare them with detailed dietary intake information. For this last step, the analyses are ongoing.

Analyses on all these sources of information allowed us to make the following observations:

Only 43% of the survivors met the national recommended dietary intakes for meat, 34% for fruit, 30% for fish, 18% for dairy products, 11% for vegetables, and 7% for combined fruit and vegetables. Results were similar for siblings and the general population. Adherence was not better for those survivors with high cardiovascular risks. In all groups, characteristics related to dietary adherence were similar.

After treatment, the prevalence of and risk factors for being overweight were the same for survivors and their peers. But, survivors treated with head radiation therapy of 20 gray or more were more often overweight after treatment. Glucocorticoid chemotherapy seemed to have no impact on overweight in the long term.

During treatment, being a boy and having been diagnosed with a specific type of leukemia (acute lymphoblastic leukemia, ALL) or lymphoma were risk factors for weight gain. Children affected by other types of cancer tended to lose initially weight before gaining weight during the second half of treatment.

Based on these results, we suggest that prevention methods for unhealthy diet and overweight can be similar for survivors as for the general population. An important exception are survivors treated with cranial radiotherapy of 20 gray or more who may need extra attention during follow-up care. Besides, patients diagnosed with ALL or lymphoma might benefit from early lifestyle interventions.

RÉSUMÉ

Une mauvaise alimentation et un surpoids augmentent le risque de problèmes de santé chroniques après un traitement contre le cancer chez les enfants. Il est donc important de mieux comprendre l'apport alimentaire des survivants et les caractéristiques personnelles et cliniques liées à l'observance des recommandations alimentaires. Il est également important de déterminer quels sont les facteurs qui peuvent provoquer une prise de poids durant et après le traitement, p.ex. type de cancer, de traitements, âge, sexe de l'enfant, etc.

Notre recherche se base sur plusieurs sources d'information. Dans le cadre du projet 'Swiss Childhood Cancer Survivor Study', nous avons envoyé deux questionnaires aux survivants d'un cancer durant l'enfance. Les anciens patients qui ont survécu au moins 5 ans ont rempli le premier questionnaire. Ce questionnaire a évalué l'observance des recommandations alimentaires, la taille et le poids pour calculer l'indice de masse corporelle (IMC). Le deuxième questionnaire était un nouveau questionnaire de suivi rempli par 1578 survivants, qui a évalué l'apport alimentaire en détail. Nous avons également relevé la taille et le poids des enfants à plusieurs reprises durant le traitement. Finalement, nous avons collecté des échantillons d'urine de 125 survivants et patients afin de les comparer aux informations détaillées sur l'apport alimentaire. Les analyses sont encore en cours pour cette dernière étape.

L'analyse de toutes ces informations nous ont permis de faire les observations suivantes:

Comparé aux lignes directrices nationales, seulement 43% des survivants respectaient les apports nutritionnels recommandés pour la viande, 34% pour les fruits, 30% pour le poisson, 18% pour les produits laitiers, 11% pour les légumes et 7% pour les fruits et légumes combinés. Les résultats étaient similaires pour les frères et sœurs et dans la population générale. Cela est également le cas pour les survivants ayant un risque cardiovasculaire élevé. Les caractéristiques liées à l'observance des recommandations alimentaires étaient semblables dans tous les groupes.

Après le traitement, la prévalence et les facteurs de risque d'être en surpoids étaient les mêmes chez les survivants et leurs pairs. Mais les survivants traités avec une radiothérapie de la tête de 20 grays ou plus étaient plus souvent en surpoids après le traitement. La chimiothérapie aux glucocorticoïde semble n'avoir aucun impact sur le surpoids à long terme.

Durant le traitement, le fait d'être un garçon et d'avoir été diagnostiqué avec un type spécifique de leucémie (la leucémie lymphoblastique aiguë, LLA) ou avec un lymphome, était un facteur de risque de prise de poids. Les enfants touchés par d'autres types de cancer avaient tendance à perdre du poids avant de prendre du poids pendant la seconde moitié du traitement.

Sur la base de ces résultats, nous suggérons que les mesures de prévention contre une mauvaise alimentation et le surpoids peuvent être similaires pour les survivants comme pour la population générale. Une attention particulière doit être donnée durant les soins de suivi aux survivants traités par une radiothérapie de plus de 20 grays à la tête. De plus, les patients diagnostiqués avec une LLA ou un lymphome pourraient bénéficier d'interventions précoces de modification du style de vie.

LIST OF ABBREVIATIONS

24HDR	24-hour dietary recalls
A	Austria
ACS	American cancer society
ACTH	Adrenocorticotropin hormone
ALCL	Anaplastic large cell
ALL	Acute lymphoblastic leukaemia
ALiCCS	Adult life after childhood cancer in Scandinavia
AML	Acute myeloid leukaemia
BCCSS	British childhood cancer survivor study
BFM	Berlin/Frankfurt/Muenster study group
BLV	“Bundesamt für Lebensmittelsicherheit und Veterinärwesen”
BMI	Body mass index
CALGB	Cancer and leukemia group B
CAYA	Childhood, adolescent, and young adult
CCG	Children’s cancer group
CCS	Childhood cancer survivor
CCSS	Childhood cancer survivor study
CCP	Childhood cancer patients
CCER	“Commission catonale d’éthique de la recherche Genève”
CER-VD	“Commission catonale d’éthique de la recherche sur l’être humain Vaud”
Ch	Chapter
CH	“Confoederatio Helvetica”, Switzerland
CHO	Carbohydrates
CHUV	“Centre hospitalier universitaire Vaudois”/ Lausanne university hospital
CI	Confidence interval
CNS	Central nervous system
COG	Children’s oncology group
COG-LTFU	Children’s oncology group long-term follow-up
CoLaus	“Cohorte Lausannoise”
Cr	Creatinine
CRT	Cranial radiation therapy
CVD	Cardiovascular disease
D	Germany
DACH	Dietary recommendations for Germany (D), Austria (A), and Switzerland (CH)
DAL	German-Austrian multicentre trial
DCOG	Dutch childhood oncology group
DRI	Dietary reference intake
Dx	Diagnosis
ESPEN	European society for clinical nutrition and metabolism
EORTC	European organisation for research and treatment of cancer
EURO	European
FFQ	Food frequency questionnaire
FOPH	Federal office of public health
FSVO	Federal food safety and veterinary office
GPOH	German society of paediatric oncology and haematology
Gy	Gray
HD	High dose / Hodgkin’s disease
HEI	Healthy eating index
HL	Hodgkin lymphoma
HR	High risk
HSCT	Haematopoietic stem cell transplantation

HUG	“Hôpital universitaire de Genève”/ Geneva university hospital
ICCC-3	International classification of childhood cancer, 3rd edition
IGHG	International guideline harmonization group
IOTF	International obesity taskforce
IQR	Interquartile range
K	Kalium, potassium
KEK-BE	“Kantonale ethikkommission Bern”, Ethics committee of the Canton of Bern
KLS	Swiss cancer league
LB	Lymphoblastic
LCH	Langerhans cell histiocytosis
LMB	B-cell non-Hodgkin’s lymphoma and B-ALL
LR	Low risk
menuCH	Swiss national nutrition survey
MRD	Minimal residual disease
n.a.	Not applicable
Na	Natrium, sodium
NHL	Non-Hodgkin lympoma
NICER	National institute of cancer epidemiology and registration
No	Number
OR	Odds ratio
ow	Overweight
PAFQ	Physical activity frequency questionnaire
PAL	Physical activity level
PanCareSurFup	PanCare childhood and adolescent cancer survivor care and follow-up studies
PO_4	Phosphate
POG	Pediatric Oncology Group
RAE	Retinol activity equivalents
R-CHOP	Rituximab cyclophosphamide hydroxyl-doxorubicin vincristine prednisone
ref	Reference
REZ	Relapse
RT	Radiotherapy
SAKK	Swiss group for clinical cancer
SCCSS	Swiss childhood cancer survivor study
SCCR	Swiss childhood cancer registry
SD	Stadard deviation
SE	Standard error
SES	Social economic status
SFCDB	Swiss food composition database
SHS	Swiss health study
SIOP	International society of paediatric oncology
SJLIFE	St. Jude lifetime cohort study
SKION LATER	“De stichting kinderoncologie Nederland lange termijn effecten na behandeling van kinderkanker”, The Netherlands
SPOG	Swiss paediatric oncology group
SSN	Swiss society of nutrition
TBI	Total body irradiation
TSH	Thyroid-stimulating hormone
UK	United Kingdom
US	United States
WCRF/AICR	World cancer research fund/ American institute for cancer research
WHO	World health organization

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Chapter 1

Introduction and outline

CHILDHOOD CANCER

Childhood cancer is rare and accounts for less than 1% of all cancer cases in Switzerland [1]. Every year between 250 and 300 children under the age of 21 are diagnosed in Switzerland, an annual number which is stable over the last twenty years [2]. The overall age-standardised incidence rate of childhood cancer in Switzerland is comparable to other European countries with 16.3 per 100,000 person-years in children aged 0-14 years of any cancer (excluding Langerhans cell histiocytosis) [2, 3].

The types and causes for cancer in children are different from adults. Some types of cancer are only found in children, whereas common adult cancers, such as carcinomas of the lung and breast, are rare in children [4]. The most common forms of childhood cancer are leukaemia (33%), central nervous system (CNS) tumours (20%), and lymphomas (12%), but this distribution differs by age category [2] (**Figure 1**). Most cancers are the results of gene mutations leading to uncontrolled cell growth. In adults, these mutations may be the result of long-term exposure of cancer-causing factors like smoking, asbestos, sun exposure, or simply the consequences of aging [4]. In children, the cause of these mutations is unknown for most cases of cancer. Inherited genetic mutations and genetic conditions like the Down syndrome can increase the risk of developing childhood cancer, but also environmental factors like pre- and postnatal irradiation [5].

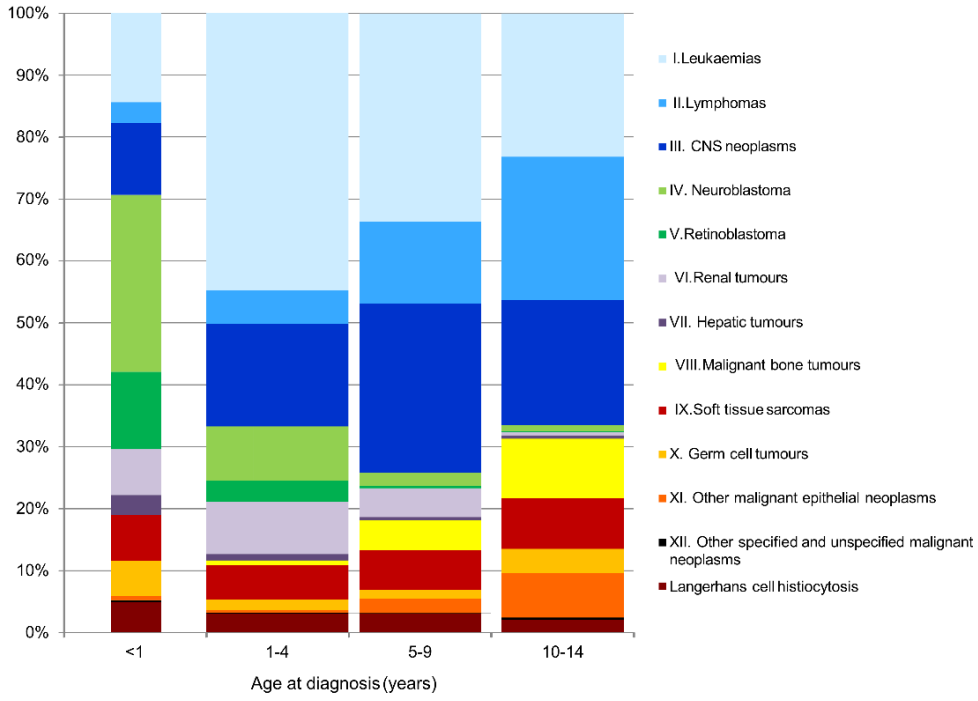

Figure 1. Main diagnostic groups of childhood cancer according to the International Classification of Childhood Cancer, third edition (ICCC-3), by age at diagnosis from the Annual Report of the Swiss Childhood Cancer Registry [2]

Swiss residents; age at diagnosis 0-14 years; period of diagnosis 1976-2016; all diagnoses (ICCC-3 or Langerhans cell histiocytosis); N=7043; with of bar represents size of population in the corresponding age group.

Although most children are successfully treated [6], cancer remains the second leading cause of death after accidents [7].

In this thesis, the term “childhood cancer” refers to cancer diagnosed before the age of 21 years including leukaemia, CNS tumours, lymphomas, and malignant solid tumours according to the ICCC-3 as well as Langerhans cell histiocytosis (LCH) [8]. The term “childhood cancer survivor (CCS)” is used for a person who survived childhood cancer at least 5 years after diagnosis. The term “childhood cancer patient (CCP)” is used for a person who receives childhood cancer treatment.

LATE EFFECTS OF CHILDHOOD CANCER

Childhood cancer treatment is a success story. Only fifty years ago, children had little hope on cure. Due to new and improved treatments survival rates among childhood cancer patients (CCP) have markedly increased over the last decades and currently exceed 80% [6]. With patients living longer, effective strategies to promote long-term overall health of childhood cancer survivors (CCS) become increasingly important. Complications and disabilities from treatment such as chemo- and radiotherapy, the cancer progress, or both can affect morbidity and mortality many years after cancer diagnosis [6, 9]. Medical assessments of 1713 adult CCS in the St. Jude Lifetime (SJLIFE) cohort study showed that, by the age of 45 years a big proportion of CCS experienced late effects. The estimated cumulative prevalence was 95% for having at least one chronic health condition and 80% for a severe, life-threatening or disabling condition [10]. Within the same cohort, Bhakta et al found that at age 45 years the burden of late effects was twice compared to the general population. CCS had on average seven or more additional chronic health conditions than the general population of whom two were severe, disabling or life-threatening. Frequently reported late effects secondary to childhood cancer or its treatment were cardiovascular disease (CVD), endocrine disorders, musculoskeletal problems, and secondary malignancies [9]. Development and severity of late effects depends on many unmodifiable or modifiable factors, e.g. age at diagnosis, type and harshness of given treatment, lifestyle (**Figure 2**). Current findings underline that post-treatment care of CCS should not only focus on preventing cancer recurrences or second malignancies but also on preventing and managing late effects, which may influence progression of other disease associated with aging or lifestyle. To anticipate on this late effects burden, both treatment related and patient specific risk factors should be taken into account.

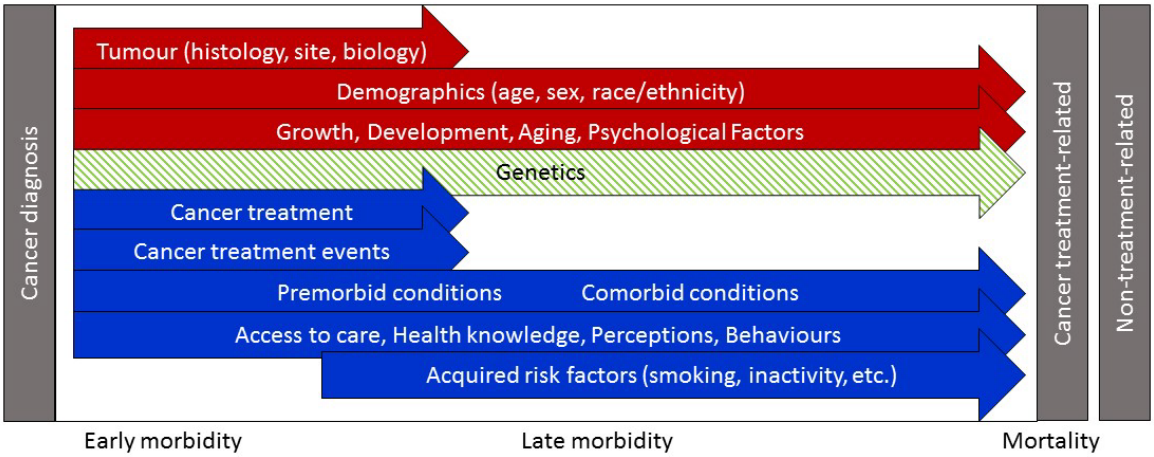

Figure 2. Risk factors for morbidity and mortality in childhood cancer survivors

Risk factors are seperated in unmodifiable risk factors (red), future plausible modifiable risk factors (green striped), and modifiable risk factors (blue)
Adapted from data source: reference [11].

Treatment related risk factors

Childhood cancer treatment and its related toxicities varies and depends on the type of cancer, tumour stage, histology, and response to treatment. In general, most children are treated with chemotherapy, radiation, surgery, or a combination of them. Although children tend to respond well to these treatments, they can have negative consequences over time (**Table I**). The emerging information of the occurrence of late effects has driven research to continously make efforts to discover and integrate novel treatments and have modified cancer treatment and follow-up care where possible. During the last years this has led to a reduction in treatment intensity for children with good prognosis while maintaining the levels of cure [12]. Due to the latency of the occurrence of many side effects, long-term follow-up remains important to determine late effects later in life as CCS are living longer.

Table I. Metabolic late effects in childhood cancer survivors and their risk factors [11, 13-15]

Late effects	Treatment-related risk factors	Patient specific risk factors
Overweight, obesity	-Glucocorticoids -Cranial radiation therapy -Total body radiation -Abdominal radiation -Hypothalamic injury; surgery or tumour growth	-Younger age at treatment -Female gender -Unhealthy diet -Physical inactivity -Older age -Mental health -Medical conditions, e.g. familial dyslipidaemia, growth hormone deficiency etc.
Metabolic syndrome, diabetes mellitus	-Cranial radiation therapy -Total body radiation -Abdominal radiation -Glucocorticoids -Alkylating agents -Haematopoietic stem cell transplantation	-Younger age at treatment - Unhealthy diet -Physical inactivity -Abdominal obesity -Family history of diabetes melllitus
Hypothalamic/pituitary dysfunction	-Cranial radiation therapy -Total body radiation -Hypothalamic injury; surgery or tumour growth -Tyrosine kinase inhibitors	-Younger age at treatment

Radiation

Radiation is frequently given to CCP and depending on the tumour can be given in different doses and locations. Although the introduction of radiation has improved survival rates, it can lead to several late effects for example subsequent neoplasms depending on the affected area and dosage [16]. With this in mind the proportion and the overall total dose of radiation per patient has been reduced over the years [16, 17]. In the North American Childhood Cancer Survivor Study (CCSS) they found that the proportion of CCS who were treated with any type of radiation decreased from 77% in the 1970s, to 54% in the 1980s, and even further to 33% in the 1990s. Median overall radiation treatment dose decreased from 30 Gy in the 1970s to 26 Gy in the 1990s [16].

Cranial radiation therapy (CRT), abdominal, and total body irradiation (TBI) have been associated with a variety of late effects, e.g. metabolic syndrome, diabetes mellitus, overweight, obesity, and hypothalamic/pituitary dysfunction like growth hormone deficiency (Table I). Dose-response relationships have been observed between radiation and these endocrine late effects, leading to efforts to either reduce or eliminate radiation completely during treatment. An example of this is the reduced use of CRT. Since the 1980s, CRT is not longer a standard element in acute lymphoblastic leukaemia (ALL) treatment protocols and cumulative doses have decreased [17-19]. In the US, the percentage of children with ALL who received CRT during treatment droped from 85% in the 1970s to only 19% in the 1990s [17]. Restricting CRT usage and decreased doses have also been observed in CNS tumour treatment protocols [17, 20].

Chemotherapy

Before 1970 cancer treatment was often based only on radiation and surgery, but survival markedly improved after the introduction of chemotherapy regimens [12]. Over the years different combinations of aggressive chemotherapies were introduced [5] and patients received more often chemotherapy including alkylating agents and anthracyclines [17]. Studies showed strong dose-response associations between the exposure of these chemotherapeutic agents and late effects. Alkylating agents increase the risk to develop gonadal dysfunction leading to infertility and anthracyclines exposure can lead to congestive heart failure which can be even further increased when CCS are also exposed to chest radiation [14, 21]. The proportion of ALL patients who received anthracyclines increased from 30% in the 1970s to 84% in the 1990s. Although the mean cumulative dose of anthracycline chemotherapy dropped from 289 mg/m^2 to almost half (158 mg/m^2), in an attempt to reduce late effects. A similar anthracycline dose reduction has been seen in children with Hodking lymphoma and Wilms tumours over the years [17].

To compensate for the reduced cranial radiation treatment in the 1980s, intrathecal and systemic chemotherapy regimens are developed to sustain CNS remissions in ALL, acute myeloid leukemia (AML), and non-Hodgkin lymphoma (NHL) patients [11, 22]. Although ALL treatment has changed little after the 1980s recent treatment advances have come from refined use of chemotherapy agents [22]. For example, overall glucocorticoids have an antileukaemic effect and are an important component in ALL treatment. But prednisone is sometimes replaced by dexamethasone due to the lower risk of relapse and improved event-free survival [22, 23]. There is still debate about the most optimal use of glucocorticoids in the treatment of ALL due to their short- and longterm side effects, e.g. weight gain, osteopenia, behavioural problems, infections. Glucocorticoids regulate maturation and metabolism of adipose tissue, which can lead to redistribution of fat deposits from arms and legs to the abdominal area with accumulating visceral fat in the long-term [24]. Furthermore, prolonged glucocorticoid use leads to increased appetite and psychological changes, which may influence dietary intake, and together with less energy expenditure due to physical inactivity could lead to weight gain [23, 25]. The choice of type, dose, and duration of glucorticoids remains a topic of dicussion within the goal of minimizing toxicity during the different phases of treatment.

Patient specific risk factors

CCP with equal treatment do not always develop the same morbidities, which suggests that the development of late effects is not only related to cancer and its treatment. Patient specific risk factors, like genetic, sociodemographic, and lifestyle factors may play a role in the development and severity of late effects. Increasing awareness of patient specific risk factors could detect chronic health conditions earlier and potentially prolong life and reduce morbidities.

Sociodemographic factors

Sociodemographic factors, like gender and age at diagnosis, are unmodifiable but investigating these factors can benefit surveillance and prevent late effects. It is suggested that cancer and its treatment negatively effects female survivors more compared to male survivors. Higher standardised all-cause mortality ratios were found in women compared to men in the CCSS performed in North America (women: 21.2: men: 10.0) [17], the Britsh Childhood Cancer Survivor Study (women: 11.7: men: 7.9) [12], as well as in the Swiss Childhood Cancer Survivor Study (SCCSS) (women: 18.4: men: 8.5) [26]. Women seem to also have a higher risk to develop chronic health conditions compared to men [27] after childhood cancer. Compared to men, women are more susceptible for cardiotoxic effects of anthracyclines and

to develop obesity after CRT [14]. The underlying mechanisms for these gender difference in late effects are not well understood and need further investigation [11].

The age at diagnosis and subsequently the age at treatment may impact the development of late effects since children experience a critical period of growth and body development. Children who receive CRT at a young age seem to be more susptible to develop endocrine late effects like obesity, diabetes mellitus, and hypothalamic/pituitary dysfunction (Table I). Young age at time of treatment is also associated with cardiac toxicity after anthracyline treatment, cardiac and pulmonary toxicity after chest radiation, and musculoskeletal growth problems after TBI [14].

Lifestyle factors

Post-treatment care may benefit from identifying modifiable risk factors that are not directly linked to late effects after cancer such as lifestyle. Risky health related behaviours including smoking, binge drinking, and an unhealthy diet may increase, whereas health promoting behaviours may reduce the risk to develop chronic diseases and second cancers [28, 29]. Despite the fact that CCS have already an elevated risk to develop late effects due to their earlier cancer and its treatment, the rates of smoking [30], frequent alcohol consumption or binge drinking [31], unsufficient sun protection [32], low physical activity [33], and having an unhealthy diet [34-38] are equally or more frequently seen in CCS compared to their siblings or the general population.

Health promoting lifestyles, including increased physical activity and improved diet, and comorbidity management could modifiy the morbidity and mortality trajectory that CCS experience due to unmodifiable cancer treatment-related and patient specific risk factors (**Figure 3**).

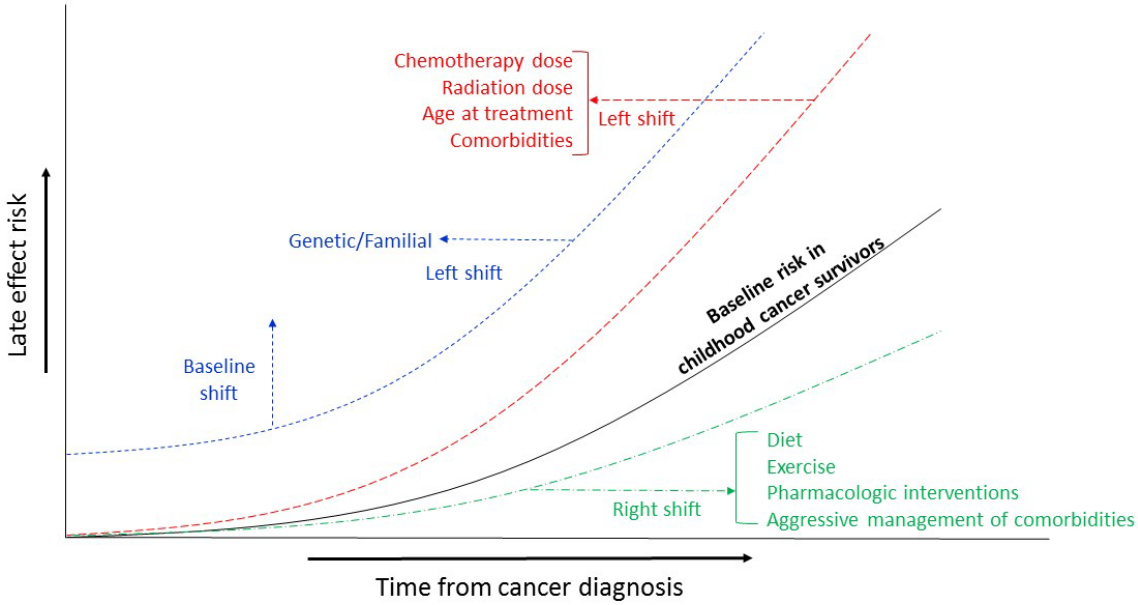

Figure 3. Conceptual schematic of late effect risk and potential modifiers in childhood cancer survivors

Adapted from data source: reference [39]

OVERWEIGHT, OBESITY, AND ITS PREDICTORS IN PATIENTS AND SURVIVORS

Childhood cancer patients and survivors face several risk factors that predispose them to overweight and obesity due to their cancer treatment received often at a very young age, e.g. reduced physical activity, unhealthy dietary intake, pituitary hormonal deficiencies, and impaired satiety signals (**Figure 4**). Overweight and obesity can occur both during and beyond cancer treatment and is seen as a modifiable patient specific risk factor to develop chronic health conditions like diabetes, dyslipidaemia, hypertension, and CVD [40]. Since CCS are more susceptible to develop these chronic health conditions due to their cancer treatment, it is important to prevent an early onset of excessive weight gain and keep a healthy weight throughout life.

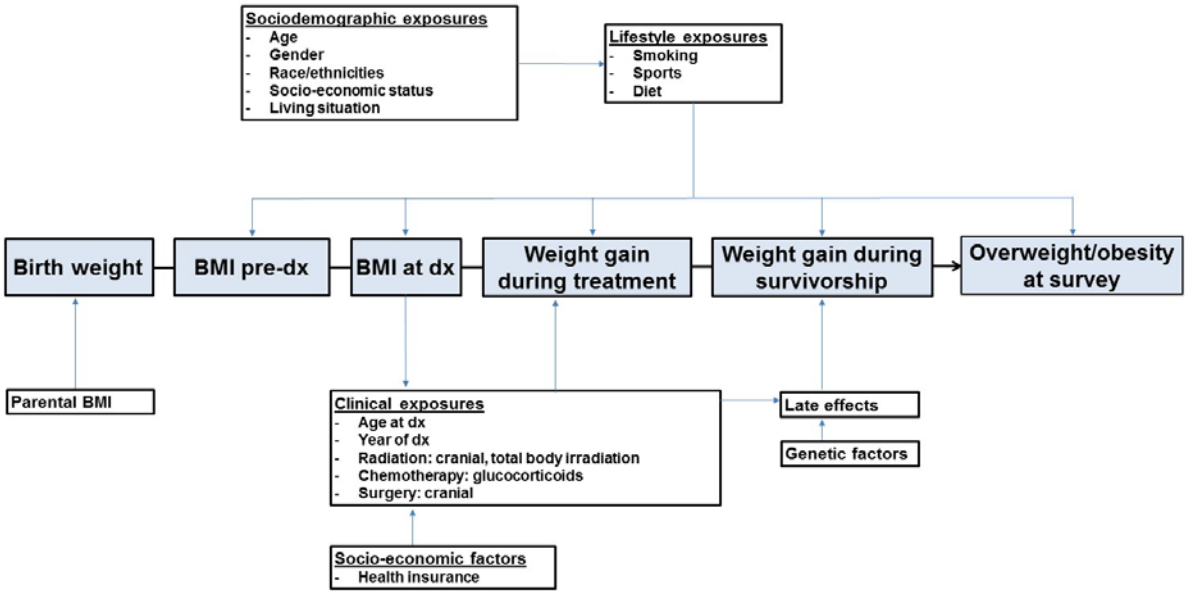

Figure 4. A schematic model of weight gain and overweight/ obesity during and beyond childhood cancer treatment
BMI, body mass index; dx, diagnosis

Overweight and obesity in acute lymphoblastic leukaemia patients and survivors

During treatment, increased weight is reported in ALL patients with obesity proportions between 9% and 48% at end of treatment versus 2% to 19% at diagnosis [41-45]. During the induction phase and early maintenance cycles, ALL patients tend to experience especially weight gain. Induction and early maintenance cycles normally contain excessive doses of glucocorticoids [43, 45-47]. These results were supported by a meta-analysis of Zhang et al. that reported results of 1791 childhood ALL patients and short-term survivors [46]. They found an overall mean increase of 0.8 (95% CI 0.3-1.4) body mass index *(*BMI) z-score from diagnosis until the end of treatment, with a tendency for a rapid weight gain during induction and during maintenance. A tendency for weight increase was also observed beyond treatment completion, with a diminishing increase in BMI Z-score over the years. These findings may suggest that weight gain during treatment is unlikely to be reversed after childhood cancer treatment, but heterogeneous results have been found. A meta-analysis of Zhang et al. showed that recent survivors tended to be more obese than those who survived longer [48]. A mean BMI z-score of 0.89 (95% CI 0.6-1.2) was found in 1391 childhood ALL survivors who were less than 5 years off treatment, and of 0.64 (95% CI 0.4-0.9) in 755 survivors 5 to 9 years off treatment. The survivors who were still mostly children and adolescents at time of evaluation had a higher BMI than the general reference population regardless of CRT receipt, gender, and age at diagnosis. Fewer studies looked at the prevalence of obesity at the long term, ≥10 years off treatment. In one of the largest long term studies, an overall similar BMI was found in 1451 adult survivors of childhood ALL 25 years after diagnosis compared to 2167 siblings. Subgroup differences were identified. ALL survivors exposed to CRT, who were

treated at a young age, and were women were more likely to have an increased BMI compared to their siblings [49]. This makes it doubtable that obesity persist long after treatment in ALL survivors.

Overweight and obesity in other types of childhood cancer patients and survivors

Studies about overweight or obesity during treatment have been mainly conducted in ALL and CNS tumour patients. In a meta-analysis of Wang et al. no difference was seen in the overweight and obesity prevalence between overall childhood brain tumour survivors and the general population, with the exception to craniopharyngiomas survivors [50]. Children with craniopharyngiomas can develop hypothalamic obesity during and after treatment [51]. Hypothalamic damage, a disruption of hormone satiety signalling, a decreased metabolic rate, and pituitary hormone deficiencies are seen due to tumour pressure or the damage caused by treatment within these CNS tumours patients [51, 52]. Besides childhood craniopharyngioma patients, also astrocytoma and ependymoma patients have been reported to be at increased risk of overweight after treatment [42, 53]. In a report of the CCSS including 14290 CCS of all types of cancer (median age 32 years, range 5-58) 24 years after diagnosis, it was found that survivors had an overall similar risk of becoming obese compared to their siblings [54]. But, a higher risk for obesity was found when survivors were treated with CRT with doses over 18 Gy which often include ALL and CNS tumour survivors.

DIETARY INTAKE OF CHILDHOOD CANCER SURVIVORS

Observational studies have shown that CCS poorly adhere to dietary guidelines [35, 36, 38, 55-57]. A low percentage of CCS meet the recommended five or more portions of fruit and vegetables per day, have inadequate amounts of vitamin D, vitamin E, calcium, magnesium, potassium, and fibre, and excessive intakes of sodium and saturated fat compared to the age-specific dietary reference intakes (**Table II**). Dietary quality based on the Healthy Eating Index (HEI) was low. A poor diet quality with a low intake of whole grain and a high intakes of sodium and empty calories was found in the St. Jude Lifetime (SJLIFE) cohort in 2570 adult CCS 24 years after diagnosis [37] and similar results are also reported by smaller studies [36, 55-58].

Dietary intake of CCS is often assessed by food frequency questionnaires (FFQ) [37, 55, 58, 59], food diaries [36], repeated 24-hour dietary recalls [56], or via food/nutrient screening questionnaires [60]. Since these self-reported assessment tools can lead to inaccuracy or under- or over-reporting, results needs to be handled with caution (**Table III**). Assessing dietary intake with a FFQ, could lead to recall bias, misreportig, or underreporting as the reported intake is limited to the food items on the list. The food item list is created to assess the habitual

intake and is therefore population and country specific. The 24-hour dietary recall is an in-depth interview to assess in detail everything the participant has eaten over the past 24-hours. This in-depth interview could lead to a good dietary intake report, but recall bias remains, and only a single recall can give a poor individual measurement. Each dietary assessment tool has its strengths and limitations to assess absolute intake (Table III). However, if we look at the relative intake instead of the absolute intake by comparing CCS to the general population we see that both groups adhere equally poor to recommended dietary intakes [36, 38]. This may be of concern, given the susceptibility of certain somatic late effects in CCS (Figure 3). Within the Chicago Healthy Living Study there was also no difference in the overall adherence to the American Cancer Society Guidelines on Nutrition and Physical Activity between 431 CCS and 361 controls [35]. Of the CCS, 10% were adherent to fibre intake, 18% to fruit and vegetables intake, 46% to red/processed meat intake, and less than 5% were adherent to all three dietary components.

With the current very limited level of evidence, the effectiveness of targeted nutritional interventions to improve nutritional intake and reduce chronic diseases later in life is lacking. Even though it seems crucial that CCS need to practice healthy behaviours equally well or better than the general population more research is needed.

Table II. Nutritional findings within the worldwide childhood cancer survivor studies[1]

	BCCSS **UK**	**CCSS** **US**	**SCCSS** **CH**	**SJLIFE** **US**
% of CCS who meet nutritional recommendations	Department of Health UK: -Alcohol *(≤21 units/week [M]/ ≤14 units/week [F])*: 76% [61]	WCRF/AICR recommendations: -Fruit and vegetables *(≥5 servings/d*): 25% [62]; +/-50% [55] -Alcohol *(<14 g/day [F]/ <28 g/d [M])*: 92% [63] only 10% consumed any alcohol [55] -Sodium *(<2400 mg/d):* 35% [55] -Red meat *(<3-4 times/week)*: 32% [63]	General findings: -Fruit and vegetables *(≥1 servings/d)*: 72% [64] -Alcohol *(<1 drink/d)*: 94% [64]	WCRF/AICR recommendations: -Fruit and vegetables *(≥5 servings/d)*: 26% [59] -Alcohol *(<14 g/d [F]/ <28 g/d [M])*: 94% [59] -Sodium *(<2400 mg/d)*: 30% [59] -Red meat *(<80 g/d)*: 10% [59] -Complex carbohydrates *(≥400 g/d)*: 48% [59]
% of DRI	-		-	-Vitamin D: 27% [37] -Vitamin E: 54% [37] -Potassium: 58% [37] -Fibre: 59% [37] -Magnesium: 84% [37] -Calcium: 90% [37] -Sodium: 155% [37] -Saturated fat: 115% [37] -71% of CCS has a DRI level of ≥0.8 g protein/kg body weight [65]
Dietary intake, mean/ median (range)	-	-Sodium (mean): 3113 mg/d [55] -Daily meat (mean): 4.6 oz (=130 g) [55] -Whole grain (mean): 1.5 servings [55]	-	-Energy (medium [range]): 1995 (1536-2543) kcal/d [65] -Fat (medium [range]): 686 (511-910) kcal/d [65] -Protein (medium [range]): 314 (241-408) kcal/d [65] -Carbohydrates (medium [range]): 965 (720-1252) kcal/d [65] -Sodium (medium [range]): 3428 (2656-4238) mg/d [65] -Fibre (medium [range]): 13 (9-17) g/d [65]
Diet quality	-	HEI-2005: 55.5 ± SE1.0 [36] Child Health and Illness Profile-Adolescent Edition: -low healthy foods in diet[2]: 32% [66] -high unhealthy foods in diet[3]: 35% [66]	-	HEI-2010: 57.9 ± 12.4 [37]

BCCSS, British Childhood Cancer Survivor Study; CCSS, Childhood Cancer Survivor Study; CH, Switzerland; CHO, carbohydrates; d, day; DRI, Dietary Reference Intakes; HEI, Healthy Eating Index; SCCSS, Swiss Childhood Cancer Survivor Study; SE, standard error; SJLIFE, St. Jude Lifetime cohort; UK, United Kingdom; US, United States of America; WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research

[1]: No nutritional findings were available for the Adult Life after Childhood Cancer in Scandinavia (ALiCCS) and "De Stichting Kinderoncologie Nederland LAnge TERmijn effecten na behandeling van kinderkanker", The Netherlands (SKION LATER)

[2]: Healthy diet behaviours was based on fruit/vegetable, lean meat, low-fat dairy, and whole grain intake within the past 4 weeks

[3]: Unhealthy diet behaviours was based on fast food, salty food, and sweets intake within the past 4 weeks

Table III. Dietary intake assessment tools and their strengths and limitations [67, 68]

Tool	Method	Strengths	Limitations
Food Frequency Questionnaire	Self-administered retrospective questionnaire based on a food item list to assess habitual diet (frequency/semi-quantitative: portion sizes) over a reference period (month/year)	-Low participant burden -Suitable for large surveys -Can be self-complete -Captures habitual intake and foods not consumed on a regular basis -Relative low costs, computerized processing -Useful to repeat dietary assessment over a number of years	-Food items may be missing and reported intake is limited to the food items on the list -Requires literacy and numeracy of participant -Population specific -Estimated portion sizes -Misreporting -Recall bias
Diet history	Retrospective structured interview method to capture detailed information on habitual food intake or food intake at a specific life stage/time period	-Usual diet in one assessment -Detailed individual foods -Captures foods not consumed on a regular basis	-Requires trained interviewers and results depend on interviewer skills -Observer bias -Recall bias -Misreporting -Not self-administered -Expensive
Technology assisted dietary assessment	Prospective electronic recording of foods and beverages consumed, photographs of consumed food with a smartphone application	-Standardisation of assessment, less prone to errors of participant/ interviewer -Less burdensome data collection and data entry -Suitable for large studies	-Internet access is needed -Computer literacy is needed -Nonresponse bias -High development costs
24-hour dietary recall	In-depth interview by a trained interviewer to assess in detail everything the participant has eaten over the past 24-hours	-Low participant burden -Suitable for large surveys -Participant does not know moment of recall, less prone for altering eating behaviour -Sensitive to ethnicity-specific eating behaviours	-Requires trained interviewers and results depend on protocol and interviewer skills -Estimated portion sizes -Recall bias -Single recall gives poor individual measurement -Expensive (time consuming, labour intense)
Food records	-Prospective food diary in which participant records details on food and beverages consumed at the time of consumption -Portion sizes can either be weighted or estimated	-Does not require recall -Detailed food descriptions and records of eating moments -Capture food eaten on a regular basis	-High participant burden -Misreporting/ can alter eating behaviour -Expensive -Irregular eaten food will not be captured -Several days of recording are needed, “study fatigue”
Weighted		-Precision of portion sizes	-Requires literacy, numeracy, and motivation of participant -Erratic lifestyle habits can be difficult with weighing and recording away from home.
Estimated		-Lower participant burden than weighted food records -Suits erratic lifestyle habits (eating outside home)	-Estimated portion sizes
Biochemical indicators of dietary intake	Collection of biological specimen from the participant	-Objective (no recall, social desirability) -Can be used to validate a dietary assessment tool -Useful assessment of the intake of certain nutrients	-Sensitive to intake, within-person variation -Focus on single agents instead of whole diet -Time integration (reflection of short-term/ long-term intake, day to day fluctuations) -Contamination -Stability during storage -No feasible biochemical indicator of intake can be available -Expensive

Dietary intake and late effects

Unhealthy dietary intake is an important element in the development of type II diabetes, metabolic syndrome, and CVD in the general population (**Table IV**). It is therefore widely recommended in populations suffering from these comorbidities to consume a diet rich in fruit, vegetables, fibre and complex carbohydrates, low in saturated and trans-fatty acids, and moderate in alcohol consumption (Table IV). Accumulating research among CCS shows that such late effects can be reduced, with diet adaptations, weight management, and physical activity [25, 58, 59, 69]. The extensively investigated Mediterranean diet, with high intakes of fish, fruit, vegetables, legumes, nuts, whole grains, and monounsaturated fats from olive oil, has shown a reduction, or even a prevention, of CVD, diabetes, obesity, metabolic syndrome, and cancer in the general population [70-74]. This makes nutrition one of the main determinants of health in the general population, and particularly relevant for people with additional risk factors, including cancer survivors. In the SJLIFE cohort study adherence to the lifestyle habits based on dietary intake, BMI, and physical activity according to the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) recommendations was associated with a lower risk of the metabolic syndrome in 1598 CCS [59]. In 117 adult survivors of childhood ALL, adherence to the Mediterranean diet was also associated with a reduced risk for the metabolic syndrome, lower visceral and subcutaneous fat, and a lower BMI [58]. In this study, each point increase on the Mediterranean diet score, representing for example an extra half serving of vegetables per day led to a 31% decrease of the metabolic syndrome risk [58].

Table IV. Long-term endocrine abnormalities and cardiovascular diseases seen in childhood cancer survivors, nutritional recommendation for prevention in the general population, and its level of evidence

Late effects seen in CCS	Nutritional recommendations for prevention or management in the general population	Level of evidence (A-C)[1]
Endocrine abnormalities		
Hypothalamic-pituitary axis-related endocrinopathies, e.g growth hormone, gonadotropin, TSH, or ACTH deficiency	-	-
Overweight, obesity, metabolic syndrome	Energy restricted/ healthy diet to achieve weight loss	A [75, 76]
	Mediterranean-type diet	B [75]
	Olive oil instead of other fats	A [75]
	Dietary Approached to Stop Hypertension diet, new Nordic diet, plant-based/vegetarian diets	B [75]
	Cereals (whole grains)	B [75]
	Fish	C [75]
	Dairy	B [75]
	Reduce/replace sugar-sweetened beverages	B-C [75]
	Moderate alcohol	B [75]
Type II diabetes, insulin resistance or insufficiency, dyslipidaemia	Low-carbohydrate or low-fat calorie restricted diets (weight loss)	A [77]
	Fibre, whole grains	B [77]
	Moderate alcohol	B [77]
	Legumes	A [75]
	Limit saturated fat	A [77]
	Fish	B [77]
	-associations found with obesity-	
Hypothyroidism, hyperthyroidism, thyroid nodules, thyroid cancer	Iodine (deficiency prevention) [78]	
	-associations found with obesity-	
Osteoporosis, osteopenia	Calcium	A [79]
	Vitamin D, dairy	B [79]
Azoospermia, Leydig cell failure, premature ovarian insuffiency	*-associations found with obesity-*	
Cardiovascular diseases		
(lowering blood pressure, low-density lipoprotein cholesterol)	Limit sodium intake [80, 81]	A - B [81]
	Limit saturated fat, trans-fat [80, 81]	A [81]
	Limit dietary cholesterol [80]	C/Insufficient [81]
	Variety of fruit and vegetables, whole grains, high-fibre foods, low-fat or fat-free diary, lean protein foods (fish, poultry, meat, alternatives), nuts, seeds, vegetables oils [80, 81]	A [81]
	Legumes	A [75]
	Whole grains	A [75]
	Nuts	A [75]
	-associations found with obesity-	

ACTH, adrenocorticotropin hormone; CCS, childhood cancer survivors; TSH, thyroid-stimulating hormone;
[1] Evidence grading system, A: strong evidence [randomised controlled trials, meta-analyses], B: moderate/intermediate evidence [cohort studies, case-control studies]; C: weak evidence [poorly controlled or uncontrolled studies, case series, case reports, expert consensus or clinical experience]

Current gaps in knowledge

So far, little is known about the dietary intake of CCS [38, 82] and its potential relationship with late effect development. Research performed to date suffers from methodological shortcomings, e.g. small sample sizes, short follow-up times, poorly detailed dietary

descriptions, are only based on self-reported questionnaire-based data instead of objective biochemical indicators of dietary intake, or lack of control groups. Well-performed studies are needed to describe dietary habits of CCS. This could help determining whether adverse somatic late effects may also be due to unhealthy lifestyle habits and malnutrition. Further, we should investigate if unhealthy habits are linked to childhood cancer, or are merely a consequence of cancer treatments, e.g. cranial surgery or CRT. It seems clear that overall malnutrition adds to the risks of comorbidity and mortality in children with cancer on short or long-terms. However, the potential harmful effects of long-standing malnutrition, the specific nutritional needs, and the exact link with adverse somatic late effects are unknown.

Studies conducted on overweight or obesity to date have been of somewhat limited relevance to CCS. Research on overweight and obesity prevalence has involved mostly ALL survivors [41, 43, 45, 49], whereas study of risk factors has led to inconsistent conclusions [48], e.g. sociodemographic, treatment, lifestyle, and pre-treatment factors like birthweight and bodyweight status at diagnosis (Figure 4). Most studies on this topic have been conducted in the US reflecting the lifestyles and eating habits of CCS in that country [43, 45, 47, 49, 54], whereas the duration of follow-up in other studies has been only short to medium term [46, 48], and many have had small sample sizes [41, 43, 45, 48]. Lastly, there is insufficient knowledge if the risk for obesity in CCS differs between cancer types with similar treatments.

Among adult cancer survivors healthy diets and weight-control management have been suggested to improve metabolic outcomes and reduce cancer recurrence and all-cause mortality [83]. This has resulted in dietary and physical activity guidelines for cancer survivors from various associations: the WCRF/AICR [84], the American Cancer Society [85], and the American College of Sports Medicine [86]. In adults, adherence to these dietary guidelines has shown encouraging results in terms of clinical outcomes, e.g. mortality and chronic disease development. However, evidence-based nutritional guidelines for children with cancer or CCS are not available to support nutritional practice. The Children's Oncology Group (COG) developed CCS guidelines, but gives general advice on nutrition and physical activity comparable to the general population [28]. Standardised international guidelines for weight management are currently lacking. Nonetheless, efforts are made by the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) to develop guidelines for metabolic syndrome surveillance, including obesity (see Appendices- Future projects).

Continuous efforts are needed to overcome the current nutrition related knowledge gaps, and promote late effects surveillance and healthy lifestyle behaviours "*so that the increasing*

numbers of successfully treated children of today do not become the chronically ill adults of tomorrow" as only "*cure is not enough*" [87].

AIM AND THESIS OUTLINE

The overall aim of this thesis is to improve our knowledge about the dietary intake in Swiss CCS and to gain insights in the potential risk factors for being overweight during and long after treatment (**Figure 5**). For this purpose, we compare the level of adherence to the national dietary recommendations in CCS, their siblings, and the general population (**Chapter 2**). In **chapter 3** we investigate the dietary intake of CCS by using a FFQ and compare it with several comparison groups representing the general Swiss population. In **chapter 4** we validated the FFQ with biomarkers assessed in urine spot samples in CCS and patients from the French-speaking region of Switzerland. In **chapter 5, 6, and 7** we show results of studies that investigated the socio-demographic, lifestyle, and clinical risk factors to develop overweight. In **chapter 5** we focus on overweight prevalence and its risk factors in childhood cancer patients from diagnosis till end of treatment. We look at weight change during treatment by type of cancer. We used data from three paediatric oncology clinics in the German speaking part of Switzerland. In **chapter 6** we assess the prevalence of overweight in CCS, with a focus on leukaemia survivors, compare it with their peers, and determine potential risk factors long after treatment. In **chapter 7** we further focus on the long-term effects of cancer treatment on overweight in CCS by looking at the cumulative dosage of glucocorticoids given during treatment. In the **appendices** we show future projects. We will compare the risk factors for overweight in ALL survivors between the US and Switzerland in a collaboration between the Childhood Cancer Survivor Study (CCSS, US, Memphis) and the SCCSS to investigate if risk factors are country specific or if they are applicable to all ALL survivors. Lastly, we will support the Obesity taskforce within the Metabolic Syndrome Working Group, IGHG in abstract reviewing and writing.

In the final chapter (**Chapter 8**), the presented results are summarized and discussed, and implications and directions for further research are presented.

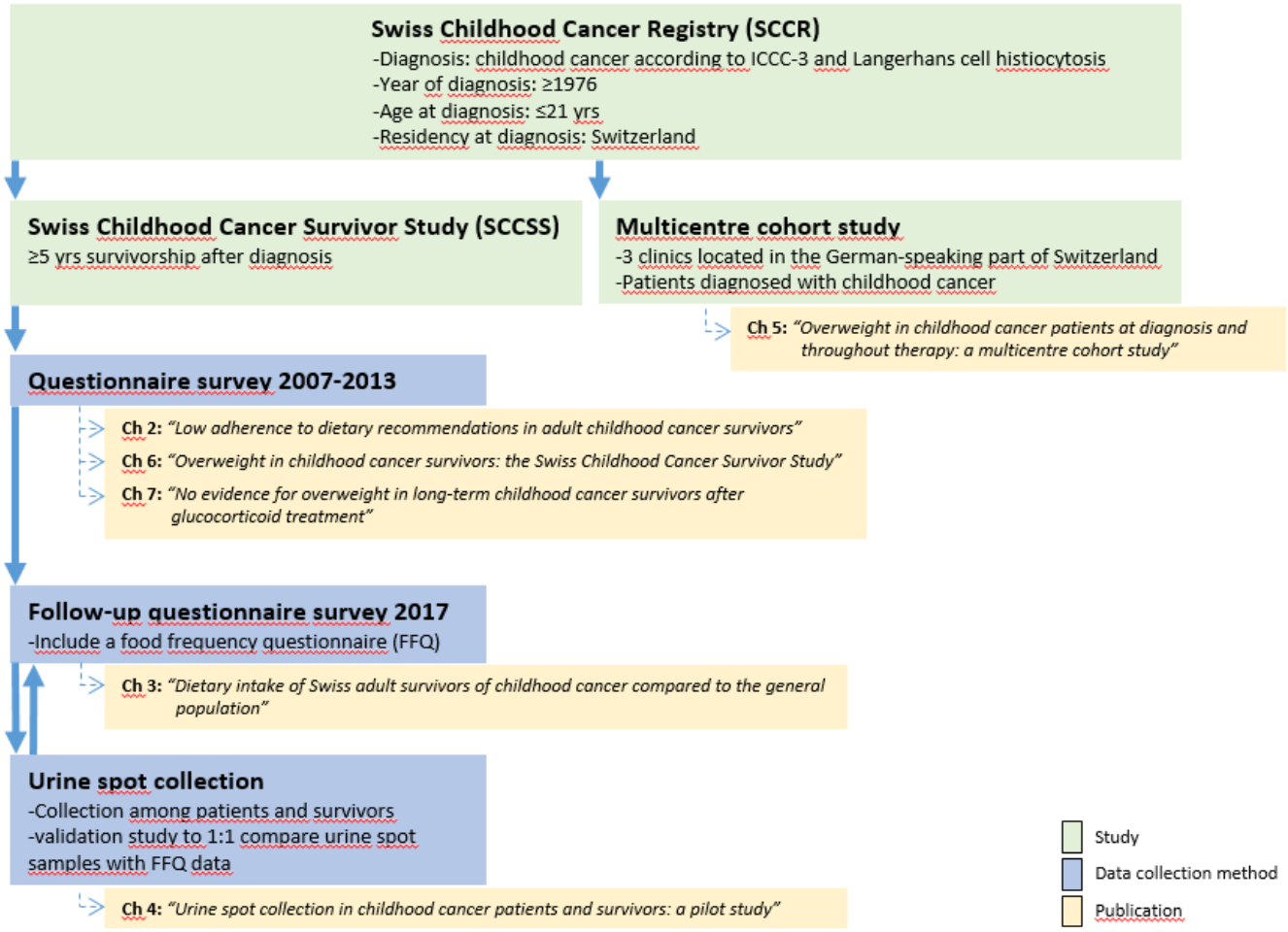

Figure 5. Overview of PhD thesis

Ch, chapter; FFQ, food frequency questionnaire; ICCC-3, International classification of childhood cancer, 3rd edition

REFERENCES

[1] Foundation National Institute for Cancer Epidemiology and Registration (NICER). Cancer incidence in Switzerland. 2010-2014.
[2] Swiss Childhood Cancer Registry. Annual report 2015-2016. Bern2017.
[3] Cancer Research UK. Children's cancers incidence statistics Childhood Cancers including Non-Malignant Brain and Central Nervous System Tumours, Age-Standardised (World) Annual Incidence Rates per Million Population, Europe, 1988-1997.
[4] Society AC. Cancer Facts and Figures 2018. Atlanta, Ga: American Cancer Society; 2018.
[5] Hewitt M, Weiner SL, Simone JV, editors. Childhood cancer survivorship: Improving care and quality of life. Washington, DC: National Academy of Sciences; 2003.
[6] Bhatia S, Armenian SH, Armstrong GT, van Dulmen-den Broeder E, Hawkins MM, Kremer LCM, et al. Collaborative Research in Childhood Cancer Survivorship: The Current Landscape. Journal of Clinical Oncology. 2015;33:3055-64.
[7] Federal Statistical Office. Causes of death statistics. In: confederation S, editor. Neuchâtel2017.
[8] Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P. International Classification of Childhood Cancer, third edition. Cancer. 2005;103:1457-67.
[9] Bhakta N, Liu Q, Ness KK, Baassiri M, Eissa H, Yeo F, et al. The cumulative burden of surviving childhood cancer: an initial report from the St Jude Lifetime Cohort Study (SJLIFE). The Lancet. 2017;390:2569-82.
[10] Hudson MM, Ness KK, Gurney JG, Mulrooney DA, Chemaitilly W, Krull KR, et al. Clinical Ascertainment of Health Outcomes among Adults Treated for Childhood Cancer: A Report from the St. Jude Lifetime Cohort Study. JAMA : the journal of the American Medical Association. 2013;309:2371-81.
[11] Dixon SB, Bjornard KL, Alberts NM, Armstrong GT, Brinkman TM, Chemaitilly W, et al. Factors influencing risk-based care of the childhood cancer survivor in the 21st century. CA: A Cancer Journal for Clinicians. 2018:n/a-n/a.
[12] Fidler MM, Reulen RC, Winter DL, Kelly J, Jenkinson HC, Skinner R, et al. Long term cause specific mortality among 34 489 five year survivors of childhood cancer in Great Britain: population based cohort study. BMJ. 2016;354.
[13] Belle FN, Weiss A, Schindler M, Goutaki M, Bochud M, Zimmermann K, et al. Overweight in childhood cancer survivors: the Swiss Childhood Cancer Survivor Study. The American Journal of Clinical Nutrition. 2018;107:3-11.
[14] Children's Oncology Group (COG). Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers 2013.
[15] Rose SR, Horne VE, Howell J, Lawson SA, Rutter MM, Trotman GE, et al. Late endocrine effects of childhood cancer. Nat Rev Endocrinol. 2016;12:319-36.
[16] Turcotte LM, Liu Q, Yasui Y, et al. Temporal trends in treatment and subsequent neoplasm risk among 5-year survivors of childhood cancer, 1970-2015. JAMA. 2017;317:814-24.
[17] Armstrong GT, Chen Y, Yasui Y, Leisenring W, Gibson TM, Mertens AC, et al. Reduction in Late Mortality among 5-Year Survivors of Childhood Cancer. New England Journal of Medicine. 2016;374:833-42.
[18] Tonorezos ES, Hudson MM, Edgar AB, Kremer LC, Sklar CA, Wallace WHB, et al. Screening and management of adverse endocrine outcomes in adult survivors of childhood and adolescent cancer. The Lancet Diabetes & Endocrinology. 2015;3:545-55.
[19] Winick N, Devidas M, Chen S, Maloney K, Larsen E, Mattano L, et al. Impact of Initial CSF Findings on Outcome Among Patients With National Cancer Institute Standard- and High-Risk B-Cell Acute Lymphoblastic Leukemia: A Report From the Children's Oncology Group. Journal of Clinical Oncology. 2017;35:2527-34.
[20] Archer TC, Mahoney EL, Pomeroy SL. Medulloblastoma: Molecular Classification-Based Personal Therapeutics. Neurotherapeutics. 2017;14:265-73.
[21] Armenian SH, Hudson MM, Mulder RL, Chen MH, Constine LS, Dwyer M, et al. Recommendations for cardiomyopathy surveillance for survivors of childhood cancer: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. The Lancet Oncology. 2015;16:e123-e36.
[22] Hudson MM, Neglia JP, Woods WG, Sandlund JT, Ching-Hon P, Kun LE, et al. Lessons from the Past: Opportunities to Improve Childhood Cancer Survivor Care through Outcomes Investigations of Historical Therapeutic Approaches for Pediatric Hematological Malignancies. Pediatric blood & cancer. 2012;58:334-43.

[23] McNeer JL, Nachman JB. The optimal use of steroids in paediatric acute lymphoblastic leukaemia: no easy answers. British Journal of Haematology. 2010;149:638-52.
[24] Rafacho A, Ortsäter H, Nadal A, Quesada I. Glucocorticoid treatment and endocrine pancreas function: implications for glucose homeostasis, insulin resistance and diabetes. Journal of Endocrinology. 2014;223:R49-R62.
[25] Zhang FF, Parsons SK. Obesity in Childhood Cancer Survivors: Call for Early Weight Management. Advances in Nutrition: An International Review Journal. 2015;6:611-9.
[26] Schindler M, Spycher BD, Ammann RA, Ansari M, Michel G, Kuehni CE, et al. Cause-specific long-term mortality in survivors of childhood cancer in Switzerland: A population-based study. International Journal of Cancer. 2016;139:322-33.
[27] Oeffinger KC, Mertens AC, Sklar CA, Kawashima T, Hudson MM, Meadows AT, et al. Chronic Health Conditions in Adult Survivors of Childhood Cancer. New England Journal of Medicine. 2006;355:1572-82.
[28] Children's Oncology Group (COG). Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancer, Staying healthy through diet and physical activity. Version 4 – October 2013.
[29] Centers for Disease Control and Prevention (CDC). Chronic Disease Prevention and Health Promotion. Atlanta, GA, USA: U.S. Department of Health & Human Services; 2016.
[30] Kasteler R, Belle FN, Schindera C, Barben J, Gumy-Pause F, Tinner E, et al. Prevalence and reasons for smoking in adolescent Swiss childhood cancer survivors. under review. 2018.
[31] Rebholz CE, Kuehni CE, Strippoli M-PF, Rueegg CS, Michel G, Hengartner H, et al. Alcohol consumption and binge drinking in young adult childhood cancer survivors. Pediatric Blood & Cancer. 2012;58:256-64.
[32] Rebholz CE, Rueegg CS, Michel G, Ammann RA, von der Weid NX, Kuehni CE, et al. Clustering of health behaviours in adult survivors of childhood cancer and the general population. British Journal Of Cancer. 2012;107:234.
[33] Rueegg CS, von der Weid NX, Rebholz CE, Michel G, Zwahlen M, Grotzer M, et al. Daily Physical Activities and Sports in Adult Survivors of Childhood Cancer and Healthy Controls: A Population-Based Questionnaire Survey. PLOS ONE. 2012;7:e34930.
[34] Belle F, Wengenroth L, Weiss A, Sommer G, Beck Popovic M, Ansari M, et al. Low adherence to dietary recommendations in adult childhood cancer survivors. Clinical Nutrition. 2017;36:1266-74.
[35] Berdan C, Tangney C, Scala C, Stolley M. Childhood cancer survivors and adherence to the American Cancer Society Guidelines on Nutrition and Physical Activity. J Cancer Surviv. 2014;8:671-9.
[36] Landy DC, Lipsitz SR, Kurtz JM, Hinkle AS, Constine LS, Adams MJ, et al. Dietary Quality, Caloric Intake, and Adiposity of Childhood Cancer Survivors and Their Siblings: An Analysis from the Cardiac Risk Factors in Childhood Cancer Survivors Study. Nutrition and Cancer. 2013;65:547-55.
[37] Zhang FF, Ojha RP, Krull KR, Gibson TM, Lu L, Lanctot J, et al. Adult Survivors of Childhood Cancer Have Poor Adherence to Dietary Guidelines. The Journal of Nutrition. 2016;146:2497-505.
[38] Zhang FF, Saltzman E, Must A, Parsons SK. Do childhood cancer survivors meet the diet and physical activity guidelines? A review of guidelines and literature. International Journal of Child Health and Nutrition. 2012;1:44-58.
[39] Ehrhardt MJ, Fulbright JM, Armenian SH. Cardiomyopathy in Childhood Cancer Survivors: Lessons from the Past and Challenges for the Future. Current Oncology Reports. 2016;18:22.
[40] National Institutes of Health. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: The Evidence Report. Obesity Research. 1998;6:51S-209S.
[41] Love E, Schneiderman JE, Stephens D, Lee S, Barron M, Tsangaris E, et al. A cross-sectional study of overweight in pediatric survivors of acute lymphoblastic leukemia (ALL). Pediatric Blood & Cancer. 2011;57:1204-9.
[42] Co-Reyes E, Li R, Huh W, Chandra J. Malnutrition and Obesity in Pediatric Oncology Patients: Causes, Consequences, and Interventions. Pediatric blood & cancer. 2012;59:1160-7.
[43] Esbenshade AJ, Simmons JH, Koyama T, Koehler E, Whitlock JA, Friedman DL. Body Mass Index and Blood Pressure Changes over the Course of Treatment of Pediatric Acute Lymphoblastic Leukemia. Pediatric blood & cancer. 2011;56:372-8.
[44] Iughetti L, Bruzzi P, Predieri B, Paolucci P. Obesity in patients with acute lymphoblastic leukemia in childhood. Italian Journal of Pediatrics. 2012;38:4-.
[45] Zhang FF, Rodday AM, Kelly MJ, Must A, MacPherson C, Roberts SB, et al. Predictors of Being Overweight or Obese in Survivors of Pediatric Acute Lymphoblastic Leukemia (ALL). Pediatric blood & cancer. 2014;61:1263-9.

[46] Zhang FF, Liu S, Chung M, Kelly MJ. Growth patterns during and after treatment in patients with pediatric ALL: A meta-analysis. Pediatric Blood & Cancer. 2015;62:1452-60.
[47] Lindemulder SJ, Stork LC, Bostrom B, Lu X, Devidas M, Hunger S, et al. Survivors of standard risk acute lymphoblastic leukemia do not have increased risk for overweight and obesity compared to non-cancer peers: A report from the Children's Oncology Group. Pediatric Blood & Cancer. 2015;62:1035-41.
[48] Zhang FF, Kelly MJ, Saltzman E, Must A, Roberts SB, Parsons SK. Obesity in Pediatric ALL Survivors: A Meta-Analysis. Pediatrics. 2014;133:e704-e15.
[49] Garmey EG, Liu Q, Sklar CA, Meacham LR, Mertens AC, Stovall MA, et al. Longitudinal Changes in Obesity and Body Mass Index Among Adult Survivors of Childhood Acute Lymphoblastic Leukemia: A Report From the Childhood Cancer Survivor Study. Journal of Clinical Oncology. 2008;26:4639-45.
[50] Wang KW, Fleming A, Johnston DL, Zelcer SM, Rassekh SR, Ladhani S, et al. Overweight, obesity and adiposity in survivors of childhood brain tumours: a systematic review and meta-analysis. Clinical Obesity. 2018;8:55-67.
[51] van Iersel L, Meijneke RWH, Schouten-van Meeteren AYN, Reneman L, de Win MM, van Trotsenburg ASP, et al. The development of hypothalamic obesity in craniopharyngioma patients: A risk factor analysis in a well-defined cohort. Pediatric Blood & Cancer. 2018:e26911-n/a.
[52] Lustig RH. Hypothalamic Obesity after Craniopharyngioma: Mechanisms, Diagnosis, and Treatment. Frontiers in Endocrinology. 2011;2:60.
[53] Siviero-Miachon AA, Spinola-Castro AM, Guerra-Junior G. Adiposity in childhood cancer survivors: insights into obesity physiopathology. Arquivos Brasileiros de Endocrinologia & Metabologia. 2009;53:190-200.
[54] Mostoufi-Moab S, Seidel K, Leisenring WM, Armstrong GT, Oeffinger KC, Stovall M, et al. Endocrine abnormalities in aging survivors of childhood cancer: A report from the Childhood Cancer Survivor Study. Journal of Clinical Oncology. 2016;34:3240-7.
[55] Robien K, Ness KK, Klesges LM, Baker KS, Gurney JG. Poor Adherence to Dietary Guidelines Among Adult Survivors of Childhood Acute Lymphoblastic Leukemia. Journal of Pediatric Hematology/Oncology. 2008;30:815-22.
[56] Zhang FF, Saltzman E, Kelly MJ, Liu S, Must A, Parsons SK, et al. Comparison of childhood cancer survivors' nutritional intake with US dietary guidelines. Pediatric Blood & Cancer. 2015;62:1461-7.
[57] Tylavsky FA, Smith K, Surprise H, Garland S, Yan X, McCammon E, et al. Nutritional intake of long-term survivors of childhood acute lymphoblastic leukemia: Evidence for bone health interventional opportunities. Pediatric Blood & Cancer. 2010;55:1362-9.
[58] Tonorezos ES, Robien K, Eshelman-Kent D, Moskowitz CS, Church TS, Ross R, et al. Contribution of diet and physical activity to metabolic parameters among survivors of childhood leukemia. Cancer Causes Control. 2013;24:313-21.
[59] Smith WA, Li C, Nottage K, Mulrooney DA, Armstrong GT, Lanctot JQ, et al. Lifestyle and metabolic syndrome in adult survivors of childhood cancer: a report from the St. Jude Lifetime Cohort Study. Cancer. 2014;120:2742-50.
[60] Badr H, Chandra J, Paxton RJ, Ater JL, Urbauer D, Cruz CS, et al. Health Related Quality of Life, Lifestyle Behaviors, and Intervention Preferences of Survivors of Childhood Cancer. Journal of cancer survivorship : research and practice. 2013;7:10.1007/s11764-013-0289-3.
[61] Frobisher C, Lancashire ER, Reulen RC, Winter DL, Stevens MCG, Hawkins MM. Extent of Alcohol Consumption among Adult Survivors of Childhood Cancer: The British Childhood Cancer Survivor Study. Cancer Epidemiology Biomarkers & Prevention. 2010;19:1174-84.
[62] Phillips-Salimi CR, Lommel K, Andrykowski MA. Physical and Mental Health Status and Health Behaviors of Childhood Cancer Survivors: Findings from the 2009 BRFSS Survey. Pediatric blood & cancer. 2012;58:964-70.
[63] Butterfield RM, Park ER, Puleo E, Mertens A, Gritz ER, Li FP, et al. Multiple risk behaviors among smokers in the childhood cancer survivors study cohort. Psycho-Oncology. 2004;13:619-29.
[64] Rebholz CE, Rueegg CS, Michel G, Ammann RA, von der Weid NX, Kuehni CE, et al. Clustering of health behaviours in adult survivors of childhood cancer and the general population. British Journal of Cancer. 2012;107:234-42.
[65] Boland AM, Gibson TM, Lu L, Kaste SC, DeLany JP, Partin RE, et al. Dietary Protein Intake and Lean Muscle Mass in Survivors of Childhood Acute Lymphoblastic Leukemia: Report From the St. Jude Lifetime Cohort Study. Physical Therapy. 2016;96:1029-38.
[66] Devine KA, Mertens AC, Whitton JA, Wilson CL, Ness KK, Marchak JG, et al. Factors associated with physical activity among adolescent and young adult survivors of early childhood cancer: A report from the childhood cancer survivor study (CCSS). Psycho-Oncology. 2018;27:613-9.

[67] Willet W. Nutritional Epidemiology, Monographs in epidemiology and biostatistics. 2nd ed: Oxford University Press; 1998.
[68] University of Cambridge. Diet, Anthropometry and Physical Acitivity (DAPA) Measurement Toolkit, Dietary assesssment 2015.
[69] Barnea D, Raghunathan N, Friedman DN, Tonorezos ES. Obesity and Metabolic Disease After Childhood Cancer. Oncology (Williston Park, NY). 2015;29:849-55.
[70] Widmer RJ, Flammer AJ, Lerman LO, Lerman A. The Mediterranean Diet, its Components, and Cardiovascular Disease. The American Journal of Medicine. 2015;128:229-38.
[71] Estruch R, Martínez-González M, Corella D, et al. Effects of a mediterranean-style diet on cardiovascular risk factors: A randomized trial. Annals of Internal Medicine. 2006;145:1-11.
[72] Kastorini C-M, Milionis HJ, Esposito K, Giugliano D, Goudevenos JA, Panagiotakos DB. The Effect of Mediterranean Diet on Metabolic Syndrome and its Components: A Meta-Analysis of 50 Studies and 534,906 Individuals. Journal of the American College of Cardiology. 2011;57:1299-313.
[73] Sofi F, Cesari F, Abbate R, Gensini GF, Casini A. Adherence to Mediterranean diet and health status: meta-analysis. BMJ. 2008;337.
[74] Rees K, Hartley L, Flowers N, Clarke A, Hooper L, Thorogood M, et al. 'Mediterranean' dietary pattern for the primary prevention of cardiovascular disease. Cochrane Database of Systematic Reviews. 2013.
[75] Pérez-Martínez P, Mikhailidis DP, Athyros VG, Bullo M, Couture P, Covas MI, et al. Lifestyle recommendations for the prevention and management of metabolic syndrome: an international panel recommendation. Nutrition Reviews. 2017;75:307-26.
[76] Garvey WT, Mechanick JI, Brett EM, Garber AJ, Hurley DL, Jastreboff AM, et al. American Association of Clinical Endocrinologists and American College of Endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. Endocrine Practice. 2016;22:1-203.
[77] American Diabetes Association. Nutrition Recommendations and Interventions for Diabetes. A position statement of the American Diabetes Association. 2008;31:S61-S78.
[78] Zimmermann MB, Boelaert K. Iodine deficiency and thyroid disorders. The Lancet Diabetes & Endocrinology. 2015;3:286-95.
[79] Weaver CM, Gordon CM, Janz KF, Kalkwarf HJ, Lappe JM, Lewis R, et al. The National Osteoporosis Foundation's position statement on peak bone mass development and lifestyle factors: a systematic review and implementation recommendations. Osteoporosis International. 2016;27:1281-386.
[80] Bowen KJ, Sullivan VK, Kris-Etherton PM, Petersen KS. Nutrition and Cardiovascular Disease—an Update. Current Atherosclerosis Reports. 2018;20:8.
[81] Eckel RH, Jakicic JM, Ard JD, de Jesus JM, Houston Miller N, Hubbard VS, et al. 2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology. 2014;63:2960-84.
[82] Ladas E. Nutritional Counseling in Survivors of Childhood Cancer: An Essential Component of Survivorship Care. Children. 2014;1:107.
[83] Demark-Wahnefried W, Rogers LQ, Alfano CM, Thomson CA, Courneya KS, Meyerhardt JA, et al. Practical clinical interventions for diet, physical activity, and weight control in cancer survivors. CA: A Cancer Journal for Clinicians. 2015;65:167-89.
[84] World Cancer Research Fund / American Institute for Cancer Research. Food, nutrition, physical activity and the prevention of cancer: a global perspective. . Washington, DC: AICR; 2007.
[85] Rock CL, Doyle C, Demark-Wahnefried W, Meyerhardt J, Courneya KS, Schwartz AL, et al. Nutrition and physical activity guidelines for cancer survivors. CA: A Cancer Journal for Clinicians. 2012;62:242-74.
[86] Schmitz KH, Courneya KS, Matthews C, Demark-Wahnefried W, GALVÃO DA, Pinto BM, et al. American College of Sports Medicine Roundtable on Exercise Guidelines for Cancer Survivors. Medicine & Science in Sports & Exercise. 2010;42:1409-26.
[87] D'Angio GJ. Pediatric cancer in perspective: Cure is not enough. Cancer. 1975;35:866-70.

Chapter 2

Low adherence to dietary recommendations in adult childhood cancer survivors

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SUMMARY

Background & aims: Poor diet may increase the risk that childhood cancer survivors (CCS) will suffer from chronic disease. We compared adherence to national dietary recommendations between CCS, their siblings and the Swiss population, identified determinants of adherence, and assessed the association of adherence with cardiovascular disease (CVD) risk profiles.

Methods: As part of the Swiss Childhood Cancer Survivor Study (SCCSS), a questionnaire was sent to all Swiss resident CCS aged <21 years at diagnosis, who survived ≥5 years and were 16-45 years old at the time of the survey. We compared dietary adherence between CCS, their siblings and participants in the Swiss Health Survey (SHS), a representative survey of the general population. A multivariable logistic regression was used to assess characteristics associated with dietary adherence. We sorted CCS into four kinds of CVD risk groups based on type of treatment (anthracyclines, chest irradiation, a combination, or neither).

Results: We included 1'864 CCS, 698 siblings and 8'258 participants of the general population. Only 43% of the CCS met the recommended dietary intakes for meat, 34% for fruit, 30% for fish, 18% for dairy products, 11% for vegetables, and 7% for combined fruit and vegetables. Results were similar for both control groups. In all groups, dietary adherence was associated with gender, parental education, migration background, language region in Switzerland, smoking, alcohol consumption and sport participation. CCS with a higher CVD risk profile because of cardiotoxic treatment had no better adherence.

Conclusions: CCS have similar food patterns as their siblings and the general population, and poorly adhere to current recommendations. Awareness of the importance of a healthy diet should be raised among CCS, to prevent chronic diseases like CVD.

INTRODUCTION

Cancer or the late effects of its treatment cause more than two-thirds of childhood cancer survivors (CCS) to develop chronic diseases later in life. Chronic diseases reduce quality of life, and increase morbidity and premature mortality [1, 2]. CCS are up to 15 times more likely to develop heart failure than their siblings, and almost 13 times more likely to die from circulatory diseases than their peers in the general population [1, 3]. This increased risk could be the result of cardiotoxic therapy effects due to anthracycline-containing chemotherapy and radiation therapy involving the heart. Unhealthy lifestyles, including unbalanced diets, physical inactivity and being overweight or obese, could also each significantly increase the risk of cardiovascular disease (CVD) [4].

Excess calorie intake, and consuming too little fish, fruit and vegetables are associated with higher risk of CVD in the general population. Better dietary habits may improve cardiovascular health [4, 5]. Unbalanced diet is a major modifiable risk factor for CVD, Type II diabetes, metabolic syndrome, and osteoporosis [4-7]. But a recent review that included 14 observational studies showed that childhood cancer patients and survivors in the US, Australia, Germany, Canada, and the UK rarely adhere to dietary recommendations [8]. CCS do not eat enough fruit and vegetables [9-11], dairy products [10, 11], whole grains [11, 12], or the micronutrients calcium and vitamin D [12]. They also eat too much sodium and meat [9].

Most studies that investigated dietary adherence had low sample sizes (N<500) [9-13], no control group [9, 10, 12, 14], and did not investigate the association between dietary adherence and CVD risk profiles based on received type of therapy [9, 10, 12-14]. Therefore, we analysed data from the Swiss Childhood Cancer Survivor Study (SCCSS) to (1) compare adherence to national dietary recommendations among CCS, their siblings and the general population, (2) identify socio-demographic and clinical factors associated with adherence to national dietary recommendations, and (3) determine if adherence to dietary recommendations in CCS differed by cardiovascular risk profiles.

METHODS

Sampling

The Swiss Childhood Cancer Survivor Study (SCCSS)

The SCCSS is a nationwide long-term follow-up study of all ≥5-year CCS registered in the Swiss Childhood Cancer Registry (SCCR), diagnosed between 1976 and 2005, and alive at the time of the study [15]. The SCCR registers children and adolescents under age 21, who are diagnosed in Switzerland with leukaemia, lymphoma, central nervous system (CNS) tumours, malignant solid tumours or Langerhans cell histiocytosis [16, 17].

From 2007 to 2012, we traced all addresses of eligible survivors for the SCCSS and sent them a long questionnaire. Non-responders were sent a second copy of the questionnaire four to six weeks later. Non-responders to the second copy were contacted by phone. We used questionnaires similar to those used in US and UK CCS studies [18, 19], but added questions about health behaviours and socio-demographic measures from the Swiss Health Survey 2007 (SHS) [20] and the Swiss Census 2000 [21]. The main domains covered by the questionnaire were quality of life, somatic health, fertility, use of current medication and health services, psychological distress, health behaviours, and socio-economic status. Detailed information on our study design was published previously [15].

The Ethics Committee of the Canton of Bern gave ethical approval to the SCCR and the SCCSS.

Sibling controls

From 2007 to 2012, when we sent out the questionnaire to CCS, we asked them to give us consent to contact their siblings and to provide sibling contact information. Beginning in 2010, we sent siblings the same questionnaire as CCS, but omitted questions about cancer history. Siblings who did not respond were sent another copy of the questionnaire four to six weeks later, but were not contacted by phone.

General population controls (Swiss Health Survey)

The second control group consisted of participants in the 2007 SHS survey. The SHS is a national representative telephone survey repeated every five years. The SHS compiled a randomly selected representative sample of 28'332 Swiss households with telephone land lines and attempted to contact one person per household. Of households called, 6'185 did not answer, and 3'414 refused to participate. The final sample included 18'760 participants (66% response rate) [20]. Sampling was stratified by region and conducted stepwise. Households were selected first, and then the survey was administered to anyone 15 or older who answered the phone.

Measurements

Dietary intake and adherence to dietary recommendations

In CCS and control groups, dietary intake was assessed with standardised open and closed questions. The same standard units and serving sizes for each food item were used in the CCS and sibling surveys. They were also the same in the SHS survey for the general population. The questionnaire to survivors and siblings offers a choice of six responses to describe frequency of intake, ranging from "never" to "several times per day". It also offers open questions where participants can indicate the portions they consume per day

(**Supplemental Figure S1**). The SHS survey offers similar options, though questions about frequency of fruit and vegetable intake were phrased slightly differently. We thus transformed the SHS questions on fruit and vegetable intake into the following daily consumption frequencies: “never”=0; “less than 1/day”=0.5; “1-2/day”=1.5; “3-4/day”=3.5 and “5+/day”=5.5. From the SHS survey, we obtained fruit and vegetable consumption by summing up fresh and conserved fruit or vegetable products and fruit or vegetable juices. The questionnaire to CCS and siblings assessed only fruit and vegetable products. Questions about fish intake also differed slightly. In the SHS survey, the general population could indicate the exact number of days per week they consumed fish, but CCS and siblings could only select from categories that specified a range.

We used current recommendations from the Swiss Society of Nutrition (SSN) to determine adequate intake of fruit, vegetable, meat, fish, and dairy products [22]. SSN recommendations are in line with those of other European countries [23-25]. We determined failure to comply with these dietary recommendations by calculating the proportion of participants who did not eat the minimum recommended daily number of servings of each food group. The lowest values of the following recommended ranges were our cut-off values: two portions of fruit (120g) per day; three portions of vegetable (120g) per day; one portion of fish (100-120g) per week, and three portions of dairy (2dl milk, 150-200g yoghurt or 30-60g cheese) per day. We used the maximum cut-off value for meat: three portions of meat (100-120g) per week.

Explanatory variables from the Swiss Childhood Cancer Survivor Study (SCCSS)

We assessed the following explanatory variables from the questionnaires submitted by CCS, siblings, and the general population: socio-demographic data (gender; age at survey; education level; parents’ education level; migration background; and, language region in Switzerland) and lifestyle factors (body mass index [BMI]); smoking; sport participation; and, alcohol consumption). Participants who were not Swiss citizens at birth, not born in Switzerland, or had at least one parent who was not a Swiss citizen were designated to have a migration background. We classed education into four categories, according to the Swiss Census: compulsory schooling only (≤9 years); vocational training (10-13 years); upper secondary education (higher vocational training or college); and, university degree. We divided highest education level of parents into three categories: primary schooling (compulsory schooling only [≤9 years]); secondary education (vocational training [10-13 years]; higher vocational training or college); and, tertiary education (university degree). We calculated BMI from self-measured height and weight, dividing weight by height in meters squared (kg/m^2). For adolescents (16–19 years at survey), we standardized BMI into z-scores for age and gender using the Swiss references [26]. BMI was classified as underweight (>19yrs:

<18.5kg/m^2; ≤19yrs: <-2 Z-scores), normal weight (>19yrs: ≥18.5 - <25kg/m^2; ≤19yrs: ≥-2 - ≤1 Z-scores), overweight (>19yrs: ≥25 - <30kg/m^2; ≤19yrs: >1 - ≤2 Z-scores), and obese (>19yrs: ≥30kg/m^2; ≤19yrs: >2 Z-scores). Sport participation was classified as ‘‘sports’’ if respondents reported engaging at least somewhat intensely in a targeted gym or sport for at least one hour per week, or ‘‘no sports’’ if participation was lower.

Explanatory variables from the Swiss Childhood Cancer Registry (SCCR)

Clinical information was extracted from the SCCR. We recorded diagnosis and the age at which cancer was diagnosed. Diagnosis was classified according to the International Classification of Childhood Cancer – 3rd Edition [27]. Chemotherapy was divided into “anthracyclines”; “other chemotherapeutic agents” or “no chemotherapy”. Radiotherapy was classified as “chest radiotherapy” if direct radiation was applied to the chest, “other radiotherapy” or “no radiotherapy”. Chest radiotherapy included total body irradiation, mantlefield irradiation or irradiation to the thorax, mediastinum, or thoracic spine. There was a record if a CCS had relapsed during follow-up time.

Statistical Analyses

Our analysis included all participants in the SCCSS (CCS and siblings) and the SHS (general population), aged 16-45 years at time of survey. Both control groups included more women and older persons than the CCS. Migrants and non-German speakers were less frequent among siblings, but more frequent in the general population. To increase the validity of the comparison between CCS and the control groups, we standardised both control groups for gender, age, migration background, and language region, according to the distribution in CCS (**Table I**). Standardisation was applied in all analyses, and was used as in previous publications [28, 29].

The first step in our analysis was to compare socio-demographic and clinical characteristics and adherence to national dietary recommendations in CCS and control groups using chi^2 tests.

Second, we used logistic regressions to determine factors associated with dietary adherence by estimating crude and adjusted odds ratios (OR) and 95% confidence intervals (95%CI). In univariable analyses, we tested each individual socio-demographic and lifestyle variable. If variables were significant on a p-value of <0.05, we included them in the multivariable analyses. We performed Wald tests to calculate global p-values. We used interaction terms to formally test differences in effects of risk factors between CCS and controls. We selected potential confounders and effect modifiers based on the literature.

Third, and in CCS only, we investigated associations between adherence to dietary recommendations and different CVD risk profiles (the profiles were based on type of

treatment). CVD risk profiles were categorized as “no chemo- and radiotherapy”, “other chemo- and/or radiotherapy” (no anthracyclines and no chest radiotherapy), “either anthracyclines or chest radiotherapy”, and “both anthracyclines and chest radiotherapy”. We conducted tests for linear trend for the ordered categorical CVD risk profiles.

We performed sensitivity analyses to compare standardised data for gender, age, migration background and language region in both control groups according to the distribution in CCS to non-standardised data. We used Stata software (version 14, Stata Corporation, Austin, Texas) for all statistical analysis. All statistical significance tests were two-sided with a significance level of 5%.

RESULTS

Characteristics of study population

We traced and contacted 3’593 of 4’116 eligible CCS. Of those we contacted, 2’527 (70%) returned the full questionnaire. We excluded 520 participants who were younger than 16 or older than 45 years, and 143 participants who did not provide data on diet. We thus included 1’864 CCS in the analysis (**Supplemental Figure S2**). We had consent to contact 1’295 siblings, of whom 733 returned the questionnaire; 32 were outside the age range, and three did not provide data on diet. Of 28’332 households surveyed, one person per each of 18’760 households (66%) replied to the survey. Of these, 8’258 were between 16-45 years old.

More CCS than controls had completed compulsory schooling only (12% vs. 7% siblings and 5% general population) and fewer CCS had earned a university degree (7% vs. 11% siblings and 10% general population; all $p<0.001$) (Table I). Mean BMI did not differ between groups, but BMI categorisation was significantly different: CCS were more likely to be underweight (4% vs. 1% siblings and 2% general population) or obese (7% vs. 4% siblings; and 4% general population; $p_{siblings}=0.001$ and $p_{SHS}<0.001$). CCS were less likely to smoke than the general population (24% vs. 34%, $p_{SHS}<0.001$). We found no significant difference between CCS and siblings for smoking. More CCS than controls consumed never or rarely alcohol (51% vs. 36% siblings and 44% general population; all $p<0.001$). CCS were less likely to engage in sports than both control groups (55% vs. 65% siblings and 64% general population; all $p<0.001$).

Among CCS, the largest diagnostic group was leukaemia (32%), followed by lymphoma (20%) and CNS tumours (14%) (**Table II**). When we divided CCS into CVD risk profiles, 17% did not receive chemo- and radiotherapy (lowest risk category), 37% had received other chemotherapeutic agents than anthracyclines and/or other radiotherapy than chest radiotherapy, 39% either anthracyclines or chest radiotherapy, and 7% had both anthracyclines and chest radiotherapy (highest risk category). Mean age at diagnosis was 8.8

± 5.5 years and mean time since diagnosis was 17.2 ± 6.9 years. Twelve percent had experienced a relapse.

Table I. General characteristics of childhood cancer survivors (CCS), their siblings and the general population (Swiss Health Survey)

	CCS (n=1864)		**Siblings[a] (n=698)**			**General population[a] (n=8258)**		
Characteristics	n	(%)	n	($\%_{std}$)	*p-value*[b]	n	($\%_{std}$)	*p-value*[c]
Gender								
Male	978	(52)	288	(53)	*n.a.*	3886	(53)	*n.a.*
Female	886	(48)	410	(47)		4372	(47)	
Age at survey (years)								
<20	449	(24)	110	(24)	*n.a.*	747	(25)	*n.a.*
20-29	886	(48)	331	(48)		1959	(47)	
30-39	438	(24)	201	(23)		3246	(23)	
≥40	91	(5)	56	(5)		2306	(5)	
Education (highest degree)								
Compulsory schooling	230	(12)	45	(7)	*<0.001*	596	(5)	*<0.001*
Vocational training	872	(47)	292	(42)		4668	(63)	
Upper secondary education	632	(34)	286	(40)		1924	(22)	
University education	130	(7)	75	(11)		1070	(10)	
Parents' education (highest degree)								
Primary schooling	169	(9)	59	(7)	*0.214*	n.a.[d]		*n.a.*
Secondary education	1351	(73)	513	(73)				
Tertiary education	344	(19)	126	(20)				
Migration								
No migration background	1423	(76)	561	(77)	*n.a.*	4901	(77)	*n.a.*
Migration background	441	(24)	137	(23)		3357	(23)	
Language region of Switzerland								
German speaking	1310	(70)	565	(71)	*n.a.*	5068	(70)	*n.a.*
French speaking	495	(27)	112	(26)		2580	(27)	
Italian speaking	59	(3)	21	(3)		610	(3)	
BMI[e]								
Underweight	72	(4)	11	(1)	*0.001*	178	(2)	*<0.001*
Normal	1324	(71)	508	(75)		5702	(76)	
Overweight	347	(19)	146	(20)		1907	(18)	
Obese	121	(7)	33	(4)		471	(4)	
Smoking								
Current smoker	443	(24)	155	(23)	*0.491*	2688	(34)	*<0.001*
Stopped smoking	210	(11)	101	(13)		1209	(10)	
Never smoked	1211	(65)	442	(64)		4361	(56)	
Alcohol								
Never/rarely	956	(51)	275	(36)	*<0.001*	3728	(44)	*<0.001*
Weekly, ≥1 std drink/week	747	(40)	358	(52)		4012	(53)	
Daily, 1 std drink/day	65	(3)	22	(3)		435	(3)	
Frequently, >1 std drink/day	96	(5)	43	(9)		83	(6)	
Sports								
Yes	1016	(55)	447	(65)	*<0.001*	4722	(64)	*<0.001*
No	848	(46)	251	(35)		3536	(36)	

BMI: body mass index; n.a.: not applicable; std: standard alcoholic drink;
[a]: Standardized on gender, age at survey, migration background and language region according to the CCS population;
[b]: p-value calculated from Chi-Square statistics comparing CCS to siblings (2-sided test);
[c]: p-value calculated from Chi-Square statistics comparing CCS to general Swiss population (2-sided test);
[d]: No data on parental education within the Swiss Health Survey available;
[e]: BMI Z-scores were calculated for subjects ≤19 years, BMI scores (kg/m^2) were calculated for adults (>19 years).

Table II. Clinical characteristics of childhood cancer survivors (CCS)

	CCS (n=1864)	
Characteristics	n	(%)
Clinical treatment		
Paediatric cancer centre[a]	1590	(85)
Other clinic	274	(15)
ICCC3 diagnosis		
I: Leukaemia	600	(32)
II: Lymphoma	371	(20)
III: CNS tumour	261	(14)
IV: Neuroblastoma	76	(4)
V: Retinoblastoma	40	(2)
VI: Renal tumour	108	(6)
VII: Hepatic tumour	11	(1)
VIII: Bone tumour	81	(4)
IX: Soft tissue sarcoma	112	(6)
X: Germ cell tumour	89	(5)
XI & XII: Other tumour	47	(3)
Langerhans Cell Histiocytosis	68	(4)
CVD risk profile		
No chemo- and RT	314	(17)
Other chemo- and/or RT (no anthracyclines and no chest RT)[b]	694	(37)
Either anthracyclines or chest RT[c]	718	(39)
Both antracyclines and chest RT	138	(7)
Age at diagnosis (years)		
<5	604	(32)
5-9	455	(24)
10-14	521	(28)
15-20	284	(15)
Time since diagnosis (years)		
<15	746	(40)
≥15	1118	(60)
History of relapse		
No	1636	(88)
Yes	228	(12)

CNS: central nervous system; CVD: cardiovascular disease; ICCC3: International Classification of Childhood Cancer, 3rd edition; RT: radiotherapy;
[a]: Including the following clinics with paediatric oncology units Kantonsspital Aarau AG, Universitäts-Kinderspital Basel, Ospedale S. Giovanni Bellinzona, Universitäts-Kinderklinik Bern, Hôpital des Enfants Genève, CHUV Lausanne, Kantonsspital Luzern, Ostschweizer Kinderspital St. Gallen, Universitäts-Kinderspital Zurich;
[b]: Other chemotherapeutic agents and radiotherapy than anthracyclines and chest radiotherapy;
[c]: Chest radiotherapy includes direct radiation applied to the chest, including total body irradiation, mantlefield irradiation or irradiation to the thorax, mediastinum, or thoracic spine.

Dietary adherence in CCS and control groups

Overall dietary adherence was low (**Figure I, Supplemental Table S1**). The highest scores on adherence were for meat (37-43%), fish (26-55%) and fruit (24-39%). The lowest scores for adherence were for the combination of two servings of fruit/day and three servings of vegetables/day (6-7%). We saw no large differences between CCS, their siblings, and the general population. CCS were slightly less adherent than their siblings to fruit intake recommendations ($p_{siblings}$=0.011), more adherent to recommendations for eating meat ($p_{siblings}$=0.011), and tended to adhere better to recommendations for eating fish ($p_{siblings}$=0.075). CCS were more adherent than the general population to recommendations for fruit (p_{SHS}<0.001), meat (p_{SHS}=0.003) or dairy products (p_{SHS}<0.001), but less adherent to recommendations for vegetables (p_{SHS}=0.009) or fish (p_{SHS}<0.001). Although these differences

were statistically significant, the absolute differences between the groups were small and clinically irrelevant.

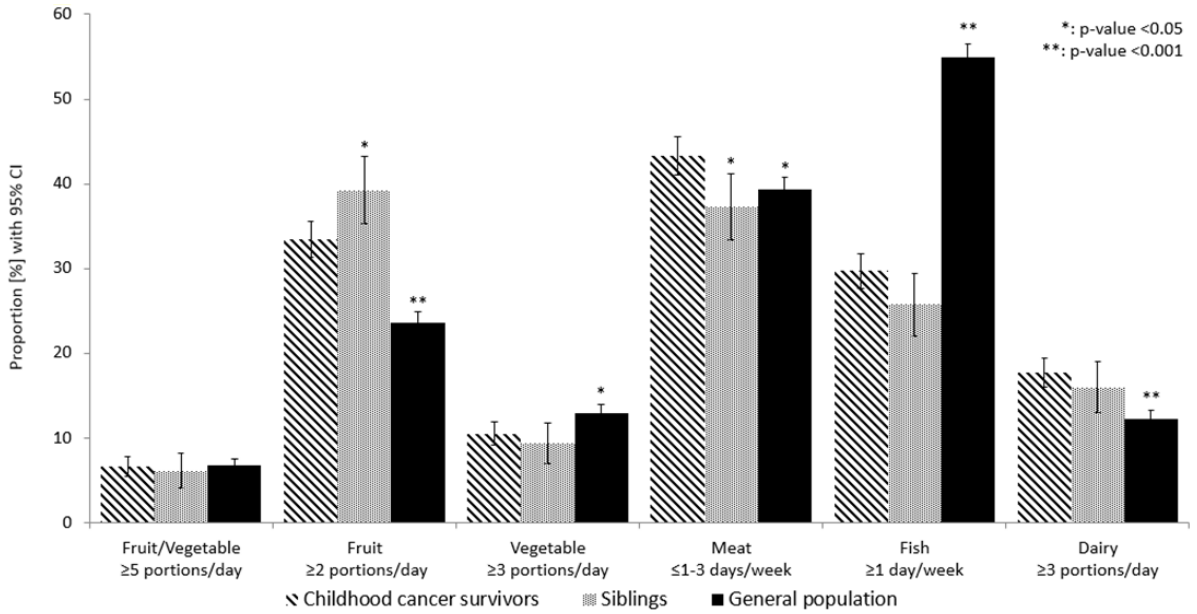

Figure 1. Adherence to dietary recommendations among childhood cancer survivors (CCS), their siblings and the general population (Swiss Health Survey)
Data are proportions with 95% confidence intervals. Siblings and the general population (SHS) are standardised on gender, age, migration background and language region according to the CCS population. P-values were calculated from Chi-Square statistics comparing CCS to siblings or CCS to the general population (SHS) (2-sided test), *: p-value<0.05, **: p-value<0.001

Determinants of dietary adherence in CCS and control groups

In univariable logistic regressions, factors associated with better adherence to dietary recommendations were female gender, age (depending on the food group), higher education, higher parental education, migration background, residence in the French or Italian speaking part of Switzerland, being underweight or having a healthy BMI, not a smoker, no-to-rarely alcohol consumption (those who ate enough fish tended to consume more alcohol), and sport participation (Results available upon request). Since all socio-demographic and lifestyle variables were significant for at least one outcome, we included all of them in the multivariable models when we investigated CCS (**Table III, Supplemental Table S2**), their siblings (Results available upon request), and the general population (**Supplemental Table S3**), and when we looked at cancer-related determinants in CCS only (**Supplemental Table S5**).

Socio-demographic and lifestyle determinants. In CCS, several socio-demographic and lifestyle factors were related to adherence to dietary recommendations in multivariable logistic regressions (Table III, Supplemental Table S2). CCS who ate enough fruit and vegetables were more often female, had more educated parents, a migration background, residence in the French-speaking part of Switzerland, participated in sports, and tended to have higher BMI. Meat adherence was associated with female gender, older age, a migration

background, residence in the French- or Italian-speaking part of Switzerland, current smoking, never-to-rare alcohol consumption, and sports participation. As with adherence to recommendations for meat intake, CCS who ate enough fish were older; had a migration background, were from the French- or Italian-speaking part of Switzerland, and participated in sports. More highly educated participants and non-smokers were more likely to eat enough fish. The opposite was true for the intake of dairy products. Maleness, younger age, and no migration background were associated with adherence to recommendations for dairy intake.

After we performed interaction tests (**Supplemental Table S4**), we found no evidence that the effect of risk factors differed between CCS and their siblings (all interaction p-values >0.05). This means that the same socio-demographic and lifestyle factors were associated with dietary adherence in both CCS and siblings. However, the strength of the associations between some risk factors and dietary adherence differed between CCS and the general population (interaction p-values <0.05) (Supplemental Table S4). When comparing effect sizes between CCS (Table III, Supplemental Table S2) and the general population (Supplemental Table S3), differences were small and hardly clinically relevant.

Cancer-related determinants. After controlling for socio-demographic and lifestyle factors, we found that cancer-related factors among CCS were not significantly associated with adherence to dietary recommendations (Supplemental Table S5). CCS diagnosed at age 5-9 were less likely to adhere to combined fruit and vegetables and vegetable recommendations than CCS diagnosed younger than five years.

We found no important differences in the sensitivity analyses that compared standardised data to non-standardised data. Both types of analyses led to the same conclusions.

Dietary adherence among different CVD risk profiles

There was no relevant difference in adherence to dietary recommendations between CVD risk profiles based on type of chemo- and radiotherapy and p-values for trend were insignificant (p>0.10) (**Figure 2**). We did see a trend for adherence to meat recommendations, which was slightly higher in all risk groups than in the group of CCS who had not received chemo- and radiotherapy.

Table III. Adherence to dietary recommendations among childhood cancer survivors, and socio-demographic predictors for adherence (retrieved from multivariable logistic regressions)

	Fruit/vegetable ≥5 portions/day (n=123)			Fruit ≥2 portions/day (n=624)			Vegetable ≥3 portions/day (n=196)		
	%[a]	OR (95%CI)[b]	p-value[c]	%[a]	OR (95%CI)[b]	p-value[c]	%[a]	OR (95%CI)[b]	p-value[c]
Gender									
Male	5	1.00 (ref)	*0.051*	26	1.00 (ref)	*<0.001*	8	1.00 (ref)	*0.002*
Female	8	1.48 (1.00; 2.18)		42	2.18 (1.77; 2.69)		13	1.67 (1.21; 2.29)	
Age at survey (years)									
<20	7	1.00 (ref)	*0.512*	35	1.00 (ref)	*0.938*	11	1.00 (ref)	*0.542*
20-29	7	1.23 (0.75; 2.02)		34	1.02 (0.78; 1.34)		11	1.18 (0.79; 1.76)	
30-39	7	1.26 (0.70; 2.25)		32	0.97 (0.70; 1.33)		9	0.91 (0.56; 1.48)	
≥40	3	0.56 (0.16; 1.96)		31	0.89 (0.53; 1.50)		9	0.83 (0.36; 1.89)	
Education (highest degree)									
Compulsory schooling	9	1.44 (0.83; 2.52)	*0.138*	36	1.20 (0.87; 1.65)	*0.416*	13	1.33 (0.84; 2.10)	*0.379*
Vocational training	6	1.00 (ref)		32	1.00 (ref)		10	1.00 (ref)	
Upper secondary education	8	1.16 (0.75; 1.79)		35	1.02 (0.81; 1.29)		12	1.19 (0.83; 1.69)	
University education	3	0.39 (0.13; 1.18)		31	0.78 (0.50; 1.21)		8	0.75 (0.36; 1.58)	
Parents' education (highest degree)									
Primary schooling	6	1.00 (ref)	*0.022*	31	1.00 (ref)	*0.055*	13	1.00 (ref)	*0.141*
Secondary education	6	1.53 (0.75; 3.12)		32	1.15 (0.79; 1.67)		10	0.91 (0.54; 1.53)	
Tertiary education	9	2.64 (1.19; 5.88)		39	1.55 (1.00; 2.39)		13	1.35 (0.74; 2.46)	
Migration									
No migration background	6	1.00 (ref)	*<0.001*	32	1.00 (ref)	*0.034*	9	1.00 (ref)	*<0.001*
Migration background	10	2.07 (1.37; 3.14)		37	1.31 (1.02; 1.68)		16	1.92 (1.36; 2.70)	
Language region									
German speaking	6	1.00 (ref)	*0.423*	32	1.00 (ref)	*0.032*	10	1.00 (ref)	*0.629*
French speaking	8	1.29 (0.85; 1.95)		38	1.31 (1.04; 1.65)		12	1.13 (0.80; 1.59)	
Italian speaking	5	0.79 (0.24; 2.63)		27	0.75 (0.41; 1.37)		9	0.75 (0.29; 1.95)	
	Meat ≤1-3 days/week (n=807)			Fish ≥1 day/week (n=554)			Dairy ≥3 portions/day (n=330)		
Gender									
Male	29	1.00 (ref)	*<0.001*	31	1.00 (ref)	*0.616*	20	1.00 (ref)	*<0.001*
Female	59	3.09 (2.52; 3.79)		28	0.95 (0.76; 1.18)		15	0.63 (0.49; 0.82)	
Age at survey (years)									
<20	38	1.00 (ref)	*0.021*	26	1.00 (ref)	*0.001*	25	1.00 (ref)	*0.004*
20-29	45	1.41 (1.08; 1.85)		27	1.14 (0.85; 1.53)		17	0.66 (0.48; 0.90)	
30-39	45	1.62 (1.18; 2.22)		38	1.76 (1.26; 2.45)		14	0.56 (0.38; 0.83)	
≥40	45	1.58 (0.95; 2.63)		37	1.76 (1.05; 2.95)		10	0.34 (0.16; 0.72)	
Education (highest degree)									
Compulsory schooling	51	1.50 (1.09; 2.06)	*0.096*	30	1.37 (0.97; 1.93)	*0.022*	21	1.01 (0.69; 1.48)	*0.517*
Vocational training	40	1.00 (ref)		25	1.00 (ref)		19	1.00 (ref)	

Upper secondary education	45	1.10 (0.88; 1.39)		32	1.25 (0.98; 1.60)		16	0.87 (0.66; 1.16)	
University education	45	1.05 (0.68; 1.60)		48	1.77 (1.17; 2.68)		11	0.66 (0.36; 1.22)	
Parents' education (highest degree)									
Primary schooling	48	1.00 (ref)	*0.356*	37	1.00 (ref)	*0.231*	11	1.00 (ref)	*0.548*
Secondary education	42	0.98 (0.68; 1.41)		28	0.83 (0.58; 1.20)		16	1.10 (0.68; 1.78)	
Tertiary education	46	1.20 (0.78; 1.83)		35	1.03 (0.67; 1.59)		24	1.29 (0.74; 2.24)	
Migration									
No migration background	41	1.00 (ref)	*0.002*	27	1.00 (ref)	*<0.001*	19	1.00 (ref)	*0.032*
Migration background	50	1.49 (1.16; 1.90)		40	1.72 (1.34; 2.21)		15	0.70 (0.51; 0.97)	
Language region									
German speaking	42	1.00 (ref)	*0.023*	24	1.00 (ref)	*<0.001*	19	1.00 (ref)	*0.196*
French speaking	46	1.18 (0.94; 1.49)		42	1.98 (1.57; 2.49)		14	0.76 (0.57; 1.03)	
Italian speaking	59	2.08 (1.17; 3.69)		44	2.25 (1.30; 3.90)		15	0.80 (0.38; 1.68)	

CI: confidence interval; OR: odds ratio;
[a]: Column percentages are given;
[b]: Adjusted for: 1) socio-demographic variables: gender, age category, education level, migration background, and language region in Switzerland and 2) lifestyle factors: BMI category, smoking status, alcohol intake, and sport participation;
[c]: global p-value for an association between adherence to national dietary recommendations and the variable as a whole (Wald test comparing models with and without the variable)

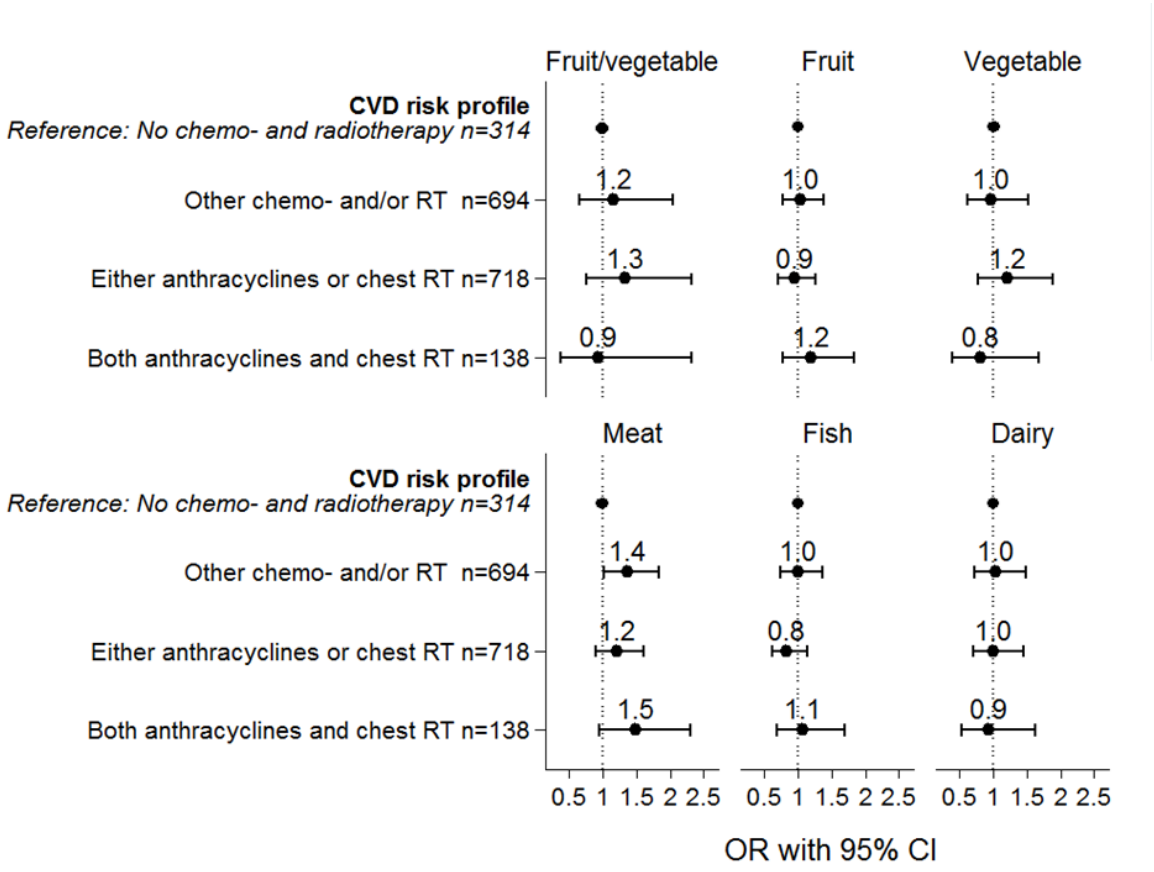

Figure 2. Adherence to dietary recommendations among childhood cancer survivors over 4 cardiovascular disease risk profiles

Dots are OR's and whiskers 95% CI. CI: confidence interval; CVD: cardiovascular disease; OR: odds ratio; RT: radiotherapy not including chest. Multivariable analysis for adherence to nutritional recommendations per CVD risk profile were adjusted for: 1) socio-demographic variables: gender, age category, education level, parental education level, migration background, and language region in Switzerland and 2) lifestyle factors: BMI category, smoking status, alcohol intake, and sport participation; All p-values for trend were insignificant (p-value>0.10) between the different CVD risk profiles for adherence to dietary recommendations;

Other chemo- and/or RT indicates other chemotherapeutic agents and radiotherapy than anthracyclines and chest radiotherapy.

DISCUSSION

Principal findings

We found that CCS poorly adhered to dietary recommendations, but that adherence of siblings and the general Swiss population was equally poor. Predictors of adherence in CCS were similar in siblings, but differed somewhat from the general population. Adherence to dietary recommendations was not better among CCS with a higher CVD risk because of cardiotoxic treatment.

Dietary adherence in Switzerland and the rest of the world

Ours is the largest study to compare the adherence of adolescents and young adult CCS and control groups to national dietary recommendations. Our findings on low adherence are in line with data from the 6th Swiss Nutrition Report [30] and the population-based cross-sectional study of de Abreu et al. 2013 in the French-speaking part of Switzerland, which reported only

39% of the participants adhered to Swiss recommendations for fruit intake, 7% for vegetables, 61% for meat, 66% for fish and 8% for dairy products [31]. We found adherence for meat was lower, probably because national recommendation guidelines for consumption of meat dropped from ≤5 days per week to ≤1-3 days per week [22] between de Abreu's and our study. Our findings also concord with the few studies that reported dietary adherence among CCS. Demark-Wahnefried et al. found that only 20% of the 209 US CCS consumed the recommended five servings of fruit and vegetables per day [32]. Similar poor adherence levels for fruit and vegetables were observed in more recent and larger US studies [13, 14]. Although meat recommendations were different in previous studies, overall meat adherence was low in CCS. Only 10% adhered to the World Cancer Research Fund/American Institute for Cancer Research guidelines to consume less than 80 grams of red meat per day [14]. A study from the US CCSS also found that less than half of CCS met the American Cancer Society (ACS) recommendations to eat less than 18 oz (+/-500g) of red and processed meat per week [13].

Dietary adherence among CCS compared to control groups

CCS and siblings had similar levels of dietary adherence, as also found by a US study based on Healthy Eating Index-2005 (HEI) scores [11]. However, our comparison of CCS to the general population revealed more significant differences in adherence. When we looked at the proportion of CCS and the general population that adhered to dietary recommendations (e.g., 18% adherence for dairy products among CCS vs. 12% among the general population) we found the observed differences were, although statistically significant, clinically irrelevant. A cross-sectional study between CCS and the general US population came to similar conclusions, finding no relevant differences after basing their analyses on adherence criteria from the ACS Guidelines on nutrition [13].

Gender and migration background differences

Females adhered better to fruit, vegetable, and meat recommendations. Males were more adherent to dairy products recommendations. These match previous Swiss [31, 33] and European [34] findings. The reasons for these gender differences are unclear. Males and females may be socialized differently, and exposed to different amounts of information about diet and health. It is also possible that males and females have different tastes, different levels of interest in healthy diets, and different eating goals. Although women were almost twice as likely to adhere to dietary recommendations for fruit, vegetable and meat intake than men were, adherence levels were still far from ideal for either gender and both need improvement.

Migration background was associated with higher adherence to recommendations for all food groups except dairy products. Much of the Swiss population with a migration background

is from Southern Europe, where people commonly eat a Mediterranean diet already rich in fruit, vegetables and fish, and poor in meat and dairy products [35].

Dietary adherence and CVD risk profiles

Low intake of fruit, vegetable, fish and dairy products are already a concern in the general population, but may have a more deleterious effect on CCS. Better adherence to dietary recommendations lowers the risk of all-cause mortality, CVD mortality, cancer incidence and mortality, and Type II diabetes mellitus among adults by 15 to 22% [6]. Since CCS are up to 15 times more likely to have heart failure than their siblings [27], risk factors like poor diet may exacerbate this [4-6]. CCS with baseline risk elevated by cancer treatment may strongly benefit from a good diet, but we found no differences in adherence levels among CCS for different CVD risk profiles. As in our study, Landy et al. found little to no difference between dietary intake and cancer diagnosis and therapy, except for exposure to cranial irradiation, which was related to even poorer adherence [11].

Implications for clinical practice

The national organisation Swiss Cancer League (www.liguecancer.ch) emphasizes in cancer prevention campaigns to increase fruit and vegetable consumption and reduce alcohol, red and processed meat intake. This could partly explain the higher levels of fruit and meat adherence in CCS. However, it is unclear to which extent CCS are aware of these dietary recommendations and if diet is perceived as a risk factor for late effects. Current CCS guidelines do not specifically focus on diet [8].

We performed a short survey among the nine Swiss paediatric oncology clinics to assess whether they discussed diet issues during follow-up visits. Six replied that they discuss diet in case CCS suffer from nutritional related late effects, and three indicated to discuss it routinely during each follow-up visit (personal communication). Given the strong evidence about diet and health in general and the increasing data for CCS, focus should be placed on the importance of good eating habits during annual long-term follow up visits. Follow-up visits are especially recommended for CCS with moderate to severe late health effects or high risk cancer treatment, a group which could benefit of dietary counselling [36].

General dietary recommendation campaigns are equally widespread between language regions within Switzerland. As regional differences in adherence are seen, campaigns should be adapted to federal state and regional level, which will not only benefit CCS but also the general population.

Strengths and limitations

Our study is limited by the fact that all available data were self-reported; so social desirability bias and subjective interpretation could have favourably biased the results. The different survey designs (questionnaire in CCS and siblings, telephone interviews in the general population) might have influenced the results. For example, respondents might list alcohol consumption more moderately in a telephone interview than a written survey. Differences in level of adherence to recommendations for fruit and fish intake between CCS and the general population may have been a product of differently worded survey answers. Our study was strengthened by its national coverage of the SCCSS, our large sample size, and the high response rate among CCS, which made our results representative. We had access to high quality clinical information extracted from the SCCR. The questionnaires gave us access to a wide variety of socio-demographic, and lifestyle factors. We compared adherence of CCS with both siblings (who share environmental factors with CCS) and a representative population-based study performed simultaneously in Switzerland (so we could account for different environmental factors).

CONCLUSION

Large-scale studies with systematic and standardised dietary assessments, such as 24h recalls and validated food frequency questionnaires would help more precisely assess nutritional intake among CCS, and determine if food intake patterns are associated with cancer diagnoses, treatments, patient characteristics, adverse somatic late effects, and survival outcomes. Finding these connections would provide incentive for CCS to eat a balanced diet because it could lessen their chance of suffering adverse late effects. Poor eating habits may predispose CCS to chronic comorbidities or increase the likelihood they will develop a secondary neoplasm [4-6, 8, 14]. More focus should be placed on improving dietary adherence during clinical follow up, especially for CCS with high CVD risk profiles.

Though no worse than their siblings or the general population, CCS adhere poorly to nutritional recommendations, and may be more susceptible to health problems caused by poor nutrition.

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AUTHORS CONTRIBUTIONS

FB conducted the statistical analyses and wrote the article; LW and CK gave support in the statistical analyses and revised critically the manuscript; All authors have critically revised and approved the final article.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

REFERENCES

[1] Oeffinger KC, Mertens AC, Sklar CA, Kawashima T, Hudson MM, Meadows AT, et al. Chronic health conditions in adult survivors of childhood cancer. N Engl J Med 2006;355:1572e82.
[2] Vonderweid N, Beck D, Caflisch U, Feldges A, Wyss M, Wagner H. Standardized assessment of late effects in long-term survivors of childhood cancer in Switzerland-results of a Swiss Pediatric Oncology Group (SPOG) pilot study. Int J Pediatr Hematol/Oncol 1996;3:483e90.
[3] Schindler M, Spycher BD, Ammann RA, Ansari M, Michel G, Kuehni CE, et al. Cause-specific long-term mortality in survivors of childhood cancer in Switzerland: a population-based study. Int J Cancer 2016;139:322e33.
[4] Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statisticsd2015 update: a report from the American heart association. Circulation 2015;131:e29e322.
[5] Atkins JL, Whincup PH, Morris RW, Lennon LT, Papacosta O, Wannamethee SG. High diet quality is associated with a lower risk of cardiovascular disease and all-cause mortality in older men. J Nutr 2014;144:673e80.
[6] Schwingshackl L, Hoffmann G. Diet quality as assessed by the healthy eating index, the alternate healthy eating index, the dietary approaches to stop hypertension score, and health outcomes: a systematic review and metaanalysis of cohort studies. J Acad Nutr Diet 2015;115:780e800. e5.
[7] Armstrong GT, Oeffinger KC, Chen Y, Kawashima T, Yasui Y, Leisenring W, et al. Modifiable risk factors and major cardiac events among adult survivors of childhood cancer. J Clin Oncol 2013;31:3673e80.
[8] Zhang FF, Saltzman E, Must A, Parsons SK. Do childhood cancer survivors meet the diet and physical activity guidelines? A review of guidelines and literature. Int J Child Health Nutr 2012;1:44e58.
[9] Robien K, Ness KK, Klesges LM, Baker KS, Gurney JG. Poor adherence to dietary guidelines among adult survivors of childhood acute lymphoblastic leukemia. J Pediatr Hematol/Oncol 2008;30:815e22.
[10] Zhang FF, Saltzman E, Kelly MJ, Liu S, Must A, Parsons SK, et al. Comparison of childhood cancer survivors' nutritional intake with US dietary guidelines. Pediatr Blood Cancer 2015;62:1461e7.
[11] Landy DC, Lipsitz SR, Kurtz JM, Hinkle AS, Constine LS, Adams MJ, et al. Dietary quality, caloric intake, and adiposity of childhood cancer survivors and their siblings: an analysis from the cardiac risk factors in childhood cancer survivors study. Nutr Cancer 2013;65:547e55.
[12] Tylavsky FA, Smith K, Surprise H, Garland S, Yan X, McCammon E, et al. Nutritional intake of long-term survivors of childhood acute lymphoblastic leukemia: evidence for bone health interventional opportunities. Pediatr Blood Cancer 2010;55:1362e9.
[13] Berdan C, Tangney C, Scala C, Stolley M. Childhood cancer survivors and adherence to the American cancer society guidelines on nutrition and physical activity. J Cancer Surviv 2014;8:671e9.
[14] Smith WA, Li C, Nottage K, Mulrooney DA, Armstrong GT, Lanctot JQ, et al. Lifestyle and metabolic syndrome in adult survivors of childhood cancer: a report from the St. Jude Lifetime Cohort Study. Cancer 2014;120:2742e50.
[15] Kuehni CE, Rueegg CS, Michel G, Rebholz CE, Strippoli M-PF, Niggli FK, et al. Cohort profile: the Swiss childhood cancer survivor study. Int J Epidemiol 2012;41:1553e64.
[16] Michel G, von der Weid NX, Zwahlen M, Adam M, Rebholz CE, Kuehni CE, et al. The Swiss childhood cancer registry: rationale, organisation and results for the years 2001e2005. Swiss Med Wkly 2007;137:502e9.
[17] Michel G, von der Weid NX, Zwahlen M, Redmond S, Strippoli MPF, Kuehni CE. Incidence of childhood cancer in Switzerland: the Swiss childhood cancer registry. Pediatr Blood Cancer 2008;50:46e51.
[18] Robison LL, Mertens AC, Boice JD, Breslow NE, Donaldson SS, Green DM, et al. Study design and cohort characteristics of the childhood cancer survivor study: a multi-institutional collaborative project. Med Pediatr Oncol 2002;38: 229e39.
[19] Hawkins MM, Lancashire ER, Winter DL, Frobisher C, Reulen RC, Taylor AJ, et al. The British childhood cancer survivor study: objectives, methods, population structure, response rates and initial descriptive information. Pediatr Blood Cancer 2008;50:1018e25.
[20] Liebherr RMJ, Storni M, Wiedenmayer G. Gesundheit und Gesundheitsverhalten in der Schweiz 2007 Schweizerische Gesundheitsbefragung. Neuchâtel Bundesamt für Statistik; 2010.
[21] Germann U. Abschlussbericht zur Volkszählung 2000. Neuchâtel, Switzerland: Bundesamt für Statistik; 2005.
[22] Swiss Society of Nutrition. Toi et moi, Les denrées alimentaires. 2014.

[23] Austrian Bundesministerium für Gesundheit. Die Ernährungspyramide im Detail - 7 Stufen zur Gesundheit. 2016.
[24] Deutsche Gesellschaft für Ernährung e.V. (DGE). DGE-Ernährungskreis. 2015.
[25] Ancellin R, Baelde D, Barthélémy L, Bellisle F, Berta (Afssa) J-L, et al. La santé vient en mangeant, le guide alimentaire pour tous Saint-Yrieix-la-Perche. Fabrègue imprimeur; 2011.
[26] Järvelä L, Niinikoski H, Lähteenmäki P, Heinonen O, Kapanen J, Arola M, et al. Physical activity and fitness in adolescent and young adult long-term survivors of childhood acute lymphoblastic leukaemia. J Cancer Surviv 2010;4:339e45.
[27] Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P. International classification of childhood cancer. third edition Cancer 2005;103:1457e67.
[28] Wengenroth L, Rueegg CS, Michel G, Essig S, Ammann RA, Bergstraesser E, et al. Life partnerships in childhood cancer survivors, their siblings, and the general population. Pediatr Blood Cancer 2014;61:538e45.
[29] Rebholz CE, Kuehni CE, Strippoli M-PF, Rueegg CS, Michel G, Hengartner H, et al. Alcohol consumption and binge drinking in young adult childhood cancer survivors. Pediatr Blood Cancer 2012;58:256e64.
[30] Keller U, Battaglia-Richi E, Beer M, Darioli R, Meyer K, Renggli A, et al. Sixth Swiss nutrition report. Berne Swiss Federal Office of Health. 2012.
[31] de Abreu D, Guessous I, Vaucher J, Preisig M, Waeber G, Vollenweider P, et al. Low compliance with dietary recommendations for food intake among adults. Clin Nutr 2013;32:783e8.
[32] Demark-Wahnefried W, Werner C, Clipp EC, Guill AB, Bonner M, Jones LW, et al. Survivors of childhood cancer and their guardians. Cancer 2005;103:2171e80.
[33] Gille D, Bütikofer U, Chollet M, Schmid A, Altintzoglou T, Honkanen P, et al. Nutrition behavior of the middle-aged and elderly: compliance with dietary recommendations of the food pyramid. Clin Nutr 2016;35(3):638. http://
dx.doi.org/10.1016/j.clnu.2015.04.002.
[34] Fruit and vegetable consumption in Europe - do Europeans get enough? Brussels: European Food Information Council (EUFIC); 2012.
[35] Trichopoulou A, Martínez-González MA, Tong TYN, Forouhi NG, Khandelwal S, Prabhakaran D, et al. Definitions and potential health benefits of the Mediterranean diet: views from experts around the world. BMC Med 2014;12:112.
[36] Rebholz CE, von der Weid NX, Michel G, Niggli FK, Kuehni CE. Follow-up care amongst long-term childhood cancer survivors: a report from the Swiss childhood cancer survivor study. Eur J Cancer 2011;47

SUPPLEMENTARY MATERIAL

Table S1. Adherence to dietary recommendations among childhood cancer survivors (CCS), their siblings and the general population (Swiss Health Survey)

	CCS (n=1864)	Siblings[a] (n=698)		General population[a] (n=8258)	
	n (%)	n ($\%_{std}$)	p-value[b]	n ($\%_{std}$)	p-value[c]
Dietary intake					
Fruit/vegetable, portion: +/-120g					
Non-adherence: <5 portions/day	1741 (93)	654 (94)		7684 (93)	
Adherence: ≥ 5 portions/day	123 (7)	44 (6)	*0.702*	574 (7)	*0.839*
Fruit, portion: +/-120g					
Non-adherence: <2 portions/day	1240 (67)	411 (61)		6350 (76)	
Adherence: ≥2 portions/day	624 (34)	287 (39)	*0.011*	1908 (24)	*<0.001*
Vegetable, portion: +/-120g					
Non-adherence: <3 portions/day	1668 (90)	632 (91)		7142 (87)	
Adherence: ≥3 portions/day	196 (11)	66 (9)	*0.421*	1116 (13)	*0.009*
Meat					
Non-adherence: ≥4-5 days/week	1057 (57)	429 (63)		4479 (61)	
Adherence: ≤1-3 days/week	807 (43)	269 (37)	*0.011*	3779 (39)	*0.003*
Fish					
Non-adherence: <1 day/week	1310 (70)[d]	531 (74)[d]		3112 (45)[d]	
Adherence: ≥1 day/week	554 (30)	167 (26)	*0.075*	5146 (55)	*<0.001*
Dairy, portion: +/-2dl, 125ml or 30-60g					
Non-adherence: <3 portions/day	1534 (82)	592 (84)		7433 (88)	
Adherence: ≥3 portions/day	330 (18)	106 (16)	*0.345*	825 (12)	*<0.001*

CCS: childhood cancer survivors;
[a]: Standardized on gender, age, migration background and language region according to the CCS population;
[b]: p-value calculated from Chi-Square statistics comparing CCS to siblings (2-sided test);
[c]: p-value calculated from Chi-Square statistics comparing CCS to general Swiss population (2-sided test);
[d]: Missing observation for fish intake: 6% (n=106), 4% (n=31), and <1% (n=10) for CCS, siblings and the general Swiss population, respectively. Missing values were assigned to medium intake

Table S2. Adherence to dietary recommendations among childhood cancer survivors, and lifestyle predictors for adherence (retrieved from multivariable logistic regressions)

	Fruit/vegetable ≥5 portions/day (n=123)			Fruit ≥2 portions/day (n=624)			Vegetable ≥3 portions/day (n=196)		
	%[a]	OR (95%CI)[b]	p-value[c]	%[a]	OR (95%CI)[b]	p-value[c]	%[a]	OR (95%CI)[b]	p-value[c]
BMI									
Underweight	7	0.99 (0.38; 2.58)	*0.303*	22	0.48 (0.27; 0.86)	*0.019*	11	1.01 (0.47; 2.19)	*0.167*
Normal	6	1.00 (ref)		34	1.00 (ref)		10	1.00 (ref)	
Overweight	7	1.29 (0.80; 2.10)		30	0.97 (0.74; 1.27)		11	1.24 (0.83; 1.85)	
Obese	10	1.82 (0.93; 3.56)		40	1.44 (0.96; 2.16)		16	1.83 (1.05; 3.17)	
Smoking									
Never smoked	7	1.00 (ref)	*0.699*	35	1.00 (ref)	*0.732*	10	1.00 (ref)	*0.468*
Stopped smoking	8	1.26 (0.70; 2.26)		33	0.95 (0.68; 1.32)		12	1.32 (0.82; 2.13)	
Current smoker	6	0.97 (0.60; 1.56)		30	0.91 (0.70; 1.16)		11	1.16 (0.80; 1.68)	
Alcohol									
Never/rarely	7	1.00 (ref)	*0.616*	36	1.00 (ref)	*0.333*	12	1.00 (ref)	*0.384*
Weekly, ≥1 std drink/week	6	0.97 (0.64; 1.49)		33	1.02 (0.82; 1.29)		10	0.94 (0.67; 1.33)	
Daily, 1 std drink/day	2	0.26 (0.03; 1.93)		25	0.84 (0.45; 1.54)		3	0.29 (0.07; 1.24)	
Frequently, >1 std drink/day	5	0.87 (0.32; 2.36)		21	0.63 (0.37; 1.08)		10	1.16 (0.55; 2.42)	
Sports									
No	7	1.00 (ref)	*0.978*	29	1.00 (ref)	*<0.001*	10	1.00 (ref)	*0.311*
Yes	6	0.99 (0.68; 1.46)		37	1.60 (1.30; 1.97)		11	1.18 (0.86; 1.61)	
	Meat ≤1-3 days/week (n=807)			**Fish ≥1 day/week (n=554)**			**Dairy ≥3 portions/day (n=330)**		
BMI									
Underweight	58	1.50 (0.90; 2.51)	*0.155*	24	0.77 (0.43; 1.37)	*0.766*	22	1.48 (0.82; 2.67)	*0.094*
Normal	44	1.00 (ref)		30	1.00 (ref)		17	1.00 (ref)	
Overweight	36	0.81 (0.62; 1.06)		32	1.07 (0.81; 1.41)		16	0.96 (0.69; 1.35)	
Obese	46	0.93 (0.62; 1.40)		29	1.05 (0.68; 1.62)		24	1.68 (1.05; 2.67)	
Smoking									
Never smoked	42	1.00 (ref)	*0.005*	30	1.00 (ref)	*0.051*	19	1.00 (ref)	*0.450*
Stopped smoking	46	1.25 (0.90; 1.72)		37	1.31 (0.94; 1.81)		13	0.75 (0.48; 1.17)	
Current smoker	45	1.50 (1.17; 1.91)		27	0.83 (0.64; 1.08)		16	0.93 (0.69; 1.27)	
Alcohol									
Never/rarely	50	1.00 (ref)	*<0.001*	27	1.00 (ref)	*0.254*	19	1.00 (ref)	*0.243*
Weekly, ≥1 std drink/week	40	0.73 (0.58; 0.91)		33	1.27 (1.00; 1.61)		16	0.85 (0.64; 1.12)	
Daily, 1 std drink/day	23	0.32 (0.17; 0.61)		35	1.19 (0.67; 2.13)		9	0.47 (0.19; 1.13)	
Frequently, >1 std drink/day	16	0.26 (0.14; 0.48)		30	1.26 (0.76; 2.08)		19	0.73 (0.41; 1.30)	
Sports									
No	43	1.00 (ref)	*0.026*	27	1.00 (ref)	*0.009*	17	1.00 (ref)	*0.409*
Yes	44	1.26 (1.03; 1.55)		32	1.33 (1.07; 1.65)		18	1.11 (0.86; 1.43)	

BMI: body mass index; CI: confidence interval; OR: odds ratio; std: standard alcoholic drink;
[a]: Column percentages are given;
[b]: Adjusted for: 1) socio-demographic variables: gender, age category, education level, migration background, and language region in Switzerland and 2) lifestyle factors: BMI category, smoking status, alcohol intake, and sport participation;
[c]: global p-value for an association between adherence to national dietary recommendations and the variable as a whole (Wald test comparing models with and without the variable).

Table S3. Adherence to dietary recommendations among the general population (Swiss Health Survey), and predictors for adherence (retrieved from multivariable logistic regressions)

	Fruit/vegetable ≥5 portions/day (n=574)			Fruit ≥2 portions/day (n=1908)			Vegetable ≥3 portions/day (n=1116)		
	%[a]	OR (95%CI)[b]	p-value[c]	%[a]	OR (95%CI)[b]	p-value[c]	%[a]	OR (95%CI)[b]	p-value[c]
Gender									
Male	5	1.00 (ref)	***<0.001***	15	1.00 (ref)	***<0.001***	10	1.00 (ref)	***<0.001***
Female	9	1.90 (1.45; 2.49)		33	2.75 (2.33; 3.25)		16	1.79 (1.46; 2.19)	
Age at survey (years)									
<20	9	1.00 (ref)	***0.004***	29	1.00 (ref)	***<0.001***	16	1.00 (ref)	***<0.001***
20-29	6	0.58 (0.41; 0.82)		22	0.60 (0.48; 0.75)		12	0.57 (0.44; 0.74)	
30-39	6	0.57 (0.41; 0.80)		22	0.60 (0.48; 0.74)		12	0.58 (0.45; 0.75)	
≥40	7	0.70 (0.49; 0.99)		23	0.64 (0.51; 0.80)		14	0.74 (0.57; 0.97)	
Education (highest degree)									
Compulsory schooling	6	0.83 (0.44; 1.57)	***0.109***	20	0.90 (0.64; 1.28)	***<0.001***	10	0.85 (0.53; 1.37)	***<0.001***
Vocational training	6	1.00 (ref)		23	1.00 (ref)		12	1.00 (ref)	
Upper secondary education	7	1.28 (0.94; 1.73)		25	1.24 (1.03: 1.49)		14	1.31 (1.05; 1.65)	
University education	8	1.49 (1.01; 2.18)		29	1.63 (1.29; 2.06)		17	1.68 (1.27; 2.23)	
Migration									
No migration background	7	1.00 (ref)	***0.850***	25	1.00 (ref)	***0.004***	13	1.00 (ref)	***0.458***
Migration background	7	0.98 (0.76; 1.26)		21	0.80 (0.68; 0.93)		13	0.93 (0.77; 1.13)	
Language region									
German speaking	5	1.00 (ref)	***<0.001***	23	1.00 (ref)	***0.005***	11	1.00 (ref)	***<0.001***
French speaking	11	2.25 (1.74: 2.91)		26	1.27 (1.08; 1.50)		19	2.09 (1.72; 2.55)	
Italian speaking	9	1.78 (1.09; 2.91)		21	0.86 (0.62; 1.19)		14	1.42 (0.97; 2.08)	
BMI									
Underweight	10	1.38 (0.71; 2.66)	***0.459***	32	1.20 (0.79; 1.82)	***0.349***	14	0.97 (0.55; 1.73)	***0.173***
Normal	7	1.00 (ref)		25	1.00 (ref)		14	1.00 (ref)	
Overweight	5	0.83 (0.60; 1.15)		20	1.04 (0.85; 1.27)		9	0.77 (0.60; 0.98)	
Obese	5	0.86 (0.48; 1.52)		17	0.76 (0.53; 1.10)		13	1.14 (0.73; 1.78)	
Smoking									
Never smoked	5	1.00 (ref)	***0.018***	18	1.00 (ref)	***<0.001***	13	1.00 (ref)	***0.226***
Stopped smoking	9	1.47 (1.06; 2.06)		28	1.24 (0.99; 1.55)		15	1.27 (0.97; 1.66)	
Current smoker	7	0.87 (0.64; 1.17)		26	0.79 (0.66; 0.94)		12	1.03 (0.83; 1.28)	
Alcohol									
Never/rarely	8	1.00 (ref)	***0.026***	28	1.00 (ref)	***0.007***	14	1.00 (ref)	***0.731***
Weekly, ≥1 std drink/week	6	0.77 (0.59; 1.00)		20	0.77 (0.66; 0.91)		12	0.95 (0.77; 1.16)	
Daily, 1 std drink/day	7	1.15 (0.57; 2.34)		22	1.22 (0.78; 1.90)		13	1.21 (0.75; 1.97)	
Frequently, >1 std drink/day	2	0.28 (0.10; 0.80)		17	1.15 (0.45; 2.99)		12	1.17 (0.44; 3.10)	
Sports									
No	5	1.00 (ref)	***<0.001***	19	1.00 (ref)	***<0.001***	11	1.00 (ref)	***<0.001***
Yes	8	1.59 (1.21; 2.10)		26	1.51 (1.28; 1.78)		14	1.43 (1.17; 1.76)	
	Meat ≤1-3 days/week (n=3779)			**Fish ≥1 day/week (n=5146)**			**Dairy ≥3 portions/day (n=825)**		
Gender									
Male	26	1.00 (ref)	***<0.001***	55	1.00 (ref)	***0.299***	15	1.00 (ref)	***<0.001***
Female	54	3.03 (2.64; 3.47)		56	1.08 (0.94; 1.24)		10	0.64 (0.52; 0.79)	
Age at survey (years)									
<20	31	1.00 (ref)	***<0.001***	50	1.00 (ref)	***<0.001***	16	1.00 (ref)	***0.004***
20-29	42	1.52 (1.24; 1.86)		54	1.15 (0.95; 1.41)		12	0.78 (0.59; 1.02)	
30-39	43	1.64 (1.35; 2.00)		61	1.60 (1.31; 1.94)		10	0.69 (0.53; 0.90)	
≥40	46	1.98 (1.61; 2.44)		62	1.69 (1.38; 2.07)		9	0.60 (0.45; 0.80)	
Education (highest degree)									
Compulsory schooling	38	0.93 (0.70; 1.23)	***<0.001***	56	0.96 (0.72; 1.28)	***0.971***	12	0.96 (0.59; 1.57)	***0.392***
Vocational training	37	1.00 (ref)		54	1.00 (ref)		13	1.00 (ref)	
Upper secondary education	43	1.14 (0.98; 1.34)		56	0.98 (0.84; 1.15)		12	1.02 (0.80; 1.29)	
University education	50	1.57 (1.27; 1.93)		61	1.03 (0.83; 1.28)		9	0.75 (0.53; 1.06)	
Migration									
No migration background	37	1.00 (ref)	***<0.001***	52	1.00 (ref)	***<0.001***	13	1.00 (ref)	***0.008***
Migration background	48	1.64 (1.44; 1.88)		65	1.62 (1.42; 1.85)		10	0.75 (0.60; 0.93)	
Language region									
German speaking	39	1.00 (ref)	***<0.001***	48	1.00 (ref)	***<0.001***	13	1.00 (ref)	***0.004***
French speaking	37	0.89 (0.77; 1.03)		71	2.62 (2.26; 3.03)		11	0.90 (0.72; 1.12)	
Italian speaking	63	2.77 (2.04; 3.74)		74	3.08 (2.31; 4.10)		6	0.41 (0.24; 0.70)	

BMI									
Underweight	62	1.47 (0.95; 2.27)	***<0.001***	59	1.15 (0.74; 1.79)	***0.805***	4	0.41 (0.19; 0.86)	***0.074***
Normal	41	1.00 (ref)		55	1.00 (ref)		12	1.00 (ref)	
Overweight	31	0.74 (0.63; 0.88)		55	0.95 (0.80; 1.12)		13	1.10 (0.85; 1.41)	
Obese	32	0.66 (0.49; 0.89)		57	1.05 (0.78; 1.41)		13	1.20 (0.78; 1.86)	
Smoking									
Never smoked	40	1.00 (ref)	***0.411***	55	1.00 (ref)	***0.042***	14	1.00 (ref)	***0.007***
Stopped smoking	45	1.15 (0.94; 1.40)		60	1.00 (0.82; 1.22)		8	0.63 (0.45; 0.87)	
Current smoker	37	1.04 (0.90; 1.21)		53	0.83 (0.72; 0.97)		11	0.77 (0.61; 0.97)	
Alcohol									
Never/rarely	45	1.00 (ref)	***0.002***	53	1.00 (ref)	***<0.001***	12	1.00 (ref)	***0.172***
Weekly, ≥1 std drink/week	35	0.80 (0.69; 0.92)		57	1.30 (1.12; 1.50)		12	0.96 (0.77; 1.19)	
Daily, 1 std drink/day	31	0.66 (0.46; 0.93)		64	1.52 (1.05; 2.20)		15	1.40 (0.85; 2.31)	
Frequently, >1 std drink/day	22	0.51 (0.27; 0.96)		45	0.54 (0.29; 1.00)		5	0.39 (0.13; 1.22)	
Sports									
No	38	1.00 (ref)	***<0.001***	54	1.00 (ref)	***0.002***	12	1.00 (ref)	***0.402***
Yes	40	1.28 (1.12; 1.47)		56	1.24 (1.08; 1.43)		12	0.91 (0.74; 1.13)	

BMI: body mass index; CI: confidence interval; OR: odds ratio; std: standard alcoholic drink;

[a.] Column percentages are given. Percentages for the general population are standardized for gender, age, migration background and language region according to the CCS population;

[b]: Adjusted for: 1) socio-demographic variables: gender, age category, education level, migration background, and language region in Switzerland and 2) lifestyle factors: BMI category, smoking status, alcohol intake, and sport participation;

[c]: global p-value for an association between adherence to national dietary recommendations and the variable as a whole (Wald test comparing models with and without the variable).

Table S4. Interaction of study group with socio-demographic and lifestyle determinants (retrieved from multivariable logistic regressions[a])

	Fruit/vegetable ≥5 portions/day p-values for interactions		**Fruit ≥2 portions/day** p-values for interactions		**Vegetable ≥3 portions/day** p-values for interactions	
	CCS vs. siblings[b]	CCS vs. general population[c]	CCS vs. siblings[b]	CCS vs. general population[c]	CCS vs. siblings[b]	CCS vs. general population[c]
Socio-demographic						
Gender	0.722	0.098	0.785	0.214	0.611	0.318
Age at survey (years)	0.379	0.194	0.273	0.235	0.733	0.125
Education (highest degree)	0.855	0.003	0.511	0.021	0.392	<0.001
Parents' education (highest degree)	0.494	n.a.	0.459	n.a.	0.972	n.a.
Migration	0.204	0.002	0.615	0.006	0.524	<0.001
Language region	0.183	0.200	0.430	0.866	0.201	0.014
Lifestyle						
BMI	0.011	0.027	0.182	<0.001	0.153	0.026
Smoking	0.969	0.452	0.272	0.173	0.498	0.411
Alcohol	0.852	0.399	0.333	0.136	0.725	0.108
Sports	0.639	0.004	0.679	0.494	0.149	0.016
	Meat ≤1-3 days/week		**Fish ≥1 day/week**		**Dairy ≥3 portions/day**	
Socio-demographic						
Gender	0.118	0.004	0.062	0.037	0.980	0.451
Age at survey (years)	0.447	0.849	0.606	0.771	0.547	0.278
Education (highest degree)	0.386	0.009	0.693	0.099	0.852	0.129
Parents' education (highest degree)	0.755	n.a.	0.065	n.a.	0.050	n.a.
Migration	0.536	0.662	0.774	0.944	0.814	0.974
Language region	0.589	0.076	0.704	0.487	0.478	0.248
Lifestyle						
BMI	0.324	0.457	0.128	0.574	0.068	0.449
Smoking	0.295	0.199	0.330	0.266	0.279	0.785
Alcohol	0.328	0.005	0.850	0.568	0.476	0.199
Sports	0.428	0.288	0.806	0.768	0.738	0.496

BMI: body mass index; CCS: childhood cancer survivors; n.a.: not applicable.

[a]: Adjusted for: 1) socio-demographic variables: gender, age category, education level, migration background, and language region in Switzerland and 2) lifestyle factors: BMI category, smoking status, alcohol intake, and sport participation;

[b]: p-value for interaction (study group: Siblings versus CCS x determinant) was calculated with the likelihood ratio test;

[c]: p-value for interaction (study group: General population versus CCS x determinant) was calculated with the likelihood ratio test.

Table S5. Cancer-related factors associated with adherence to dietary recommendations among childhood cancer survivors (CCS) (retrieved from multivariable logistic regressions)

	Fruit/vegetable ≥5 portions/day		Fruit ≥2 portions/day		Vegetable ≥3 portions/day		Meat ≤1-3 days/week		Fish ≥1 day/week		Dairy ≥3 portions/day	
	OR (95%CI)[a]	***p-value***[b]	OR (95%CI)[a]	***p-value***[b]	OR (95%CI)[a]	***p-value***[b]	OR (95%CI)[a]	***p-value***[b]	OR (95%CI)[a]	***p-value***[b]	OR (95%CI)[a]	***p-value***[b]
Clinical treatment												
Paediatric cancer centre[c]	1.00 (ref)	***0.959***	1.00 (ref)	***0.918***	1.00 (ref)	***0.703***	1.00 (ref)	***0.230***	1.00 (ref)	***0.796***	1.00 (ref)	***0.732***
Other clinic	1.02 (0.57; 1.80)		1.02 (0.74; 1.39)		1.10 (0.69; 1.75)		0.83 (0.60; 1.13)		0.96 (0.70; 1.31)		0.93 (0.61; 1.42)	
ICCC3 diagnosis												
I: Leukaemia	1.00 (ref)	***0.230***	1.00 (ref)	***0.349***	1.00 (ref)	***0.320***	1.00 (ref)	***0.667***	1.00 (ref)	***0.897***	1.00 (ref)	***0.277***
II: Lymphoma	0.76 (0.44; 1.32)		1.16 (0.87; 1.55)		0.79 (0.51; 1.23)		0.98 (0.73; 1.30)		0.96 (0.72; 1.30)		0.79 (0.55; 1.14)	
III: CNS tumour	0.66 (0.35; 1.24)		1.12 (0.81; 1.55)		0.64 (0.38; 1.08)		1.01 (0.74; 1.39)		0.98 (0.70; 1.38)		0.87 (0.59; 1.27)	
IV: Neuroblastoma	1.09 (0.44; 2.69)		1.33 (0.79; 2.23)		1.04 (0.49; 2.20)		0.89 (0.53; 1.50)		1.19 (0.69; 2.04)		0.91 (0.50; 1.69)	
V: Retinoblastoma	-		0.62 (0.29; 1.34)		0.14 (0.02; 1.05)		0.67 (0.33; 1.37)		1.65 (0.83; 3.27)		0.46 (0.16; 1.35)	
VI: Renal tumour	0.45 (0.16; 1.30)		1.03 (0.66; 1.62)		0.79 (0.40; 1.57)		1.20 (0.77; 1.88)		0.94 (0.58; 1.54)		0.96 (0.57; 1.64)	
VII: Hepatic tumour	1.97 (0.39; 9.97)		3.84 (1.07; 13.76)		2.19 (0.54; 8.91)		0.79 (0.21; 2.90)		0.58 (0.14; 2.35)		0.90 (0.18; 4.56)	
VIII: Bone tumour	0.98 (0.39; 2.43)		0.90 (0.53; 1.53)		0.96 (0.45; 2.05)		0.58 (0.34; 0.99)		1.27 (0.76; 2.13)		0.71 (0.36; 1.40)	
IX: Soft tissue sarcoma	0.75 (0.31; 1.82)		1.32 (0.85; 2.05)		0.97 (0.50; 1.88)		0.89 (0.57; 1.39)		0.79 (0.48; 1.28)		0.65 (0.36; 1.18)	
X: Germ cell tumour	0.58 (0.20; 1.69)		1.19 (0.73; 1.95)		0.64 (0.28; 1.46)		0.86 (0.53; 1.41)		1.03 (0.62; 1.71)		0.69 (0.36; 1.34)	
XI & XII: Other tumour	2.46 (1.08; 5.64)		1.05 (0.56; 1.99)		1.70 (0.79; 3.68)		1.40 (0.73; 2.67)		0.88 (0.46; 1.70)		1.97 (0.97; 4.03)	
Langerhans Cell Histiocytosis	0.77 (0.26; 2.26)		1.68 (0.98; 2.87)		0.76 (0.31; 1.84)		1.07 (0.62; 1.86)		0.97 (0.54; 1.74)		1.37 (0.76; 2.47)	
CVD risk profile												
No chemo- and RT	1.00 (ref)	***0.705***	1.00 (ref)	***0.676***	1.00 (ref)	***0.474***	1.00 (ref)	***0.145***	1.00 (ref)	***0.361***	1.00 (ref)	***0.978***
Other chemo- and/or RT[d]	1.16 (0.66; 2.04)		1.03 (0.77; 1.38)		0.97 (0.62; 1.52)		1.36 (1.02; 1.83)		1.01 (0.75; 1.36)		1.04 (0.72; 1.49)	
Either anthracyclines or chest RT[e]	1.32 (0.76; 2.32)		0.94 (0.70; 1.26)		1.21 (0.78; 1.88)		1.20 (0.90; 1.61)		0.83 (0.61; 1.13)		1.01 (0.70; 1.45)	
Both antracyclines and chest RT	0.93 (0.38; 2.31)		1.19 (0.77; 1.84)		0.81 (0.39; 1.67)		1.48 (0.96; 2.30)		1.08 (0.69; 1.69)		0.93 (0.53; 1.62)	
Age at diagnosis (years)												
<5	1.00 (ref)	***0.155***	1.00 (ref)	***0.481***	1.00 (ref)	***0.066***	1.00 (ref)	***0.737***	1.00 (ref)	***0.510***	1.00 (ref)	***0.579***
5-9	0.54 (0.31; 0.94)		1.12 (0.85; 1.47)		0.57 (0.37; 0.90)		1.06 (0.81; 1.38)		0.94 (0.70; 1.25)		0.85 (0.62; 1.16)	
10-14	0.93 (0.58; 1.49)		1.11 (0.85; 1.45)		0.99 (0.68; 1.46)		0.98 (0.76; 1.28)		1.11 (0.84; 1.47)		0.82 (0.59; 1.12)	
15-20	0.77 (0.41; 1.42)		1.30 (0.93; 1.82)		0.80 (0.49; 1.33)		0.87 (0.62; 1.22)		0.89 (0.63; 1.26)		0.83 (0.53; 1.28)	
Time since diagnosis (years)												
<15	1.00 (ref)	***0.643***	1.00 (ref)	***0.920***	1.00 (ref)	***0.830***	1.00 (ref)	***0.074***	1.00 (ref)	***0.606***	1.00 (ref)	***0.617***
≥15	1.11 (0.72; 1.71)		0.99 (0.78; 1.25)		1.04 (0.73; 1.47)		1.24 (0.98; 1.56)		1,07 (0.83; 1.37)		1.07 (0.81; 1.43)	
History of relapse												
No	1.00 (ref)	***0.286***	1.00 (ref)	***0.508***	1.00 (ref)	***0.607***	1.00 (ref)	***0.292***	1.00 (ref)	***0.888***	1.00 (ref)	***0.161***
Yes	1.33 (0.79; 2.24)		1.11 (0.82; 1.50)		1.12 (0.72; 1.76)		1.18 (0.87; 1.59)		1.02 (0.75; 1.40)		1.29 (0.90; 1.83)	

CI: confidence interval; CNS: central nervous system; CVD: cardiovascular disease; ICCC3: International Classification of Childhood Cancer, 3rd edition; OR: odds ratio; RT: radiotherapy;

[a]: Multivariable analysis for adherence to nutritional recommendations were adjusted for: 1) socio-demographic variables: gender, age category, education level, parental education level, migration background, and language region in Switzerland and 2) lifestyle factors: BMI category, smoking status, alcohol intake, and sport participation;

[b]: global p-value for an association between high/frequent dietary intake and the variable as a whole (Wald test comparing models with and without the variable);

[c]: Including the following clinics with paediatric oncology units Kantonsspital Aarau AG, Universitäts-Kinderspital Basel, Ospedale S. Giovanni Bellinzona, Universitäts-Kinderklinik Bern, Hôpital des Enfants Genève, CHUV Lausanne, Kantonsspital Luzern, Ostschweizer Kinderspital St. Gallen, Universitäts-Kinderspital Zurich;

[d]: Other chemotherapeutic agents and radiotherapy than anthracyclines and chest radiotherapy;
[e]: Chest radiotherapy includes direct radiation applied to the chest, including total body irradiation, mantlefield irradiation or irradiation to the thorax, mediastinum, or thoracic spine.

Alimentation

90. **Combien de jours** par semaine, **en général,** mangez-vous de la viande ou de la saucisse et du poisson?

	Jamais	Moins de 1 fois par semaine	1 - 3 jours par semaine	4 - 5 jours par semaine	Quotidien-nement	Plusieurs fois par jour
Viande/ saucisse	☐	☐	☐	☐	☐	☐
Poisson	☐	☐	☐	☐	☐	☐

91. Combien des portions de **fruits, légumes et lait/ produits laitiers** prenez-vous **par jour** en moyenne?

	Combien de portions par jour?
Fruits 1 portion de fruits= taille du votre poing (ou bien 120g)	_____ portions par jour
Légumes (sans les pommes de terre et le maïs) 1 portion de légumes= taille du votre poing (ou bien 120g)	_____ portions par jour
Lait/Produits laitiers 1 portion= 2dl de lait ou 1 yoghourt/fromage blanc ou 30-60g de fromage	_____ portions par jour

92. **Combien de jours par semaine** mangez-vous habituellement **dans un snack-bar ou dans la rue** (par ex. Mc Donalds, Migros Take Away etc.)?

_____ jours par semaine

Ernährung

90. **An wie vielen Tagen** pro Woche konsumieren Sie im Allgemeinen **Fleisch oder Wurstwaren und Fisch?**

	Nie	Seltener als 1 Tag pro Woche	1 - 3 Tage pro Woche	4 - 5 Tage pro Woche	Täglich	Mehrmals pro Tag
Fleisch/ Wurstwaren	☐	☐	☐	☐	☐	☐
Fisch	☐	☐	☐	☐	☐	☐

91. Wie viele Portionen **Früchte, Gemüse und Milch/Milchprodukte** nehmen Sie **pro Tag** im Durchschnitt zu sich?

	Wieviele Portionen pro Tag?
Früchte 1 Portion Früchte= Grösse Ihrer Faust (oder etwa 120g)	_____ Portionen pro Tag
Gemüse (ohne Kartoffeln und Mais) 1 Portion Gemüse= Grösse Ihrer Faust (oder etwa 120g)	_____ Portionen pro Tag
Milch/Milchprodukte 1 Portion= 2 dl Milch oder 1 Joghurt/Quark oder 30-60g Käse	_____ Portionen pro Tag

92. An **wie vielen Tagen pro Woche** essen Sie gewöhnlich in einem **Fast Food Lokal** (z.B. Mc Donalds, Migros Take Away usw.)?

An _____ Tagen pro Woche

Figure S1. Swiss Childhood Cancer Survivor Study questionnaire, French and German version

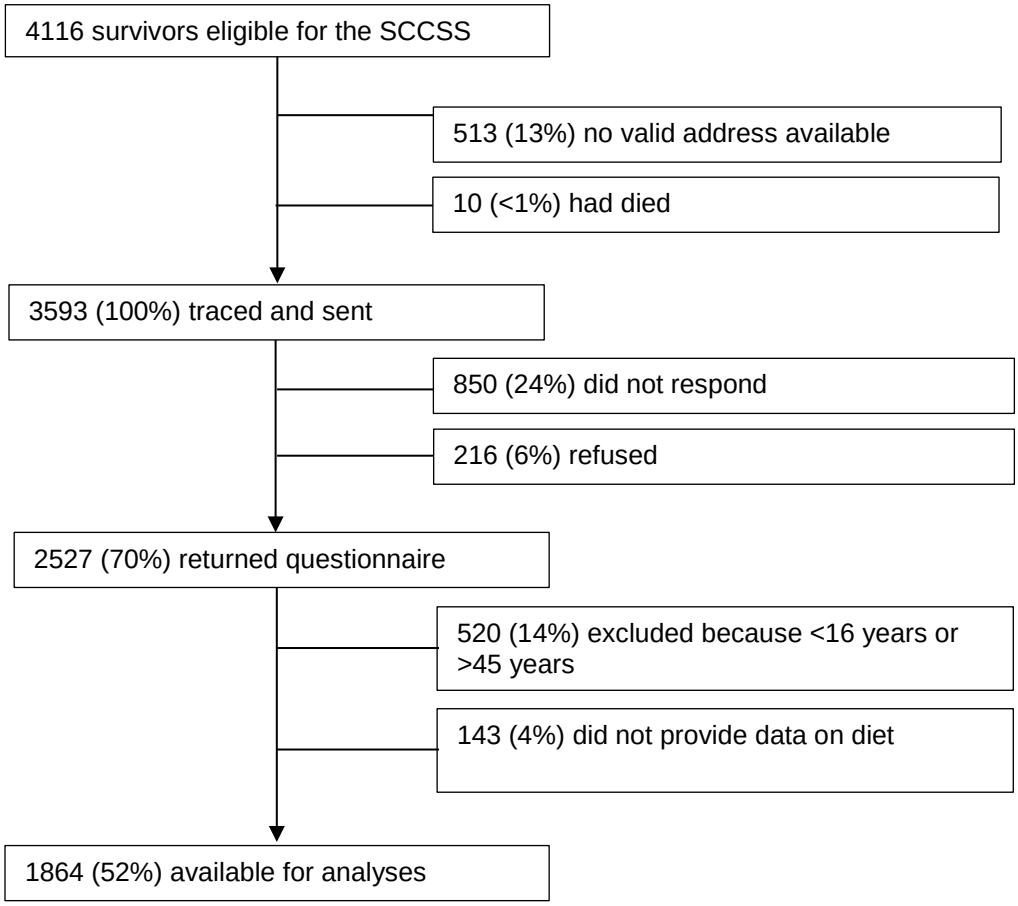

Figure S2. Participants of the Swiss Childhood Cancer Survivor Study

Flow diagram of our study population starting from those eligible in the Swiss Childhood Cancer Registry to those included in the analysis.

Chapter 3

Dietary intake of Swiss adult survivors of childhood cancer compared to the general population

First results

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INTRODUCTION

An unhealthy dietary intake is seen as a modifiable factor that can prevent or delay the development of chronic diseases like type II diabetes, metabolic syndrome, and CVD [1-3]. It is therefore widely recommended in populations suffering from these comorbidities to consume a diet rich in fruit, vegetables, fibre, and complex carbohydrates, low in saturated and trans-fatty acids, and moderate in alcohol consumption. Accumulating research among childhood cancer survivors (CCSs) shows that chronic diseases secondary to childhood cancer or its treatment can be reduced, with diet adaptations, weight management, and physical activity [4-7]. This makes nutrition particularly relevant for CCSs with an increased risk to develop chronic diseases, but few studies have evaluated the dietary intake or quality of CCSs [8, 9]. Within the St. Jude Lifetime cohort a poor dietary adherence to the 2010 Dietary Guidelines for Americans and a poor diet quality based on the Healthy Eating Index-2010 (HEI-2010, 58% of the maximum score) were found in 2570 adult long-term CCSs [10]. They found an even poorer dietary quality for those CCSs diagnosed young and treated with abdominal radiation therapy. Similar results were observed in other smaller studies from the United States (US), CCSs poorly adhered to dietary recommendations and diet quality ranged from 33-56% of the maximum score [5, 6, 11-13].

Studies outside the US, with different lifestyle and eating habits, are limited and suffer from methodological shortcomings, e.g. small sample sizes, short follow-up times, poorly detailed dietary descriptions, and only focus on specific cancer diagnoses. Almost all studies performed to date lack control groups to compare dietary intake between CCSs and the general population. Therefore, we analyzed data from the Swiss Childhood Cancer Survivor Study (SCCSS) to assess dietary intake and quality of CCSs in comparison to the general population and whether clinical characteristics have an impact on CSSs long-term dietary intake.

METHODS

Study populations

The Swiss Childhood Cancer Survivor Study (SCCSS)

The SCCSS is a population-based, long-term follow-up study in all childhood cancer patients registered in the Swiss Childhood Cancer Registry (SCCR; available from: www.childhoodcancerregistry.ch) who have been diagnosed with leukemia, lymphoma, central nervous system (CNS) tumors, malignant solid tumors, or Langerhans cell histiocytosis; who survived ≥5 y after initial diagnosis of cancer; who were under the age of 21 y; and who were alive at the time of the study [14-16]. Ethical approval of the SCCR and the SCCSS was granted by the Ethics Committee of the Canton of Bern (KEK-BE: 166/2014). This study was registered at clinicaltrials.gov as NCT03297034.

As part of the SCCSS, we traced all addresses of CCSs diagnosed between 1976 and 2005, who filled in a baseline questionnaire between 2007 and 2013 [14], and who were at time of the follow-up questionnaire in 2017 at least 20 y. Nonresponders received a reminder of the follow-up questionnaire 6 wks later. If they again did not respond, we contacted them again by sending a second questionnaire reminder. Our questionnaire included core questions from the US and UK CCS studies [17, 18], with added questions about dietary intake [19, 20], health behaviors, and sociodemographic measures from the Swiss Health Survey (SHS) [21] and the Swiss Census [22].

Comparison groups

We used 3 random samples of the general Swiss population represented by data from Bus Santé, CoLaus, and the Swiss National Nutrition Survey.

Bus Santé is a cross-sectional, on-going population based study in the canton of Geneva, as previously described [23]. Every year since 1993, a representative sample of non-institutionalized men and women aged 35-74 y are recruited. Eligible participants are identified with a standardized procedure using a residential list established by the local government. Random sampling in age and sex-specific strata is proportional to the corresponding frequencies in the population. Non-responders after 3 mailings and 7 phone calls were replaced using the same selection protocol as above, but those who refused to participate were not replaced. Included participants were not eligible for future recruitments and surveys. Participants received a self-administered questionnaire to collect data on socio-demographic characteristics, health behaviors, and dietary intake at home before receiving an invite for a health examination in a clinic or a mobile medical unit. During the examination, trained staff checked the questionnaires for completion.

The “Cohorte Lausannoise” (CoLaus) study is a prospective, population-based study conducted in the city of Lausanne to identify biological and genetic determinants of cardiovascular disease. From June 2003 until May 2006 participants aged 35-75 y were recruited for the baseline study. Participants were invited to the outpatient clinic of the University Hospital of Lausanne for an interview, physical assessment, and blood and urine collections. Those who participated in the baseline study were asked to participate in the follow-up study between April 2009 and September 2012 [24]. In the follow-up study, dietary intake was assessed with a food frequency questionnaire (FFQ).

The Swiss National Nutrition Survey is a cross-sectional nutrition survey conducted from January 2014 till February 2015 in 18-75 y old adults living in one of the 3 main linguistic regions of Switzerland (German, French, and Italian) [20]. Trained dieticians collected the data. Each participant got 2 24-hour dietary recalls (24HDR), the first was face-to-face and the second by phone 2-6 wk later. Prior to the face-to-face interview, participants received a 49-

item questionnaire including e.g. questions on socio-demographic characteristics and health behaviors. Interviews were carried out in either German, French or Italian.

Measurements

Dietary intake

In CCSs and among participants of the Bus Santé and CoLaus survey, dietary intake was assessed with the same self-administered, semi quantitative FFQ including portion sizes [25, 26]. The FFQ was originally developed and validated for the French-speaking Swiss adult population [19, 23, 25, 27]. It provides information on consumption frequency and portion sizes during the 4 previous wk for 97 fresh and prepared food items organized in 12 different food groups (dietary supplements not accounted for). Consumption frequencies ranges from “never during the last 4 wk” to “2 or more times per day” and portions are dived in 3 sizes: smaller, equal, or larger than the reference size. The reference portions were defined as common household measures representing the median portion size of a previous validation study [19]. The “smaller” and “larger” portions represented the first and third quartiles of this distribution. The French Centre d’Information sur la Qualité des Aliments food-composition table was used to convert the portions into macro- and micronutrients.

In the Swiss National Nutrition Survey (www.menuch.ch) dietary intake was assessed by 2 non-consecutive 24HDR during all seasons, weekdays and weekends. The GloboDiet software [28, 29] was used which was complemented with a comprehensive picture book [30] and a set of real dishes adapted to the Swiss specific food market to support survey participants in quantifying amounts of consumed foods. Conversion into macro- and micronutrients was performed on the basis of the Swiss Food Composition Database (SFCDB) [31]. We took the average dietary intake of the 2 24HDRs per participant. To account for non-response and national population representativeness all data was corrected by sample weights [20].

In CCSs we extended the used FFQ with 15 additional food products, based on data of the Swiss National Nutrition Survey [20]. Since CCS could live in whole Switzerland we investigate if most frequent dietary products consumed in the German and Italian-speaking part of Switzerland were also included in the FFQ, as the original FFQ was developed for the French-speaking part of Switzerland. The 15 additional food products were all reported more than 70 times (>2%) during the 24h recall assessments.

Data collected

For all CCSs and comparison groups, we collected self-reported data on sex, age at survey, educational level, country of birth, language region in Switzerland, living situation, physical activity, smoking status, and BMI at survey. Physical activity was differently assessed in CCSs

and comparison groups. In the SCCSS and the Swiss National Nutrition Survey we dichotomized physical activity according the WHO guidelines of physical activity for adults: lower (inactive) or equal or more (active) than 150 minutes of moderate intense or 75 minutes of vigorous intense or a combination of moderate and vigorous intense physical activity per week [32]. In Bus Santé and CoLaus physical activity were assessed with a self-administered validated physical activity frequency questionnaire (PAFQ) [33] and dichotomized in lower (inactive) or equal or more than the first quartile of total weekly physical activity time excluding sleep (active). For all CCSs we had information on weight and height at time of survey from the self-administered questionnaires. We asked CCSs to report their weight without clothes and their height without shoes. Within the 3 random samples of the general Swiss population, body weight and height were measured with participants standing without shoes in light indoor clothes. Body weight was measured in kilograms to the nearest 100 g using a calibrated electronic scale (Seca®, Hamburg Germany). Height was measured to either the nearest 5 or 10 mm using a Seca® height gauge. We calculated BMI by dividing weight in kilograms by height in meters squared (kg/m^2) in all groups. BMI in adults was classified as underweight (<18.5 kg/m^2), normal weight (≥18.5 to <25 kg/m^2), overweight (≥25 to <30 kg/m^2), or obesity (≥30 kg/m^2) [34]. For the CCSs population, we extracted additional clinical information from the Swiss Childhood Cancer Registry (SCCR). This included information on cancer diagnosis and the age at diagnosis. Diagnosis was classified according to the *International Classification of Childhood Cancer, 3rd Edition* [35]. Radiotherapy was classified as “any”, “cranial”, “chest”, “total body irradiation and/or abdominal” or “no radiotherapy”. Cranial radiation was considered if the survivor had received direct radiation to the brain and/or skull. Chest radiotherapy was considered direct radiation applied to the chest including total body irradiation, mantlefield irradiation, or irradiation to the thorax, mediastinum, or thoracic spine. Cumulative dosage of radiotherapy was obtained from medical records and categorized based on the Children’s Oncology Group Long-Term Follow-up (COG-LTFU) Guidelines for cranial into: <18 Gray (Gy) versus ≥18 Gy; chest: <30 Gy versus ≥30 Gy, and total body irradiation and/or abdominal versus neither [36]. Chemotherapy was divided into “glucocorticoids”; “anthracyclines”; or “alkylating agents”. Glucocorticoids, prednisone and/ or dexamethasone, intake was based on cancer protocol adherence as described previously [37]. We also retrieved records on hematopoietic stem cell transplantation (HSCT) and relapse during follow-up time.

Statistical Analyses

We included all CCSs and the participants of the general population (Bus Santé, CoLaus, Swiss National Nutrition Survey), who were aged ≤50 years at time of survey, who provided reliable dietary intake information, and were not pregnant nor lactating during the survey (**Supplemental Figure 1**). For better comparison between CCSs and peers, we standardized comparison groups for sex, age at survey, and language region as previously described [38-

40]. The first step in our analyses was to evaluate if CCS and their peers met the dietary recommendations for Germany (D), Austria (A), and Switzerland (CH) (DACH) [41]. We compared the mean intake to the recommended intake or, when not available, the adequate intake. We calculated the mean intake based on age and sex recommendations, weighted by the age and sex distribution of the study population. Nutritional goals were set at 100 when the mean intake met the recommended or adequate intake. Total energy intake was calculated including calories from alcohol consumption. To estimate the diet quality of CCS and peers we used the Alternative Healthy Eating Index (AHEI) [42]. All AHEI score components score from zero (worst) to 10 (best), and the total AHEI score ranges from zero (nonadherence) to 100 (perfect adherence). We compared whether the AHEI score differed between CCS and peers. Furthermore, we assessed if CCSs' dietary quality differed by cancer diagnosis and treatment with the use of ANCOVA while adjusting for sex and age. Because education level attained, smoking habits, physical activity, and BMI can be affected by cancer diagnosis, treatment exposures, and late effects occurrence (i.e., intermediates on the causal pathway), these covariates were not adjusted in the analysis to avoid over adjustment. We used Stata software (version 14, Stata Corporation, Austin, Texas) for all statistical analysis.

FIRST RESULTS

Response rate of the study populations

Among 1832 eligible CCSs, we traced and contacted 1578, of whom 918 (58%) returned a questionnaire. We excluded 29 survivors who were over 50 y old, 11 who were pregnant or lactating, 34 who did not reported their dietary intake, and a further 70 who had unreliable dietary intake. We thus included 774 CCSs in this study (**Supplemental Figure S1**). Of 20,125 participants within the Bus Santé survey, 10,851 were over 50 y old, and 310 who had unreliable dietary intake information. Participation rates ranged from 55 to 75% [43]. Of 5064 participants (41% response rate) within the CoLaus survey, 3616 were over 50 y old, 126 had no dietary intake information, and 46 had unreliable dietary intake. Within the Swiss National Nutrition Survey we excluded from 2085 participants (38% response rate), 857 who were older than 50 y and 39 who were younger than 20 y, 27 who were pregnant or lactating, one participant who did not reported his dietary intake, and 27 participants with unreliable dietary intake information (**Table I**).

Among CCSs, the most common cancers were leukemia, lymphoma, and central nervous system tumors (**Table II**). The median age at diagnosis was 9 y (IQR: 4-14 y). The median time from diagnosis to survey was 26 y (IQR: 20-31 y).

Table I. Characteristics of childhood cancer survivors and comparison groups[1]

	CCSs (*n* = 774)	**Bus Santé[2] (*n* = 8964)**		**CoLaus[2] (*n* = 1276)**		**Menu.CH[2] (*n* = 1134)**	
Characteristics		n (%std)	***P*[3]**	n (%std)	***P*[3]**	n (%std)	***P*[3]**
Sex, *n (%)*							
Men	386 (50)	4345 (55)	***NA***	628 (49)	***NA***	498 (51)	***NA***
Age at survey, *n (%)*							
20-24 y	69 (9)	-	***NA***	-	***NA***	169 (9)	***NA***
25-29 y	179 (23)	-		-		188 (23)	
30-34 y	163 (21)	-		-		150 (22)	
35-39 y	156 (20)	3027 (45)		-		146 (20)	
40-44 y	123 (16)	2997 (32)		552 (62)		211 (16)	
45-50 y	84 (11)	2940 (23)		724 (38)		270 (11)	
Language region, *n (%)*							
German speaking	554 (72)	-	***NA***	-	***NA***	740 (71)	***NA***
French speaking	202 (26)	8964 (100)		1276 (100)		280 (27)	
Italian speaking	18 (2)	-		-		114 (2)	
Country of birth, *n (%)*							
Switzerland	737 (95)	4811 (54)	***<0.001***	750 (58)	***<0.001***	934 (81)	***<0.001***
Other	37 (5)	4153 (46)		526 (42)		200 (19)	
Education (highest degree), *n (%)*							
Lower than university	537 (69)	5336 (59)	***<0.001***	916 (71)	***0.817***	741 (61)	***<0.001***
University	237 (31)	3628 (41)		360 (29)		393 (39)	
Living situation, *n (%)*							
Alone	161 (21)	2192 (24)	***0.038***	237 (19)	***0.526***	170 (16)	***0.012***
Other	613 (79)	6772 (76)		1039 (81)		964 (84)	
Physical activity[4], *n (%)*							
Inactive	159 (21)	662 (8)	***<0.001***	267 (21)	***<0.001***	220 (19)	***0.051***
Active	613 (79)	2700 (33)		905 (71)		900 (80)	
Missing	*2 (<1)*	*5602 (58)*		*104 (8)*		*14 (1)*	
Smoking status, *n (%)*							
Never	523 (68)	4005 (44)	***<0.001***	567 (46)	***<0.001***	521 (44)	***<0.001***
Former	129 (17)	2460 (27)		398 (30)		320 (28)	
Current	122 (16)	2499 (29)		311 (24)		293 (28)	
BMI at survey, *n (%)*							
Underweight	17 (2)[5]	241 (3)	***<0.001***	19 (2)	***<0.001***	34 (3)	***0.023***
Normal	513 (66)	5536 (62)		649 (51)		687 (60)	
Overweight	170 (22)	2491 (28)		451 (36)		306 (28)	
Obese	74 (10)	696 (8)		157 (12)		107 (9)	

[1] BMI, body mass index; CCS, childhood cancer survivors; NA, not applicable; std, standardized.

[2] Standardized on sex, age at survey, and language region according to CCSs.

[3] *P* value calculated from Chi-Square statistics comparing comparison groups with CCSs (2-sided test).

[4] CCSs and Swiss National Nutrition Survey (Menu.CH): < or ≥150 minutes of moderate intense or 75 minutes of vigorous intense or a combination of moderate and vigorous intense physical activity per week. Bus Santé and CoLaus: < or ≥ 1st quartile of total weekly physical activity time excluding sleep.

[5] Self-reported BMI in CCSs.

Table 2. Dietary intake in childhood cancer survivors and the general Swiss population: Bus Santé, CoLaus and Menu.CH compared to the DACH dietary recommendations[1]

	DACH recommendations[3]		CCSs (*n* = 774)		Bus Santé[2] (*n* = 8964)		CoLaus[2] (*n* = 1276)		Menu.CH[2] (*n* = 1134)	
Nutrients	men	women	mean ± SD	% DACH[4]	mean ± SD	% DACH[4]	mean ± SD	% DACH[4]	mean ± SD	% DACH[4]
Total energy, kcal[5]	2300-3400	1800-2600	1639 ± 582	65	2022 ± 688	79	1885 ± 658	75	2283 ± 720	90
Macronutrients										
Protein, g	57	48	66.1 ± 29.5	126	78.7 ± 29.5	149	73.3 ± 29.1	140	86.9 ± 37.2	165
% of energy[6]	10-20	10-20	16.1 ± 3.6	108	15.7 ± 3.1	105	15.6 ± 3.4	104	15.4 ± 4.6	103
Vegetal, g			18.1 ± 7.6		23.6 ± 10.0		21.8 ± 9.6			
Animal, g			48.0 ± 26.9		55.1 ± 24.8		51.4 ± 24.3			
Carbohydrates, g[7]	225-275	225-275	180 ± 74	72	230 ± 91	92	220 ± 88.9	88	246 ± 89	98
% of energy[6, 7]	45-55	45-55	43.9 ± 8.8	88	45.5 ± 8.6	91	46.6 ± 8.2	93	43.2 ± 8.1	86
Mono/disaccharides, g			86 ± 46		105 ± 52		107 ± 53		110 ± 54	
Polysaccharides, g			94 ± 44		124 ± 60		113 ± 57		83 ± 49	
Total fiber, g[7]	≥30	≥30	12.2 ± 6.4	41	15.7 ± 8.0	52	15.0 ± 8.1	50	20.3 ± 8.9	68
Total fat, g			68.2 ± 28.2		79.0 ± 31.1		72.2 ± 28.2		91.8 ± 35.1	
Total fat, % of energy[6]	30-40	30-40	37.4 ± 6.9	107	35.2 ± 6.8	101	34.6 ± 6.3	99	36.1 ± 6.9	103
Saturated fat, g			25.2 ± 11.6		29.4 ± 13.4		26.8 ± 12.2		33.6 ± 14.8	
Saturated fat, % of energy[8]	<10	<10	13.7 ± 3.2	137	13.0 ± 3.3	130	12.8 ± 3.1	128	13.2 ± 3.6	132
Monounsaturated fat, g			28.6 ± 12.7		31.4 ± 13.0		29.0 ± 11.7		23.2 ± 12.6	
Polyunsaturated fat, g			8.6 ± 3.8		11.6 ± 5.3		10.2 ± 4.6		8.6 ± 5.3	
Cholesterol, mg[6]	300	300	343 ± 208	114	343 ± 167	114	316 ± 141	106	261 ± 194	87
Micronutrients										
Vitamins										
A, mg-RE[9]	1.0	0.8	0.7 ± 0.7	79	0.9 ± 0.7	99	0.8 ± 0.7	89	0.7 ± 1.1	77
D, µg	20	20	2.4 ± 2.0	12	2.8 ± 2.1	14	2.6 ± 1.9	13	2.3 ± 2.2	11
Minerals										
Calcium, mg	1000	1000	889 ± 471	89	1079 ± 563	108	1021 ± 529	102	732 ± 391	73
Iron, mg	10[4]	15	9.0 ± 3.6	72	11.2 ± 3.9	91	10.6 ± 3.9	85	7.4 ± 3.5	59
Alcohol, g[10]	20	10	5.7 ± 7.8	38	11.7 ± 16.4	75	8.7 ± 12.2	58	11.8 ± 18.0	78

[1] CCS, childhood cancer survivors, DACH, Dietary recommendations for Germany (D), Austria (A) and Switzerland (CH).
[2] Standardized on sex, age at survey, and language region according to CCSs.
[3] DACH recommendations for the general population age 20-50 y, excluding pregnant and lactating women.
[4] Percentage of mean intake in relation to the DACH recommended intake level * 100. Recommended intake is estimated on the basis of the age-sex groups of the DACH guidelines, weighted by the age and sex distribution of the study population. For alcohol intake the maximum tolerated dosage was taken.
[5] Depending on physical activity level (PAL, 1.4-1.8) and age.
[6] Federal Food Safety and Veterinary Office FSVO, www.naehrwertdaten.ch.
[7] BLV (2009). Kohlenhydrate in unserer Ernährung – Empfehlungen des BLV. www.blv.admin.ch.
[8] BLV (2012). Fett in unserer Ernährung – Empfehlung des BLV. www.blv.admin.chv, Recommendations as a percentage of the daily energy demand and based on a daily energy intake of 2000 kcal.
[9] Total vitamin A= retinol + carotene/12, expressed in µg RAE.
[10] Maximum tolerated dosage.

Table 3. Diet quality in childhood cancer survivors by clinical characteristics (retrieved from ANCOVA)[1, 2]

	CCS (*n* = 774)		
Characteristics	*n (%)*	AHEI score (95%CI)	*P*
ICCC-3 diagnosis			
I: Leukemia	237 (31)	48.3 (46.8, 49.8)	0.078
II: Lymphoma	163 (21)	49.6 (47.8, 51.4)	
III: CNS tumor	79 (10)	45.5 (42.9, 48.2)	
Other	295 (38)	47.5 (46.2, 48.9)	
Age at diagnosis, y			
<5	251 (32)	47.2 (45.5, 48.8)	0.390
5-9	163 (21)	48.7 (46.9, 50.6)	
10-14	224 (29)	47.6 (46.0, 49.2)	
15-20	136 (18)	49.3 (47.0, 51.5)	
Time since diagnosis			
≤25	366 (47)	49.1 (47.6, 50.6)	0.092
>25	408 (53)	47.0 (45.6, 48.4)	
History of relapse			
No	691 (89)	47.9 (47.0, 48.8)	0.711
Yes	83 (11)	48.4 (45.9, 51.0)	
Cranial radiation			
No	654 (85)	48.2 (47.3, 49.1)	0.247
Yes	120 (16)	46.8 (44.5, 49.0)	
Chest radiation			
No	688 (89)	47.9 (47.0, 48.8)	0.748
Yes	86 (11)	48.4 (45.6, 51.2)	
TBI and/or abdominal radiation			
No	707 (91)	48.0 (47.2, 48.9)	0.746
Yes	67 (9)	47.5 (44.6, 50.5)	
Glucocorticoids			
No	444 (57)	47.5 (46.1, 48.9)	0.420
Yes	330 (43)	48.6 (46.8, 50.4)	
Anthracyclines			
No	482 (62)	47.6 (46.5, 48.7)	0.345
Yes	292 (38)	48.6 (47.1, 50.0)	
Alkylating agents			
No	455 (59)	47.6 (46.5, 48.8)	0.372
Yes	319 (41)	48.5 (47.1, 49.8)	
Hematopoietic stem cell transplantation			
No	744 (96)	48.1 (47.2, 48.9)	0.246
Yes	30 (4)	45.5 (41.2, 49.8)	

[1] CNS, central nervous system; CCS, childhood cancer survivors; ICCC3, *International Classification of Childhood Cancer, 3rd edition.*

[2] Adjusted for sex, age at survey, and ICCC-3 diagnosis.

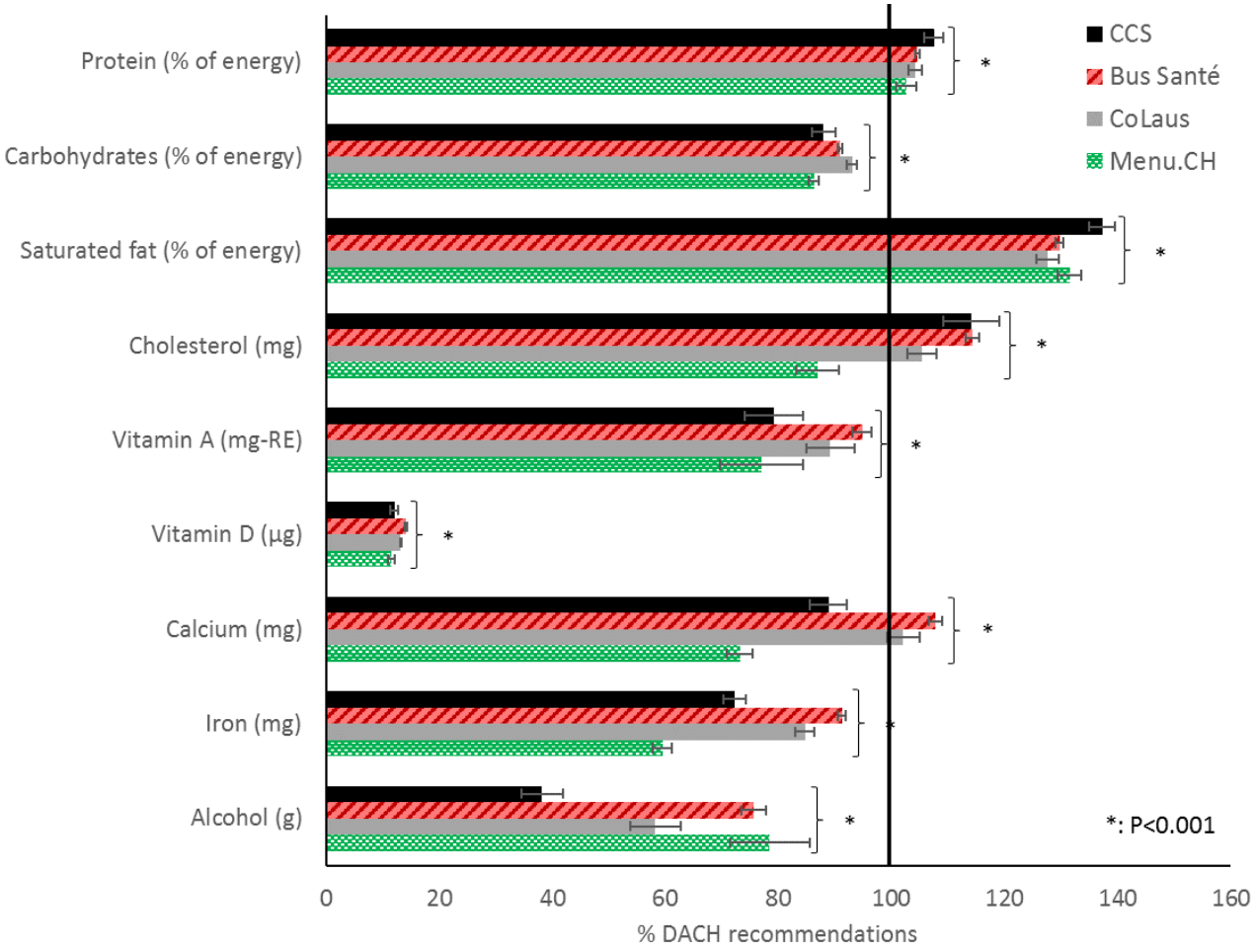

Figure 1. Dietary intakes of nutrients compared with DACH recommended intakes or limits in childhood cancer survivors and the general Swiss population: Bus Santé, CoLaus, and Menu.CH.

The length of the bar per nutrient corresponds to the percentage of mean intake (95% CIs) to the recommended intake level * 100. Recommended intake is estimated on the basis of age and sex according to dietary recommendations for Germany (D), Austria (A) and Switzerland (CH) (DACH), weighted by the age and sex distribution per study population. For alcohol intake the maximum tolerated dosage was taken. Nutritional goals were set at 100 when the mean intake met the recommended intake or limit.
All *P* values were calculated from ANOVA.

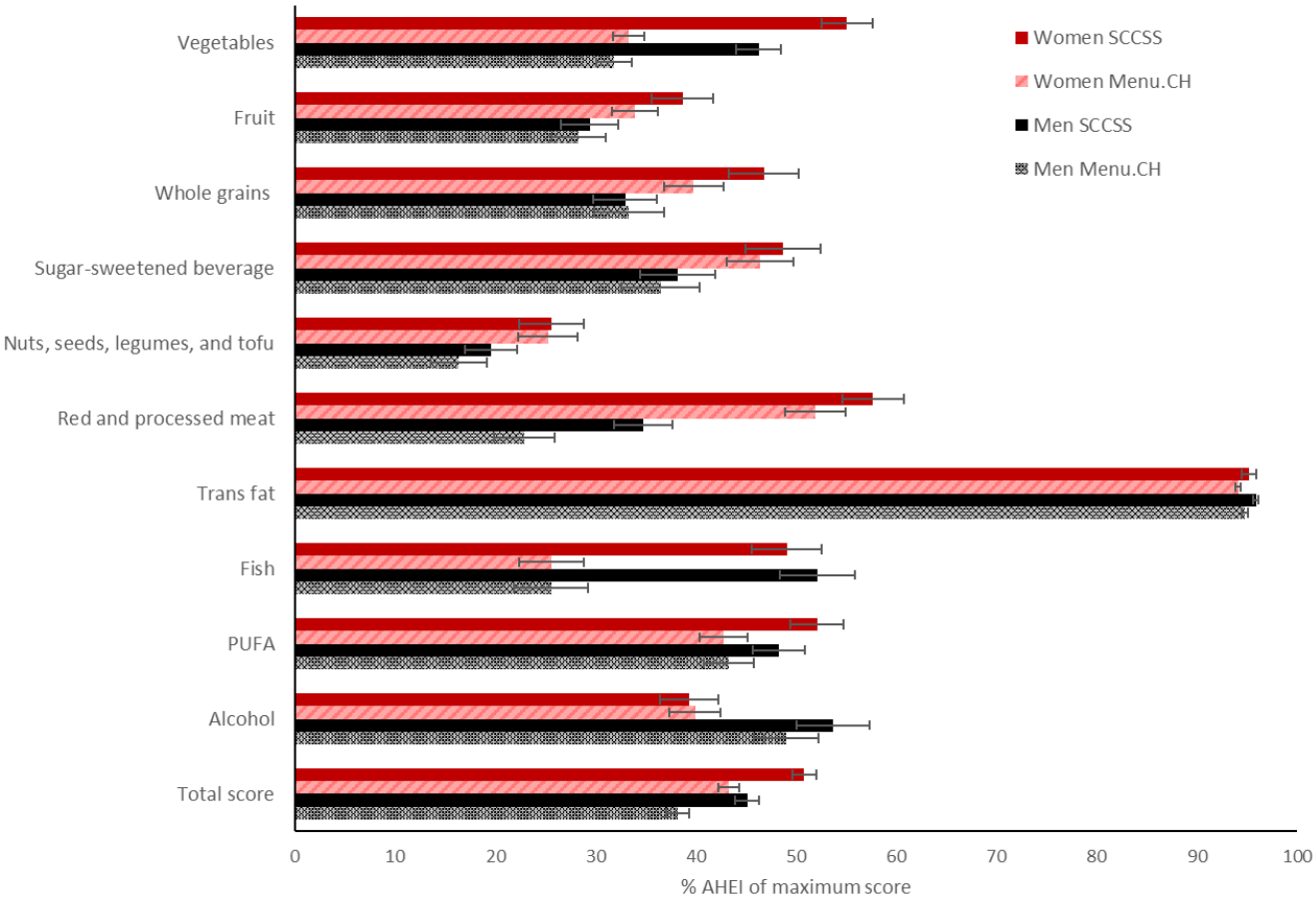

Figure 2. Percentage of mean Alternate Healthy Eating Index[1,2] scores with 95% CIs to the maximum scores in childhood cancer survivors and the general population (Menu.CH)[3] by sex

[1] Adapted from Chiuve et al. J Nutr 2012 142(6):1009-18.
[2] Intermediate food intake was scored proportionately between the minimum score 0 and the maximum score 10.
[3] Adjusted for sex, age at survey, and ICCC-3 diagnosis, Menu.CH standardized on sex, age at survey, and language region according to CCSs.

REFERENCES

[1] Pérez-Martínez P, Mikhailidis DP, Athyros VG, Bullo M, Couture P, Covas MI, de Koning L, Delgado-Lista J, Díaz-López A, Drevon CA, et al. Lifestyle recommendations for the prevention and management of metabolic syndrome: an international panel recommendation. Nutrition Reviews 2017;75(5):307-26. doi: 10.1093/nutrit/nux014.
[2] American Diabetes Association. Nutrition Recommendations and Interventions for Diabetes. A position statement of the American Diabetes Association 2008;31(Supplement 1):S61-S78. doi: 10.2337/dc08-S061.
[3] Eckel RH, Jakicic JM, Ard JD, de Jesus JM, Houston Miller N, Hubbard VS, Lee IM, Lichtenstein AH, Loria CM, Millen BE, et al. 2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology 2014;63(25, Part B):2960-84. doi: https://doi.org/10.1016/j.jacc.2013.11.003.
[4] Barnea D, Raghunathan N, Friedman DN, Tonorezos ES. Obesity and Metabolic Disease After Childhood Cancer. Oncology (Williston Park, NY) 2015;29(11):849-55.
[5] Tonorezos ES, Robien K, Eshelman-Kent D, Moskowitz CS, Church TS, Ross R, Oeffinger KC. Contribution of diet and physical activity to metabolic parameters among survivors of childhood leukemia. Cancer Causes Control 2013;24(2):313-21. doi: 10.1007/s10552-012-0116-6.
[6] Smith WA, Li C, Nottage K, Mulrooney DA, Armstrong GT, Lanctot JQ, Chemaitilly W, Laver JH, Srivastava DK, Robison LL, et al. Lifestyle and metabolic syndrome in adult survivors of childhood cancer: a report from the St. Jude Lifetime Cohort Study. Cancer 2014;120(17):2742-50. doi: 10.1002/cncr.28670.
[7] Zhang FF, Parsons SK. Obesity in Childhood Cancer Survivors: Call for Early Weight Management. Advances in Nutrition: An International Review Journal 2015;6(5):611-9. doi: 10.3945/an.115.008946.
[8] Zhang FF, Saltzman E, Must A, Parsons SK. Do childhood cancer survivors meet the diet and physical activity guidelines? A review of guidelines and literature. International Journal of Child Health and Nutrition 2012;1(1):44-58.
[9] Ladas E. Nutritional Counseling in Survivors of Childhood Cancer: An Essential Component of Survivorship Care. Children 2014;1(2):107.
[10] Zhang FF, Ojha RP, Krull KR, Gibson TM, Lu L, Lanctot J, Chemaitilly W, Robison LL, Hudson MM. Adult Survivors of Childhood Cancer Have Poor Adherence to Dietary Guidelines. The Journal of Nutrition 2016;146(12):2497-505. doi: 10.3945/jn.116.238261.
[11] Zhang FF, Saltzman E, Kelly MJ, Liu S, Must A, Parsons SK, Roberts SB. Comparison of childhood cancer survivors' nutritional intake with US dietary guidelines. Pediatric Blood & Cancer 2015;62(8):1461-7. doi: 10.1002/pbc.25521.
[12] Landy DC, Lipsitz SR, Kurtz JM, Hinkle AS, Constine LS, Adams MJ, Lipshultz SE, Miller TL. Dietary Quality, Caloric Intake, and Adiposity of Childhood Cancer Survivors and Their Siblings: An Analysis from the Cardiac Risk Factors in Childhood Cancer Survivors Study. Nutrition and Cancer 2013;65(4):547-55. doi: 10.1080/01635581.2013.770042.
[13] Robien K, Ness KK, Klesges LM, Baker KS, Gurney JG. Poor Adherence to Dietary Guidelines Among Adult Survivors of Childhood Acute Lymphoblastic Leukemia. Journal of Pediatric Hematology/Oncology 2008;30(11):815-22. doi: 10.1097/MPH.0b013e31817e4ad9.
[14] Kuehni CE, Rueegg CS, Michel G, Rebholz CE, Strippoli M-PF, Niggli FK, Egger M, von der Weid NX, Group ftSPO. Cohort Profile: The Swiss Childhood Cancer Survivor Study. International Journal of Epidemiology 2012;41(6):1553-64. doi: 10.1093/ije/dyr142.
[15] Michel G, von der Weid NX, Zwahlen M, Adam M, Rebholz CE, Kuehni CE, Swiss CCR, Swiss POGS. The Swiss Childhood Cancer Registry: rationale, organisation and results for the years 2001-2005. Swiss Medical Weekly 2007;137(35-36):502-9.
[16] Michel G, von der Weid NX, Zwahlen M, Redmond S, Strippoli MPF, Kuehni CE. Incidence of childhood cancer in Switzerland: The Swiss childhood cancer registry. Pediatric Blood & Cancer 2008;50(1):46-51. doi: 10.1002/pbc.21129.
[17] Robison LL, Mertens AC, Boice JD, Breslow NE, Donaldson SS, Green DM, Li FP, Meadows AT, Mulvihill JJ, Neglia JP, et al. Study design and cohort characteristics of the childhood cancer survivor study: A multi-institutional collaborative project. Medical and Pediatric Oncology 2002;38(4):229-39. doi: 10.1002/mpo.1316.
[18] Hawkins MM, Lancashire ER, Winter DL, Frobisher C, Reulen RC, Taylor AJ, Stevens MCG, Jenney M. The British Childhood Cancer Survivor Study: Objectives, methods, population structure, response rates and initial descriptive information. Pediatric Blood & Cancer 2008;50(5):1018-25. doi: 10.1002/pbc.21335.

[19] Morabia A, Bernstein M, Kumanyika S, Sorenson A, Mabiala I, Prodolliet B, Rolfo I, Luong B. Development and validation of a semi-quantitative food questionnaire based on a population survey. Sozial-und Praventivmedizin 1994;39(6):345-69.
[20] Bochud M, Chatelan A, Blanco J-M, Beer-Borst S. Anthropometric characteristics and indicators of eating and physical activity behaviors in the Swiss adult population, Results from menuCH 2014-2015, Report on behalf of the Federal Office of Public Health and the Food Safety and Veterinary Office. 2017.
[21] Liebherr R MJ, Storni M, Wiedenmayer G. Gesundheit und Gesundheitsverhalten in der Schweiz 2007 Schweizerische Gesundheitsbefragung. Neuchâtel Bundesamt für Statistik, 2010.
[22] Germann U. Abschlussbericht zur Volkszählung 2000. Neuchâtel, Switzerland: Bundesamt für Statistik, 2005.
[23] Morabia A, Bernstein M, Héritier S, Ylli A. Community-Based Surveillance of Cardiovascular Risk Factors in Geneva: Methods, Resulting Distributions, and Comparisons with Other Populations. Preventive Medicine 1997;26(3):311-9. doi: http://dx.doi.org/10.1006/pmed.1997.0146.
[24] Marques-Vidal P, Bochud M, Bastardot F, von Känel R, Aubry J, Gaspoz J, Paccaud F, Urwyler A, Lüscher T, Hoch C. Assessing the association between mental disorders, cardiovascular risk factors, and cardiovascular disease: the CoLaus/PsyCoLaus study. Raisons de santé 2011;182:1-28.
[25] Bernstein L, Huot I, Morabia A. Amélioration des performances d'un questionnaire alimentaire semi-quantitatif comparé à un rappel des 24 heures [Improvement of the effectiveness of a food frequency questionnaire compared with a 24 hour recall survey]. Santé Publique 1995;7(4):403-13.
[26] Bernstein M, Morabia A, Costanza M, Landis J, Ross A, Flandre P, Luong B, Kumanyika S, Sorenson A, Localio R. Nutritional balance of the diet of the adult residents of Geneva. Sozial-und Praventivmedizin 1994;39(6):333-44.
[27] Beer-Borst S, Costanza M, Pechere-Bertschi A, Morabia A. Twelve-year trends and correlates of dietary salt intakes for the general adult population of Geneva, Switzerland. European journal of clinical nutrition 2009;63(2):155.
[28] Slimani N, Casagrande C, Nicolas G, Freisling H, Huybrechts I, Ocké M, Niekerk E, Van Rossum C, Bellemans M, De Maeyer M. The standardized computerized 24-h dietary recall method EPIC-Soft adapted for pan-European dietary monitoring. European journal of clinical nutrition 2011;65(S1):S5.
[29] Slimani N, Deharveng G, Charrondière RU, van Kappel AL, Ocké MC, Welch A, Lagiou A, van Liere M, Agudo A, Pala V. Structure of the standardized computerized 24-h diet recall interview used as reference method in the 22 centers participating in the EPIC project. Computer methods and programs in biomedicine 1999;58(3):251-66.
[30] Camenzind-Frey E, Zuberbühler C. menuCH - SCHWEIZERISCHES FOTOBUCH / LIVRE PHOTO SUISSE / MANUALE FOTOGRAFICO SVIZZERO. Bern: Bundesamt für Gesundheit (BAG) & Bundesamt für Lebensmittelsicherheit und Veterinärwesen (BLV), 2014.
[31] Swiss Confederation, Federal Department of Home Affairs FDHA, Federal Food Safety and Veterninary Office FSVO. Internet: http://naehrwertdaten.ch/request?xml=MessageData&xml=MetaData&xsl=Start&lan=en&pageKey=Start.
[32] World Health Organization (WHO). Internet: http://www.who.int/dietphysicalactivity/physical-activity-recommendations-18-64years.pdf?ua=1.
[33] Bernstein M, Sloutskis D, Kumanyika S, Sparti A, Schutz Y, Morabia A. Data-based approach for developing a physical activity frequency questionnaire. American Journal of Epidemiology 1998;147(2):147-54.
[34] World Health Organization (WHO). Obesity: Preventing and managing the global epidemic. Report of a WHO Consultation on obesity. Geneva: WHO, 2000.
[35] Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P. International Classification of Childhood Cancer, third edition. Cancer 2005;103(7):1457-67. doi: 10.1002/cncr.20910.
[36] Children's Oncology Group (COG). Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers 2013.
[37] Belle FN, Kasteler R, Schindera C, Bochud M, Ammann RA, von der Weid NX, Kuehni CE. No evidence for overweight in long-term childhood cancer survivors after glucocorticoid treatment. Cancer 2018. doi: 10.1002/cncr.31599.
[38] Belle F, Wengenroth L, Weiss A, Sommer G, Beck Popovic M, Ansari M, Bochud M, Kuehni C, Ammann R, Angst R, et al. Low adherence to dietary recommendations in adult childhood cancer survivors. Clinical Nutrition 2017;36(5):1266-74. doi: 10.1016/j.clnu.2016.08.012.
[39] Belle FN, Weiss A, Schindler M, Sommer G, Goutaki M, Bochud M, Zimmermann K, Ammann RA, Kuehni CE. Overweight in Childhood Leukemia Survivors: the Swiss Childhood Cancer Survival Study. American Journal of Clinical Nutrition 2017.

[40] Kasteler R, Weiss A, Schindler M, Sommer G, Latzin P, von der Weid NX, Ammann RA, Kuehni CE, Swiss Pediatric Oncology G. Long-term pulmonary disease among Swiss childhood cancer survivors. Pediatric Blood & Cancer:e26749-n/a. doi: 10.1002/pbc.26749.
[41] D-A-CH-Referenzwerte für die Nährstoffzufuhr. 2015.
[42] Chiuve SE, Fung TT, Rimm EB, Hu FB, McCullough ML, Wang M, Stampfer MJ, Willett WC. Alternative Dietary Indices Both Strongly Predict Risk of Chronic Disease. The Journal of Nutrition 2012;142(6):1009-18. doi: 10.3945/jn.111.157222.
[43] Marques-Vidal P, Rousi E, Paccaud F, Gaspoz J-M, Theler J-M, Bochud M, Stringhini S, Guessous I. Dietary Intake according to Gender and Education: A Twenty-Year Trend in a Swiss Adult Population. Nutrients 2015;7(11):5481.

SUPPLEMENTARY MATERIAL

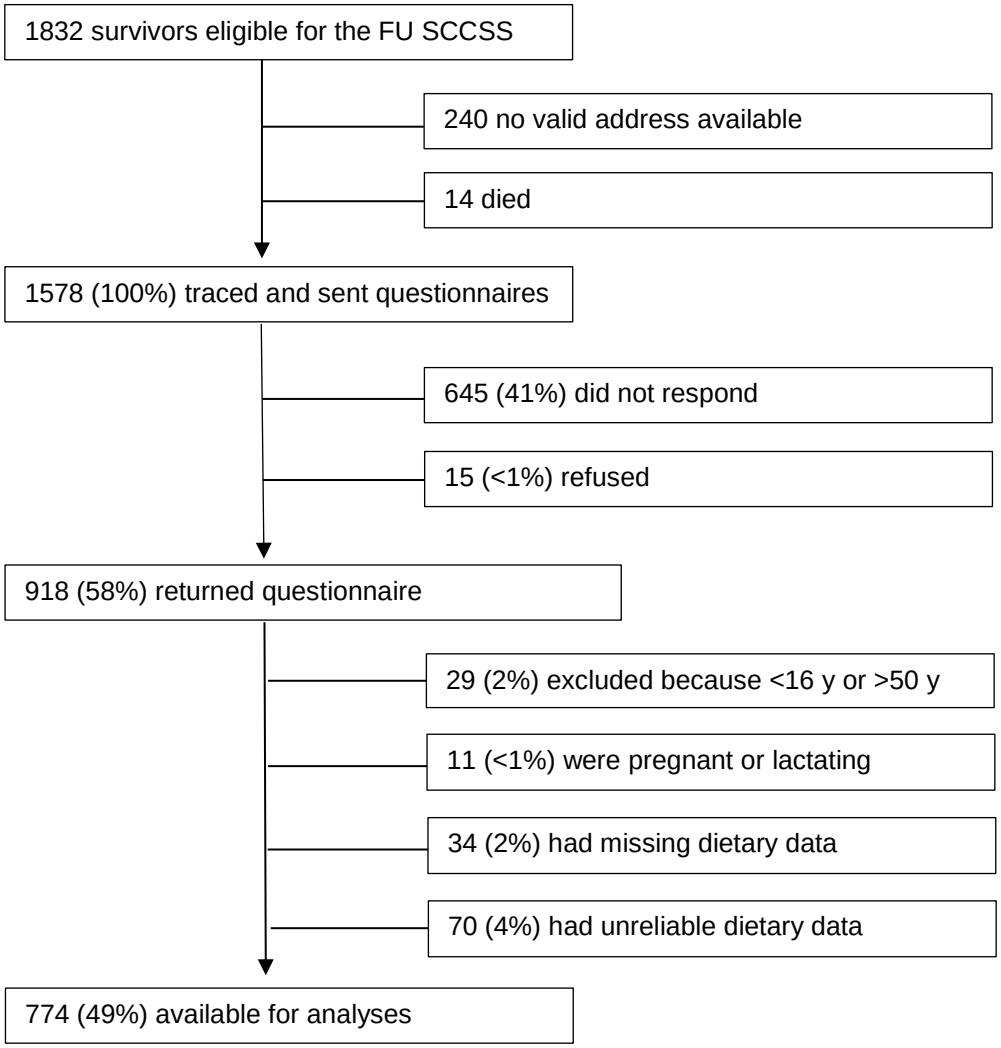

Figure S1. Response rates in the follow-up Swiss Childhood Cancer Survivor Study[1]

[1] FU, follow-up; SCCSS, Swiss Childhood Cancer Survivor Study.

Table S1. Clinical characteristics of childhood cancer survivors[1]

Characteristics	**CCSs (*n* = 774)**
ICCC3 diagnosis, *n (%)*	
I: Leukemia	237 (31)
II: Lymphoma	163 (21)
III: CNS tumor	79 (10)
IV: Neuroblastoma	28 (4)
V: Retinoblastoma	12 (2)
VI: Renal tumor	52 (7)
VII: Hepatic tumor	6 (1)
VIII: Bone tumor	49 (6)
IX: Soft tissue sarcoma	64 (8)
X: Germ cell tumor	40 (5)
XI & XII: Other tumor	25 (3)
Langerhans cell histiocytosis	19 (2)
Age at diagnosis, *n (%)*	
<5 y	251 (32)
5-9 y	163 (21)
10-14 y	224 (29)
15-20 y	136 (18)
Time since diagnosis,[2] y	25.7 (20.1-31.1)
History of relapse, *n (%)*	83 (11)
Radiation, *n (%)*	
Any	276 (36)
Cranial	120 (16)
<18 Gy	27 (3)
≥18 Gy	93 (12)
Chest	86 (11)
<30 Gy	33 (4)
≥30 Gy	53 (7)
TBI and/or abdominal	67 (9)
Glucocorticoids, *n (%)*	330 (43)
Anthracyclines, *n (%)*	292 (38)
Alkylating agents, *n (%)*	319 (41)
Hematopoietic stem cell transplantation, *n (%)*	30 (4)

[1] CCS, childhood cancer survivor; CNS, central nervous system; Gy, gray; ICCC3, *International Childhood Cancer Classification, 3rd edition.*

[2] Values are medians (IQRs).

Table S2. Dietary intake in childhood cancer survivors by sex compared to the DACH dietary recommendations[1]

Nutrients	DACH recommendations[2]		CCSs (*n* = 774)			
	men	women	men (*n* = 386)		women (*n* = 388)	
			mean ± SD	% DACH[4]	mean ± SD	% DACH[4]
Total energy, kcal[3]	2300-3400	1800-2600	1743 ± 632	61	1535 ± 508	70
Macronutrients						
Protein, g	57	48	73.8 ± 33.8	129	58.5 ± 22.1	122
% of energy[5]	10-20	10-20	16.9 ± 3.7	112	15.4 ± 3.4	103
Vegetal, g			18.3 ± 7.7		18.0 ± 7.5	
Animal, g			55.5 ± 30.7		40.6 ± 19.9	
Carbohydrates, g[6]	225-275	225-275	187 ± 76.2	75	174 ± 71	70
% of energy[5, 6]	45-55	45-55	42.8 ± 8.4	86	45.2 ± 9.1	90
Mono/disaccharides, g			87 ± 46		84 ± 46	
Polysaccharides, g			98 ± 46		90 ± 42	
Total fiber, g[6]	≥30	≥30	11.5 ± 5.8	38	12.9 ± 6.9	43
Total fat, g			72.2 ± 30.2		64.2 ± 25.4	
Total fat, % of energy[5]	30-40	30-40	37.2 ± 6.6	106	37.5 ± 7.2	107
Saturated fat, g			27.3 ± 12.5		23.1 ± 10.4	
Saturated fat, % of energy[7]	<10	<10	14.0 ± 2.9	140	13.5 ± 3.4	135
Monounsaturated fat, g			29.9 ± 13.3		27.3 ± 11.9	
Polyunsaturated fat, g			9.0 ± 3.9		8.2 ± 3.6	
Cholesterol, mg[5]	300	300	376 ± 209	125	310 ± 202	103
Micronutrients						
Vitamins						
A, mg-RE[8]	1.0	0.8	0.7 ± 0.7	71	0.7 ± 0.7	89
D, µg	20	20	2.5 ± 2.0	12	2.3 ± 2.0	12
Minerals						
Calcium, mg	1000	1000	908 ± 502	91	869 ± 437	87
Iron, mg	10[4]	15	9.7 ± 3.9	97	8.3 ± 3.1	56
Alcohol, g[9]	20	10	7.5 ± 7.9	37	4.0 ± 7.2	40

[1] CCS, childhood cancer survivors, DACH, Dietary recommendations for Germany (D), Austria (A) and Switzerland (CH).
[2] DACH recommendations for the general population age 20-50 y, excluding pregnant and lactating women.
[3] Depending on physical activity level (PAL, 1.4-1.8) and age.
[4] Percentage of mean intake to the DACH recommended intake level * 100. Recommended intake is estimated on the basis of the age-sex groups of the DACH guidelines, weighted by the age and sex distribution of the study population. For alcohol intake the maximum tolerated dosage was taken.
[5] Federal Food Safety and Veterinary Office FSVO, www.naehrwertdaten.ch.
[6] BLV (2009). Kohlenhydrate in unserer Ernährung – Empfehlungen des BLV. www.blv.admin.ch.
[7] BLV (2012). Fett in unserer Ernährung – Empfehlung des BLV. www.blv.admin.chv, Recommendations as a percentage of the daily energy demand and based on a daily energy intake of 2000 kcal.
[8] Total vitamin A= retinol + carotene/12, expressed in µg RAE.
[9] Maximum tolerated dosage.

Table S3. Scoring method and mean scores (95%CI) of components of the modified Alternate Healthy Eating Index[1,2] in childhood cancer survivors and the general population (Menu.CH) by sex

Components	Criteria for minimum score (0)	Criteria for maximum score (10)	Score in CCSs[12] mean (95%CI)		Score in Menu.CH[13] mean (95%CI)	
			men (*n* = 386)	women (*n* = 388)	men (*n* = 498)	women (*n* = 636)
Vegetables, excluding potatoes (servings/day)[3]	0	≥ 5	4.6 (4.4, 4.9)	5.5 (5.3, 5.7)	3.2 (3.2, 3.2)	3.3 (3.3, 3.3)
Fruit, excluding juice (servings/day)[4]	0	≥ 4	2.9 (2.6, 3.2)	3.9 (3.6, 4.2)	2.9 (2.9, 2.9)	3.4 (3.4, 3.5)
Whole grains (g/day)[5]						
Men	0	≥ 90	3.3 (3.0, 3.6)		3.4 (3.4, 3.4)	
Women	0	≥ 75		4.7 (4.4, 5.0)		4.0 (4.0, 4.0)
Sugar-sweetened beverage and fruit juice (servings/day)[6]	≥ 1	0	3.8 (3.4, 4.2)	4.9 (4.5, 5.3)	3.8 (3.7, 3.9)	4.8 (4.7, 4.9)
Nuts, seeds, legumes, and tofu (servings/day)[7]	0	≥ 1	1.9 (1.6, 2.2)	2.6 (2.3, 2.9)	1.7 (1.6, 1.7)	2.5 (2.5, 2.6)
Red and processed meat (servings/day)[8]	≥ 1.5	0	3.5 (3.2, 3.8)	5.8 (5.5, 6.1)	2.3 (2.3, 2.4)	5.2 (5.2, 5.2)
Trans fat (% of total energy intake)[9]	≥ 4	≤ 0.5	9.6 (9.5, 9.7)	9.5 (9.5, 9.6)	9.5 (9.5, 9.5)	9.4 (9.4, 9.4)
Fish, excluding processed products (g/day)	0	32.4	5.2 (4.8, 5.5)	4.9 (4.6, 5.3)	2.6 (2.6, 2.6)	2.6 (2.6, 2.6)
PUFA (% of total energy intake)[10]	≤2	≥10	4.8 (4.6, 5.1)	5.2 (4.9, 5.5)	4.4 (4.3, 4.4)	4.3 (4.3, 4.3)
Alcohol (drinks/day)[11]						
Men	≥ 3.5	0.5 - 2.0	5.4 (5.0, 5.7)		5.0 (4.9, 5.0)	
Women	≥ 2.5	0.5 - 1.5		3.9 (3.6, 4.3)		4.0 (4.0, 4.1)
Total	**0**	**100**	**45.0 (43.8, 46.2)**	**50.9 (49.7, 52.1)**	**38.7 (38.4, 38.9)**	**43.8 (43.6, 44.0)**

[1] Adapted from Chiuve et al. J Nutr 2012 142(6):1009-18.
[2] Intermediate food intake was scored proportionately between the minimum score 0 and the maximum score 10.
[3] One serving was equal to 118.3g of raw or cooked vegetables or 250g of vegetable soup. Dried vegetables were not included.
[4] One serving was equal to 118.3g of raw or cooked fruit. Dried fruit was not included.
[5] Whole grain products like whole grain bread and muesli were included.
[6] One serving was equal to 226.8g.
[7] One serving was equal to 28.4g.
[8] One serving was equal to 113.4g of red meat or 42.5g of processed meat.
[9] Consumption was estimated based on the assumption that each food contains max. 2g of trans fat per 100g of total fat, as defined in the Swiss regulation.
[10] The highest score was given to individuals with ≥10% of total energy intake from poly-unsaturated fatty acids (PUFA).
[11] One drink was 113.4g of wine, 340.2g of beer or 42.5g of liquor. A score of 2.5 was given to non-drinkers.
[12] Adjusted for age at survey and ICCC-3 diagnosis
[13] Adjusted for age at survey and standardized on sex, age at survey, and language region according to CCSs.

Chapter 4

Urine spot collection in childhood cancer patients and survivors: a pilot study

First results

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Maja Beck Popovic
Marc Ansari
Claudia Kuehni
Murielle Bochud

SUMMARY

Background: Urine analyses are an objective way to quantify intake of different nutrients, and can therefore complement self-reported information on nutrition from food frequency questionnaires (FFQs). We compared urine spot sample outcomes 1:1 with FFQs and evaluated the study conduct to investigate the possibility for a future national study.

Methods: In an observational multicentre pilot study, we determined dietary intake with a FFQ. First and second morning urine spot samples were asked of patients hospitalised in the university hospitals of Lausanne (CHUV) or Geneva (HUG) and first morning spot samples of outpatients previously treated in CHUV or HUG. We analyse the content of sodium, potassium, urea, urate, creatinine, and phosphate in urinary samples. Currently, analyses are ongoing to compare the urine spot sample outcomes 1:1 with the FFQ dietary assessment tool.

Results: We included 6 patients (response rate 75%) and 119 outpatients (response rate 50%). The recruitment target was not met for patients (6 out of 50), but was met for outpatients (119 out of 100). Study recruitment in patients was difficult for several reasons, e.g. patient was too young, too sick, or did not needed an overnight stay, or recruitment was impossible due to understaffed paediatric oncology departments.

Conclusions: Study feasibility in childhood cancer patients is poor if there is not a direct patient benefit. With the current information we recommend a future study only in outpatients as the response rate was relatively high. The quality of outpatients' samples still need to be investigated.

BACKGROUND

Biochemical indicators are an objective way to quantify intake of different nutrients, and can therefore complement self-reported information on nutrition from food frequency questionnaires (FFQs). This can be done by direct assays of the nutrient or the metabolic product in tissue or fluid, e.g. nails, faeces, blood, or urine. 24h urinary assessment of alkali minerals (sodium, potassium), halide ions (chloride, iodine and fluorine) and protein intakes are potential more valid indicators of nutrition than questionnaire-based data [1]. However, collection of 24h urine involves a considerable burden for subjects, and may introduce bias due to undetected incomplete sample collection and low response rate. Recently, research has therefore focused on the utility of single spot urines to estimate 24h urinary assessments [2, 3]. This is less burdensome for subjects, potential under- or over-collection is irrelevant and it is easier to incorporate in nutritional studies, as collection can be done during a single encounter. By adjusting for parameters such as age, sex, height and weight, and by taking urinary creatinine into account, samples can be converted into interpretable results. This makes spot urine samples a practical and costs saving alternative to 24h urine excretion to estimate population levels.

This pilot study was set up to:
1) compare the urine spot sample outcomes 1:1 with the FFQ dietary assessment tool. This will give more information about the reliability of the FFQ, the actual dietary intake of CCS and help to investigate if there is an association between diet and somatic late effects occurrence.
2) evaluate the pilot study, e.g.

- to determine feasibility (response rate, costs, quality) of analysing objective dietary markers in spot urine of CCS.
- to observe if there are potential differences in study conduct, response rate and quality of the samples among two categories of participants:
    - patients followed at the oncology clinic, and
    - outpatients, former patients of CHUV or HUG
- based on this experience, define the feasibility of a future national study to determine objectively dietary intake.

METHODS

Study population

Inclusion criteria

This multicentre observational pilot study was performed in the paediatric cancer centre in Lausanne (CHUV) and Geneva (HUG). For this pilot study we aimed to recruit 50 patients and

100 outpatients (**Figure 1**). This was perceived as the maximal feasible sample size within the study period of 2 years, both because of logistical reasons and patient availability.

Participants were eligible to participate if they were: 1) childhood cancer patients (i.e. cancer diagnosed before the age of 21 years) newly diagnosed or in treatment, aged ≥8 years, and who were at time of the pilot study hospitalised in the oncology department of CHUV or HUG or 2) SCCSS study participants ≥16 years who visited in the past the oncology department of CHUV or HUG and filled in the FFQ as part of the SCCSS follow-up questionnaire. If the informed consent was signed and the urine specimen was sufficient to fulfil the pilot study protocol, participants were automatically enrolled. Study participants were excluded if they had end stage renal disease, or were pregnant or lactating.

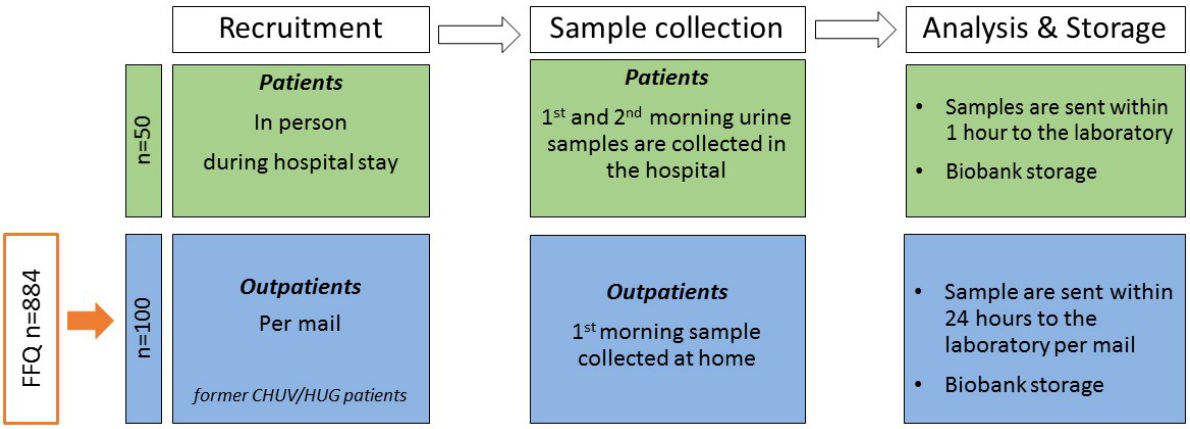

Figure 1. Pilot study flowchart.

Recruitment and Screening

Patients received a verbal briefing, and/or an information letter and informed consent in person from the project leader or their treating oncologist to ask for their willingness to participate. During recruitment it was made clear that this study would not lead to a direct benefit for the patient, but could benefit childhood cancer survivors in an attempt to reduce treatment related late effects. In case the patient and/or the legal representative signed the informed consent, the urine collection kit was handed over to collect a first and second morning urine sample the following day. It was hypothesized that the urine spot samples of this group would have the highest quality compared to outpatients. A high quality was expected as these patients received supervision of hospital staff during the pilot study, samples were considered to be stored quicker under the protocol storage procedures, and it was ensured that first and second morning urine spot samples were collected. Therefore, the urine spot samples of outpatients were compared to the ones of patients. The urine samples of patients were transferred as soon as possible, preferably within 1h to 1 day after collection handed over to the CHUV laboratory for analyses.

Outpatients received by post mail an information letter signed by the project leader. If the patient did not rejected to participate, an urine collection kit and informed consent were shipped to the participant's home address to collect a first morning sample within 2 weeks. After sample collection, the urine spot was asked to be transferred by mail within 24 hours to the CHUV laboratory for analyses.

Information about medication and type of treatment was extracted from clinical records for all participants.

Measurements

Up to 70 ml of a fresh first morning urine sample was asked to an eligible recruited participant during hospitalisation (patients) or via post mail (outpatients) (Figure 1). Second morning urine samples were asked only during hospitalisation. Response rate, feasibility, quality of samples, and correspondence between self-reported nutrition and objective measurements were assessed (**Table I**).

For analyses, levels of potassium, sodium, phosphate, urate, urea, and creatinine were measured using routine laboratory procedures (Table I). Urinary potassium-to-creatinine ratio was used to estimate dietary potassium intake; similar calculations were done for sodium, phosphate, urate, and protein intakes (estimated by urea excretion, Table II). The central laboratory of CHUV, performed all biochemical analyses of all samples coming from both CHUV and HUG. Urine samples were frozen and stored in a biobank for further analyses corresponding to the topic of research, and to complete and increase the power of a possible further similar investigation within the larger cohort of the SCCCS.

Table I. Primary and secondary endpoint/ outcomes of interest in the urine spot pilot study

Endpoints/outcomes	Method:	Quality promotion	(Expected) time point/window
Detailed dietary intake, macro- and micronutrients	Dietary intake was assessed using a validated FFQ which provided information on consumption frequency and portion sizes during the 4 previous wks for 97 fresh and prepared food items organized in 12 different food groups. *-The FFQ was not validated and adapted to children-*	A validated FFQ earlier used in the Bus Santé and CoLaus study was slightly adapted to meet study objectives	Participants were expected to fill in and return the FFQ within +/- 10 wks. After 4-6 wks, the participants received their 1st reminder by sending the FFQ again. In case of non-response, they received a 2nd reminder. The FFQ was sent before the start of this pilot study to all SCCSS participants (≥16 yrs).
Urinary measurements, e.g. Na, K, urea, urate, creatine, PO_4	Laboratory tests	Standard laboratory procedures	Measurements were done at the same time the routine analyses were performed in the hospital laboratory. Measurements were performed during the whole time period of the pilot study
General response rate and in subgroups	- Patients: the investigator kept track of the number of CCS that were not willing to participate. - Outpatients: the SCCSS tracking system kept track of the number of CCS that did not responded or were not willing to participate.	n.a.	After finalising the pilot study

Costs	All costs were recorded, e.g. laboratory, mailing, printing, urine collection sample kits.		Mid-term evaluation and after finalising the pilot study
Quality of obtained urine spots	FFQ vs. urine spots were compared between subgroups. To investigate if storage circumstances among subgroups did not substantially impact the quality of urine measurements, a subset of 10 patients 1st morning samples (20%) mimicked to potential outpatients' conditions. This means, that 1st morning samples of 10 patients were split into 2 subsamples. The 1st subsample (3 x 3ml) was kept 4 hrs at room temperature before urine chemistry and final storage at -80°C. The 2nd subsample (9 x 3ml) followed standard protocol storage procedures. The outcomes of the urine chemistry analyses of the 2 subsamples were 1:1 compared.	Standard laboratory procedures	Mid-term evaluation and after finalising the pilot study
Study feasibility for both hospital and study participants	Difficulties in the study conduct among study participants or at the study centres (CHUV and HUG) were recorded for final evaluation.	n.a.	Mid-term evaluation and after finalising the pilot study

CCS, childhood cancer survivor; CHUV, Centre Hospitalier Universitaire Vaudois; FFQ, food frequency questionnaire; HUG, Hôpital Universitaire de Genève; K, potassium; Na, sodium; PO_4, phosphate; SCCSS, Swiss Childhood Cancer Survivor Study

Table II. Performed urinary measurements and their estimated dietary intake

Urinary measurement	Estimation of dietary intake
sodium (Na)	• Dietary sodium intake • Na/Cr ratio
potassium (K)	• Dietary potassium intake (fruit and vegetables) • K/Cr ratio
urea	• Protein intake. Main end-product of the catabolism of amino acids • Protein/Cr ratio
urate	• Production of uric acid – diet rich in protein
creatinine (Cr)	• Completeness of urine collection
phosphate (PO_4)	• Phosphate intake (dairy products, meat, whole grain, nuts, eggs, additives in processed food) • PO_4/Cr ratio

STATUS

The urine pilot study includes in total 125 participants: 6 patients and 119 outpatients (**Figure 2**). The study was terminated prematurely on 01.04.2018 (**Table III**). Currently, data analyses are ongoing.

Table III. Pilot study elements and duration

Pilot study duration	Date
Ethical approval	
CER-VD	15.03.2016
CCER	21.07.2017
Date first participant in	03.02.2017
Date last participant in	10.12.2017
FFQ data entered	23.03.2018
End of study	01.04.2018

CCER, Commission Catonale d'éthique de la recherche Genève; CER-VD, Commission Catonale d'éthique de la recherche sur l'être humain Vaud

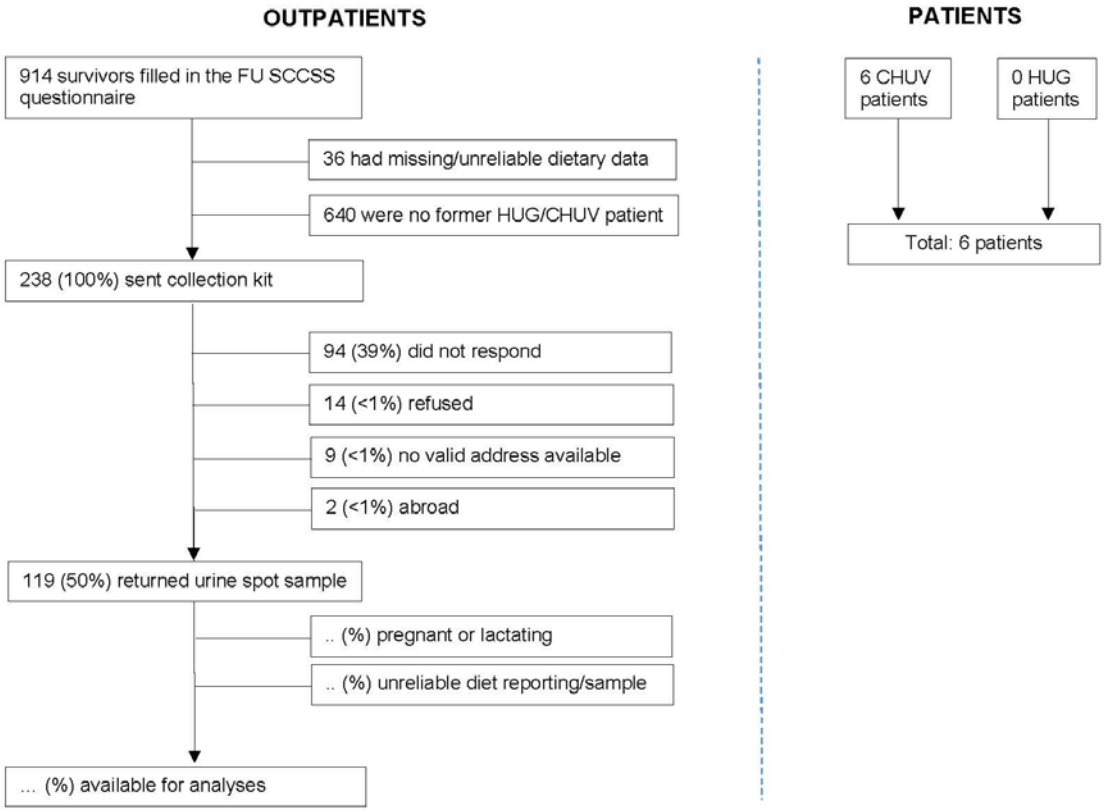

Figure 2. Response rates per study arm in the Swiss Childhood Cancer Survivor Study (SCCSS) Urine Pilot Study

STUDY CHALLENGES

This study has not met its initial target number of participants due to difficulties with patient recruitment. Initially this study contained three study arms:

1. Patients: childhood cancer patients hospitalised in the paediatric oncology department of CHUV or HUG
2. Clinical visit: CCS with regular clinical visits at CHUV or HUG, meaning at least one planned visit during study duration
3. Outpatients: CCS with unregularly clinical visits in CHUV or HUG, meaning no planned visit during study duration

The original target participant number was 200 (patients N=50, clinical visit N=50, outpatients N=100) of which we enrolled 125 (patients N=6, clinical visit N=0, outpatients N=119).

Patients

Reasons why the target for the study arm 'patients' was not met were:

- patients did not met the inclusion criteria. Hospital staff often had difficulties with the age limitation of ≥ 8 years as a high proportion of patients were younger;
- patients were too sick;
- patients resigned sooner than expected (no overnight stay);
- under staffed paediatric oncology departments, no time for recruitment, sample collection etc., and because of
- refusal of patient and/or legal guardian(s) (minority)

Clinical visit and outpatients

Because of recruitment difficulties, understaffed paediatric oncology departments, and time restrictions we decided to include a second study centre (HUG) and drop the study arm: 'clinical visit'. This gave us the opportunity to include more eligible 'outpatients' due to the overlap between the study arms 'clinical visit' and 'outpatients'. We aimed for an as high as possible eligible outpatients number as we expected potential recruitment difficulties. Outpatients were asked to collect and send their urine samples during the week and bring the sample to the post office as the sample did not fitted the opening of a mailbox. Although a low response rate was expected we managed to recruit more outpatients than planned. Due to good response, we did not send the planned reminder. The recruitment target for 'outpatients' was met due to the:

- high number of eligible CCS, national coverage of SCCR;
- direct contact possibilities with the potential participants;
- up to date address list, personal information etc. of SCCR, and
- because CCS were more often capable to participate to the study (less restricted to illness) compared to patients and highly motivated.

CONCLUSION

We can conclude that the study feasibility in childhood cancer patients is poor if there is not a direct patient benefit. With the current information we recommend a future study only in outpatients as the response rate was relatively high. The quality of outpatients' samples still need to be investigated.

REFERENCES

[1] Willet W. Nutritional Epidemiology, Monographs in epidemiology and biostatistics, 2nd ed, Vol 30, 1998, Oxford University Press
[2] Huang L, Crino M, Wu JHY, Woodward M, Barzi F, et al. Mean population salt intake estimated from 24-h urine samples and spot urine samples: a systematic review and meta-analysis. International Journal of Epidemiology. 2016;45(1): 239-250.
[3] Mente A, O'Donnell MJ, Dagenais G, Wielgosz A, Lear SA, McQueen MJ, et al. Validation and comparison of three formulae to estimate sodium and potassium excretion from a single morning fasting urine compared to 24-h measures in 11 countries. Journal of Hypertension. 2014;32(5): 1005-1015.

Chapter 5

Overweight in childhood cancer patients at diagnosis and throughout therapy: a multicentre cohort study

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SUMMARY

Background: Childhood cancer patients (CCP) have been reported to be at increased risk of becoming overweight during treatment. We assessed prevalence of overweight in CCP at diagnosis and at the end of treatment, determined risk factors, and identified weight change during treatment by type of cancer.

Objective: In a multicentre cohort study, we collected height and weight measurements of CCP at diagnosis and repeatedly during treatment. We calculated age- and sex-adjusted BMI Z-scores using references of the International Obesity Taskforce for children. Risk factors were described by multivariable linear regression, and weight change during treatment by multilevel segmented linear regression.

Results: The study included 327 CCP with a median age of 7 years (IQR 3-12) at diagnosis (55% boys), who had been diagnosed with acute lymphoblastic leukaemia (ALL, 29%), lymphoma (16%), central nervous system (CNS) tumours (13%), sarcoma (18%), and other types of cancer (24%). At diagnosis, 27 CCP (8%) were overweight. This increased to 43 (13%) at end of treatment, on average 0.7 years after diagnosis. Being a boy ($p=0.005$) and having been diagnosed with ALL or lymphoma ($p<0.001$) were risk factors for weight gain during treatment. During the first half of treatment, BMI Z-scores increased in ALL (regression slope $\beta=0.4$, 95% CI 0.1–0.7) and lymphoma ($\beta=1.5$, 95% CI 0.2–2.9) patients, whereas for patients with CNS tumours ($\beta=-1.4$, 95% CI -2.7 to -0.2), sarcoma ($\beta=-1.4$, 95% CI -2.0 to -0.7), or other types of cancer ($\beta=-0.3$, 95% CI -1.5–0.9) BMI Z-scores tended to drop initially. During the second half of treatment BMI Z-scores of all patients tended to increase. Exploratory analyses showed that BMI Z-scores of younger ALL patients (<7 years at diagnosis) increased during induction ($\beta= 3.8$, 95% CI 0.5–7.0). The inverse was seen for older ALL patients (≥7 years at diagnosis), in whom BMI Z-scores tended to decrease during induction ($\beta= -1.5$, -5.1–2.2), both groups tended to increase afterwards.

Conclusions: CCP diagnosed with ALL or lymphoma are at increased risk of weight gain during treatment, and might particularly benefit from early lifestyle interventions.

INTRODUCTION

Childhood cancer survival has substantially improved in recent decades, but chronic health problems are common in survivors [1]. Overweight is reported as a frequent late effect, particularly in patients with acute lymphoblastic leukaemia (ALL) and brain tumours [2, 3]. Some studies have suggested that patients diagnosed with other cancers such as sarcomas and lymphomas are also affected [2, 4]. The consequences of overweight and obesity in childhood cancer patients (CCP) are manifold: reduced health-related quality of life, more comorbidities in later life, and increased risk for relapse, second primary tumours, and mortality [4, 5].

Studies of overweight or obesity during treatment have been conducted mainly in ALL and brain tumour patients, and have reported varying results. At diagnosis, 10-36% of ALL patients were reported to be overweight and 2-19% obese [4, 6-9]. At the end of treatment, 19-49% were reported as overweight and 9-48% as obese [4, 6-9]. In patients with craniopharyngiomas, obesity was reported in 50% of the patients after tumour resection [10, 11].

Data on risk factors for overweight in CCP are inconclusive [4, 12]. A meta-analysis has concluded that childhood ALL patients have substantial weight gain from diagnosis to start of maintenance treatment and beyond, independent of gender, cranial radiation therapy, and weight status at diagnosis [13]. For brain tumour patients, female gender and younger age were described as risk factors for obesity [10, 14]. Yet few studies have covered the whole diagnostic spectrum of childhood cancer. Comparable information on overweight prevalence at diagnosis, during, and at the end of cancer treatment between diagnostic groups in CCP is also lacking, but is crucial for initiating individualised preventive measures at an early stage.

The goals of this multicentre cohort study were to 1) determine overweight prevalence of CCP at diagnosis and at the end of treatment, 2) determine potential risk factors for weight change from diagnosis until the end of treatment, and 3) describe weight change during treatment by type of cancer, with a focus on ALL patients during the different treatment phases.

METHODS

Study population

Eligible patients for this retrospective cohort study were CCP aged <18 years at diagnosis who were diagnosed 2003–2006 and treated with chemotherapy and/or percutaneous radiotherapy in three tertiary care centres for paediatric haematology/oncology in Basel, Bern, and Zürich in the German-speaking part of Switzerland. Prospectively collected data on type of cancer, treatment, and demographic information were extracted from the Swiss Childhood Cancer Registry (SCCR, www.childhoodcancerregistry.ch) [15, 16]. Height and weight measurements were obtained from a retrospective chart review. Detailed information on our study design was

published previously [17]. Ethical approval of the SCCR was granted by the Ethics Committee of the Canton of Bern (KEK-BE: 166/2014).

Measurements

Body weight and BMI Z-scores

Body mass index (BMI), expressed in kg/m^2 was used to define overweight. BMI Z-scores were calculated according to Cole's LMS method [18] based on the reference values of the International Obesity Taskforce (IOTF). For children under two years of age, we used the standards of the World Health Organization [19]. Underweight (thinness grade I-III), normal weight, and overweight (including obesity and morbid obesity) was classified according to BMI cut-offs recommended by the IOTF (**Supplementary Table S1**) [20]. The observation period started with the first measurement at diagnosis and ended with the last measurement before the end of anticancer treatment or when the patient died, relapsed, or was transferred to a nonparticipating hospital for ongoing anticancer treatment [17]. This study used all weight and height measurements available from medical charts.

We obtained birth weights from medical records and by using probabilistic record linkage of the SCCR and birth records from the Swiss Federal Statistical Office, as described previously [21]. Birth weight was classified into three categories: low (<2500 g), normal (2500-4000 g), and high (>4000 g) [22].

Sociodemographic and clinical characteristics

Participants who were not Swiss citizens at birth, not born in Switzerland, or had at least one parent who was not a Swiss citizen were classified as having a migration background. Diagnosis was classified according to the International Classification for Childhood Cancer, 3rd edition (ICCC-3) [23], and grouped into five main categories: ALL, lymphomas, CNS tumours, sarcomas, and other types of cancer. These categories were chosen in accordance with other studies [2, 4]. Radiotherapy was classified as cranial radiation therapy (CRT) if the patient had received direct radiation to the brain and/or skull. Cumulative dosage of CRT was obtained from medical records and categorized as <20 Gray (Gy) or ≥20 Gy. We also extracted information on parenteral and/or enteral nutritional support during treatment.

Statistical Analyses

We first compared the changes in prevalence of overweight and BMI Z-scores between diagnosis and the end of treatment by sociodemographic and clinical characteristics. The time of end of treatment was replaced with time at relapse, death, or end of data collection if these occurred during treatment.

Second, we used linear regression to determine risk factors associated with change in BMI during treatment, from diagnosis till end of treatment. We selected the following potential

risk factors a priori based on a literature review: gender, age at diagnosis, ICCC-3 diagnosis, cumulative CRT, parenteral/enteral nutrition support, birthweight, and BMI Z-score at diagnosis. Variables with p-values <0.05 in univariable models were jointly included in a multivariable model. F-tests were used to test the association between the outcome and the covariates. Age at diagnosis and BMI Z-scores at diagnosis were included as continuous variables after testing for linearity of their association with BMI-change using likelihood ratio tests.

Third, to assess whether the slope of BMI change was different between early and late treatment phases we fit multilevel segmented linear regression models with BMI Z-score as dependent variable and therapy duration in years as independent variable. We separated analyses for each diagnostic group. The piecewise linear regression line allowed for a change in trend at a specified breakpoint set to the median treatment duration among patients of the given diagnostic group. For ALL patients, we performed separate analyses with breakpoints at the end of the induction period (33 days, 0.09 years) and the start of the maintenance period (99 days, 0.27 years), based on the cancer protocols used in the study. All regression models included a random effect term on patient level, allowing for intra-individual correlation. The models were adjusted for gender, age at diagnosis, cumulative CRT, parenteral/enteral nutrition support, and BMI Z-score at diagnosis. For these analyses, we included only 311 CCP who had at least five height and weight measurements available.

BMI Z-score curves of individual patients were highly variable, and fitting a single trend by diagnostic group is clearly an oversimplification. In additional exploratory analyses in ALL patients, we therefore fit separate segmented linear regressions with a flexible breakpoint to the BMI Z-score of each patient. We then grouped patients according to whether the initial slope was positive or negative and compared groups according to gender and age (below and above median of 7 years) at diagnosis using chi-square tests. We found that BMI Z-scores tended to initially increase in younger patients, but decreased in older patients (p=0.002). The groups differed little in gender composition (p=0.117). In post hoc analyses we therefore repeated our main analysis for ALL (with specified breakpoints at the end of the induction period and the start of the maintenance period), stratifying patients by these age groups. We used Stata (version 14, Stata Corporation, Austin, Texas) and R (version 3.2.0) for all analyses. The command xtmixed was used for multilevel segmented linear regression analysis.

RESULTS

We included 327 patients in the analysis whose median age at diagnosis of 7 years (interquartile range [IQR] 3-12). ALL was the most common diagnosis among CSS with 95 patients (29%), followed by sarcomas (18%), lymphoma (16%), CNS tumours (13%), other types of cancer (24%) including acute myeloid leukaemia, nephroblastoma, and

neuroblastoma (**Table I**). The median time from diagnosis until the end of treatment was 0.7 years (IQR 0.4-1.8) for all patients and varied by type of cancer: ALL 2.0 (IQR 2.0-2.3), lymphoma 0.4 (IQR 0.3-0.6), CNS tumours 0.7 (IQR 0.3-1.2), sarcomas 0.7 (IQR 0.5-0.9), and other types of cancer 0.6 (IQR 0.4-0.7) years. Median time interval between successive weight and height measurements was 13 days (IQR 10-19 days), and 267 patients were observed until the end of their anticancer treatment (82%), 23 patients (7%) relapsed during therapy, 12 patients (4%) died, and 25 patients (8%) were lost to follow up. Other patient and clinical characteristics are shown in Table I.

Overweight prevalence and BMI Z-scores at diagnosis and at the end of treatment

At diagnosis, 27 patients (8%) were overweight. This proportion increased to 43 (13%) at the end of treatment (Table I). Mean BMI Z-score was -0.1 (SD 1.1) at diagnosis and -0.1 (SD 1.3) at the end of treatment (**Table II**). Prevalence of overweight at diagnosis increased during treatment in boys and girls, all age groups, all types of cancer except "other types," and patients with and without parenteral or enteral nutrition support (**Figure 1**). BMI Z-scores tended to increase during treatment in boys, patients below the age of five years, those diagnosed with ALL or lymphoma, with no or <20 Gy CRT, no parenteral or enteral nutrition support, and those who were underweight at diagnosis (Table II).

Risk factors for weight change during treatment among childhood cancer patients

In adjusted models, risk factors for weight gain during treatment were being a boy (β=0.3; 95%CI: 0.1, 0.5) and being diagnosed with ALL (β=0.5; 0.2, 0.8) or lymphoma (β=0.6; 0.2, 1.0). Weight loss was associated with older age at diagnosis (β=-0.03; -0.05, 0.01, per year increase), ≥20 Gy CRT (β=-0.6; -1.0, 0.1), receiving parenteral/enteral nutrition support (β=-0.3; -0.5, 0.1), and a higher BMI at diagnosis (β=-0.3; -0.4, 0.2, per BMI Z-score) (**Table III**).

Table I. General characteristics of the study population *(*n=327)

Characteristics	**Total (n=327)** *n* (%)	**Overweight at diagnosis (n=27)** *n* (%)	**Overweight at the end of treatment (n=43)** *n* (%)
Sociodemographic characteristics			
Gender			
Girl	146 (45)	15 (56)	17 (40)
Boy	181 (55)	12 (44)	26 (60)
Age at diagnosis, median years (IQR)	6.8 (2.9, 12.0)	9.2 (1.5, 13.0)	7.0 (3.9, 13.7)
<5	132 (40)	11 (41)	18 (42)
5-9	86 (26)	5 (19)	9 (21)
10-14	71 (22)	6 (22)	8 (19)
≥15	38 (12)	5 (19)	8 (19)
Migration			
No migration background	239 (73)	19 (70)	31 (72)
Migration background	88 (27)	8 (30)	12 (28)
Clinical characteristics			
ICCC-3 diagnosis			
Ia: ALL	95 (29)	7 (26)	17 (40)
II: Lymphoma	53 (16)	2 (7)	7 (16)
III: CNS tumour	42 (13)	5 (19)	6 (14)
VIII-IX: Sarcoma	59 (18)	4 (15)	7 (16)
Other	78 (24)	9 (33)	6 (14)
Treatment centre			
Centre 1	152 (46)	19 (70)	22 (51)
Centre 2	113 (35)	6 (22)	14 (33)
Centre 3	62 (19)	2 (7)	7 (16)
Time from dx until end of treatment, median years (IQR)	0.7 (0.4, 1.8)	-	-
Cranial radiation therapy			
No	284 (87)	20 (74)	38 (88)
<20 Gy	16 (5)	4 (15)	3 (7)
≥20 Gy	27 (8)	3 (11)	2 (5)
Chemotherapy			
No	3 (1)	2 (7)	2 (5)
Yes	324 (99)	25 (93)	41 (95)
Parenteral/ enteral nutrition support			
No	229 (70)	21 (78)	32 (74)
Yes	98 (30)	6 (22)	11 (26)
BMI at diagnosis			
Underweight	63 (19)	-	-
Normal	237 (72)	-	24 (56)
Overweight	20 (6)	20 (74)	13 (30)
Obese	7 (2)	7 (26)	6 (14)
BMI at end of treatment			
Underweight	72 (22)	-	-
Normal	212 (65)	8 (30)	-
Overweight	35 (11)	13 (48)	35 (81)
Obese	8 (2)	6 (22)	8 (19)
Birthweight, gram			
Low: <2500	18 (6)	-	2 (5)
Normal: 2500-4000	239 (73)	18 (67)	31 (72)
High: >4000	29 (9)	2 (7)	3 (7)
Missing	*41 (13)*	*7 (26)*	*7 (16)*

ALL, acute lymphoblastic leukaemia; BMI, body mass index; CNS, central nervous system; Gy, gray; ICCC-3, International Classification of Childhood Cancer, 3rd edition; IQR, interquartile range

Table II. BMI Z-scores at diagnosis and at the end of treatment

	BMI Z-score mean (SD)		
	Diagnosis (n=327)	**End of treatment (n=327)**	**Difference between diagnosis and end of treatment**
All CCS	-0.10 (1.1)	-0.08 (1.3)	0.02 (1.1)
Gender			
Girl	-0.13 (1.2)	-0.30 (1.3)	-0.17 (1.1)
Boy	-0.08 (1.1)	0.10 (1.3)	0.18 (1.0)
Age at diagnosis			
<5	-0.19 (1.2)	0.02 (1.3)	0.21 (1.2)
5-9	-0.18 (1.0)	-0.19 (1.4)	-0.01 (1.1)
10-14	-0.05 (1.0)	-0.18 (1.2)	-0.14 (0.9)
≥15	0.26 (1.1)	0.03 (1.4)	-0.23 (0.9)
ICCC-3 diagnosis			
Ia: ALL	-0.14 (1.2)	0.28 (1.1)	0.42 (1.0)
II: Lymphoma	-0.07 (1.0)	0.22 (1.1)	0.29 (0.9)
III: CNS tumour	-0.25 (1.4)	-0.60 (1.6)	-0.35 (1.3)
VIII-IX: Sarcoma	-0.08 (0.9)	-0.32 (1.2)	-0.24 (0.8)
Other	-0.02 (1.1)	-0.26 (1.3)	-0.24 (1.2)
Cranial radiation therapy			
No	-0.14 (1.1)	-0.04 (1.3)	0.10 (1.1)
<20 Gy	0.41 (1.6)	0.55 (1.4)	0.14 (0.9)
≥20 Gy	-0.05 (1.1)	-0.84 (1.3)	-0.79 (1.0)
Parenteral/ enteral nutrition support			
No	-0.04 (1.1)	0.06 (1.2)	0.11 (1.0)
Yes	-0.24 (1.1)	-0.41 (1.4)	-0.17 (1.3)
BMI at diagnosis			
Underweight	-1.64 (0.6)	-0.98 (1.1)	0.66 (1.0)
Normal	0.07 (0.6)	-0.04 (1.1)	-0.11 (1.1)
Overweight	1.98 (0.7)	1.70 (1.3)	-0.29 (0.9)

ALL, acute lymphoblastic leukaemia; BMI, body mass index; CCS, childhood cancer survivors; CNS, central nervous system; Dx, diagnosis; Gy, gray; ICCC-3, International Classification of Childhood Cancer, 3rd edition; OW, overweight; SD, standard deviation

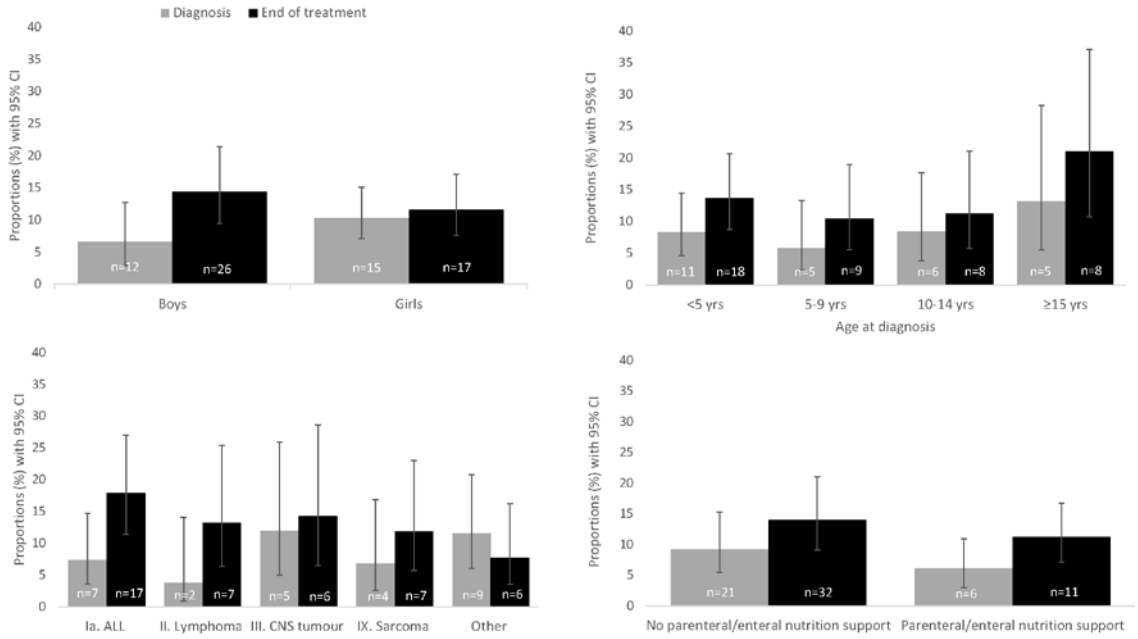

Figure 1. Prevalence of overweight at diagnosis and end of treatment for childhood cancer patients by gender, age at diagnosis, type of cancer, and nutritional support
CI, confidence interval; ALL, acute lymphoblastic leukaemia; CNS, central nervous system

Table III. Risk factors for change in BMI per Z-score from diagnosis until end of treatment (retrieved from univariable and multivariable linear regression models)

	β (95% CI) for change in BMI per Z-score from diagnosis until end of treatment			
	Univariable		**Multivariable**[a]	
	β (95% CI)	p-value[b]	β (95% CI)	p-value[b]
Gender				
Girl	Ref		Ref	
Boy	0.35 (0.12–0.59)	***0.003***	0.30 (0.09–0.51)	***0.005***
Age at diagnosis, years	-0.03 (-0.05 to 0.01)	***0.007***	-0.03 (-0.05 to 0.01)	***0.010***
ICCC-3 diagnosis				
Other	Ref		Ref	
Ia: ALL	0.66 (0.35–0.98)		0.54 (0.24–0.84)	
II: Lymphoma	0.53 (0.17–0.90)		0.57 (0.20–0.95)	
III: CNS tumour	-0.11 (-0.50 to 0.28)		0.10 (-0.30 to 0.50)	
VIII-IX: Sarcoma	0.01 (-0.35 to 0.36)	***<0.001***	0.11 (-0.24 to 0.46)	***<0.001***
Cranial radiotherapy				
No	Ref		Ref	
<20 Gy	0.05 (-0.49 to 0.58)		0.30 (-0.20 to 0.80)	
≥20 Gy	-0.88 (-1.30 to 0.46)	***<0.001***	-0.58 (-1.02 to 0.14)	***0.015***
Parenteral/ enteral nutrition support				
No	Ref		Ref	
Yes	-0.28 (-0.53 to 0.02)	***0.035***	-0.29 (-0.53 to 0.06)	***0.016***
Birthweight				
Low: <2500	0.03 (-0.50 to 0.55)		-	-
Normal: 2500-4000	Ref			
High: >4000	0.06 (-0.36 to 0.49)	***0.992***		
BMI at diagnosis (BMI Z-scores)	-0.29 (-0.40 to 0.19)	***<0.001***	-0.29 (-0.39 to 0.20)	***<0.001***

ALL, acute lymphoblastic leukaemia; BMI, body mass index; CI, confidence interval; CNS, central nervous system; Gy, gray; ICCC3, International Classification of Childhood Cancer, 3rd edition; OR, odds ratio

[a]: Adjusted for gender, age at diagnosis, ICCC-3, CRT, parenteral/enteral nutrition support, and weight at diagnosis

[b]: p-value calculated from F-test

Weight change during treatment by type of cancer

Using multilevel segmented linear regressions, we found that BMI Z-scores tended to increase throughout treatment in ALL patients ($\beta_{0\text{-}0.6\ yrs}$: 0.4; 95%CI: 0.1, 0.7; $\beta_{\geq 0.6\ yrs}$: 0.3; 0.2, 0.5) (**Table IV**), especially during early treatment from diagnosis until end of the induction phase ($\beta_{0\text{-}0.1\ yrs}$: 2.3; 95%CI: -0.2, 4.8) (**Figure 2, Supplementary Table S2**). BMI Z-score also tended to increase throughout the whole treatment period in lymphoma patients ($\beta_{0\text{-}0.2\ yrs}$: 1.5; 0.2, 2.9; $\beta_{\geq 0.2\ yrs}$: 0.6; 0.2, 1.1). In patients with CNS tumours, sarcoma, and other types of cancer BMI Z-scores tended to drop during the first half of the treatment period (β_{CNS}: -1.4; -2.7, 0.2; $\beta_{sarcoma}$: -1.4; -2.0, 0.7; β_{other}: -0.3; -1.5, 0.9), but tended to increase thereafter ($coef_{CNS}$: 0.2; -0.5, 0.9; $coef_{sarcoma}$: 1.2; 0.7, 1.7, $coef_{other}$: 0.6; 0.1, 1.1) (Table IV).

In post hoc analyses of ALL patients, BMI Z-scores of ALL patients who were <7 years at diagnosis tended to increase during treatment ($\beta_{0\text{-}33\ days}$: 3.8; 0.5, 7.0; $\beta_{34\text{-}99\ days}$: -0.4; -1.9, 1.0; $\beta_{\geq 100\ days}$: 0.2; 0.1, 0.3) (Supplementary Table S2, **Supplementary Figure S1A**). BMI Z-scores of older ALL patients tended to drop during the induction phase of their cancer treatment protocol ($\beta_{0\text{-}33\ days}$: -1.5; -5.1, 2.2), and increase thereafter ($\beta_{34\text{-}99\ days}$: 0.5; -1.3, 2.2; $\beta_{\geq 100\ days}$: 0.3; 0.2, 0.4) (Supplementary Table S2, **Supplementary Figure S1B**).

Table IV. Slopes of change in BMI Z-score from multilevel segmented linear regression models[a] for childhood cancer patients by cancer type

ICCC-3 diagnosis	slope 1 β (95%CI)	slope 2 β (95%CI)	Break point, years[b]
ALL	0.38 (0.08–0.69)	0.32 (0.19–0.45)	0.61
Lymphoma	1.53 (0.18–2.87)	0.62 (0.17–1.07)	0.22
CNS	-1.44 (-2.73 to 0.16)	0.22 (-0.46 to 0.89)	0.37
Sarcoma	-1.39 (-2.04 to 0.74)	1.18 (0.72–1.65)	0.34
Other	-0.28 (-1.50 to 0.89)	0.61 (0.09–1.14)	0.27

ALL, acute lymphoblastic leukaemia; BMI, body mass index; CI, confidence interval; CNS, central nervous system; ICCC-3, International Classification of Childhood Cancer, 3rd ed.

[a] Adjusted for gender, age, cumulative cranial radiation therapy, parenteral/enteral nutrition support, and BMI at diagnosis with a random effect on patient level.

[b] Breakpoint defined at the median treatment duration within each diagnostic group

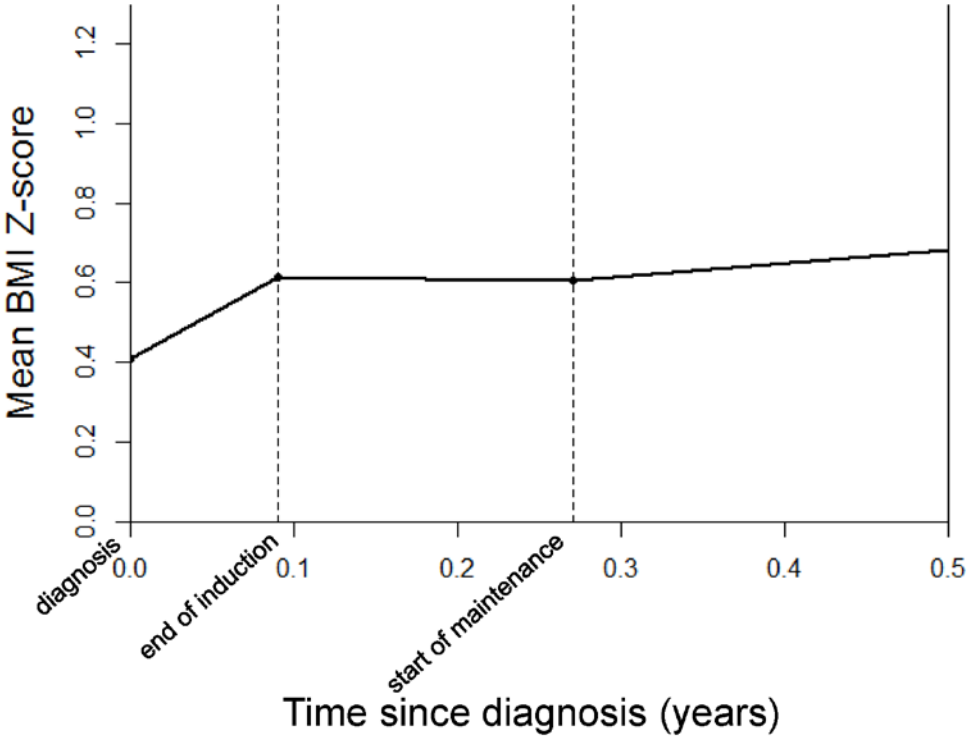

Figure 2. Slope of change in BMI Z-score from a multilevel segmented linear regression model[a] for childhood acute lymphoblastic leukaemia patients (n=95)

[a] Adjusted for gender, age at diagnosis, cranial radiation therapy, parenteral/enteral nutrition support, and BMI at diagnosis with a random effect on patient level. Breakpoints defined at the end of the induction period (33 days, 0.09 years) and the start of the maintenance period (99 days, 0.27 years).

DISCUSSION

The prevalence of overweight at diagnosis of Swiss CCP increased from 8% at diagnosis to 13% at the end of treatment. Being a boy and being diagnosed with ALL or lymphoma were risk factors for weight gain during treatment. Patients with ALL and lymphoma showed a continuously increasing trend in BMI Z-scores over the treatment period. The increase was particularly steep during early treatment in ALL patients, from diagnosis until end of induction. However, in older ALL patients (≥7 years at diagnosis) BMI initially tended to drop and increase later.

Prevalence of overweight and BMI Z-scores in comparison with other studies

Direct comparison with other studies is limited due to the lack of studies including all types of cancers and different overweight definitions that were used. A Dutch prospective study in 133 CCP with a median age of 8 years, found that 5% of the children were overweight at diagnosis, and 10% one year later [12]. They used higher cut-offs to define overweight than we did, which might explain the lower prevalence. We found similar overweight prevalence in the general Swiss population; 12% in the general population versus 8% in CCP at diagnosis to 13% at the end of treatment [24]. In a study in the US, 55% of 183 patients were overweight at diagnosis and 69% at the end of treatment [6] while in another US-based study 21% of 83 ALL patients were overweight and this rose to almost 40% at the end of treatment [8]. The BMI Z-scores of these respective ALL patients increased between diagnosis and end of treatment from 0.2 to 0.8 and 0.6 to 1.1 respectively [6, 8]. These studies are in accord with the higher prevalence of overweight seen in the general US population, with around 33% of the children being overweight [25]. We observed a lower prevalence of overweight, 7%, at diagnosis, and 18% at the end of treatment. In our study mean BMI Z-score in ALL patients increased from -0.1 to 0.3 during the observation period, with an accentuated weight increase during early treatment potentially due to the high doses of glucocorticoids given during this treatment period in all patients with ALL. Glucocorticoids may also effect linear growth suppression which could be associated with a BMI increase [26, 27]. The overall increase in BMI we observed in ALL patients is in line with previous literature [6-8, 13, 28, 29].

Patients with CNS tumours, especially those diagnosed with craniopharyngioma, astrocytoma, or ependymoma have been reported to be at increased risk of overweight after treatment [2, 4]. We could not confirm this. We found that the BMI Z-score of CNS patients dropped during the first four months of treatment, but tended to increase afterwards. These results are in contrast to 36 CNS patients in the Dutch study mentioned above in whom a rapid increase in BMI Z-scores was observed after diagnosis [12]. The differences in these results might be due to the higher proportion of medulloblastoma patients in our study who are often undernourished [17], whereas the opposite is seen for patients diagnosed with astrocytoma and craniopharyngioma.

Risk factors for weight gain during treatment in relation to other studies

Mixed results are reported in literature. Female gender [4, 7, 10, 14], and male gender have been associated with becoming overweight during treatment [9, 30, 31], while no gender association has also been observed [13]. We found that boys were more likely to gain weight than girls, which is in line with the gender differences found in the general Swiss child population [32]. Furthermore, we found that ALL patients who were older at diagnosis (≥7 years) tended to show a decline in BMI during the induction treatment phase, after which BMI

tended to increase. This initial drop may reflect the physiological and psychosocial burden of a cancer diagnosis among children who are old enough to fully understand its consequences and hazards. We observed the same tendency for all cancer diagnosis groups combined. Weight at diagnosis was associated with overweight at the end of treatment in other studies [8, 9, 33]. This has not been seen, however, in meta-analysis: weight gain during treatment was independent of weight at diagnosis, but patients who were underweight at diagnosis showed a greater BMI increase than normal and overweight patients [13]. We saw an inverse association between BMI at diagnosis and change of BMI during treatment with an overall increase in BMI Z-scores in underweight patients and a decrease in overweight patients; however, the majority of overweight patients at diagnosis stayed overweight at end of treatment (70%).

Limitations and strengths of the study

Our study is limited by its retrospective study design. Weight and height measurements were based on routine, clinically indicated measurements, documented in charts, and were not taken at specific times during patients' treatments. Second, BMI Z-scores do not measure the ratio of lean to fat mass or the fat distribution. Although BMI Z-scores are an easy, low cost, and appropriate method to assess overweight, they correlate less with body fat than other methods such as skinfold measurements, underwater weighing, dual energy X-ray, or magnetic resonance imaging [34], and are not recommended as a sole overweight indicator in childhood cancer patients [35]. Third, we did not collect data on lifestyle and social factors like diet, physical activity, and parenting style that could potentially affect weight gain during treatment. Finally, the multilevel segmented linear regression models were a poor fit to the highly variable BMI Z-score curves of individual patients. More complex analyses are required to take this heterogeneity into account among patients.

Despite these limitations, our study is among the few to have captured weight at diagnosis and end of treatment in childhood cancer patients of all diagnoses. We chose the IOTF cut-off values [20], which are stricter than national cut-offs [6-8], to define overweight for international comparability. Finally, we had access to detailed clinical information of patients from the SCCR.

Implications for future recommendations

Overweight plays a significant role in childhood cancer treatment [3, 4, 33] and has been reported to affect treatment-related toxicity, relapse rates, and (event-free) survival rates [3, 4, 36]. Weight gain during treatment tends to persist in ALL patients beyond treatment completion [13]. Early weight management should therefore be emphasized. Furthermore, in overweight CCP lower emotional, cognitive, and social functioning has been reported compared to

children with a normal weight [5]. This can reveal new target areas for overweight interventions because awareness of influential factors can help to proactively introduce and specifically review current methods. Since early overweight is a risk factor for overweight later in life, weight management interventions should be individually tailored and provided especially to patients who have a high risk of developing overweight during treatment. Overweight later in life is associated with development of chronic cardiac disorders and type II diabetes [37]. As CCP already have an increased risk of developing these disorders, early overweight management could prevent long-term consequences [1]. Purposeful prevention and treatment measures should be developed and implemented with regard to encouraging a balanced diet and sufficient physical exercise. Focus should lie on the prevention of overweight and underweight as 19% of the patients were underweight at diagnosis and 22% at end of treatment. Both overweight and underweight CCP have a reduced health-related quality of life compared to normal weight CCP [5]. Therefore, future research needs to focus on testing interventions that aim to improve the nutritional status of children with cancer and behavioural interventions should be well grounded in theory and empirical evidence as they are complex.

CONCLUSION

This multicentre cohort study found that overall prevalence of overweight markedly increased in CCP within an average treatment duration of less than one year. Lifestyle interventions to prevent overweight development should start early during treatment, particularly for patients diagnosed with ALL or lymphoma.

ACKNOWLEDGEMENTS

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AUTHORS CONTRIBUTIONS

FB conducted the statistical analyses and wrote the final article, JWZ performed initial statistical analyses and wrote the first draft of the article, KZ designed the study and collected the complementary registry data, and BS, KZ, and CK gave support in the statistical analyses. All authors have participated in the data interpretation, and have revised and approved the final article.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures

REFERENCES

[1] Hudson MM, Ness KK, Gurney JG, Mulrooney DA, Chemaitilly W, Krull KR, et al. Clinical Ascertainment of Health Outcomes among Adults Treated for Childhood Cancer: A Report from the St. Jude Lifetime Cohort Study. JAMA : the journal of the American Medical Association. 2013;309:2371-81.
[2] Siviero-Miachon AA, Spinola-Castro AM, Guerra-Junior G. Adiposity in childhood cancer survivors: insights into obesity physiopathology. Arquivos Brasileiros de Endocrinologia & Metabologia. 2009;53:190-200.
[3] Reilly JJ. Obesity during and after treatment for childhood cancer. Endocrinopathy After Childhood Cancer Treatment: Karger Publishers; 2009. p. 40-58.
[4] Co-Reyes E, Li R, Huh W, Chandra J. Malnutrition and Obesity in Pediatric Oncology Patients: Causes, Consequences, and Interventions. Pediatric blood & cancer. 2012;59:1160-7.
[5] Brinksma A, Sanderman R, Roodbol PF, Sulkers E, Burgerhof JGM, de Bont ESJM, et al. Malnutrition is associated with worse health-related quality of life in children with cancer. Supportive Care in Cancer. 2015;23:3043-52.
[6] Esbenshade AJ, Simmons JH, Koyama T, Koehler E, Whitlock JA, Friedman DL. Body Mass Index and Blood Pressure Changes over the Course of Treatment of Pediatric Acute Lymphoblastic Leukemia. Pediatric blood & cancer. 2011;56:372-8.
[7] Iughetti L, Bruzzi P, Predieri B, Paolucci P. Obesity in patients with acute lymphoblastic leukemia in childhood. Italian Journal of Pediatrics. 2012;38:4-.
[8] Zhang FF, Rodday AM, Kelly MJ, Must A, MacPherson C, Roberts SB, et al. Predictors of Being Overweight or Obese in Survivors of Pediatric Acute Lymphoblastic Leukemia (ALL). Pediatric blood & cancer. 2014;61:1263-9.
[9] Love E, Schneiderman JE, Stephens D, Lee S, Barron M, Tsangaris E, et al. A cross-sectional study of overweight in pediatric survivors of acute lymphoblastic leukemia (ALL). Pediatric Blood & Cancer. 2011;57:1204-9.
[10] Iughetti L, Bruzzi P. Obesity and craniopharyngioma. Italian Journal of Pediatrics. 2011;37:38-.
[11] Bereket A, Kiess W, Lustig RH, Muller HL, Goldstone AP, Weiss R, et al. Hypothalamic obesity in children. Obesity Reviews. 2012;13:780-98.
[12] Brinksma A, Roodbol PF, Sulkers E, Kamps WA, de Bont ESJM, Boot AM, et al. Changes in nutritional status in childhood cancer patients: A prospective cohort study. Clinical Nutrition. 2015;34:66-73.
[13] Zhang FF, Liu S, Chung M, Kelly MJ. Growth patterns during and after treatment in patients with pediatric ALL: A meta-analysis. Pediatric Blood & Cancer. 2015;62:1452-60.
[14] Brouwer CAJ, Gietema JA, Kamps WA, de Vries EGE, Postma A. Changes in body composition after childhood cancer treatment: Impact on future health status - A review. Critical Reviews in Oncology / Hematology. 2007;63:32-46.
[15] Michel G, von der Weid NX, Zwahlen M, Adam M, Rebholz C, Kühni C. The Swiss Childhood Cancer Registry: rationale, organisation and results for the years 2001-2005. Swiss medical weekly. 2007;137:502-9.
[16] Michel G, von der Weid NX, Zwahlen M, Redmond S, Strippoli MPF, Kuehni CE. Incidence of childhood cancer in Switzerland: The Swiss childhood cancer registry. Pediatric Blood & Cancer. 2008;50:46-51.
[17] Zimmermann K, Ammann RA, Kuehni CE, De Geest S, Cignacco E. Malnutrition in pediatric patients with cancer at diagnosis and throughout therapy: A multicenter cohort study. Pediatric Blood & Cancer. 2013;60:642-9.
[18] Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. BMJ : British Medical Journal. 2000;320:1240-.
[19] World Health Organization. WHO child growth standards: methods and development: length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age. Geneva: World Health Organization. 2006.
[20] Cole TJ, Lobstein T. Extended international (IOTF) body mass index cut-offs for thinness, overweight and obesity. Pediatric Obesity. 2012;7:284-94.
[21] Belle FN, Weiss A, Schindler M, Goutaki M, Bochud M, Zimmermann K, et al. Overweight in childhood cancer survivors: the Swiss Childhood Cancer Survivor Study. American Journal of Clinical Nutrition. 2018;107:3-11.
[22] International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10). Chapter XVI, Certain conditions originating in the perinatal period (P00-P96), Disorders related to length of gestation and fetal growth (P05-P08) 2010.

[23] Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P. International Classification of Childhood Cancer, third edition. Cancer. 2005;103:1457-67.
[24] Stamm H, Gebert A, Guggenbühl L, Lamprecht M. Excess weight among children and adolescents in Switzerland-prevalence and correlates for the early 2010s. Swiss Med Wkly. 2014;144:w13956.
[25] Skinner AC, Perrin EM, Skelton JA. Prevalence of obesity and severe obesity in US children, 1999-2014. Obesity. 2016;24:1116-23.
[26] Ahmed SF, Tucker P, Mushtaq T, Wallace AM, Williams DM, Hughes IA. Short-term effects on linear growth and bone turnover in children randomized to receive prednisolone or dexamethasone. Clinical Endocrinology. 2002;57:185-91.
[27] Touyz LM, Cohen J, Neville KA, Wakefield CE, Garnett SP, Mallitt K-A, et al. Changes in body mass index in long-term survivors of childhood acute lymphoblastic leukemia treated without cranial radiation and with reduced glucocorticoid therapy. Pediatric Blood & Cancer. 2016:n/a-n/a.
[28] Esbenshade AJ, Simmons JH, Koyama T, Lindell RB, Friedman DL. Obesity and insulin resistance in pediatric acute lymphoblastic leukemia worsens during maintenance therapy. Pediatric blood & cancer. 2013;60:10.1002/pbc.24489.
[29] Ness KK, Armenian SH, Kadan-Lottick N, Gurney JG. Adverse effects of treatment in childhood acute lymphoblastic leukemia: general overview and implications for long-term cardiac health. Expert review of hematology. 2011;4:185-97.
[30] Razzouk BI, Rose SR, Hongeng S, Wallace D, Smeltzer MP, Zacher M, et al. Obesity in Survivors of Childhood Acute Lymphoblastic Leukemia and Lymphoma. Journal of Clinical Oncology. 2007;25:1183-9.
[31] Nathan PC, Jovcevska V, Ness KK, Mammone D'Agostino N, Staneland P, Urbach SL, et al. The prevalence of overweight and obesity in pediatric survivors of cancer. The Journal of Pediatrics. 2006;149:518-25.e2.
[32] Murer SB, Saarsalu S, Zimmermann MB, Aeberli I. Pediatric adiposity stabilized in Switzerland between 1999 and 2012. European Journal of Nutrition. 2014;53:865-75.
[33] Withycombe JS, Smith LM, Meza JL, Merkle C, Faulkner MS, Ritter L, et al. Weight Change during Childhood Acute Lymphoblastic Leukemia Induction Therapy Predicts Obesity: A Report from the Children's Oncology Group. Pediatric blood & cancer. 2015;62:434-9.
[34] Cole TJ, Rolland-Cachera MF. Measurement and definition. Child and adolescent obesity: Causes, consequences, prevention, and management. 2002:3-27.
[35] Nething J, Ringwald-Smith K, Williams R, Hancock ML, Hale GA. Establishing the Use of Body Mass Index as an Indicator of Nutrition Risk in Children With Cancer. Journal of Parenteral and Enteral Nutrition. 2007;31:53-7.
[36] Orgel E, Sposto R, Malvar J, Seibel NL, Ladas E, Gaynon PS, et al. Impact on Survival and Toxicity by Duration of Weight Extremes During Treatment for Pediatric Acute Lymphoblastic Leukemia: A Report From the Children's Oncology Group. Journal of Clinical Oncology. 2014;32:1331-7.
[37] National Institutes of Health. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: The Evidence Report. Obesity Research. 1998;6:51S-209S.

SUPPLEMENTARY MATERIAL

Table S1. Cut-off values[a] by gender for BMI, Z-scores, and percentiles for thinness, normal weight, overweight, obesity, and morbid obesity [20]

	BMI at age 18 (kg/m^2)		**BMI Z-score**		**Percentile**	
	Girls	Boys	Girls	Boys	Girls	Boys
Thinness (grade I-III)	<18.5	<18.5	<-0.975	<-1.014	<16.5	<15.5
Normal	18.5	18.5	-0.975	-1.014	16.5	15.5
Overweight	25	25	1.244	1.310	89.3	90.5
Obesity	30	30	2.192	2.288	98.6	98.9
Morbid obesity	35	35	2.822	2.930	99.76	99.83

[a] upper cut-off value for thinness and lower cut-off values for normal, overweight, obesity, and morbid obesity

Table S2. Slopes of change in BMI Z-score from multilevel segmented linear regression models[a] for childhood acute lymphoblastic leukaemia patients by age at diagnosis

ICCC-3 diagnosis	slope 1 β (95%CI)	slope 2 β (95%CI)	slope 3 β (95%CI)	Break points, days[b]
ALL	2.28 (-0.22; 4.78)	-0.02 (-1.14; 1.09)	0.33 (0.22; 0.45)	33 (=induction) 99 (=maintenance)
<7 years	3.75 (0.48; 7.03)	-0.41 (-1.86; 1.04)	0.20 (0.13; 0.27)	33 (=induction) 99 (=maintenance)
≥7 years	-1.47 (-5.14; 2.21)	0.48 (-1.29; 2.24)	0.28 (0.17; 0.39)	33 (=induction) 99 (=maintenance)

ALL, acute lymphoblastic leukaemia; BMI, body mass index; CI, confidence interval

[a] Adjusted for gender, age, cumulative cranial radiation therapy, parenteral/ enteral nutrition, and BMI at diagnosis with a random effect on patient level.

[b] Breakpoints defined at end of induction (33 days, 0.09 years) and start of maintenance period (99 days, 0.27 years).

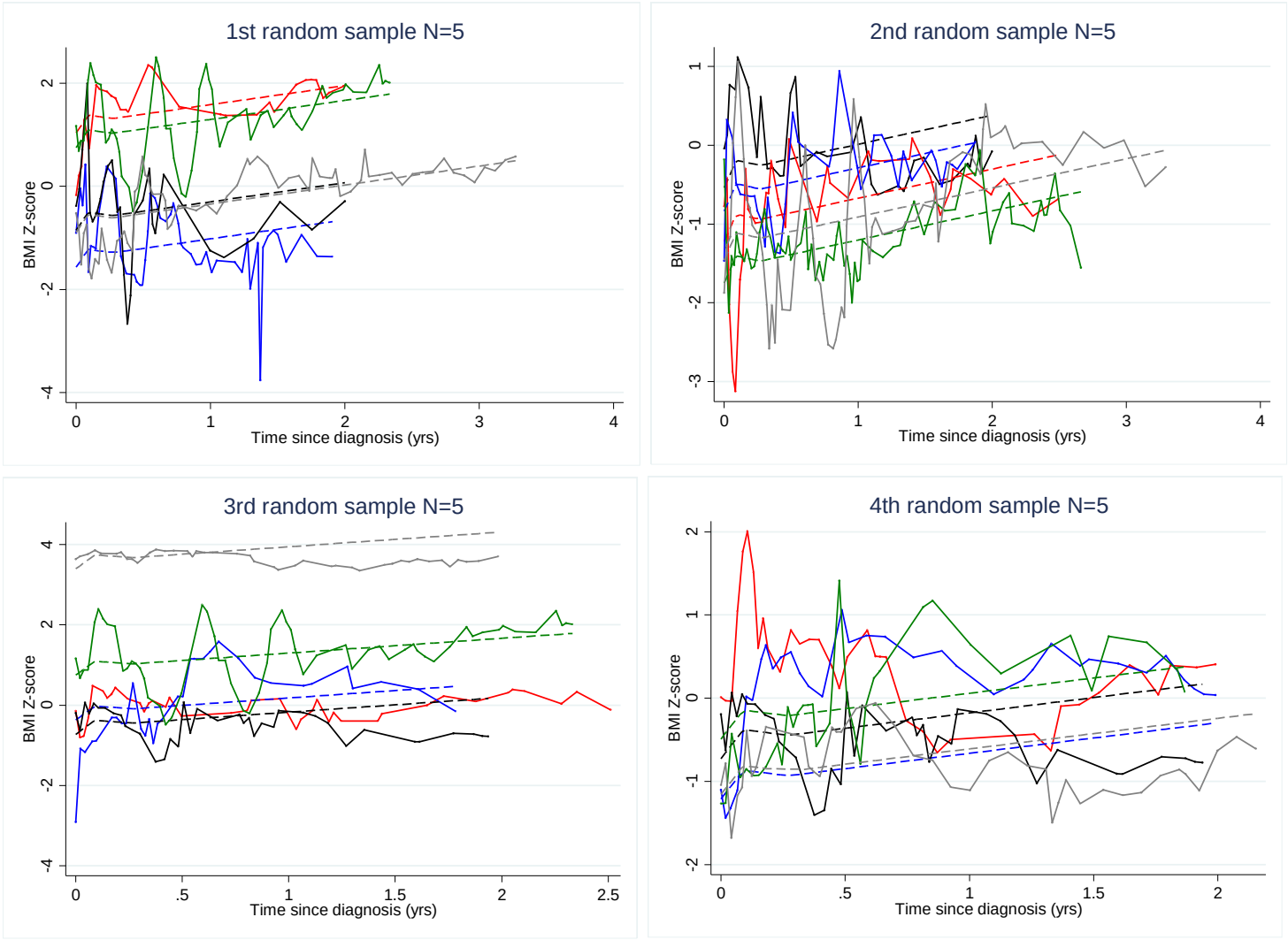

Figure S1A. Observed individual BMI Z-score curves of random samples (N=5) of ALL patients age <7 years (N=5) at diagnosis and estimated trend from multilevel segmented linear regression models with fixed breakpoints[a]

BMI Z-score per patient since diagnosis over time shown in *solid line* and fitted multilevel segmented linear regression based on predicted random effects on patient level shown in *dashed line.*

[a] Adjusted for gender and age at diagnosis with a random effect on patient level. Breakpoints were defined at end of induction (33 days, 0.09 years) and start of maintenance period (99 days, 0.27 years).

Figure S1B. Observed individual BMI Z-score curves of random samples (N=5) of ALL patients age ≥7 years (N=5) at diagnosis and estimated trend from multilevel segmented linear regression models with fixed breakpoints[a]

BMI Z-score per patient since diagnosis over time shown in *solid line* and fitted multilevel segmented linear regression based on predicted random effects on patient level shown in *dashed line.*

[a] Adjusted for gender and age at diagnosis with a random effect on patient level. Breakpoints were defined at end of induction (33 days, 0.09 years) and start of maintenance period (99 days, 0.27 years).

Chapter 6

Overweight in childhood cancer survivors: the Swiss Childhood Cancer Survivor Study

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SUMMARY

Background: An increased risk of becoming overweight has been reported for childhood cancer survivors (CCSs), in particular leukemia survivors, although the evidence is inconclusive.

Objective: We assessed the prevalence of overweight in CCSs, with a focus on leukemia survivors, compared it with their peers, and determined potential risk factors.

Design: As part of the Swiss Childhood Cancer Survivor Study, we sent a questionnaire between 2007 and 2013 to all Swiss resident CCSs aged <21 y at diagnosis who had survived ≥5 y. We calculated body mass index (BMI) from medical records at diagnosis and self-reported heights and weights at survey. We calculated BMI *z* scores by using Swiss references for children and compared overweight prevalence in CCSs, their siblings, and the general population with the use of the Swiss Health Survey (SHS) and assessed risk factors for being overweight by using multivariable logistic regression.

Results: The study included 2365 CCSs, 819 siblings, and 9591 SHS participants. At survey, at an average of 15 y after diagnosis, the prevalence of overweight in CCSs overall (26%) and in leukemia survivors (26%) was similar to that in siblings (22%) and the general population (25%). Risk factors for being overweight in CCSs were male sex (OR: 1.8; 95% CI: 1.5, 2.1), both young (OR for ages 5–14 y: 1.6; 95% CI: 1.2, 2.3) and older (range—OR for ages 25–29 y: 1.7; 95% CI: 1.2, 2.4; OR for ages 40–45 y: 4.0; 95% CI: 2.5, 6.5) age at study, lower education (OR: 1.4; 95% CI: 1.1, 1.8), migration background (OR: 1.3; 95% CI: 1.1, 1.7), and no sports participation (OR: 1.4; 95% CI: 1.1, 1.7). Risk factors for overweight were similar in peers. CCSs treated with cranial radiotherapy (≥20 Gy) were more likely to be overweight than their peers (OR: 1.6; 95% CI: 1.2, 2.2).

Conclusions: The prevalence of and risk factors for being overweight are similar in long-term CCSs and their peers. This suggests that prevention methods can be the same as in the general population. An important exception is CCSs treated with cranial radiotherapy ≥20 Gy who may need extra attention during follow-up care. This study was registered at clinicaltrials.gov as NCT03297034.

INTRODUCTION

Overweight and obesity are well-known risk factors for chronic diseases, such as diabetes, dyslipidemia, hypertension, and cardiovascular disease [1]. Fortunately, these risk factors are modifiable: primary- and secondary-prevention methods can reduce morbidity and mortality. Childhood cancer survivors (CCSs) already have an elevated burden of chronic diseases due to cancer treatment, which increases with age [2, 3]. It is thus important to avoid additional, preventable risk factors such as obesity by identifying CCSs at high risk and offering them targeted interventions.

Whether CCSs are more overweight in the long term after treatment is not clear. Two meta-analyses suggested that obesity was more common in childhood acute lymphoblastic leukemia (ALL) survivors within 5 y of treatment (BMI *z* score: 0.89), but obesity diminished 5–9 y post-treatment (BMI *z* score: 0.64) compared with their healthy peers [4, 5]. Results are inconclusive for those ≥10 y post-treatment, although overweight prevalence (34–46%) in these long-term ALL survivors seemed to be similar to that in noncancer comparison groups [4]. Risk factors for overweight in the general population are sedentary lifestyle, low (≤2.5 kg) and high (>4 kg) birth weights [6, 7], and overweight during early childhood [8]. In CCSs, most risk factors were the same as in the general population, but no study has considered birth weight. ALL and lymphoma survivors who were overweight at diagnosis were substantially more likely to be overweight or obese 12 y after treatment [9]. The same was true for cranial radiation therapy (CRT); ALL survivors treated with CRT were more likely to be overweight or obese than their siblings 21–25 y after diagnosis [10, 11].

Studies of overweight conducted to date have been of somewhat limited relevance to CCSs. Research on overweight prevalence has involved mostly ALL survivors [9–19], whereas study of risk factors has led to inconsistent conclusions [4]. Studies conducted in the United States reflect the lifestyles and eating habits of CSSs in that country [10–13, 16, 17, 19–22], whereas the duration of follow-up in other studies has been only short to medium term [4, 5], and many have had small (<250 participants) sample sizes [4, 11, 13–15, 17–19]. With this background of research in mind, we analyzed data from the Swiss Childhood Cancer Survivor Study (SCCSS) to *1*) assess overweight prevalence in CCSs overall and for specific, different diagnoses; *2*) compare overweight prevalence in CCSs with that in their siblings and the Swiss general population; and *3*) identify sociodemographic and clinical risk factors for excessive weight.

METHODS

Study populations

The SCCSS

The SCCSS is a population-based, long-term follow-up study in all childhood cancer patients registered in the Swiss Childhood Cancer Registry (SCCR; available from: www.childhoodcancerregistry.ch) who have been diagnosed with leukemia, lymphoma, central nervous system (CNS) tumors, malignant solid tumors, or Langerhans cell histiocytosis; who survived ≥5 y after initial diagnosis of cancer; who were under the age of 21 y; and who were alive at the time of the study [23–25]. Ethical approval of the SCCR and the SCCSS was granted by the Ethics Committee of the Canton of Bern (KEK-BE: 166/2014). This study was registered at clinicaltrials.gov as NCT03297034.

As part of the SCCSS, we traced all addresses of CCSs diagnosed between 1976 and 2005 and sent them a questionnaire between 2007 and 2013. Nonresponders received a second copy of the questionnaire 4–6 wk later. If they again did not respond, we contacted them by phone. Our questionnaire included core questions from the US and UK CCS studies [26, 27], with added questions about health behaviors and sociodemographic measures from the Swiss Health Survey (SHS) [28] and the Swiss Census [29]. The main domains covered by the questionnaire were quality of life, somatic health, fertility, current medication and health services use, psychological distress, health behaviors, and socioeconomic status. Detailed information on our study design was published previously [23].

Comparison groups

We used 2 comparison groups for this study: siblings of the CCSs and a random sample of the general Swiss population represented by data from the SHS. The sibling survey was conducted from 2009 to 2012. We asked CCSs for consent to contact siblings and for their contact information. We sent siblings the same questionnaire as CCSs, omitting questions about cancer history. Siblings who did not respond received another copy of the questionnaire 4–6 wk later, but were not contacted by phone [23]. The second comparison group consisted of participants in the 2012 SHS [30]. The SHS is a representative national telephone survey repeated every 5 y. The SHS compiled a randomly selected representative sample of Swiss households with landline telephones and attempted to contact 1 person/household. Sampling was stratified by region and conducted in a stepwise manner. Households were selected first, and then the survey was administered to anyone aged ≥15 y who answered the phone.

Measurements

Body weight and BMI

We obtained information on participants' weight and height. For all CCSs and both comparison groups, we had information on weight and height at time of survey from the self-administered questionnaires. Study participants were instructed to record height without shoes and weight without clothes. For leukemia survivors diagnosed between 1990 and 2005 and treated in a specialized pediatric cancer clinic, we also had information on weight and height at diagnosis and at birth. Weight and height at diagnosis were obtained via a retrospective medical record audit. We obtained 98% of birth weights by using a probabilistic linkage procedure (G-LINK 2.3; Statistics Canada) to link CCSs and anonymous birth statistics with no personal identifiers, which was collected by the Swiss Federal Statistical Office. Information on sex, date of birth, first name, nationality, municipality of residence at birth, and parental birth dates was used for linking. The remaining birth weights (2%) were obtained from medical records. We calculated BMI by dividing weight in kilograms by height in meters squared (kg/m^2). BMI in adults was classified as underweight (<18.5), normal weight (≥18.5 to <25), or overweight (≥25) [1]. As recommended for children aged ≤19 y, we calculated BMI *z* scores by using the latest available Swiss growth curves [31]. BMI *z* scores were classified as underweight (<–2), normal weight (–2 to 1), or overweight (>1 for age >5 y, >2 for age ≤5 y) [32]. Birth weight was classified into 3 categories: low (<2500 g), normal (2500–4000 g), and high (>4000 g) [33].

Risk factors for being overweight at time of survey

For all 3 study populations, we assessed sex, age at survey, educational level, migration background, language region in Switzerland, and participation in sports at time of survey as potential sociodemographic risk factors for being overweight. Participants who were not Swiss citizens at birth, not born in Switzerland, or had ≥1 parent who was not a Swiss citizen were classified as having a migration background. We classified education into 3 categories: primary education (compulsory schooling only; ≤9 y), secondary education (vocational training; 10–13 y), and tertiary education (higher vocational training, college, or university degree). Sports participation was classified as sports if respondents reported engaging in a specific gym or sports activity for ≥1/wk, or no sports with less or no such participation.

For the CCS population, we extracted additional clinical information from the SCCR. This included information on cancer diagnosis and age at diagnosis. Diagnosis was classified according to the *International Classification of Childhood Cancer, 3rd Edition* [34]. Radiotherapy was classified as CRT if the survivor had received direct radiation to the brain, skull, or both. The cumulative dosage of CRT was obtained from medical records and

categorized as either <20 Gy or ≥20 Gy. We also retrieved records on hematopoietic stem cell transplantation, chemotherapy, and relapse during follow-up time.

Statistical analyses

We included all participants in the SCCSS (CCSs and their siblings) and the SHS (general population) who were aged ≤45 y at time of survey and who provided self-reported height and weight (**Supplemental Figure S1**). For better comparison between CCSs and peers, we standardized comparison groups for sex, age at survey, migration background, and language region, as previously described [35–37]. The first step in our analyses was to assess the overall prevalence of overweight in CSSs at survey and stratify diagnostic groups. We divided BMI into 2 categories: overweight (overweight and obesity) and nonoverweight (underweight and normal weight) as separate categories were small and logistic regression outcomes for the categories of overweight and obesity were in the same direction and magnitude as for the category of overweight or obesity combined. We then compared the prevalence of overweight between CCSs and comparison groups by using chi-square tests. Finally, we determined risk factors for being overweight at survey within each group separately by using multivariable logistic regression. We identified potential sociodemographic, lifestyle, and clinical risk factors and included them in uni- and multivariable logistic regressions. To test for statistical significance, we used likelihood ratio tests for unstandardized groups and Wald tests for standardized groups. We investigated whether birth weight and BMI at diagnosis were additional risk factors for overweight at survey in a subgroup of leukemia survivors who had been diagnosed between 1990 and 2005. Interaction terms were used to formally test differences in effects of risk factors between CCSs and comparison groups. We also included both CCSs and comparison groups in multivariable logistic regression models to investigate whether the risk of being overweight was similar between groups stratified for CRT. We used Stata software (version 14; StataCorp) for all statistical analysis.

RESULTS

Response rate and characteristics of the study populations

Among 4116 eligible CCSs, we traced and contacted 3577, of whom 2527 returned a questionnaire. We excluded 119 questionnaires that did not report height and weight, and a further 43 from survivors who were >45 y old. We thus included 2365 CCSs in this study, of whom 770 were leukemia survivors and 461 of whom were diagnosed between 1990 and 2005 (Supplemental Figure S1). We received consent to contact 1530 siblings, of whom 866 returned the questionnaire. Twenty-seven were outside the age range and 20 did not report height and weight; thus, 819 siblings were finally included in the analyses. Of 41,008 households surveyed in the general population (SHS), 21,597 households replied to the

survey. In those responding households, 9591 persons who were ≤45 y old were included in the analysis.

Among CCSs, the most common cancers were leukemia (predominantly ALL; 88%), lymphoma, and CNS and renal tumors (**Table I**). The median age at diagnosis was 7 y (IQR: 3–12 y) for CCSs overall and 5 y (IQR: 3–9 y) for leukemia. The median time from diagnosis to survey was 15 y (IQR: 10–21 y) for CCSs overall and 16 y (IQR: 11–22 y) for leukemia survivors. Most leukemia survivors received chemotherapy. Among the subgroup of leukemia survivors diagnosed between 1990 and 2005, 10% had a high birth weight and 6% were overweight at diagnosis (**Supplemental Table S1**).

Table I. Clinical characteristics of CCSs and childhood leukemia survivors[1]

Characteristics	**CCSs (*n*= 2365)**	**Leukemia (*n*= 770)**
ICCC3 diagnosis, *n* (%)		
I: Leukemia	770 (33)	770 (100)
II: Lymphoma	424 (18)	-
III: CNS neoplasm	341 (14)	-
IV: Neuroblastoma	118 (5)	-
V: Retinoblastoma	72 (3)	-
VI: Renal tumor	144 (6)	-
VII: Hepatic tumor	20 (1)	-
VIII: Malignant bone tumor	96 (4)	-
IX: Soft tissue sarcoma	137 (6)	-
X: Germ cell tumor	106 (4)	-
XI & XII: Other tumor	54 (2)	-
Langerhans cell histiocytosis	83 (4)	-
Age at diagnosis, *n* (%)		
<5 y	1,413 (60)	389 (51)
≥5 y	952 (40)	381 (49)
Year of diagnosis, *n* (%)		
Before 1990	762 (32)	291 (38)
1990-2000	977 (41)	299 (39)
After 2000	626 (26)	180 (23)
Time since diagnosis,[2] y	15.0 (10.0-20.9)	15.6 (10.7-22.0)
Chemotherapy[3], *n* (%)		
No	509 (22)	-
Yes	1,856 (78)	767 (100)
CRT, *n* (%)		
None	1,950 (82)	599 (78)
<20 Gy	157 (7)	95 (12)
≥20 Gy	258 (11)	76 (10)
HSCT, *n* (%)		
No	2,248 (95)	709 (92)
Yes	117 (5)	61 (8)
History of relapse, *n* (%)		
No	2,081 (88)	670 (87)
Yes	284 (12)	100 (13)

[1] CCS, childhood cancer survivor; CNS, central nervous system; CRT, cranial radiation therapy; HSCT, hematopoietic stem cell transplantation; ICCC3, *International Classification of Childhood Cancer, 3rd edition*
[2] Values are medians (IQRs)
[3] *n*=3 missing (<1%)

Sociodemographic characteristics were mostly identical across CCSs and the comparison groups. Fewer CCSs than siblings had parents who completed tertiary education, however,

and the educational level of CCSs was slightly lower than that of their peers (**Table II**). CCSs engaged in fewer sports than their siblings but more than the general population.

Overweight prevalence among CCSs and comparison groups

Overall, the prevalence of overweight among CCSs was 26% (median BMI in those aged >19 y: 27; IQR: 26–30; median BMI *z* score in those aged ≤19 y: 1; IQR: 1–2), which was similar to overweight prevalence in the comparison groups: 22% in siblings (*P* = 0.07; median BMI in those aged >19 y: 27; IQR: 26–29; median BMI *z* score in those aged ≤19 y: 1; IQR: 1–2), 25% in the general population (*P* = 0.64; median BMI in those aged >19 y: 27; IQR: 26–29; median BMI *z* score in those aged ≤19 y: 1; IQR: 1–2). However, CCS diagnostic groups differed: 31% of CNS neoplasm survivors were overweight, whereas only 13% of neuroblastoma and 18% of soft tissue sarcoma survivors were overweight; the prevalence differences were significant (*P* < 0.001, *P* < 0.001, and *P* = 0.04, respectively; **Figure 1**). The prevalence of overweight in leukemia survivors (26%) was similar to the average of all CCSs.

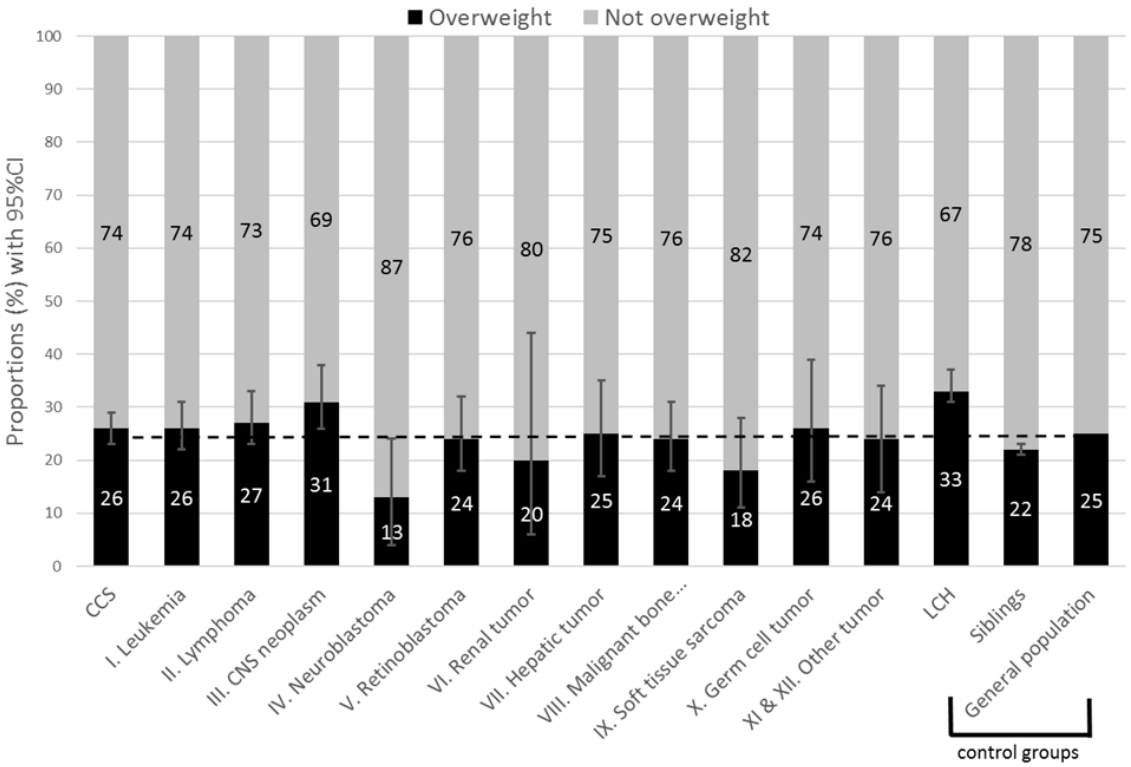

Figure 1. Overweight in childhood cancer survivors and comparison groups.
The BMI distribution of comparison groups is standardized on sex, age at survey, migration background, and language region according to childhood cancer survivors. The dotted line reflects the overweight prevalence of the general population. CCS, childhood cancer survivors; CNS, central nervous system; LCH, Langerhans cell histiocytosis; Malignant bone..., malignant bone tumor.

Table II. General characteristics of CCSs and comparison groups[1]

	CCSs, *n* (%)		Siblings[2] (*n* =819)		General population[2] (*n* =9,591)	
Characteristics	CCSs (*n* =2,365)	Leukemia (*n* =770)	*n* (%std)	*p-value*[3]	*n* (%std)	*p-value*[3]
Sex, *n* (%)						
Female	1,086 (46)	367 (48)	473 (45)		4,946 (46)	
Male	1,279 (54)	403 (52)	346 (55)	***n.a.***	4,645 (54)	***n.a.***
Age at survey, *n* (%)						
5-14 y	329 (14)	121 (16)	94 (18)		-	
15-19 y	541 (23)	184 (24)	142 (20)		1,518 (33)	
20-24 y	530 (22)	167 (22)	162 (19)		1,440 (23)	
25-29 y	401 (17)	136 (18)	168 (19)		1,174 (13)	
30-34 y	277 (12)	87 (11)	115 (12)		1,424 (11)	
35-39 y	185 (8)	47 (6)	84 (8)		1,601 (9)	
40-45 y	102 (4)	28 (4)	54 (5)	***n.a.***	2,434 (10)	***n.a.***
Parents' education (highest degree)[4], *n* (%)						
Primary schooling	62 (7)	26 (9)	8 (3)		n.a.	
Secondary education	469 (54)	165 (54)	115 (47)			
Tertiary education	339 (39)	114 (37)	113 (50)	***0.007***		
Personal education[5], *n* (%)						
Primary schooling	117 (8)	36 (8)	24 (4)		691 (8)	
Secondary education	1,010 (68)	337 (72)	359 (61)		4,549 (62)	
Tertiary education	368 (25)	92 (20)	200 (35)	***<0.001***	2,833 (30)	***<0.001***
Migration, *n* (%)						
No migration background	1,762 (75)	573 (74)	657 (75)		6,137 (77)	
Migration background	603 (26)	197 (26)	162 (25)	***n.a.***	3,454 (23)	***n.a.***
Language region of Switzerland, *n* (%)						
German speaking	1,658 (70)	571 (74)	650 (70)		6,300 (70)	
French speaking	630 (27)	172 (22)	143 (27)		2,620 (27)	
Italian speaking	77 (3)	27 (4)	26 (3)	***n.a.***	671 (3)	***n.a.***
Sports participation, *n* (%)						
Yes	1,623 (69)	544 (71)	593 (75)		5,598 (64)	
No	742 (31)	226 (29)	226 (25)	***0.002***	3,993 (36)	<***0.001***
BMI at survey[6], *n* (%)						
Underweight	127 (5)	43 (6)	20 (2)		349 (3)	
Normal	1,632 (69)	525 (68)	602 (76)		6,354 (72)	
Overweight	606 (26)	202 (26)	197 (22)	<***0.001***	2,888 (25)	<***0.001***

[1] CCS, childhood cancer survivor; n.a., not applicable, std, standardized

[1] Standardized on sex, age at survey, migration background and language region according to CCSs

[2] p-value calculated from Chi-Square statistics comparing comparison group to CCSs (2-sided test)

[3] Highest parental education level of CCSs and siblings <20 y at time of survey

[4] Highest personal education level of CCSs, siblings, and the general population ≥20 y at time of survey

[5] BMI Z-scores were calculated for CCSs, siblings, and the general population ≤19 y, BMI scores (kg/m^2) were calculated for adults (>19 y)

Risk factors for being overweight among CCSs and comparison groups

In a multivariable regression, we found associations between all sociodemographic factors and being overweight. In all 3 study populations, male participants, those who were older at survey, and those who did not take part in sports activities were more likely to be overweight (**Table III**). Also associated with being overweight were lower education (CCSs, leukemia survivors), migration background (CCSs, the general population), and living in the German-speaking part of Switzerland (siblings, the general population). Results of univariable logistic regression are shown in **Supplemental Table S2**.

Table III. Overweight prevalence and risk factors associated with overweight in CCSs or comparison groups (from multivariable logistic regression)[1]

	CCSs				Siblings[2] (*n* =819)		General population[2] (*n* =9,591)	
	CCSs (*n* =2,365)		Leukemia (*n* =770)					
Sociodemographic characteristics	*%ow*	OR (95% CI) ***p-value***[3]	*%ow*	*OR (95% CI)* ***p-value***[3]	*%ow*	OR (95% CI) ***p-value***[4]	*%ow*	OR (95% CI) ***p-value***[4]
Sex								
Female	(20)	1.00 (ref) ***<0.001***	(20)	1.00 (ref) ***<0.001***	(17)	1.00 (ref) ***<0.001***	(17)	1.00 (ref) ***<0.001***
Male	(30)	1.76 (1.45, 2.14)	(32)	1.95 (1.38, 2.76)	(27)	2.20 (1.51, 3.18)	(32)	2.42 (2.16, 2.71)
Age at survey								
5-14 y	(25)	1.64 (1.16, 2.32) ***<0.001***	(29)	2.05 (1.16, 3.64) ***<0.001***	(12)	1.48 (0.65, 3.36) ***<0.001***	-	***<0.001***
15-19 y	(17)	1.00 (ref)	(16)	1.00 (ref)	(11)	1.00 (ref)	(16)	1.00 (ref)
20-24 y	(21)	1.30 (0.94, 1.78)	(21)	1.25 (0.71, 2.20)	(20)	2.17 (1.07, 4.40)	(23)	1.58 (1.30, 1.92)
25-29 y	(25)	1.71 (1.24, 2.38)	(23)	1.62 (0.90, 2.90)	(25)	2.87 (1.49, 5.54)	(28)	2.07 (1.70, 2.52)
30-34 y	(34)	2.76 (1.94, 3.91)	(40)	3.64 (1.97, 6.70)	(34)	4.64 (2.33, 9.25)	(31)	2.39 (1.98, 2.88)
35-39 y	(43)	3.80 (2.58, 5.60)	(53)	6.13 (2.94, 12.78)	(43)	7.04 (3.40, 14.58)	(37)	3.00 (2.50, 3.60)
40-45 y	(41)	4.03 (2.50, 6.48)	(39)	3.81 (1.54, 9.42)	(46)	8.53 (3.65, 19.94)	(41)	3.73 (3.15, 4.42)
Age at diagnosis								
≥5 y	(26)	1.00 (ref) ***0.107***	(26)	1.00 (ref) ***0.161***	*n.a*		*n.a*	
<5 y	(25)	1.20 (0.96, 1.49)	(27)	1.29 (0.90, 1.86)				
Education[5]								
Primary schooling	(28)	1.45 (0.98, 2.15) ***0.008***	(31)	2.06 (1.03, 4.12) ***0.010***	(31)	1.75 (0.65, 4.72) ***0.268***	*n.a.*	
Secondary education	(27)	1.42 (1.13, 1.78)	(29)	1.88 (1.22, 2.89)	(24)	1.36 (0.90, 2.05)		
Tertiary education	(22)	1.00 (ref)	(18)	1.00 (ref)	(19)	1.00 (ref)		
Migration								
No migration background	(25)	1.00 (ref) ***0.011***	(26)	1.00 (ref) ***0.368***	(22)	1.00 (ref) ***0.189***	(23)	1.00 (ref) ***<0.001***
Migration background	(29)	1.34 (1.07, 1.68)	(27)	1.21 (0.80, 1.81)	(23)	1.37 (0.86, 2.18)	(31)	1.34 (1.19, 1.50)
Language region of Switzerland	(26)	1.00 (ref) ***0.287***	(27)	1.00 (ref) ***0.638***	(25)	1.00 (ref) ***0.017***	(26)	1.00 (ref) ***0.019***
German speaking	(24)	0.84 (0.67, 1.05)	(25)	0.95 (0.63, 1.44)	(16)	0.46 (0.27, 0.79)	(23)	0.85 (0.74, 0.96)
French speaking	(25)	0.94 (0.55, 1.63)	(19)	0.62 (0.22, 1.74)	(18)	0.69 (0.19, 2.46)	(24)	0.84 (0.67, 1.04)
Italian speaking								
Sports participation								
Yes	(23)	1.00 (ref) ***0.004***	(24)	1.00 (ref) ***0.427***	(19)	1.00 (ref) ***0.002***	(23)	1.00 (ref) ***<0.001***
No	(31)	1.35 (1.10, 1.66)	(31)	1.17 (0.80, 1.70)	(34)	1.90 (1.27, 2.85)	(30)	1.42 (1.27, 1.60)

[1] CCS, childhood cancer survivor; na, not applicable; ref, reference
[2] Standardized on sex, age at survey, migration background, and language region according to CCSs; multivariable logistic regressions are separately for each study population
[3] p-values were calculated from likelihood ratio test
[4] Global p-values for an association between prevalence of overweight/obesity and the variables as a whole (Wald test comparing models with and without the variable)
[5] Highest parental (aged <20 y at time at survey) or personal (aged ≥20 y at time of survey) education

Interaction tests (**Supplemental Table S3**) showed that most effects of sociodemographic factors did not differ between CCSs and the comparison groups (all *P*-interaction ≥ 0.05), suggesting that the direction and strength of the associations between these risk factors and overweight were similar. The only difference was the effect of sex, which was weaker in CCSs (OR: 1.7; 95% CI: 1.45, 2.14) than in the general population (OR: 2.42; 95% CI: 2.16, 2.71; Table III, Supplemental Table S3). Among clinical factors, only ≥20 Gy CRT was associated with overweight. After combining all diagnostic groups, we saw that CCSs who received ≥20 Gy CRT, of whom 29% were diagnosed with leukemia and 45% with CNS neoplasms, were around 1.5 times more likely to be overweight in comparison to their peers (OR for CCSs compared with siblings: 1.5; 95% CI: 1.1, 2.2; OR for CCSs compared with the general population: 1.6; 95% CI: 1.2, 2.2; **Figure 2**).

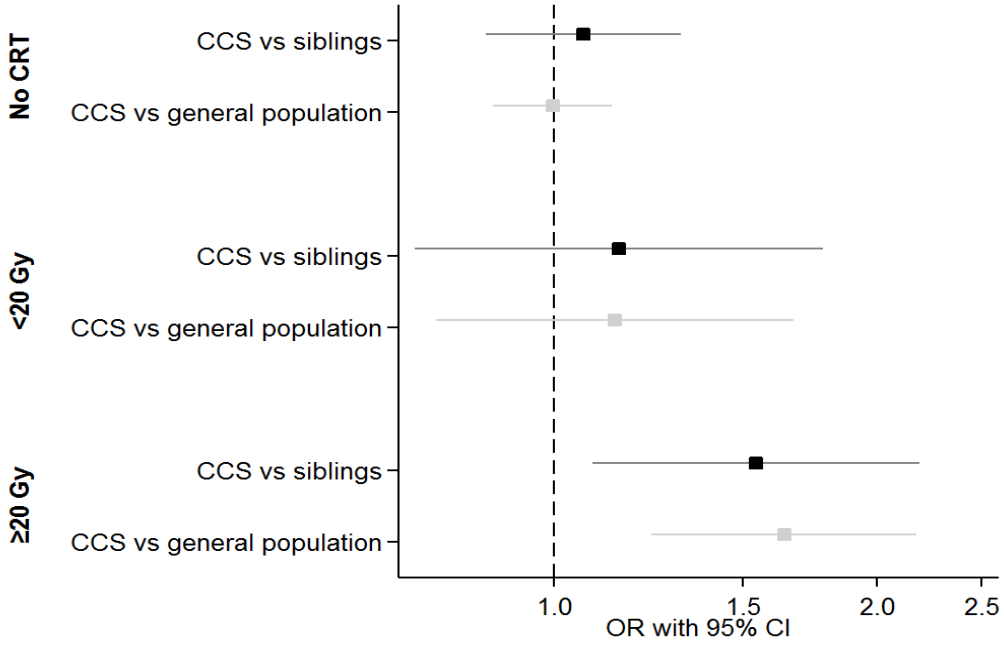

Figure 2. CRT-specific ORs (95% CIs) for overweight in childhood cancer survivors and comparison groups (from multivariable logistic regression).
Both comparison groups were standardized on sex, age at survey, migration background, and language region according to childhood cancer survivors. Values were adjusted for sex, age, education, migration background, language region of Switzerland, and sports participation. CCS, childhood cancer survivors; CRT, cranial radiation therapy; Gy, Gray.

We found no association between being overweight at survey and birth weight (*P* = 0.523) in a subgroup of 461 leukemia survivors diagnosed between 1990 and 2005. However, being overweight at diagnosis was associated with being overweight at survey (OR: 9.86; 95% CI: 3.97, 24.51) (**Supplemental Table S4**). Results of univariable logistic regression are shown in **Supplemental Table S5**. Of 27 leukemia survivors who were overweight at diagnosis, 18 (67%) remained overweight at survey.

DISCUSSION

Principal findings

At a median of 15 y after cancer diagnosis, 26% of all CCSs were overweight. This prevalence is comparable to that of their healthy peers, but there were differences between diagnostic groups. Survivors of CNS neoplasms were most likely to be overweight, whereas survivors of neuroblastoma and soft tissue sarcoma were least likely to be overweight. Sociodemographic factors for being overweight were similar in CCSs, their siblings, and the general population. Among clinical factors, we confirmed that receiving ≥20 Gy CRT was associated with being overweight.

Strengths and limitations

Height and weight at survey were self-reported; both under- and overreporting could have occurred. However, because height and weight were self-reported in all study populations we expected the degree of nondifferential error of BMI assessment to be similar across CCSs and comparison groups. BMI calculations are practical and inexpensive measures of overweight and are therefore widely used in population-based studies, and BMI values derived from self-reported height and weight can be as reliable as measured values in the estimation of health risks [38]. The prevalence of overweight might be underestimated because having a higher BMI at diagnosis is associated with poorer survival. This could have resulted in excluding more overweight CCSs due to our exclusion criteria of ≥5 y of survival after initial diagnosis of cancer [39]. Furthermore, our results could have been biased by reverse causation (e.g., a lack of sports participation could have been due to overweight).

Long-term follow-up is a strength of this study, as are the national coverage of the SCCSS and our high CCS response rate, which makes this the largest such study in Europe to date. We also had access to high-quality clinical information extracted from the SCCR, including extended information about clinical factors, birth weight, and height and weight at diagnosis for a large subgroup of leukemia patients. The questionnaire also allowed us to assess a wide variety of sociodemographic factors. Finally, we included not 1 but 2 comparison groups: siblings of CCSs (who share environmental factors with CCSs) and the general population with data derived from a population-based study performed simultaneously in Switzerland.

Overweight prevalence: results in relation to other studies

Studies investigating overweight or obesity among CCSs other than ALL survivors are scarce. Meta-analyses have suggested that overweight or obesity is common among short-term ALL survivors who are still in childhood or early adolescence compared with reference populations [4, 5], and potentially increased among late-adolescent and adult long-term ALL survivors aged

≥15 y at survey [40]. In our study, the prevalence of overweight among CCSs overall and leukemia survivors was similar to that in the general population but increased for CNS neoplasms. CNS neoplasm survivors are exposed to several risk factors (e.g., CRT, hypothalamic tumors, and surgical damage) that might lead to hypothalamic obesity, and more research on adequate management is needed [41, 42].

A contributor to differences in overweight prevalence between our results and those of pertinent studies across the literature included in meta-analyses may be the lack of detailed treatment information on CRT and dose-dependent associations with overweight in those studies. Our findings do agree with those of a recent US-based study in 14,290 CCSs [median of 24 y (5–39 y) after diagnosis] and 4031 siblings in which self-reported obesity in CCSs and siblings was similar to our results, and the 4100 survivors treated with ≥18 Gy of CRT were more likely to be obese [20]. In contrast, a study in 7195 survivors of a variety of cancer types ≥5 y after diagnosis reported underweight in CCSs treated for different cancers, including neuroblastoma and soft tissue sarcoma, when compared with the general population [22], and an increased likelihood of obesity was observed in both male and female ALL survivors who received CRT ≥20 Gy [12, 22].

Potential mechanisms and risk factors: results in relation to other studies

CRT affects the hypothalamic-pituitary axis, which may lead to growth hormone deficiency and leptin insensitivity, which could, in turn, place CCSs at risk of neuroendocrine abnormalities such as obesity [13]. However, previous studies of overweight in CCSs and CRT have shown mixed results that vary from weak to strong associations [4]. Older studies usually showed a clear association between overweight and CRT [9, 10, 12, 14], whereas those with children treated more recently with no or lower-dose CRT have shown a smaller effect [15–17, 43]. We found an association only between ≥20 Gy CRT and overweight. Overall, CCSs and leukemia survivors treated with ≥20 Gy CRT were more likely to be overweight, which suggests that ≥20 Gy CRT is a risk factor for obesity in all CCSs irrespective of the diagnosis. The positive association between CRT and obesity has also been seen in adult survivors of a variety of different childhood cancer types [22, 44]. Although CRT was not stratified by dose amount, survivors in these studies were diagnosed between 1970–1986 [22] and 1966–1996 [44], and the majority might have received high-dose CRT.

Female sex also has been reported as a risk factor for obesity in ALL adult survivors [10, 12, 22]. We could not confirm this. On the contrary, we found that men were more likely to be overweight or obese. This was the same in our comparison groups. Two systematic reviews on overweight in CCSs published in 2014 and 2015 reported no conclusive effect due to sex

[4, 5]. This suggests that sex differences mainly reflect social and cultural differences. We also found that leukemia survivors who are overweight at diagnosis have a substantially higher risk of being overweight later in life. This is in line with previous observations of survivors of leukemia [11, 17–19] and other childhood cancers [44] and the general population, in all of whom overweight tends to track strongly throughout life [45]. As in our study, others have found that more than two-thirds of ALL survivors who were overweight at diagnosis remained overweight at the end of, or after, treatment [18, 19].

Implications and recommendations

Overweight and obesity are associated with chronic diseases that are frequently seen among CCSs, such as type 2 diabetes and cardiovascular disease [46, 47]. Poor diet and a sedentary lifestyle could further increase these already elevated risks. Personal counseling should be offered to childhood cancer patients and their parents throughout treatment and beyond, and special attention should be given to patients with an increased BMI [48]. However, counseling during this period, when patients and families face the crisis of a life-threatening illness and nutritional status is not a first priority, is challenging. In addition, children may receive high steroid doses, which increase appetite and fatty tissue, and they may experience fatigue or be immobilized for some time, which reduces their physical activity. During clinical follow-up, special attention should focus on CNS tumor and leukemia survivors treated with ≥20 Gy CRT, who have the highest risk of becoming overweight. Follow-up services with multi-profession teams, including physicians, dieticians, nurses, and physiotherapists, might be a promising approach.

Conclusions

This national survey in Switzerland found that the prevalence of and risk factors for overweight were similar in CCSs overall and in healthy peers, suggesting that prevention methods and interventions can be the same as in the general population. Important exceptions are CCSs treated with ≥20 Gy CRT who may need extra attention during follow-up care.

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FB conducted the statistical analyses and wrote the article; CK contributed to the concept and the design of the study; and AW, MS, and CK gave support in the statistical analyses. All authors have revised earlier drafts and approved the final article.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures

REFERENCES

[1] National Institutes of Health. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: the evidence report. Obes Res 1998;6(Suppl 2):51S–209S.
[2] Hudson MM, Ness KK, Gurney JG, Mulrooney DA, Chemaitilly W, Krull KR, Green DM, Armstrong GT, Nottage KA, Jones KE, et al. Clinical ascertainment of health outcomes among adults treated for childhood cancer: a report from the St. Jude Lifetime Cohort Study.
JAMA 2013;309(22):2371–81.
[3] Zhang FF, Parsons SK. Obesity in childhood cancer survivors: call for early weight management. Adv Nutr 2015;6(5):611–9.
[4] Zhang FF, Kelly MJ, Saltzman E, Must A, Roberts SB, Parsons SK. Obesity in pediatric ALL survivors: a meta-analysis. Pediatrics 2014;133(3):e704–15.
[5] Zhang FF, Liu S, Chung M, Kelly MJ. Growth patterns during and after treatment in patients with pediatric ALL: a meta-analysis. Pediatr Blood Cancer 2015;62(8):1452–60.
[6] Woo Baidal JA, Locks LM, Cheng ER, Blake-Lamb TL, Perkins ME, Taveras EM. Risk factors for childhood obesity in the first 1,000 days. Am J Prev Med 2016;50(6):761–79.
[7] Jornayvaz FR, Vollenweider P, Bochud M, Mooser V, Waeber G, Marques-Vidal P. Low birth weight leads to obesity, diabetes and increased leptin levels in adults: the CoLaus study. Cardiovasc Diabetol 2016;15:73.
[8] Aarestrup J, Bjerregaard LG, Gamborg M, Angquist L, Tjonneland A, Overvad K, Linneberg A, Osler M, Mortensen EL, Gyntelberg F, et al. Tracking of body mass index from 7 to 69 years of age. Int J Obes 2016;40:1376–83.
[9] Geenen MM, Bakker PJM, Kremer LCM, Kastelein JJP, Leeuwen FEv. Increased prevalence of risk factors for cardiovascular disease in long-term survivors of acute lymphoblastic leukemia and Wilms tumor treated with radiotherapy. Pediatr Blood Cancer 2010;55(4):690–7.
[10] Garmey EG, Liu Q, Sklar CA, Meacham LR, Mertens AC, Stovall MA, Yasui Y, Robison LL, Oeffinger KC. Longitudinal changes in obesity and body mass index among adult survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. J Clin Oncol 2008;26(28):4639–45.
[11] Razzouk BI, Rose SR, Hongeng S, Wallace D, Smeltzer MP, Zacher M, Pui C-H, Hudson MM. Obesity in survivors of childhood acute lymphoblastic leukemia and lymphoma. J Clin Oncol 2007;25(10):1183–9.
[12] Oeffinger KC, Mertens AC, Sklar CA, Yasui Y, Fears T, Stovall M, Vik TA, Inskip PD, Robison LL. Obesity in adult survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. J Clin Oncol 2003;21(7):1359–65.
[13] Janiszewski PM, Oeffinger KC, Church TS, Dunn AL, Eshelman DA, Victor RG, Brooks S, Turoff AJ, Sinclair E, Murray JC, et al. Abdominal obesity, liver fat, and muscle composition in survivors of childhood acute lymphoblastic leukemia. J Clin Endocrinol Metab
2007;92(10):3816–21.
[14] Veringa SJE, van Dulmen-den Broeder E, Kaspers GJL, Veening MA. Blood pressure and body composition in long-term survivors of childhood acute lymphoblastic leukemia. Pediatr Blood Cancer 2012;58(2):278–82.
[15] Karakurt H, Sarper N, Kılıc SC, Gelen SA, Zengin E. Screening survivors of childhood acute lymphoblastic leukemia for obesity, metabolic syndrome, and insulin resistance. Pediatr Hematol Oncol 2012;29(6):551–61.
[16] Withycombe JS, Post-White JE, Meza JL, Hawks RG, Smith LM, Sacks N, Seibel NL. Weight patterns in children with higher risk ALL: a report
from the Children's Oncology Group (COG) for CCG 1961. Pediatr
Blood Cancer 2009;53(7):1249–54.
[17] Esbenshade AJ, Simmons JH, Koyama T, Koehler E, Whitlock JA, Friedman DL. Body mass index and blood pressure changes over the course of treatment of pediatric acute lymphoblastic leukemia. Pediatr Blood Cancer 2011;56(3):372–8.
[18] Love E, Schneiderman JE, Stephens D, Lee S, Barron M, Tsangaris E, Urbach S, Staneland P, Greenberg M, Nathan PC. A cross-sectional study of overweight in pediatric survivors of acute lymphoblastic leukemia (ALL). Pediatr Blood Cancer 2011;57(7):1204–9.
[19] Zhang FF, Rodday AM, Kelly MJ, Must A, MacPherson C, Roberts SB, Saltzman E, Parsons SK. Predictors of being overweight or obese in survivors of pediatric acute lymphoblastic leukemia (ALL). Pediatr Blood Cancer 2014;61(7):1263–9.
[20] Mostoufi-Moab S, Seidel K, Leisenring WM, Armstrong GT, Oeffinger KC, Stovall M, Meacham LR, Green DM, Weathers R, Ginsberg JP. Endocrine abnormalities in aging survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. J Clin Oncol 2016;34(27):3240–7.

[21] Lindemulder SJ, Stork LC, Bostrom B, Lu X, Devidas M, Hunger S, Neglia JP, Kadan-Lottick NS. Survivors of standard risk acute lymphoblastic leukemia do not have increased risk for overweight and obesity compared to non-cancer peers: a report from the Children's Oncology Group. Pediatric Blood Cancer 2015;62(6):1035–41.
[22] Meacham LR, Gurney JG, Mertens AC, Ness KK, Sklar CA, Robison LL, Oeffinger KC. Body mass index in long-term adult survivors of childhood cancer. Cancer 2005;103(8):1730–9.
[23] Kuehni CE, Rueegg CS, Michel G, Rebholz CE, Strippoli MPF, Niggli FK, Egger M, von der Weid NX. Cohort profile: the Swiss Childhood Cancer Survivor Study. Int J Epidemiol 2012;41(6):1553–64.
[24] Michel G, von der Weid NX, Zwahlen M, Adam M, Rebholz CE, Kuehni CE. The Swiss Childhood Cancer Registry: rationale, organisation and results for the years 2001–2005. Swiss Med Wk 2007;137(35–36):502–9.
[25] Michel G, von der Weid NX, Zwahlen M, Redmond S, Strippoli MPF, Kuehni CE. Incidence of childhood cancer in Switzerland: the Swiss Childhood Cancer Registry. Pediatr Blood Cancer 2008;50(1):46–51.
[26] Robison LL, Mertens AC, Boice JD, Breslow NE, Donaldson SS, Green DM, Li FP, Meadows AT, Mulvihill JJ, Neglia JP, et al. Study design and cohort characteristics of the childhood cancer survivor study: a multi-institutional collaborative project. Med Pediatr Oncol 2002;38(4):229–39.
[27] Hawkins MM, Lancashire ER, Winter DL, Frobisher C, Reulen RC, Taylor AJ, Stevens MCG, Jenney M. The British Childhood Cancer Survivor Study: objectives, methods, population structure, response rates and initial descriptive information. Pediatr Blood Cancer 2008;50(5):1018–25.
[28] Liebherr RMJ, Storni M, Wiedenmayer G. Health and health behaviour in Switzerland 2007 Swiss Health Survey. Neuchatel (Switzerland): Swiss Federal Statistical Office; 2010 (in German).
[29] Germann U. Final Census report 2000. Neuchatel (Switzerland): Swiss Federal Statistical Office; 2005 (in German).
[30] Swiss confederation Federal Statistical Office (BFS). The Swiss Health Survey 2012 in short, concept, method, execution. Neuchatel (Switzerland): Swiss Federal Statistical Office; 2013 (in German).
[31] Braegger C, Jenni O, Konrad D, Mollonari L. New growth curves for Switzerland. Paediatrica 2011;22(1):9–11.
[32] De Onis M, Lobstein T. Defining obesity risk status in the general childhood population: which cut-offs should we use? Int J Pediatr Obes 2010;5(6):458–60.
[33] WHO. Certain conditions originating in the perinatal period (P00-P96), Disorders related to length of gestation and fetal growth (P05-P08). In: International statistical classification of diseases and related health problems. 10th revision. Geneva: WHO; 2015.
[34] Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P. International classification of childhood cancer, third edition. Cancer 2005;103(7):1457–67.
[35] Wengenroth L, Rueegg CS, Michel G, Essig S, Ammann RA, Bergstraesser E, Kuehni CE; Swiss Paediatric Oncology Group. Life partnerships in childhood cancer survivors, their siblings, and the general population. Pediatr Blood Cancer 2014;61(3):538–45.
[36] Weiss A, Sommer G, Kasteler R, Scheinemann K, Grotzer M, Kompis M, Claudia CE. Long-term auditory complications after childhood cancer: a report from the Swiss Childhood Cancer Survivor Study. Pediatr Blood Cancer 2017;64(2):364–73.
[37] Belle F, Wengenroth L, Weiss A, Sommer G, Beck Popovic M, Ansari M, Bochud M, Kuehni C. Low adherence to dietary recommendations in adult childhood cancer survivors. Clin Nutr 2017;36(5):1266–74.
[38] Stommel M, Schoenborn CA. Accuracy and usefulness of BMI measures based on self-reported weight and height: findings from the NHANES & NHIS 2001–2006. BMC Public Health 2009;9(1):1–10.
[39] Orgel E, Genkinger JM, Aggarwal D, Sung L, Nieder M, Ladas EJ. Association of body mass index and survival in pediatric leukemia: a meta-analysis. Am J Clin Nutr 2016;103(3):808–17.
[40] Nam GE, Kaul S, Wu PY, Nelson RE, Wright J, Fluchel MN, Hacking CC, Kirchhoff AC. A meta-analysis of body mass index of adolescent and adult survivors of pediatric acute lymphoblastic leukemia. J Cancer Surviv 2015;9(3):412–21.
[41] Wang KW, Chau R, Fleming A, Banfield L, Singh SK, Johnston DL, Zelcer SM, Rassekh SR, Burrow S, Valencia M, et al. The effectiveness of interventions to treat hypothalamic obesity in survivors of childhood brain tumours: a systematic review. Obes Rev 2017;18(8): 899–914.

[42] Wang K-W, Fleming A, Singh SK, Banfield L, de Souza RJ, Thabane L, Samaan MC. Evaluating overweight and obesity prevalence in survivors of childhood brain tumors: a systematic review protocol. Syst Rev 2017;6:43.
[43] Skoczen S, Tomasik PJ, Bik-Multanowski M, Surmiak M, Balwierz W, Pietrzyk JJ, Sztefko K, Gozdzik J, Galicka-Latała D, Strojny W. Plasma levels of leptin and soluble leptin receptor and polymorphisms of leptin gene -18G>A and leptin receptor genes K109R and Q223R, in survivors of childhood acute lymphoblastic leukemia. J Exp Clin Cancer Res 2011;30(1):64.
[44] van Santen HM, Geskus RB, Raemaekers S, van Trotsenburg ASP, Vulsma T, van der Pal HJH, Caron HN, Kremer LCM. Changes in body mass index in long-term childhood cancer survivors. Cancer 2015;121(23):4197–204.
[45] Faienza MF, Wang DQH, Fruhbeck G, Garruti G, Portincasa P. The dangerous link between childhood and adulthood predictors of obesity and metabolic syndrome. Intern Emerg Med 2016;11(2):175–82.
[46] Smith KB, Smith MS. Obesity statistics. Prim Care 2016;43(1):121–35.
[47] Oeffinger KC, Mertens AC, Sklar CA, Kawashima T, Hudson MM, Meadows AT, Friedman DL, Marina N, Hobbie W, Kadan-Lottick NS, et al. Chronic health conditions in adult survivors of childhood cancer. N Engl J Med 2006;355(15):1572–82.
[48] Saultier P, Auquier P, Bertrand Y, Vercasson C, Oudin C, Contet A, Plantaz D, Poiree M, Ducassou S, Kanold J, et al. Metabolic syndrome in long-term survivors of childhood acute leukemia treated without hematopoietic stem cell transplantation: an L.E.A. study. Haematologica 2016;101(12):1603–10.

SUPPLEMENTARY MATERIAL

Table S1. Sociodemographic and clinical characteristics of childhood leukemia survivors, subgroup diagnosed between 1990-2005

Characteristics	**Leukemia (*n* =461)**
Sociodemographic characteristics	
Sex, *n* (%)	
Female	212 (46)
Male	249 (54)
Age at survey, *n* (%)	
5-14 y	121 (26)
15-19 y	183 (40)
≥20 y	157 (34)
Parents' education (highest degree)[1], *n* (%)	
Primary schooling	26 (9)
Secondary education	165 (54)
Tertiary education	113 (37)
Personal education[2], *n* (%)	
Primary schooling	23 (15)
Secondary education	115 (73)
Tertiary education	19 (12)
Migration, *n* (%)	
No migration background	309 (67)
Migration background	152 (33)
Language region of Switzerland, *n* (%)	
German speaking	333 (72)
French speaking	113 (25)
Italian speaking	15 (3)
Sports participation, *n* (%)	
Yes	350 (76)
No	111 (24)
BMI at survey[3], *n* (%)	
Underweight	24 (5)
Normal	336 (73)
Overweight	101 (22)
Birth weight[4], *n* (%)	
Low: <2500 g	28 (6)
Normal: 2500-4000 g	337 (73)
High: >4000 g	45 (10)
Clinical characteristics	
BMI at diagnosis[5], *n* (%)	
Underweight	24 (5)
Normal	366 (79)
Overweight	27 (6)
Age at diagnosis, *n* (%)	
≥5 y	228 (49)
<5 y	233 (51)
Year of diagnosis, *n* (%)	
1990-2000	287 (62)
After 2000	174 (38)
CRT, *n* (%)	
None	366 (79)
<20 Gy	65 (14)
≥20 Gy	30 (7)

CRT, cranial radiation therapy
[1] Highest parental education level reported for CCS <20 y at time of survey
[2] Highest personal education level of CCS ≥20 y at time of survey
[3] BMI Z-scores were calculated for CCS ≤19 y, BMI scores (km/m2) were calculated for adults (>19 y)
[4] *n*=51 missing (11%)
[5] *n*=44 missing (10%).

Table S2. Overweight prevalence and risk factors associated with overweight in CCSs and comparison groups (from univariable logistic regression)[1]

	CCSs				**Siblings**[2] **(*n* =819)**		**General population**[2] **(*n* =9591)**	
	CCS (*n* =2365)		**Leukemia (*n* =770)**					
Sociodemographic characteristics	*%ow* OR (95% CI)	*p-value*[3]	*%ow* OR (95% CI)	*p-value*[3]	*%ow* OR (95% CI)	*p-value*[4]	*%ow* OR (95% CI)	*p-value*[4]
Gender								
Female	(20) 1.00 (ref)	*<0.001*	(20) 1.00 (ref)	*<0.001*	(17) 1.00 (ref)	*0. 001*	(17) 1.00 (ref)	*<0.001*
Male	(30) 1.70 (1.41, 2.06)		(32) 1.90 (1.36, 2.64)		(27) 1.80 (1.28, 2.53)		(32) 2.20 (1.97, 2.45)	
Age at survey								
5-14 y	(25) 1.58 (1.13, 2.21)	*<0.001*	(29) 2.09 (1.20, 3.64)	*<0.001*	(12) 1.08 (0.48, 2.45)	*<0.001*	-	*<0.001*
15-19 y	(17) 1.00 (ref)		(16) 1.00 (ref)		(11) 1.00 (ref)		(16) 1.00 (ref)	
20-24 y	(21) 1.27 (0.94, 1.73)		(21) 1.36 (0.79, 2.34)		(20) 2.03 (1.01, 4.07)		(23) 1.58 (1.30, 1.91)	
25-29 y	(25) 1.62 (1.18, 2.23)		(23) 1.52 (0.87, 2.65)		(25) 2.66 (1.36, 5.17)		(28) 2.07 (1.70, 2.51)	
30-34 y	(34) 2.48 (1.78, 3.46)		(40) 3.46 (1.93, 6.17)		(34) 4.02 (2.02, 7.99)		(31) 2.44 (2.03, 2.93)	
35-39 y	(43) 3.54 (2.46, 5.11)		(53) 5.83 (2.91, 11.67)		(43) 5.87 (2.86, 12.06)		(37) 3.09 (2.59, 3.69)	
40-45 y	(41) 3.33 (2.12, 5.23)		(39) 3.32 (1.41, 7.80)		(46) 6.66 (2.97, 14.97)		(41) 3.70 (3.14, 4.36)	
Education[5]								
Primary schooling	(28) 1.36 (0.94, 1.97)	*<0.001*	(31) 1.95 (1.03, 3.72)	*0.009*	(31) 1.91 (0.79, 4.57)	*0.170*	*n.a*	
Secondary education	(27) 1.29 (1.05, 1.60)		(29) 1.80 (1.20, 2.68)		(24) 1.34 (0.93, 1.94)			
Tertiary education	(22) 1.00 (ref)		(18) 1.00 (ref)		(19) 1.00 (ref)			
Migration								
No migration background	(25) 1.00 (ref)	*0.047*	(26) 1.00 (ref)	*0.664*	(22) 1.00 (ref)	*0.819*	(23) 1.00 (ref)	*<0.001*
Migration background	(29) 1.23 (1.00, 1.52)		(27) 1.08 (0.75, 1.56)		(23) 1.05 (0.69, 1.61)		(31) 1.48 (1.33, 1.64)	
Language region of Switzerland								
German speaking	(26) 1.00 (ref)	*0.574*	(27) 1.00 (ref)	*0.552*	(25) 1.00 (ref)	*0.046*	(26) 1.00 (ref)	*0.101*
French speaking	(24) 0.89 (0.72, 1.11)		(25) 0.90 (0.61, 1.34)		(16) 0.55 (0.34, 0.89)		(23) 0.88 (0.78, 0.99)	
Italian speaking	(25) 0.92 (0.54, 1.56)		(19) 0.62 (0.23, 1.65)		(18) 0.67 (0.22, 2.06)		(24) 0.93 (0.75, 1.15)	
Sports participation								
Yes	(23) 1.00 (ref)	*<0.001*	(24) 1.00 (ref)	*0.083*	(19) 1.00 (ref)	*<0.001*	(23) 1.00 (ref)	*<0.001*
No	(31) 1.45 (1.19, 1.76)		(31) 1.36 (0.96, 1.92)		(34) 2.22 (1.54, 3.20)		(30) 1.45 (1.31, 1.62)	
Clinical characteristics								
ICCC-3 diagnosis								
I: Leukemia	(26) 1.00 (ref)	*0.003*	*n.a*		*n.a*		*n.a*	
II: Lymphoma	(27) 1.06 (0.81, 1.38)							
III: CNS neoplasm	(31) 1.29 (0.97, 1.70)							
IV: Neuroblastoma	(13) 0.41 (0.23, 0.72)							
V: Retinoblastoma	(24) 0.87 (0.49, 1.53)							
VI: Renal tumor	(20) 0.71 (0.46, 1.10)							
VII: Hepatic tumor	(25) 0.94 (0.34, 2.61)							
VIII: Malignant bone tumor	(24) 0.89 (0.54, 1.45)							

IX: Soft tissue sarcoma	(18) 0.60 (0.37, 0.95)					
X: Germ cell tumor	(26) 1.01 (0.64, 1.60)					
XI & XII: Other tumor	(24) 0.89 (0.47, 1.70)					
Langerhans cell histiocytosis	(33) 1.36 (0.83, 2.21)					
Age at diagnosis						
≥5 y	(26) 1.00 (ref)	*0.339*	(26) 1.00 (ref)	*0.749*	*n.a*	*n.a*
<5 y	(25) 0.91 (0.75, 1.10)		(27) 1.05 (0.76, 1.45)			
Year of diagnosis						
Before 1990	(32) 1.00 (ref)	*0.001*	(34) 1.00 (ref)	*<0.001*	*n.a*	*n.a*
1990-2000	(23) 0.62 (0.50, 0.77)		(19) 0.47 (0.33, 0.69)			
After 2000	(22) 0.60 (0.47, 0.77)		(26) 0.68 (0.45, 1.02)			
CRT						
None	(24) 1.00 (ref)	*<0.001*	(24) 1.00 (ref)	*<0.001*	*n.a*	*n.a*
<20 Gy	(26) 1.13 (0.78, 1.63)		(17) 0.63 (0.36, 1.11)			
≥20 Gy	(38) 1.98 (1.51, 2.60)		(53) 3.45 (2.12, 5.61)			
HSCT						
No	(26) 1.00 (ref)	*0.270*	(27) 1.00 (ref)	*0.212*	*n.a*	*n.a*
Yes	(21) 0.78 (0.50, 1.23)		(20) 0.67 (0.35, 1.29)			
Chemotherapy						
No	(29) 1.00 (ref)	*0.060*	*n.a*		*n.a*	*n.a*
Yes	(25) 0.81 (0.65, 1.01)					
History of relapse						
No	(25) 1.00 (ref)	*0.299*	(26) 1.00 (ref)	*0.504*	*n.a*	*n.a*
Yes	(28) 1.16 (0.88, 1.53)		(29) 1.17 (0.74, 1.87)			

[1] CCS, childhood cancer survivor; CNS, central nervous system; HSCT, hematopoietic stem cell transplantation; ICCC3, *International Classification of Childhood Cancer, 3rd edition*
[2] Standardized on gender, age at survey, migration background and language region according to CCS
[3] p-value calculated from likelihood ratio test
[4] Global p-value for an association between prevalence of overweight/obesity and the variables as a whole (Wald test comparing models with and without the variable)
[5] Highest parental (<20 years at time at survey) or personal education (≥20 years at time of survey)

Table S3. Interaction of study group with sociodemographic determinants (retrieved from multivariable logistic regressions[1])

Sociodemographic determinants	**CCS except leukemia vs. leukemia[3]**	**CCS vs. siblings[2,3]**	**CCS vs. general population[2,3]**
Gender	0.446	0.381	<0.001
Age at survey, year	0.723	0.438	0.156
Education	0.471	0.807	0.500
Migration	0.708	0.457	0.249
Language region	0.497	0.193	0.806
Sports	0.400	0.075	0.828

CCS, childhood cancer survivors; n.a., not applicable

[1] Adjusted for sex, age category, education level, migration background, language region in Switzerland, sports participation; the model including only CCSs, is additionally adjusted for age at diagnosis, year of diagnosis, and cranial radiation therapy

[2] Standardized on sex, age at survey, migration background, and language region according to CCSs

[3] p-value for interaction (study group, CCSs versus comparison group x determinant) was calculated with the likelihood ratio test

Table S4. Overweight prevalence and risk factors associated with overweight in childhood leukemia survivors, subgroup diagnosed between 1990-2005 (from multivariable logistic regression)

	Leukemia (*n* =461)		
Characteristics	(‰$_{ow}$)	OR (95% CI)	*p-value*[1]
Sociodemographic characteristics			
Sex			
Female	(17)	1.00 (ref)	*0.026*
Male	(26)	1.76 (1.06, 2.90)	
Age at survey			
5-14 y	(29)	1.61 (0.74, 3.50)	*0.049*
15-19 y	(16)	1.00 (ref)	
≥20 y	(23)	2.18 (1.08, 4.38)	
Education			
Primary education	(27)	1.50 (0.61, 3.38)	*0.242*
Secondary education	(24)	1.67 (0.91, 3.09)	
Tertiary education	(17)	1.00 (ref)	
Migration			
No migration background	(19)	1.00 (ref)	*0.066*
Migration background	(27)	1.66 (0.97, 2.84)	
Language region in Switzerland			
German speaking	(22)	1.00 (ref)	*0.233*
French speaking	(23)	1.04 (0.58, 1.84)	
Italian speaking	(7)	0.22 (0.03, 1.84)	
Sports participation			
Yes	(23)	1.00 (ref)	*0.854*
No	(19)	0.94 (0.51, 1.73)	
Clinical characteristics			
Birth weight[2]			
Low: <2500 g	(32)	1.68 (0.65, 4.35)	*0.523*
Normal: 2500-4000 g	(22)	1.00 (ref)	
High: >4000 g	(18)	0.70 (0.30, 1.66)	
BMI at diagnosis[3]			
Underweight	(13)	0.49 (0.14, 1.78)	*<0.001*
Normal	(20)	1.00 (ref)	
Overweight/Obese	(67)	9.86 (3.97, 24.51)	
Age at diagnosis			
≥5 y	(21)	1.00 (ref)	*0.338*
<5 y	(23)	1.36 (0.73, 2.54)	
Year of diagnosis			
1990-2000	(19)	1.00 (ref)	*0.278*
After 2000	(26)	1.48 (0.73, 2.99)	
CRT			
None	(23)	1.00 (ref)	*0.057*
<20 Gy	(15)	0.45 (0.22, 0.95)	
≥20 Gy	(25)	1.53 (0.43, 5.37)	

[1] p-value calculated from likelihood ratio test
[2] *n*=51 missing (11%)
[3] *n*=44 missing (10%)

Table S5. Overweight prevalence and risk factors associated with overweight in childhood leukemia survivors, subgroup diagnosed between 1990-2005 (from univariable logistic regression)

	Leukemia (*n* =461)		
Characteristics	(‰$_{ow}$)	OR (95% CI)	*p-value*[1]
Sociodemographic characteristics			
Sex			
Female	(17)	1.00 (ref)	*0.018*
Male	(26)	1.73 (1.09, 2.73)	
Age at survey, year			
5-14 y	(29)	2.08 (1.19, 3.61)	*0.033*
15-19 y	(16)	1.00 (ref)	
≥20 y	(23)	1.52 (0.88, 2.60)	
Education			
Primary education	(27)	1.81 (0.83, 3.95)	*0.193*
Secondary education	(24)	1.54 (0.90, 2.63)	
Tertiary education	(17)	1.00 (ref)	
Migration			
No migration background	(19)	1.00 (ref)	*0.068*
Migration background	(27)	1.53 (0.97, 2.42)	
Language region in Switzerland			
German speaking	(22)	1.00 (ref)	*0.258*
French speaking	(23)	1.05 (0.63, 1.74)	
Italian speaking	(7)	0.25 (0.03, 1.93)	
Sports			
Yes	(23)	1.00 (ref)	*0.376*
No	(19)	0.79 (0.46, 1.35)	
Clinical characteristics			
Birth weight[2]			
Low: <2500 g	(32)	1.71 (0.74, 3.95)	*0.562*
Normal: 2500-4000 g	(22)	1.00 (ref)	
High: >4000 g	(18)	0.78 (0.35, 1.75)	
BMI at diagnosis[3]			
Underweight	(13)	0.58 (0.17, 2.01)	*<0.001*
Normal	(20)	1.00 (ref)	
Overweight/Obese	(67)	8.17 (3.52, 18.93)	
Age at diagnosis			
≥5 y	(21)	1.00 (ref)	*0.645*
<5 y	(23)	1.11 (0.71, 1.73)	
Year of diagnosis			
1990-2000	(19)	1.00 (ref)	*0.069*
After 2000	(26)	1.52 (0.97, 2.37)	
CRT			
None	(23)	1.00 (ref)	*0.257*
<20 Gy	(15)	0.59 (0.31, 1.15)	
≥20 Gy	(25)	1.10 (0.35, 3.51)	
HSCT			
No	(23)	1.00 (ref)	*0.190*
Yes	(14)	0.57 (0.23, 1.39)	
History of relapse			
No	(22)	1.00 (ref)	*0.828*
Yes	(21)	0.93 (0.46, 1.87)	

[1] p-value calculated from likelihood ratio test
[2] *n*=51 missing (11%)
[3] *n*=44 missing (10%)

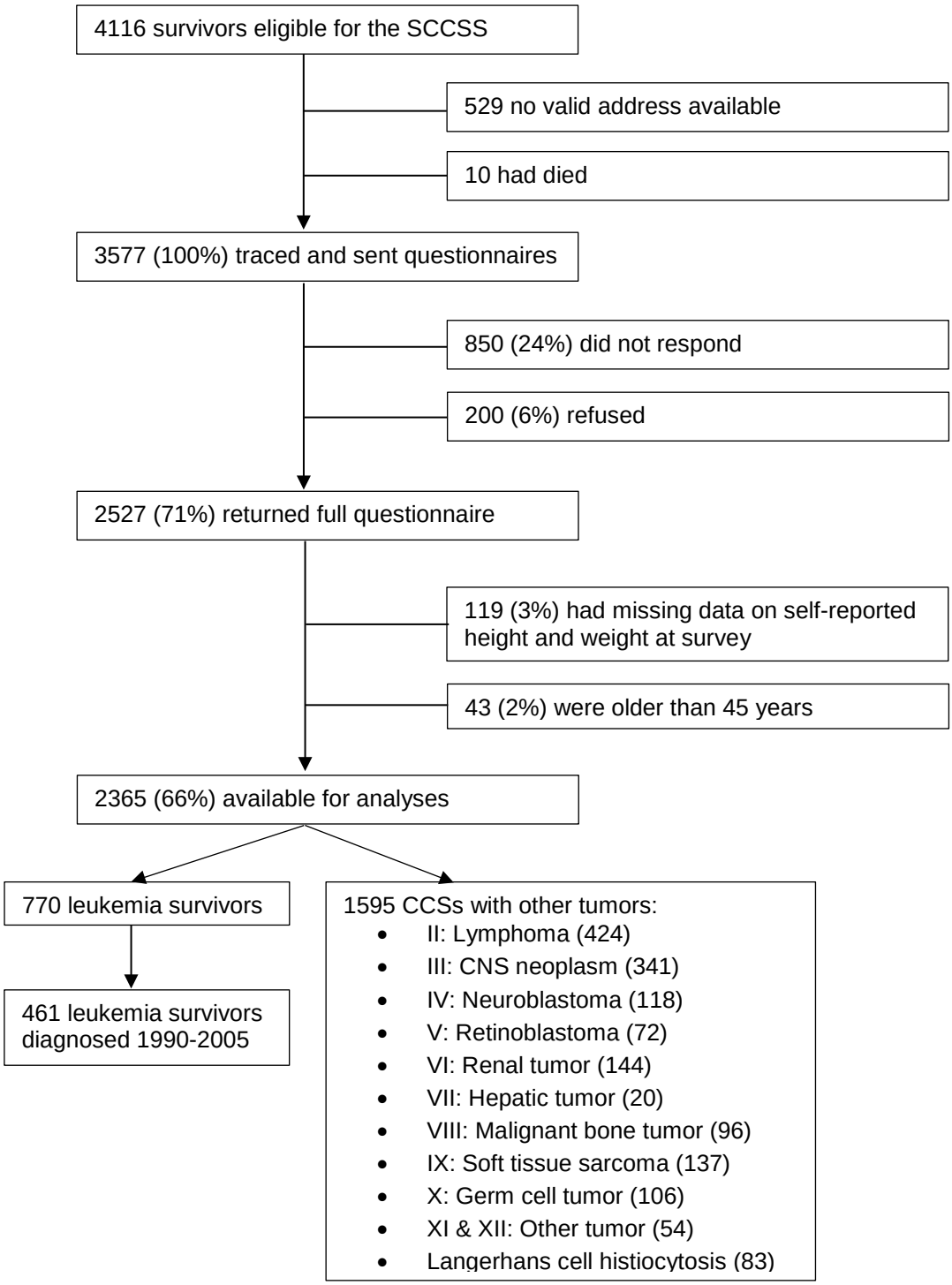

Figure S1. Response rates in the Swiss Childhood Cancer Survivor Study (SCCSS)
CCS, childhood cancer survivor

Chapter 7

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

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SUMMARY

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

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

RESULTS: The study included 1936 CCS, 546 siblings, and 9591 SHS participants. Median (interquartile range) age of the CCS at survey was 24 (20-31) years and median time since diagnosis was 17 (12-22) years. At survey, 26% of CCS were overweight, a proportion comparable to that among siblings (24%) and the SHS participants (25%). Prevalence of overweight was 24% in CCS treated with glucocorticoids only (n=686), 37% in those with cranial radiation therapy (CRT) (n=127), and 49% in those with both glucocorticoids and CRT (n=101), $p<0.001$. We found no evidence for a dose-response relationship between cumulative glucocorticoid doses and overweight and no evidence that CRT modified the effect of cumulative glucocorticoid dose treatment on overweight.

CONCLUSION: This study suggests that glucocorticoids used for the treatment of childhood cancer are not associated with long-term risk of overweight.

INTRODUCTION

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

Glucocorticoids might, therefore, be implicated in excessive weight gain during cancer treatment [3, 7]. But whether glucocorticoids have a longer-lasting effect on weight is uncertain, and any such effect may depend on the dose and duration of treatment. Research has yielded contradictory results. One small (N=169) study of ALL survivors reported a six-fold increased risk of being overweight or obese in ALL survivors with the highest cumulative doses of glucocorticoids (≥10,000 mg/m^2) compared to the lowest doses (<7500 mg/m^2) five years after diagnosis [9], while another US study found no dose-response effects ≥10 years after diagnosis [10]. In an US study glucocorticoid treatment was associated with obesity 25 years after diagnosis in 776 CCS who were treated with CRT, but cumulative dose and type of glucocorticoid were not assessed [11]. Previous studies have mainly focused on acute effects of glucocorticoids during or shortly after treatment [9, 12-16], have not assessed cumulative glucocorticoid dose [11, 13], and often have relatively low numbers of participants (<200) [9, 12-18]. Thus it remains unclear whether glucocorticoids affect overweight in CCS long after treatment.

We analyzed data from the Swiss Childhood Cancer Survivor Study (SCCSS) to investigate whether 1) overweight in long-term CCS (on average 17 years after diagnosis) is associated with the cumulative glucocorticoid dose received, 2) there is a dose-response relationship between cumulative glucocorticoid dose and BMI, and 3) the respective effects of prednisone and dexamethasone differ. We studied the entire group of CCS, and separately the three cancer types treated most frequently with glucocorticoids (ALL, NHL, and HL).

METHODS

Sampling

The Swiss Childhood Cancer Survivor Study

The Swiss Childhood Cancer Survivor Study (SCCSS) is a long-term follow-up study of patients registered in the Swiss Childhood Cancer Registry (SCCR, www.childhoodcancerregistry.ch) who have been diagnosed since 1976 and survived ≥5 years after cancer diagnosis [19]. The SCCR is a population-based registry that includes all children and adolescents under age 21 in Switzerland who are diagnosed with leukemia, lymphoma, central nervous system (CNS) tumors, malignant solid tumors, or Langerhans cell histiocytosis [20, 21]. Ethical approval of the SCCR and the SCCSS has been given by the Ethics Committee of the Canton of Bern to (KEK-BE: 166/2014).

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

Comparison groups

We used two comparison groups in this study: siblings of the CCS and a random sample of the general Swiss population represented by data from the Swiss Health Survey (SHS). The sibling survey was conducted from 2009 to 2012. We asked CCS for consent to contact siblings and for contact information. We sent siblings the same questionnaire as CCS, omitting questions about cancer history. Siblings who did not respond received another copy of the questionnaire four to six weeks later, but were not contacted by phone [19].

The second comparison group consisted of participants in the SHS questionnaire 2012 [24]. This is a nationally representative telephone survey repeated every five years. The SHS

compiled a randomly selected sample of Swiss households with telephone landlines and attempted to contact someone in each household. Sampling was stratified by region and in the selected households the survey was administered to the consenting household member, age 15 years or older, who first answered the phone.

Measurements

Body weight and BMI

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

Glucocorticoids

We calculated prednisone and/or dexamethasone doses based on the intended doses in the cancer treatment protocol and, if applicable, the treatment arm. Glucocorticoid tapering was taken into account if protocols indicated this. In the event tapering information on duration and dosage was missing, we assumed that the dosage decreased by 50% of the prior dose in three steps over three days. The few protocols (3%) that prescribed glucocorticoids by body weight (mg/kg) were converted into dose per body surface area (mg/m^2) by multiplying the dose in mg/kg by a conversion factor of 30, which represents an average of the factors for persons weighing 20 and 60 kg [30]. Glucocorticoids administered by intrathecal route and for supportive care or immunosuppression, were not taken into consideration [1]. Treatment protocols that were included came from the Swiss Pediatric Oncology Group (31%), Pediatric Oncology Group (29%), Berlin/Frankfurt/Muenster study group (24%), German Society of Pediatric Oncology and Hematology (7%), and others (9%) (**Supplementary Table S1**). In 67 cases in which the study arm was unknown, survivors were assigned to the protocol arm with the lowest glucocorticoid dosage. We calculated the total cumulative glucocorticoid dose in equivalent of prednisone for each patient using the formula cumulative glucocorticoid dose = cumulative prednisone dose + (cumulative dexamethasone dose x 6.67) in mg/m^2 [31]. The recommended cumulative glucocorticoid doses dropped over time when all cancer types were combined, and specifically for each type of cancer with the exception of ALL protocols, in which doses increased (**Supplementary Figure S1**). We assessed other clinical and sociodemographic variables as described previously [26].

Statistical analysis

We included all SCCSS survivors and their siblings, and the SHS participants in the general population, who were aged 15-45 years at time of survey and provided self-reported height and weight (**Supplementary Figure S2**). We excluded CCS with hematopoietic stem cell transplantation (HSCT); this specific group is at substantial risk of underweight due to chronic graft-versus-host disease and long-term immunosuppression with recurrent infections [32]. For better comparison between CCS and peers, we standardized comparison groups for gender, age at survey, migration background, and language region as described previously [26]. First, we assessed whether overweight at survey was associated with the cumulative glucocorticoid dose during treatment. We determined these associations using multivariable logistic regression within all CCS, and within patients with the three cancer types frequently treated with glucocorticoids. We divided BMI into two categories: overweight (overweight and obesity) versus non-overweight (underweight and normal) because the group of obese people was small and the glucocorticoids and CRT risk estimates for the two categories overweight and obesity had the same direction and comparable magnitude. Cumulative prednisone and glucocorticoid usage was divided into three categories: lower than the median intake of all CCS, median to third quartile, and equal to or higher than the third quartile. Cumulative dexamethasone was divided into two categories: lower than the median intake of all CCS, and equal to or higher than the median. We adjusted the models for gender, age at diagnosis, time since diagnosis, and cumulative CRT and/or glucocorticoid dose. We used interaction terms to test whether age, gender, and the clinical variables e.g. age at diagnosis, year of diagnosis, time since diagnosis, and CRT modified the effect of cumulative glucocorticoid dose treatment on overweight since these variables are related to the total dose. Second, we illustrated the dose-response relationship by comparing the distribution of BMI by cumulative glucocorticoid dose in steps of 1000 mg/m^2 (prednisone and total glucocorticoids) or 100 mg/m^2 (dexamethasone) with boxplots. Because 26% of CCS were 15-19 years at survey, we used BMI Z-scores for all CCS. We used trend tests to test for an ordered relationship between cumulative glucocorticoid dose categories and BMI Z-scores. Third, we examined whether effects differed between dexamethasone and prednisone treatment again using multivariable logistic regression models. Finally, we performed sensitivity analyses to compare standardized data for gender, age, migration background, and language region in all comparison groups according to the distribution in CCS to non-standardized data. For the 67 survivors for whom the study arm was unknown we performed sensitivity analyses in which they were excluded or were assigned to the protocol arm with the highest glucocorticoid dose instead of the lowest. We used Stata (version 14, Stata Corporation, Austin, Texas) for all statistical analyses.

RESULTS

Response rate and characteristics of the study populations

Among 4116 eligible CCS we traced and contacted 3593 of whom 2527 returned the SCCSS questionnaire. We excluded 119 participants who did not report height and weight, 355 who were younger than 15 or older than 45 years, and a further 117 who had received HSCT. We thus included 1936 CCS in this study, of whom 546 had been treated for ALL, 114 NHL, 195 HL, and 1081 for other types of cancer (Supplementary Figure S2).

We received consent to contact 1530 siblings, of whom 866 returned the questionnaire; 300 were outside the age range, and 20 did not report height and weight, thus 546 siblings were finally included in the analyses. Of 41,008 households surveyed in the general population (SHS), 21,597 replied to the survey. In those responding households, 9591 persons who were aged 15-45 years were included in the analysis.

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

Table I. Clinical characteristics of childhood cancer survivors

	CCS (*n*=1936)		ALL survivors (*n*=546)			NHL survivors (*n*=114)			HL survivors (*n*=195)		
Characteristics	*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%).

[d]: 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 II. General characteristics of childhood cancer survivors, their siblings, and the general population (Swiss Health Survey)

	CCS (*n*=1936)		Siblings[a] (*n*=725)			General population[a] (*n*=9591)		
Characteristics	*n*	(%)	*n*	($\%_{std}$)	***p-value***[b]	*n*	($\%_{std}$)	***p-value***[b]
Gender								
Male	1034	(53)	301	(54)	***n.a.***	4645	(54)	***n.a.***
Age at survey, y								
15-19	509	(26)	142	(26)	***n.a.***	1518	(33)	***n.a.***
20-24	504	(26)	162	(24)		1440	(23)	
25-29	388	(20)	168	(23)		1174	(13)	
30-34	259	(13)	115	(13)		1424	(11)	
35-45	276	(14)	138	(14)		4035	(19)	
Parents' education (highest degree)[c]								
Primary	33	(6)	6	(4)	***0.243***	n.a.		
Secondary	302	(59)	77	(54)				
Tertiary	174	(34)	59	(42)				
Personal education[d]								
Primary	108	(8)	24	(4)	***<0.001***	691	(8)	***<0.001***
Secondary	966	(68)	359	(62)		4549	(62)	
Tertiary	353	(25)	200	(35)		2833	(30)	
Migration background	453	(23)	132	(23)	***n.a.***	3454	(23)	***n.a.***
Sports[e]	1281	(66)	506	(71)	***0.041***	5598	(64)	***0.051***
BMI at survey								
Underweight	113	(6)	19	(2)	***<0.001***	349	(3)	***<0.001***
Normal	1321	(68)	523	(74)		6354	(72)	
Overweight	372	(19)	149	(20)		2285	(24)	
Obese	130	(7)	34	(4)		603	(6)	

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

Overweight and glucocorticoid therapy

The prevalence of overweight among all CCS was 26% at survey. This was similar to the overweight prevalence in the comparison groups after standardization according to CCS: 24% in siblings (p=0.34) and 25% in the general population (p=0.48) (Table II, **Supplementary Figure S3**). When we stratified CCS by treatment, we found that the prevalence of overweight was 23% in CCS treated with no glucocorticoids and no CRT (205 of 889), 24% in those treated with glucocorticoids alone (166 of 686), 37% in CCS treated with ≥20 Gy CRT (47 of 127, p<0.01), and 49% in those treated with both glucocorticoids and ≥20 Gy CRT (49 of 101, p<0.001) (**Figure 1**). There was a weak trend (p=0.08), suggesting an interaction that the effect of CRT tended to be higher in CCS also treated with glucocorticoids.

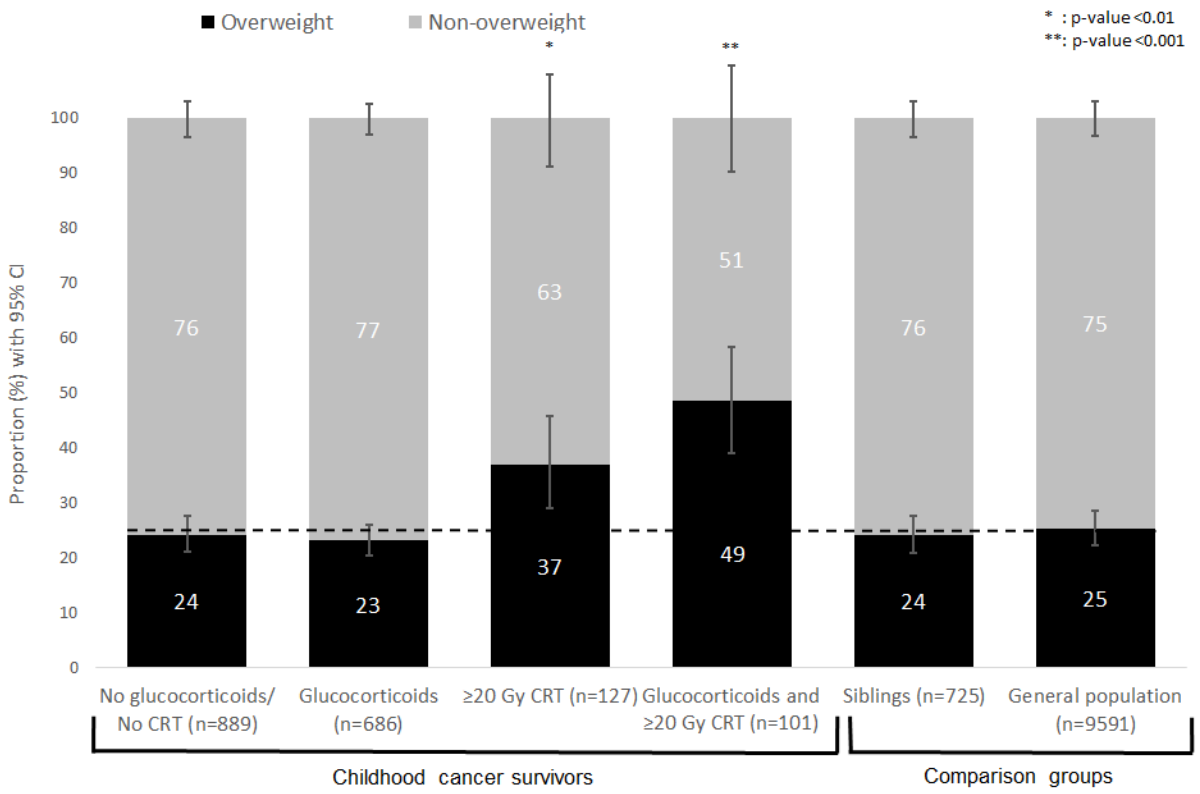

Figure 1. Prevalence of overweight in long-term childhood cancer survivors, by treatment with glucocorticoids and ≥20 Gray cranial radiation.
CI, confidence interval; CRT, cranial radiation therapy; Gy, gray;
Comparison groups were standardized on gender, age at survey, migration background, and language 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

In multivariable logistic regression models we found that overweight was not associated with cumulative glucocorticoid dose either in CCS overall or in the three cancer types treated frequently with glucocorticoids (**Table III**). But, CCS and ALL survivors treated with ≥20 Gy CRT were more likely to be overweight. Interaction tests did not suggest that the cumulative effect of glucocorticoids differed by gender, age, year of diagnosis, time since diagnosis, chemotherapy, CRT, or history of relapse (**Supplemental Table S2**).

Dose-response relationship between overweight and glucocorticoids

We found no evidence supporting a dose-response relationship between cumulative prednisone, dexamethasone, or both combined and BMI Z-scores, either when stratifying for CRT ($p_{trend\ no\ CRT}$=0.994, $p_{trend\ <20Gy}$=0.510, and $p_{trend\ ≥20Gy}$= 0.174, **Figure 2**), or when analyzing the entire CCS group adjusted for cumulative CRT dose ($p_{trend\ prednisone}$=0.085, $p_{trend\ dexamethasone}$=0.176, and $p_{trend\ glucocorticoids}$ =0.583 **Supplementary Figure S4**). CCS who got high prednisone doses (≥8000 mg/m^2) tended to have higher BMI Z-scores. In ALL survivors we also observed no dose-response relationship ($p_{trend\ prednisone}$=0.223, $p_{trend\ dexamethasone}$=0.063, and $p_{trend\ glucocorticoids}$ =0.512, **Supplementary Figure S5)**.

Table III. 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)		
	n_{ow}/n_{total}	Crude OR (95% CI)	Adj OR (95% CI)[a]	n_{ow}/n_{total}	Crude OR (95% CI)	Adj OR (95% CI)[a]	n_{ow}/n_{total}	Crude OR (95% CI)	Adj OR (95% CI)[a]	n_{ow}/n_{total}	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)
p-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)	-	-	-	-	-	-
p-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)
p-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	-	-
p-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

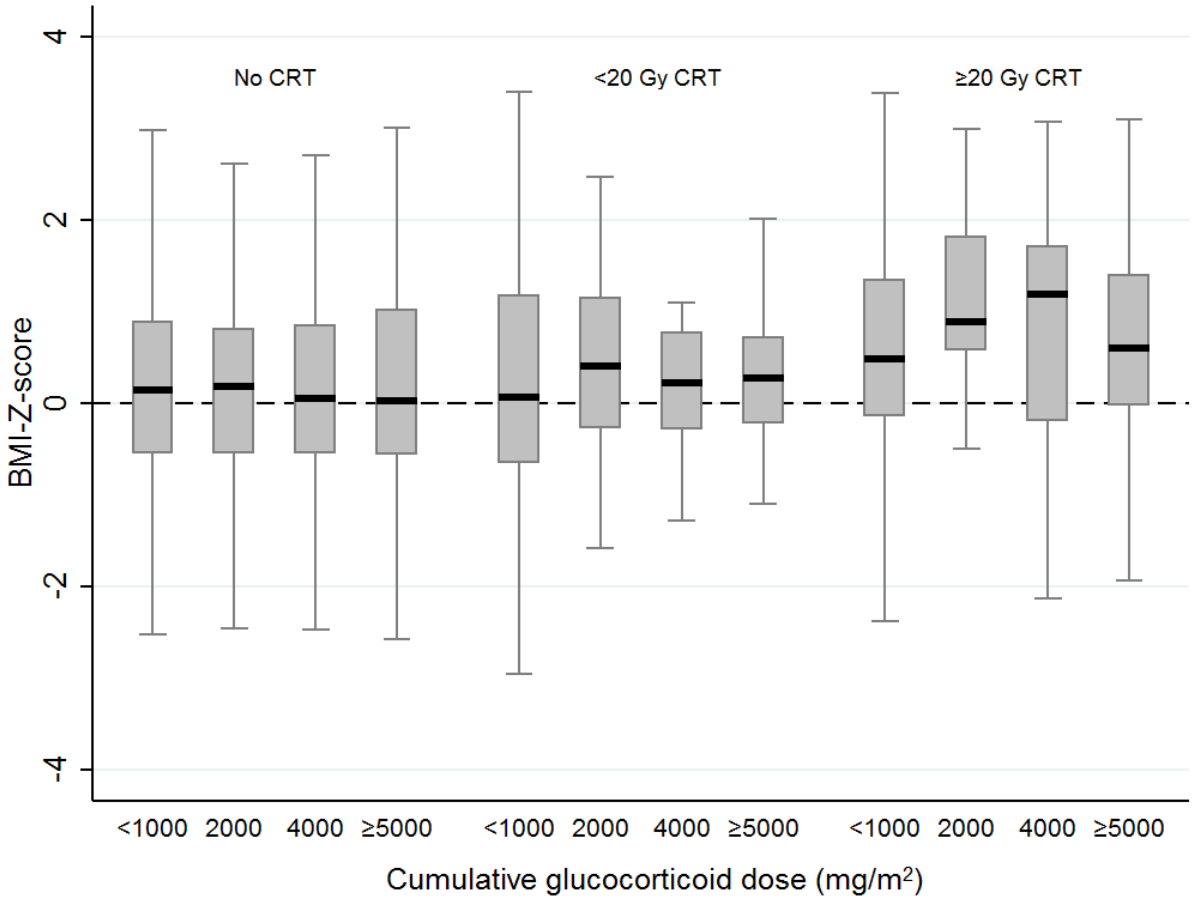

Figure 2. Box-plot of the dose-response relationship between BMI Z-score and cumulative glucocorticoid dose stratified by cranial radiation therapy in childhood cancer survivors (N=1936)
BMI, body mass index; CRT, cranial radiation therapy; Gy, gray
p-values for trend for no CRT 0.658, <20 Gy CRT 0.937, and ≥20 Gy CRT 0.309

Prednisone versus dexamethasone

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

DISCUSSION

At a median 17 years after cancer diagnosis, 26% of CCS in Switzerland were overweight. This prevalence is comparable to that in siblings and healthy peers in the general population. Prevalence of overweight was 23% in those CCS treated with glucocorticoids, but higher for CCS treated with cranial radiation ≥20 Gy (37%), and yet higher among CCS treated with both

glucocorticoids and cranial radiation ≥20 Gy (49%). The effect of CRT on overweight tended to be higher if CCS were also treated with glucocorticoids, but power for interaction tests was low. There was no evidence for a dose-response relationship between the cumulative glucocorticoid dose and being overweight, except for a possible effect at the highest doses (prednisone ≥8000 mg/m^2).

Overweight and obesity during treatment is frequent in ALL patients who receive high doses of glucocorticoids [33], but the long-tern impact of glucocorticoids on overweight has not been well studied. An US study of 784 ALL survivors followed over 26 years found an association of obesity with CRT, but not cumulative glucocorticoid dose. That finding is similar to ours, but ALL survivors with low glucocorticoid doses in the US study received high CRT doses. This could have masked an association between glucocorticoids and obesity [34]. A Dutch study of 113 ALL survivors 10 years after treatment found that higher cumulative prednisone doses led to higher BMI Z-scores at end of treatment and shortly thereafter, but not in the long-term [18]. The cumulative prednisone doses in the study were much higher than ours; of the 65 survivors who received only prednisone 60 (92%) survivors had received a cumulative dose of 9800 mg/m^2, or more. We also found post hoc evidence that higher cumulative prednisone doses (≥8000 mg/m^2) lead to more overweight, but after multivariable adjustment this effect disappeared. A dose-response association between cumulative glucocorticoid dose and BMI was also seen in a longitudinal single-center study in the US of 165 ALL survivors. BMI was assessed five years after diagnosis and again, cumulative glucocorticoid doses were higher (around 50% had a cumulative dose of >9000 mg/m^2) [9]. We found in univariable analyses that survivors who got the highest cumulative prednisone dose (≥5824 mg/m^2) were more likely to be overweight. After adjustment, the association was similar in magnitude and direction, but was no longer significant. We did not find an association between cumulative dexamethasone and overweight in CCS. However, follow-up time was longer in CCS treated with prednisone because dexamethasone was introduced more recently. ALL survivors who got a cumulative dexamethasone dose of ≥1260 mg/m^2 were even less likely to be overweight than those who were treated with a lower dosage. The dose-response relationship between cumulative dexamethasone and BMI Z-scores showed a dent with higher doses of dexamethasone. Given the wide confidence intervals this finding is most likely due to chance. The dint could also be a surrogate for more severe disease and more intense treatment, leading to less weight gain over time. Studies that look at the association between glucocorticoids and overweight in survivors of tumors other than ALL are limited. In 88 HL survivors in complete continuous remission for 16 years, no difference in BMI was found between those treated with and without prednisone [17]. The glucocorticoid dose is lower and chemotherapy duration is shorter in HL

compared to ALL survivors. We saw no association between glucocorticoids and overweight in either survivor group.

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

Treatment of childhood cancer increases survivors' risk of chronic diseases. Overweight can worsen disease burden, in particular when it involves development of endocrine complications such as type II diabetes. While our study does not suggest glucocorticoids are associated with long-term overweight, advice on weight control, a healthy lifestyle, and physical activity should always be part of survivorship care, with a special focus on patients who received CRT as well as potentially those who received very high doses of glucocorticoids.

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

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AUTHOR CONTRIBUTIONS

FNB conducted the statistical analyses and wrote the article; RK, CS, MB, RAA, NXvdW, and CEK contributed to the concept and the design of the study; CS, NXvdW, and RAA gave support in calculating cumulative doses of glucocorticoids, and RK, MB, and CEK gave support in the statistical analyses. All authors have revised earlier drafts and approved the final article.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

REFERENCES

[1] McNeer JL, Nachman JB. The optimal use of steroids in paediatric acute lymphoblastic leukaemia: no easy answers. British Journal of Haematology. 2010;149: 638-652.
[2] Fardet L, Fève B. Systemic Glucocorticoid Therapy: a Review of its Metabolic and Cardiovascular Adverse Events. Drugs. 2014;74: 1731-1745.
[3] Warris LT, van den Akker ELT, Bierings MB, et al. Acute Activation of Metabolic Syndrome Components in Pediatric Acute Lymphoblastic Leukemia Patients Treated with Dexamethasone. PLoS ONE. 2016;11: e0158225.
[4] Janiszewski PM, Oeffinger KC, Church TS, et al. Abdominal Obesity, Liver Fat, and Muscle Composition in Survivors of Childhood Acute Lymphoblastic Leukemia. The Journal of Clinical Endocrinology & Metabolism. 2007;92: 3816-3821.
[5] Tonorezos ES, Hudson MM, Edgar AB, et al. Screening and management of adverse endocrine outcomes in adult survivors of childhood and adolescent cancer. The Lancet Diabetes & Endocrinology. 2015;3: 545-555.
[6] Inaba H, Pui C-H. Glucocorticoid use in acute lymphoblastic leukemia: comparison of prednisone and dexamethasone. The Lancet Oncology. 2010;11: 1096-1106.
[7] Iughetti L, Bruzzi P, Predieri B, Paolucci P. Obesity in patients with acute lymphoblastic leukemia in childhood. Italian Journal of Pediatrics. 2012;38: 4-4.
[8] Zhang FF, Kelly MJ, Saltzman E, Must A, Roberts SB, Parsons SK. Obesity in Pediatric ALL Survivors: A Meta-Analysis. Pediatrics. 2014;133: e704-e715.
[9] Chow EJ, Pihoker C, Hunt K, Wilkinson K, Friedman DL. Obesity and hypertension among children after treatment for acute lymphoblastic leukemia. Cancer. 2007;110: 2313-2320.
[10] Sklar CA, Mertens AC, Walter A, et al. Changes in body mass index and prevalence of overweight in survivors of childhood acute lymphoblastic leukemia: Role of cranial irradiation. Medical and Pediatric Oncology. 2000;35: 91-95.
[11] Wilson CL, Liu W, Yang JJ, et al. Genetic and clinical factors associated with obesity among adult survivors of childhood cancer: a report from the St. Jude Lifetime cohort. Cancer. 2015;121: 2262-2270.
[12] Arpe M-LH, Rørvig S, Kok K, Mølgaard C, Frandsen TL. The association between glucocorticoid therapy and BMI z-score changes in children with acute lymphoblastic leukemia. Supportive Care in Cancer. 2015;23: 3573-3580.
[13] Collins L, Zarzabal LA, Nayiager T, Pollock BH, Barr RD. Growth in Children With Acute Lymphoblastic Leukemia During Treatment. Journal of pediatric hematology/oncology. 2010;32: e304-e307.
[14] Jansen H, Postma A, Stolk RP, Kamps WA. Acute lymphoblastic leukemia and obesity: increased energy intake or decreased physical activity? Supportive Care in Cancer. 2009;17: 103-106.
[15] Asner S, Ammann RA, Ozsahin H, Beck-Popovic M, von der Weid NX. Obesity in long-term survivors of childhood acute lymphoblastic leukemia. Pediatric Blood & Cancer. 2008;51: 118-122.
[16] Murphy AJ, Wells JC, Williams JE, Fewtrell MS, Davies PS, Webb DK. Body composition in children in remission from acute lymphoblastic leukemia. The American Journal of Clinical Nutrition. 2006;83: 70-74.
[17] van Beek RD, van den Heuvel-Eibrink MM, Hakvoort-Cammel FG, et al. Bone Mineral Density, Growth, and Thyroid Function in Long-Term Survivors of Pediatric Hodgkin's Lymphoma Treated with Chemotherapy Only. The Journal of Clinical Endocrinology & Metabolism. 2009;94: 1904-1909.
[18] Van Dongen-Melman JEWM, Hokken-Koelega ACS, Hahlen K, Groot AD, Tromp CG, Egeler RM. Obesity after Successful Treatment of Acute Lymphoblastic Leukemia in Childhood. Pediatr Res. 1995;38: 86-90.
[19] Kuehni CE, Rueegg CS, Michel G, et al. Cohort Profile: The Swiss Childhood Cancer Survivor Study. International Journal of Epidemiology. 2012;41: 1553-1564.
[20] Michel G, von der Weid NX, Zwahlen M, et al. The Swiss Childhood Cancer Registry: rationale, organisation and results for the years 2001-2005. Swiss Medical Weekly. 2007;137: 502-509.
[21] Michel G, von der Weid NX, Zwahlen M, Redmond S, Strippoli MPF, Kuehni CE. Incidence of childhood cancer in Switzerland: The Swiss childhood cancer registry. Pediatric blood & cancer. 2008;50: 46-51.
[22] Robison LL, Mertens AC, Boice JD, et al. Study design and cohort characteristics of the childhood cancer survivor study: A multi-institutional collaborative project. Medical and Pediatric Oncology. 2002;38: 229-239.
[23] Hawkins MM, Lancashire ER, Winter DL, et al. The British Childhood Cancer Survivor Study: Objectives, methods, population structure, response rates and initial descriptive information. Pediatric blood & cancer. 2008;50: 1018-1025. 15

[24] Schweizerische Eidgenossenschaft Bundesamt für Statistik BFS. Die Schweizerische Gesundheitsbefragung 2012 in Kürze, Konzept, Methode, Durchführung. Neuchâtel: Swiss confederation, 2013.
[25] Germann U. Abschlussbericht zur Volkszählung 2000. Neuchâtel, Switzerland: Bundesamt für Statistik, 2005.
[26] Belle FN, Weiss A, Schindler M, et al. Overweight in childhood cancer survivors: the Swiss Childhood Cancer Survivor Study. The American Journal of Clinical Nutrition. 2018;107: 3-11.
[27] National Institutes of Health. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: The Evidence Report. Obesity Research. 1998;6: 51S-209S.
[28] Braegger C, Jenni O, Konrad D, Molinari L. Neue Wachstumskurven für die Schweiz. Paediatrica. 2011;22.
[29] International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10). Available from URL: http://apps.who.int/classifications/icd10/browse/2010/en#/P05-P08.
[30] U.S. Department of Health and Human Services; Food and Drug Administration (FDA); Center for Drug Evaluation and Research (CDER). Guidance for Industry, Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers Available from URL: https://www.fda.gov/downloads/Drugs/.../Guidances/UCM078932.pdf [accessed 06.09, 2017].
[31] Haynes RJ, Murad F. Adrenocorticotropic hormone; adrenocortical steroids and their analogs; inhibitors of adrenocortical steroid biosynthesis. 7 ed. New York, NY: Mac-millan Publishing Company, 1985.
[32] Inaba H, Yang J, Kaste SC, et al. Longitudinal Changes in Body Mass and Composition in Survivors of Childhood Hematologic Malignancies After Allogeneic Hematopoietic Stem-Cell Transplantation. Journal of Clinical Oncology. 2012;30: 3991-3997.
[33] Zhang FF, Rodday AM, Kelly MJ, et al. Predictors of Being Overweight or Obese in Survivors of Pediatric Acute Lymphoblastic Leukemia (ALL). Pediatric Blood & Cancer. 2014;61: 1263-1269.
[34] Nottage KA, Ness KK, Li C, Srivastava D, Robison LL, Hudson MM. Metabolic Syndrome and Cardiovascular Risk among Long-Term Survivors of Acute Lymphoblastic Leukaemia - From the St. Jude Lifetime Cohort. British Journal of Haematology. 2014;165: 364-374.
[35] Caplan A, Fett N, Rosenbach M, Werth VP, Micheletti RG. Prevention and management of glucocorticoid-induced side effects: A comprehensive review: Ocular, cardiovascular, muscular, and psychiatric side effects and issues unique to pediatric patients. Journal of the American Academy of Dermatology. 2017;76: 201-207.

SUPPLEMENTARY MATERIAL

Table S1. 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; 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; R-CHOP, rituximab cyclophosphamide hydroxyl-doxorubicin vincristine prednisone; 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

Table S2. 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	0.672	0.373	0.665	0.971
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

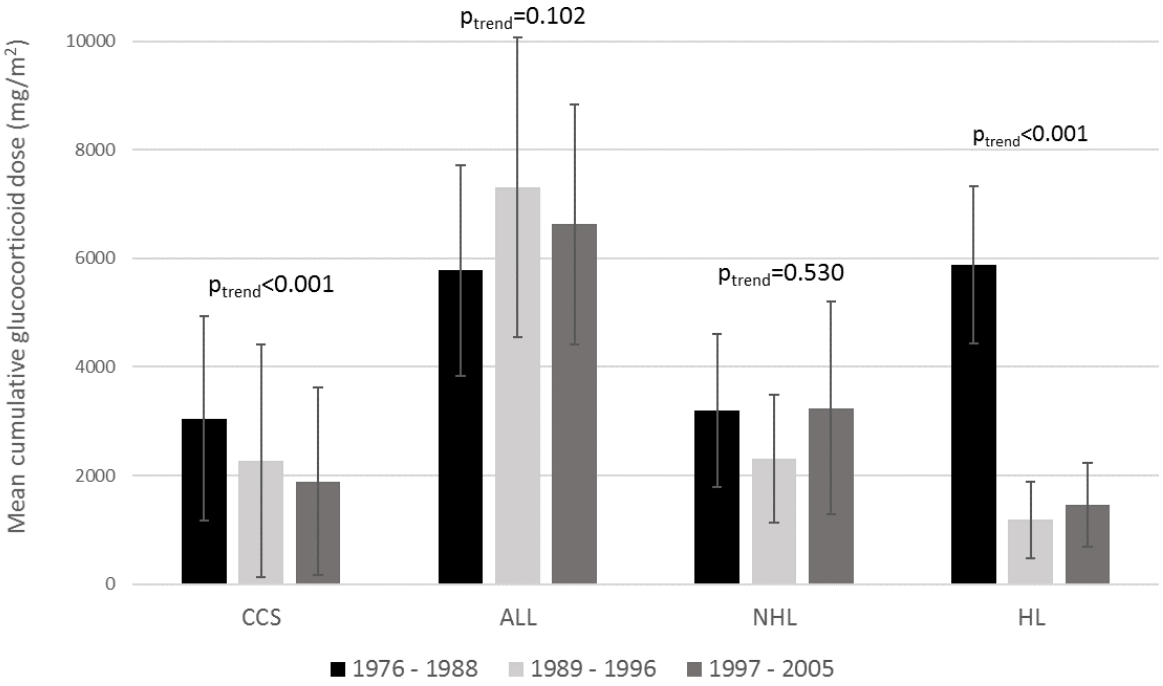

Figure S1. Time trends in exposure to glucocorticoids (cumulative dose) during treatment in CCS, ALL, NHL, and HL survivors

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

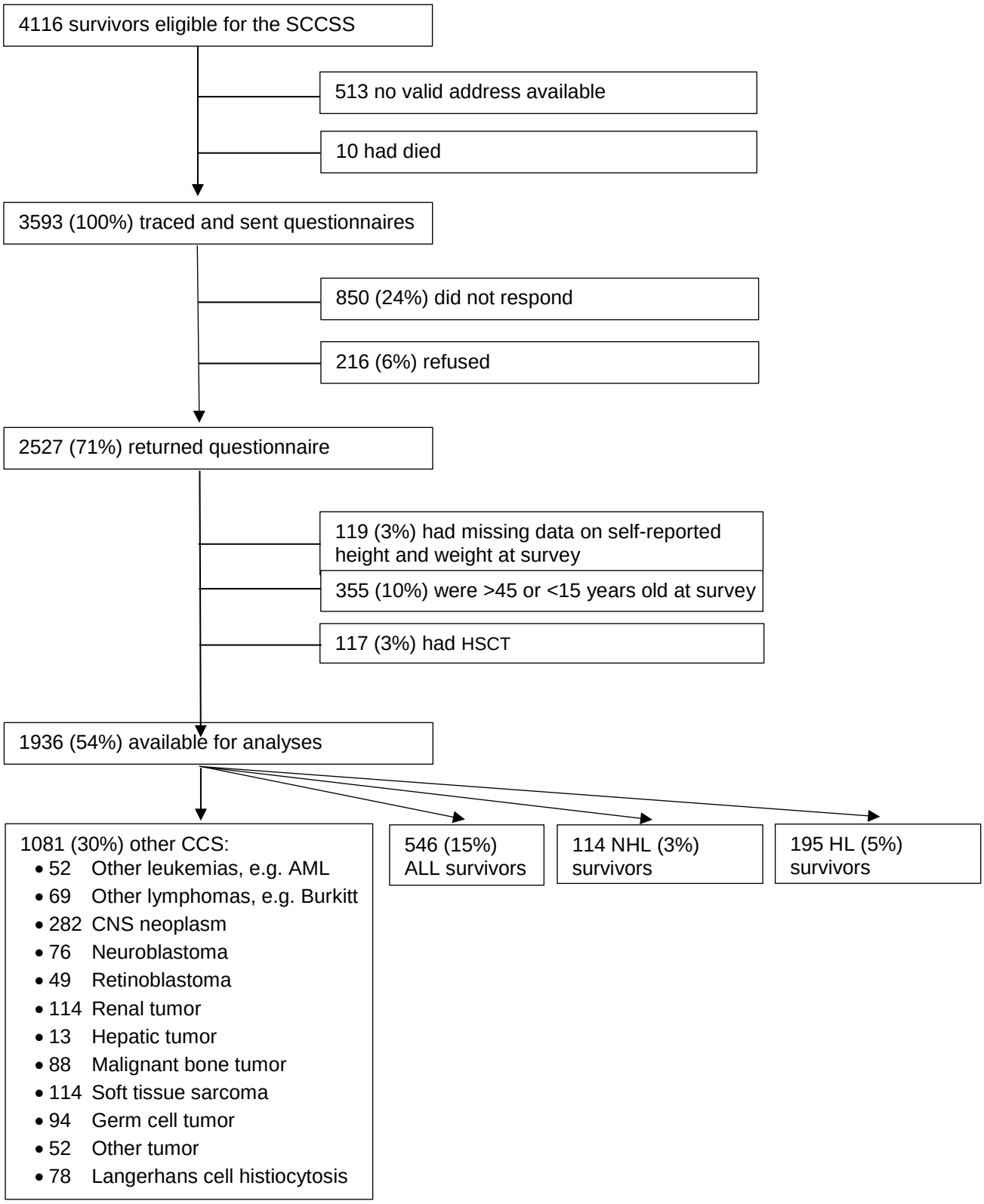

Figure S2. Response rates and study populations in the Swiss Childhood Cancer Survivor Study

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

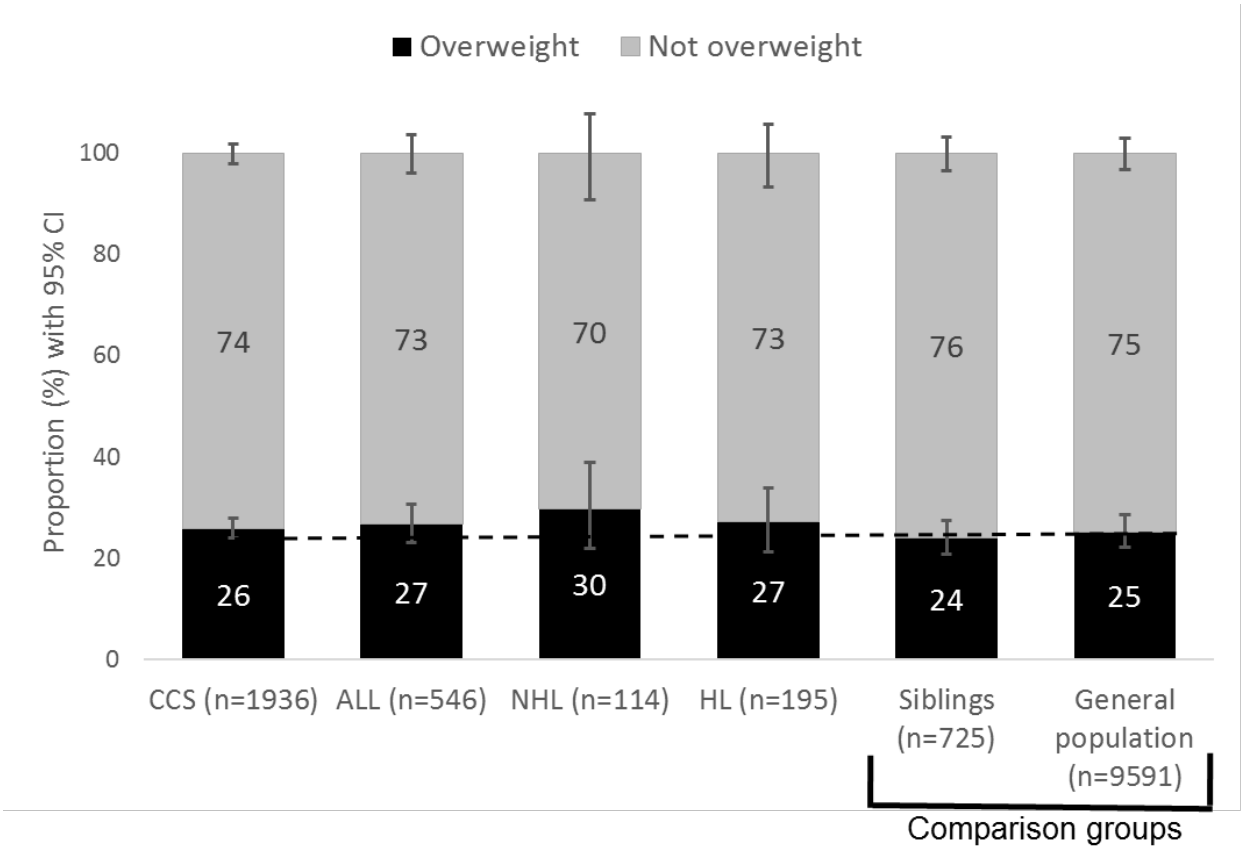

Figure S3. Prevalence of overweight in childhood cancer survivors, their siblings, and the general population

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

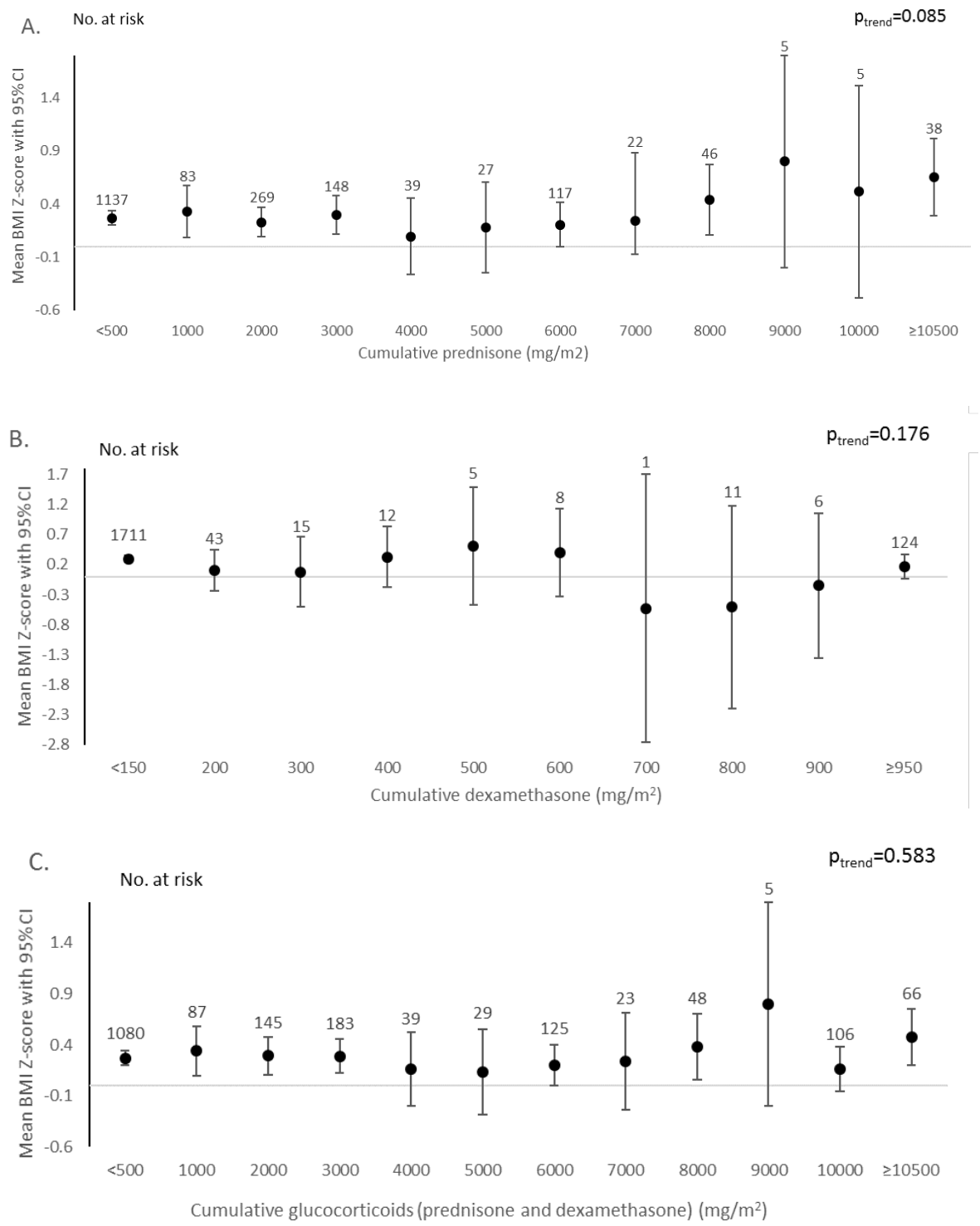

Figure S4. Dose-response relationship between cumulative A. Prednisone, B. Dexamethasone, C. Glucocorticoids combined (prednisone and dexamethasone) and BMI Z-score in childhood cancer survivors (N=1936), adjusted for cumulative dose of cranial radiation therapy

BMI, body mass index; CI, confidence interval; No, number;
p-values for testing trend of BMI Z-score across cumulative glucocorticoid dose

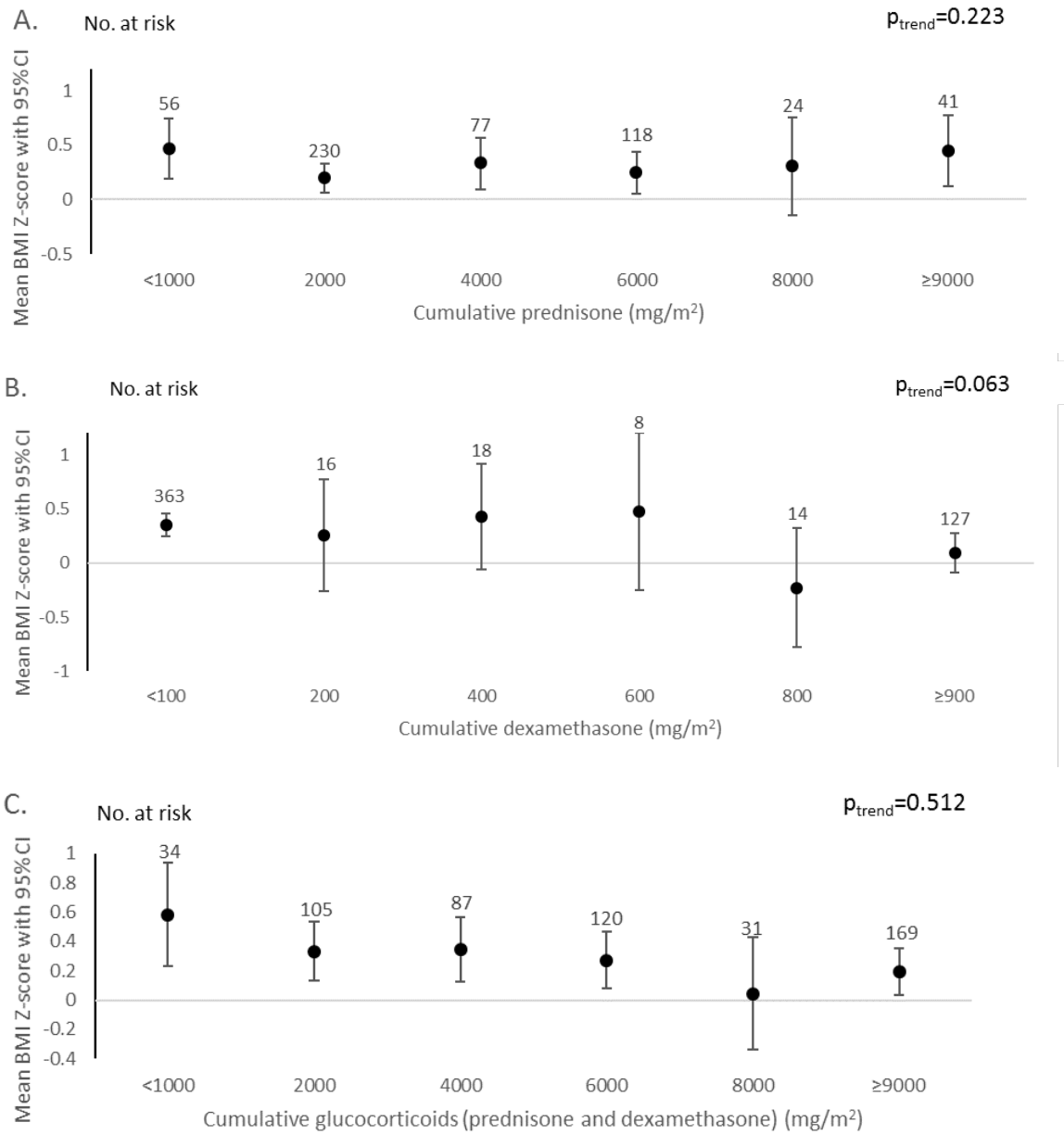

Figure S5. Dose-response relationship between cumulative A. Prednisone, B. Dexamethasone, C. Glucocorticoids combined (prednisone and dexamethasone) and BMI Z-score in ALL survivors (N=546), adjusted for cumulative dose of cranial radiation therapy

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

Chapter 8

General discussion

This thesis addressed dietary adherence, its determinants, and the prevalence and risk factors for being overweight during and long after childhood cancer treatment. For this purpose, I used *1)* available data from the first questionnaire of the Swiss Childhood Cancer Survivor Study (SCCSS); *2)* new data from a follow-up questionnaire including a food frequency questionnaire which I developed and mailed to adolescent and adult survivors; *3)* new data from a multicentre validation study which I set up. This study compared dietary intake assessed via the food frequency questionnaire with urine spot samples from survivors and patients (analyses ongoing), and *4)* available data from childhood cancer patients in a multicentre cohort study (**Introduction, Figure 5**).

MAIN FINDINGS IN CONTEXT OF OTHER LITERATURE

An overview of the studies in this thesis can be found in **Table I**. Our results do not indicate that childhood cancer survivors (CCS) adhere better to dietary recommendations than their peers. In addition, prevalence and risk factors for overweight in CCS are similar to peers. Within patients we saw that being diagnosed with acute lymphoblastic leukaemia (ALL) and lymphoma were both risk factors for weight gain.

"Low adherence to dietary recommendations in adult childhood cancer survivors" (Chapter 2)

According to our research, CCS poorly adhered to dietary recommendations, but equally poor as their siblings and the general Swiss population. Our findings on low adherence are in line with previously published data within the general Swiss population [1, 2] and CCS in other countries [3-9]. In line with our results, previous studies reported no relevant differences in level of dietary adherence between CCS and comparison groups [3, 8]. We found that predictors of adherence in CCS were similar in siblings and the general population. Adherence to dietary recommendations was not better among CCS with a higher cardiovascular disease (CVD) risk because of cardiotoxic treatment. As in accord to our study, a small US study in 91 CCS found little to no difference between dietary intake and cancer diagnosis and therapy [8]. An exception was exposure to cranial radiation therapy (CRT), which was related to even poorer adherence.

"Dietary intake of Swiss adult survivors of childhood cancer compared to the general population" (Chapter 3) and *"Urine spot collection in childhood cancer patients and survivors: a pilot study" (Chapter 4)*

We assessed CCS' dietary intake in more detail with a food frequency questionnaire (FFQ, Chapter 3) and compared the FFQ with nutrient measurements in urine spot samples (analyses ongoing, Chapter 4). Till now far, only two reports on detailed dietary intake

information have been published within a large CCS study population (≥500) [4, 10]. Both reports where from the St. Jude Lifetime Cohort Study, US.

"Overweight in childhood cancer patients at diagnosis and throughout therapy: a multicentre cohort study" (Chapter 5)

We found that the prevalence of overweight of Swiss childhood cancer patients (CCP) increased from 8% at diagnosis to 13% at the end of treatment. A smaller Dutch prospective study in 133 CCP with a medium age of 8 years found a lower prevalence (diagnosis: 5%; one year after diagnosis: 10%). This was likely due to the used cut-offs to define overweight (>2 standard deviations), which were less conservative than in our study where we used cut-offs of the International Obesity Taskforce [11]. US studies found higher prevalences of overweight at diagnosis: 21-55% and at end of treatment: 40-69% [12, 13]. This is in accord with the higher prevalences also seen in the general US population [14]. ALL and lymphoma patients in our study showed a continuously increasing trend in BMI Z-scores over time during treatment in line with previous literature [12, 13, 15-18].

"Overweight in childhood cancer survivors: the Swiss Childhood Cancer Survivor Study" (Chapter 6)

Long after cancer diagnosis (median 15 years), we found that 26% of all CCS were overweight. This prevalence was comparable to that of their healthy peers (siblings: 22%; general population: 25%). However, CCS diagnostic groups differed: 31% of central nervous system (CNS) tumour survivors were overweight, whereas only 13% of neuroblastoma and 18% of soft tissue sarcoma survivors were overweight. CNS tumour survivors are exposed to several risk factors that might lead to hypothalamic obesity such as CRT, hypothalamic tumours, and surgical damage [19-21]. In line with previous studies, we confirmed that receiving ≥20 Gy CRT was associated with being overweight [22-24]. The US Childhood Cancer Survivor Study (CCSS) in 7195 CCS reported also that those who were treated for neuroblastoma and soft tissue sarcoma were less likely to be obese compared to the general population [24].

"No evidence for overweight in long-term childhood cancer survivors after glucocorticoid treatment" (Chapter 7)

We saw that CCS who received CRT and glucocorticoids were more overweight than CCS who were only treated with CRT, 49% versus 37%. However, there was no evidence for a dose-response relationship between the cumulative glucocorticoid dose and being overweight, except for a possible effect at the highest doses (prednisone ≥8000 mg/m^2). In contrast, dose-response relationships were observed at end of treatment and shortly after (<5 years) in studies among ALL survivors [25, 26], but the given cumulative glucocorticoid dosages were

higher than in our study population. Similar to our study, no long-term association between cumulative glucocorticoid dose and obesity was found in 784 US ALL survivors who were followed over 26 years [27]. But, the association between glucocorticoids and obesity could have been masked as ALL survivors with low glucocorticoid doses in this US study received high CRT doses.

Table I. Overview of the studies and main findings presented in this thesis

Ch.	Design	Population, *n*	Aim	Findings
			Dietary intake	
2	Cohort	Survivors, *1864* *Comparison groups:* -Siblings, *698* -SHS, *8258*	Dietary adherence of food groups and determinants for adherence	-% of CCS which met recommended dietary intakes: meat (43%), fruit (34%), fish (30%), dairy products (18%), vegetables (11%), combined fruit and vegetables (7%). -Dietary adherence was associated with: gender, parental education, migration background, language region in Switzerland, smoking, alcohol consumption, and sport participation.
3	Cohort	Survivors, *878* *Comparison groups:* -Bus Santé, *9216* -CoLaus, *1311* -menuCH, *1189*	Detailed dietary intake and quality (FFQ) and clinical determinants	-Analyses are ongoing
4	Validation	Patients, *6* Survivors, *119*	Correspondence between FFQ and urine spot samples	-Response rate: patients (75%), outpatients (50%). -Patient recruitment is difficult. -Analyses are ongoing.
			Overweight	
5	Cohort	Patients, *327*	Weight development during treatment and risk factors for weight gain	-During the first half of treatment, BMI Z-scores increased in acute lymphoblastic leukaemia (ALL) and lymphoma patients, whereas for patients with central nervous system tumours, sarcoma, or other types of cancer BMI Z-scores tended to drop initially. During the second half of treatment BMI Z-scores of all patients tended to increase. -Risk factors for weight gain: being a boy, diagnosed with ALL or lymphoma.
6	Cohort	Survivors, *2365* *Comparison groups:* -Siblings, *819* -SHS, *9591*	Overweight prevalence and sociodemographic risk factors	-Overweight prevalence: 26% -Risk factors for being overweight: male sex, both young and older age at study, lower education, migration background, no sports participation, and being treated with cranial radiotherapy (≥20 gray)
7	Cohort	Survivors, *1936* *Comparison groups:* -Siblings, *546* -SHS, *9591*	Association between cancer treatment and overweight	-No dose-response relationship between cumulative glucocorticoid doses and overweight -No evidence that cranial radiotherapy modified the effect of cumulative glucocorticoid dose treatment on overweight.

BMI, body mass index; FFQ, food frequency questionnaire; SHS, Swiss Health Survey

METHODOLOGICAL CONSIDERATIONS

Most of the methodological considerations of the studies included in this thesis are discussed in the corresponding chapter. We focus here on the relevant epidemiological issues as a whole to interpret the results, e.g. internal and external validity of the observed observation and causation.

Internal validity

Challenges in dietary intake assessment

Within the SCCSS, dietary intake was assessed with self-reported general brief questions at the time of first survey. These questions on fruit, vegetables, meat, fish, milk(-products), and fast-food were derived from the Swiss Health Survey (SHS 2007). In this thesis, I attempt to improve the available dietary intake information among CCS in the SCCSS follow-up questionnaire. We made use of a validated FFQ which was send to all CCS who filled in the first questionnaire and who were 16 years or older at time of the follow-up survey, used urine spot samples as an objective biomarker, and included comparison groups in which diet was assessed with the same FFQ.

The used FFQ in the SCCSS follow-up questionnaire was originally only developed and validated for the French speaking language region of Switzerland [28, 29]. As the SCCSS is a nationwide study we investigated if most frequent food products consumed in the German and Italian speaking language regions were also included and extended the FFQ with 15 additional food products.

Between 1993-2012 a small decrease in total energy intake was seen in the "Bus Santé" Geneva study [30]. This may suggest that the dietary habits over time including a higher consumption of processed food changed minimal in the French speaking language region of Switzerland. Therefore, although the FFQ was already developed in 1991 [28], we believe that our conclusions would not have substantially differed if we would have had a more up-to-date dietary intake assessment tool.

The assessed absolute dietary intake needs to be interpreted with caution. Reporting bias could have occurred; overweight CCS tend to underreport their total energy intake but whether this is done in a similar degree as in the general population is unknown [31]. To adjust for reporting bias we excluded CCS with a potential unreliable dietary intake, e.g. extreme energy intakes and unrealistic values for nutrient intakes. Furthermore, in conjunction with self-reported dietary intake from the FFQ we used urine biomarkers.

Challenges in body weight and height assessment

In the studies of this thesis, we used BMI calculations as an indirect measure of overweight and obesity. In the performed studies, we had information on weight and height at time of survey from self-administered questionnaires for CCS and most comparison groups. Study participants were instructed to record height without shoes and weight without clothes. Differential misclassification could have occurred, as overweight and obese adult participants tend to underestimate their weight more than normal weight participants do [32, 33].

The indirect measurement of body fat with BMI, instead of direct measurements like underwater weighting (densitometry) and dual-energy x-ray absorptiometry has several shortcomings. First, BMI calculations do not take age, gender, and muscle mass percentage into account. Second, body fat increases and lean mass decreases with age and the relationship between BMI and body fat differs between men and women [34]. Thus, participants with a similar BMI could have different body fat percentages.

Several errors in height and weight report could have occurred. Height and weight might be better monitored in CCS than in the general population. This could make CCS more aware of their true height and weight than the general population, which could have caused surveillance bias. Reporting bias could have occurred as the questionnaire first asks CCS about late effects and then about height and weight. For example, participants with chronic health conditions could have underreported their weight more as they became aware of their health status than participants without chronic health conditions. However, because height and weight were self-reported in most of our study populations we expected the degree of nondifferential error of BMI assessment to be similar across CCS and comparison groups. An exception are the comparison groups in chapter 3, e.g. participants of the studies Bus Santé, CoLaus ("Cohorte Lausannoise"), and menuCH as their height and weight were measured by study staff.

Finally, we divided BMI into two categories: overweight (overweight and obesity) versus non-overweight (underweight and normal) although obesity is a chronic disease associated with multiple co-morbidities, whereas overweight is only a stage of pre-obesity. We dichotomized BMI as separate categories were small and outcomes for the categories overweight and obesity were in the same direction and magnitude as for the category overweight or obesity combined.

Confounding

Potential bias by confounding is common in observational studies and can bias the association of interest. Studies in this thesis (Chapter 2, 3, and 5) and other studies show that CCS with a good adherence to dietary guidelines and healthy body weight seem to be a more health conscious group who adopted various healthy lifestyle habits [4, 10]. They are more likely to be non-smokers [3, 10, 35] and have a higher physical activity level [10, 36-38] than those with a poor dietary adherence and high body weight. These differences between demographic and lifestyle factors between survivors (overweight/obese CCS versus those with a healthy body weight and CCS with a good versus a poor dietary adherence) could have affected our results. For this reason, we evaluated several potential lifestyle and health status-confounding factors in our regression models. Nevertheless, residual confounding can never be completely ruled out.

Like in the general population, CCS with a poor health status seem to have a lower social economic status (SES) [39]. Within epidemiological studies, participant's education level is a common used marker for SES and a strong predictor for good health and a healthy lifestyle [40, 41]. Within the SCCSS, some CCS were too young to reach their final level of education at time of survey or completed their final educational achievement with some delay [42]. For this reason, we used both the education level of CCS and their parents as a marker for SES. Adjusting for individual income would have misclassified participants as some CCS were still studying or chose to stay home for their children. Information on household income was often missing. Furthermore, simultaneous adjustment for educational level as a SES marker and other lifestyle factors could potentially have led to overadjustment of lifestyle factors.

External validity

In this section, we discuss the heterogeneity of the study population and the representativeness of the study results.

Heterogeneity of the study populations

We combined survivors of all childhood cancer diagnoses in several chapters of this thesis although each type of cancer has its own treatment protocols. For example, treatment duration, type, and dosage may vary per type of cancer as well as side effects and treatment related late effects. Within the different paediatric oncology clinics, we also saw differences in the used cancer treatment protocols for the same cancer type. For example in the past, clinics in the German speaking region of Switzerland tended to use more often protocols of the "Berlin/Frankfurt/Muenster study group" compared to the other language regions, where US protocols were more common.

The risk profiles of the study populations would have been more homogenous if we would have investigated CCS diagnosed with the same cancer type and treated with similar cancer protocols. However, as childhood cancer is rare and therefore numbers are low we combined all types of cancer to have sufficient power and performed subgroup analyses where possible.

Representativeness of study populations

The representativeness of the study populations is important for the translation of our findings to the whole population of CCS. Within the SCCSS, selection bias in CCS could have occurred due to nonresponse and nonparticipation. To reduce nonresponse, eligible survivors who did not filled in the first questionnaire were send a second copy of the questionnaire. Non-responders to the second copy were contacted by phone. This resulted in a response rate of 70%. Rueegg et al. estimated the effect of nonresponse bias on selected prevalence estimates

(somatic health, medical care, mental health, and health behaviours) in 930 early responders, 671 late responders, and 727 nonresponders to the first SCCSS questionnaire by constructing the complete population using inverse probability of participation weights. They found that nonresponse might only play a minor role, suggesting that responders were generalizable to the whole Swiss CCS population [43]. However, they did found differences in socio-demographic characteristics between responders and nonresponders. Responders were more likely to be women and non-immigrants but did not have a higher socioeconomic position based on neighbourhood level. From studies in the general population, we know that survey participants have more often a higher SES and education level, are less likely to be obese, and have in general a healthier lifestyle, e.g. are less likely to smoke, to drink frequently, to have a poor diet quality, and have less health conditions compared to nonparticipants [44-46]. Thus, the observed dietary intake could have been better and the obesity prevalence in CCS could have been lower than in reality.

For the follow-up questionnaire we selected only those survivors that filled in the first questionnaire. Non-responders to the follow-up questionnaire were send a second and if needed a third copy of the questionnaire. We obtained a response rate of 58%.

Survival bias could have also occurred within the SCCSS as CCS who survive longer tend to have an overall better health [47]. Furthermore, CCS who are underweight or obese at diagnosis and during survivorship tend to have a higher mortality and relapse rate [48-51]. Therefore, survivors with a healthier lifestyle and normal body weight could have been more likely to be eligible to participate, since the SCCSS included only survivors who survived at least five years after diagnosis.

In this thesis, we made use of several comparison groups reflecting the general population. Response rates in these comparison groups were overall lower than in CCS; SHS 2007 (66%), siblings (57%), Bus Santé (55-75%), SHS 2012 (53%), CoLaus (41%), and Swiss National Nutrition Survey (38%). These lower response rates could have affected the representativeness of the study populations for the general population.

To increase the validity of the comparison between CCS and the comparison groups, we standardised comparison groups for gender, age, migration background, and language region, according to the distribution in CCS. Within the used comparison groups, more women and older persons were included than within CCS. Also migrants and non-German speakers were less frequent among siblings, but more frequent in the general population than within CCS. The Bus Santé and CoLaus studies included only participants from the French language region in Switzerland.

Causation

No statement on causation can be made based of the currently conducted observational studies. In chapter 2, 3, 6, and 7, we made use of cohort studies with cross-sectional data. Since we did not have prospective follow-up data we could not assess the timing of an unhealthy dietary intake and weight status before, during and after treatment in CCS. Reverse causation could have biased our results, e.g. a lack of sports participation could have been due to overweight.

IMPLICATIONS FOR PUBLIC HEALTH AND CLINICAL PRACTICE

The national organisation Swiss Cancer League (www.liguecancer.ch) emphasizes in cancer prevention campaigns to increase fruit and vegetable consumption and reduce alcohol, red and processed meat intake. This could partly explain the higher levels of adherence for fruit and meat intake in CCS (Chapter 2). However, it is unclear to which extent CCS are aware of these dietary recommendations and if diet is perceived as a risk factor for late effects. Current CCS guidelines do not specifically focus on diet [52] or have general dietary recommendations [53, 54]. However, given the strong evidence about diet and health in general and the increasing data for CCS, focus should be placed on the importance of good eating habits and physical activity during annual long-term follow-up visits. Follow-up visits are especially recommended for CCS with moderate to severe late health effects or high risk cancer treatment, a group which could benefit of dietary and lifestyle counselling [55]. However, nutritional counselling seems not to be the standard in Switzerland in follow-up care. We performed a short survey among the heads of the nine Swiss paediatric oncology clinics to assess whether they discussed diet issues during follow-up visits. Six replied that they discuss diet in case CCS suffer from nutritional related late effects, and three indicated to discuss it routinely during each follow-up visit (personal communication). The growing research on dietary intake in CCS could help clinicians in the future to provide consistent uniform and comprehensive nutritional counselling during and after treatment.

This thesis showed risk factors for overweight development in childhood cancer patients and survivors (Chapter 5, 6, 7). Since overweight prevalence and risk factors for being overweight were similar in CCS as to the general population prevention methods can be the same as in the general population. An important exception are CNS tumour and leukaemia survivors treated with ≥20 Gy CRT and patients diagnosed with ALL and lymphoma, who have the highest risk of becoming overweight. The importance of obesity on long-term health needs to be raised especially in these patients and survivors. Since early overweight is a risk factor for overweight later in life, weight management interventions should be individually tailored during treatment. However, counselling during this period, when patients and families face the crisis

of a life-threatening illness and nutritional status is not a first priority, is challenging. In addition, children may receive high steroid doses, which increase appetite and fatty tissue, and they may experience fatigue or be immobilized for some time, which reduces their physical activity. During clinical follow-up, visits with multi-profession teams, including physicians, dieticians, nurses, and physiotherapists, might be a promising approach. Existing surveillance recommendations should be harmonised using an evidence-based approach to effectively implement standardised care in Switzerland and the rest of the world. International harmonised recommendation could benefit early detection, prevention, and intervention of overweight.

FUTURE RESEARCH PERSPECTIVES

Based on current evidence and the conclusions in this thesis, future research needs to be performed before evidence-based and standardised dietary and overweight/obesity surveillance guidelines for CCS can be composed. We recommend several future research opportunities in dietary assessment and weight management below.

Future research opportunities in dietary assessment

• We made use of a FFQ that was developed and validated only for the French-speaking Swiss adult population. I extended the FFQ with additional food products based on data of the Swiss National Nutrition Survey to include frequent food products consumed in the German and Italian-speaking part of Switzerland. Since the currently used FFQ is not validated for whole Switzerland, a new FFQ should be developed suitable for all language regions (Chapter 3).

• Although FFQs have become the primary method for measuring dietary intake in epidemiologic studies [56], continues efforts are needed to develop a new dietary assessment tool. This new tool should be easier to complete, rely less on memory, have correct portion sizes, not be restricted to a given food list, and rely less on question interpretation. Assessment via a smart phone application with a photo function could be the base for a new tool.

• In this thesis, we made the first steps to investigate the dietary intake of CCS long after treatment, when late effects could already have occurred and might influence dietary intake. Prospective and repeated dietary assessments from treatment onwards could investigate the potential association between dietary intake and late chronic health effects. As a next step, I recommend to investigate dietary interventions to prevent or reduce nutrition-related late effects during early survivorship.

• Evidence based dietary guidelines specific for CCS are needed to avoid long-term morbidity in this vulnerable population. Future epidemiologic studies should be performed in different types of childhood cancer so that dietary recommendations, if relevant, could be adapted to diagnosis and treatment exposures. A detailed and standardized survey among all paediatric

oncologists in Switzerland would give more information about the current situation in nutritional counselling practice.

• Currently, it is unclear to which extent CCS are aware of dietary recommendations and if diet is perceived as a risk factor for late effects. Therefore, I recommend a survey among CCS to investigate their attitude and knowledge of nutrition.

Future research opportunities in weight management

• Most research to date on overweight and obesity in CCP and CCS are based on BMI calculations from self-reported height and weight. I recommend direct body fat measurements as indirect measurements can introduce differential misclassification, which may result in a bias towards or away from the null. Furthermore, direct body fat measurements will give more insights in CCS body composition; lean mass versus fat mass. If direct body fat measurements are impossible to perform, I recommend BMI calculations with standardised measured height and weight by medical staff.

• Future studies are needed to investigate risk factors for overweight and obesity development over time, to which extent the risk for overweight and obesity differs between cancer types, and if there are any lifestyle interventions that can alter this risk. Our results indicated that CRT is a risk factor for overweight in CCS (Chapter 6 and 7), but less is known about abdominal radiation, TBI, and other fields, their potential dosage cut-off values, and if fractionation matters. We found that glucocorticoid treatment is not a reason for concern for long term overweight in CCS but this needs to be confirmed in other studies with exact patient dose levels, bigger study population of CCS treated with dexamethasone, and direct measurements of body fat and lean body mass (Chapter 7).

• We do not know if risk factors for overweight/obesity are country specific or if they are applicable to all CCS worldwide. Therefore, we will investigate if the effect of risk factors on overweight and obesity are the same in US and Swiss CCS within a collaboration with the US CCSS, Duke Cancer Institute Durham, Cancer Survivor Program - Children`s Health Care of Atlanta, and the Memorial Sloan Kettering Cancer Center New York (Appendices- Future projects).

• International evidence-based clinical practice guidelines for surveillance of overweight and obesity in CCS are needed to combine all available information and look for areas of concordance and discordance across existing guidelines. The metabolic syndrome workgroup of the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG, www.ighg.org), in which I am a member, is working on the development of these surveillance guidelines (Appendices- Future projects).

REFERENCES

[1] Keller U, Battaglia-Richi E, Beer M, Darioli R, Meyer K, Renggli A, et al. Sixth Swiss nutrition report. Berne Swiss Federal Office of Health; 2012.
[2] de Abreu D, Guessous I, Vaucher J, Preisig M, Waeber G, Vollenweider P, et al. Low compliance with dietary recommendations for food intake among adults. Clinical Nutrition. 2013;32:783-8.
[3] Berdan C, Tangney C, Scala C, Stolley M. Childhood cancer survivors and adherence to the American Cancer Society Guidelines on Nutrition and Physical Activity. J Cancer Surviv. 2014;8:671-9.
[4] Smith WA, Li C, Nottage K, Mulrooney DA, Armstrong GT, Lanctot JQ, et al. Lifestyle and metabolic syndrome in adult survivors of childhood cancer: a report from the St. Jude Lifetime Cohort Study. Cancer. 2014;120:2742-50.
[5] Demark-Wahnefried W, Werner C, Clipp EC, Guill AB, Bonner M, Jones LW, et al. Survivors of childhood cancer and their guardians. Cancer. 2005;103:2171-80.
[6] Robien K, Ness KK, Klesges LM, Baker KS, Gurney JG. Poor Adherence to Dietary Guidelines Among Adult Survivors of Childhood Acute Lymphoblastic Leukemia. Journal of Pediatric Hematology/Oncology. 2008;30:815-22.
[7] Zhang FF, Saltzman E, Kelly MJ, Liu S, Must A, Parsons SK, et al. Comparison of childhood cancer survivors' nutritional intake with US dietary guidelines. Pediatric Blood & Cancer. 2015;62:1461-7.
[8] Landy DC, Lipsitz SR, Kurtz JM, Hinkle AS, Constine LS, Adams MJ, et al. Dietary Quality, Caloric Intake, and Adiposity of Childhood Cancer Survivors and Their Siblings: An Analysis from the Cardiac Risk Factors in Childhood Cancer Survivors Study. Nutrition and Cancer. 2013;65:547-55.
[9] Tylavsky FA, Smith K, Surprise H, Garland S, Yan X, McCammon E, et al. Nutritional intake of long-term survivors of childhood acute lymphoblastic leukemia: Evidence for bone health interventional opportunities. Pediatric Blood & Cancer. 2010;55:1362-9.
[10] Zhang FF, Ojha RP, Krull KR, Gibson TM, Lu L, Lanctot J, et al. Adult Survivors of Childhood Cancer Have Poor Adherence to Dietary Guidelines. The Journal of Nutrition. 2016;146:2497-505.
[11] Brinksma A, Roodbol PF, Sulkers E, Kamps WA, de Bont ESJM, Boot AM, et al. Changes in nutritional status in childhood cancer patients: A prospective cohort study. Clinical Nutrition. 2015;34:66-73.
[12] Esbenshade AJ, Simmons JH, Koyama T, Koehler E, Whitlock JA, Friedman DL. Body Mass Index and Blood Pressure Changes over the Course of Treatment of Pediatric Acute Lymphoblastic Leukemia. Pediatric blood & cancer. 2011;56:372-8.
[13] Zhang FF, Rodday AM, Kelly MJ, Must A, MacPherson C, Roberts SB, et al. Predictors of Being Overweight or Obese in Survivors of Pediatric Acute Lymphoblastic Leukemia (ALL). Pediatric blood & cancer. 2014;61:1263-9.
[14] Skinner AC, Perrin EM, Skelton JA. Prevalence of obesity and severe obesity in US children, 1999-2014. Obesity. 2016;24:1116-23.
[15] Iughetti L, Bruzzi P, Predieri B, Paolucci P. Obesity in patients with acute lymphoblastic leukemia in childhood. Italian Journal of Pediatrics. 2012;38:4-.
[16] Zhang FF, Liu S, Chung M, Kelly MJ. Growth patterns during and after treatment in patients with pediatric ALL: A meta-analysis. Pediatric Blood & Cancer. 2015;62:1452-60.
[17] Ness KK, Armenian SH, Kadan-Lottick N, Gurney JG. Adverse effects of treatment in childhood acute lymphoblastic leukemia: general overview and implications for long-term cardiac health. Expert review of hematology. 2011;4:185-97.
[18] Esbenshade AJ, Simmons JH, Koyama T, Lindell RB, Friedman DL. Obesity and insulin resistance in pediatric acute lymphoblastic leukemia worsens during maintenance therapy. Pediatric blood & cancer. 2013;60:10.1002/pbc.24489.
[19] Wang KW, Chau R, Fleming A, Banfield L, Singh SK, Johnston DL, et al. The effectiveness of interventions to treat hypothalamic obesity in survivors of childhood brain tumours: a systematic review. Obesity Reviews. 2017;18:899-914.
[20] van Iersel L, Meijneke RWH, Schouten-van Meeteren AYN, Reneman L, de Win MM, van Trotsenburg ASP, et al. The development of hypothalamic obesity in craniopharyngioma patients: A risk factor analysis in a well-defined cohort. Pediatric Blood & Cancer. 2018:e26911-n/a.
[21] Lustig RH. Hypothalamic Obesity after Craniopharyngioma: Mechanisms, Diagnosis, and Treatment. Frontiers in Endocrinology. 2011;2:60.
[22] Mostoufi-Moab S, Seidel K, Leisenring WM, Armstrong GT, Oeffinger KC, Stovall M, et al. Endocrine abnormalities in aging survivors of childhood cancer: A report from the Childhood Cancer Survivor Study. Journal of Clinical Oncology. 2016;34:3240-7.

[23] Oeffinger KC, Mertens AC, Sklar CA, Yasui Y, Fears T, Stovall M, et al. Obesity in Adult Survivors of Childhood Acute Lymphoblastic Leukemia: A Report from the Childhood Cancer Survivor Study. Journal of Clinical Oncology. 2003;21:1359-65.
[24] Meacham LR, Gurney JG, Mertens AC, Ness KK, Sklar CA, Robison LL, et al. Body mass index in long-term adult survivors of childhood cancer. Cancer. 2005;103:1730-9.
[25] Chow EJ, Pihoker C, Hunt K, Wilkinson K, Friedman DL. Obesity and hypertension among children after treatment for acute lymphoblastic leukemia. Cancer. 2007;110:2313-20.
[26] Van Dongen-Melman JEWM, Hokken-Koelega ACS, Hahlen K, Groot AD, Tromp CG, Egeler RM. Obesity after Successful Treatment of Acute Lymphoblastic Leukemia in Childhood. Pediatr Res. 1995;38:86-90.
[27] Nottage KA, Ness KK, Li C, Srivastava D, Robison LL, Hudson MM. Metabolic Syndrome and Cardiovascular Risk among Long-Term Survivors of Acute Lymphoblastic Leukaemia - From the St. Jude Lifetime Cohort. British journal of haematology. 2014;165:364-74.
[28] Morabia A, Bernstein M, Kumanyika S, Sorenson A, Mabiala I, Prodolliet B, et al. Development and validation of a semi-quantitative food questionnaire based on a population survey. Sozial-und Praventivmedizin. 1994;39:345-69.
[29] Bernstein L, Huot I, Morabia A. Amélioration des performances d'un questionnaire alimentaire semi-quantitatif comparé à un rappel des 24 heures [Improvement of the effectiveness of a food frequency questionnaire compared with a 24 hour recall survey]. Santé Publique. 1995;7:403-13.
[30] Marques-Vidal P, Rousi E, Paccaud F, Gaspoz J-M, Theler J-M, Bochud M, et al. Dietary Intake according to Gender and Education: A Twenty-Year Trend in a Swiss Adult Population. Nutrients. 2015;7:5481.
[31] Love E, Schneiderman JE, Stephens D, Lee S, Barron M, Tsangaris E, et al. A cross-sectional study of overweight in pediatric survivors of acute lymphoblastic leukemia (ALL). Pediatric Blood & Cancer. 2011;57:1204-9.
[32] Maukonen M, Männistö S, Tolonen H. A comparison of measured versus self-reported anthropometrics for assessing obesity in adults: a literature review. Scandinavian Journal of Public Health. 2018;0:1403494818761971.
[33] Danubio ME, Miranda G, Vinciguerra MG, Vecchi E, Rufo F. Comparison of self-reported and measured height and weight: Implications for obesity research among young adults. Economics & Human Biology. 2008;6:181-90.
[34] Rothman KJ. BMI-related errors in the measurement of obesity. International Journal Of Obesity. 2008;32:S56.
[35] Butterfield RM, Park ER, Puleo E, Mertens A, Gritz ER, Li FP, et al. Multiple risk behaviors among smokers in the childhood cancer survivors study cohort. Psycho-Oncology. 2004;13:619-29.
[36] Tonorezos ES, Robien K, Eshelman-Kent D, Moskowitz CS, Church TS, Ross R, et al. Contribution of diet and physical activity to metabolic parameters among survivors of childhood leukemia. Cancer Causes Control. 2013;24:313-21.
[37] Rueegg CS, von der Weid NX, Rebholz CE, Michel G, Zwahlen M, Grotzer M, et al. Daily Physical Activities and Sports in Adult Survivors of Childhood Cancer and Healthy Controls: A Population-Based Questionnaire Survey. PLOS ONE. 2012;7:e34930.
[38] Murphy-Alford AJ, White M, Lockwood L, Hallahan A, Davies PSW. Body composition, dietary intake and physical activity of young survivors of childhood cancer. Clinical Nutrition. 2018.
[39] Hudson MM, Mertens AC, Yasui Y, et al. Health status of adult long-term survivors of childhood cancer: A report from the childhood cancer survivor study. JAMA. 2003;290:1583-92.
[40] Winkleby MA, Jatulis DE, Frank E, Fortmann SP. Socioeconomic status and health: how education, income, and occupation contribute to risk factors for cardiovascular disease. American Journal of Public Health. 1992;82:816-20.
[41] Liberatos P, Link BG, Kelsey JL. The measurement of social class in epidemiology. Epidemiol Rev. 1988;10:87-121.
[42] Kuehni CE, Strippoli MPF, Rueegg CS, Rebholz CE, Bergstraesser E, Grotzer M, et al. Educational achievement in Swiss childhood cancer survivors compared with the general population. Cancer. 2012;118:1439-49.
[43] Rueegg CS, Gianinazzi ME, Michel G, Zwahlen M, von der Weid NX, Kuehni CE, et al. No evidence of response bias in a population-based childhood cancer survivor questionnaire survey — Results from the Swiss Childhood Cancer Survivor Study. PLOS ONE. 2017;12:e0176442.
[44] Honningsvåg L-M, Linde M, Håberg A, Stovner LJ, Hagen K. Does health differ between participants and non-participants in the MRI-HUNT study, a population based neuroimaging study? The Nord-Trøndelag health studies 1984–2009. BMC Medical Imaging. 2012;12:23.

[45] Nohr EA, Liew Z. How to investigate and adjust for selection bias in cohort studies. Acta Obstetricia et Gynecologica Scandinavica. 2018;97:407-16.
[46] Silva Junior SHAd, Santos SM, Coeli CM, Carvalho MS. Assessment of participation bias in cohort studies: systematic review and meta-regression analysis. Cadernos de Saúde Pública. 2015;31:2259-74.
[47] Asdahl PH, Ojha RP, Winther JF, Holmqvist AS, de Fine Licht S, Gudmundsdottir T, et al. Measuring childhood cancer late effects: evidence of a healthy survivor effect. European Journal of Epidemiology. 2017;32:1089-96.
[48] Amankwah EK, Saenz AM, Hale GA, Brown PA. Association between body mass index at diagnosis and pediatric leukemia mortality and relapse: a systematic review and meta-analysis. Leukemia & Lymphoma. 2015:1-9.
[49] Orgel E, Genkinger JM, Aggarwal D, Sung L, Nieder M, Ladas EJ. Association of body mass index and survival in pediatric leukemia: a meta-analysis. The American Journal of Clinical Nutrition. 2016;103:808-17.
[50] den Hoed MAH, Pluijm SMF, de Groot-Kruseman HA, te Winkel ML, Fiocco M, van den Akker ELT, et al. The negative impact of being underweight and weight loss on survival of children with acute lymphoblastic leukemia. Haematologica. 2015;100:62-9.
[51] Cox CL, Nolan VG, Leisenring W, Yasui Y, Ogg SW, Mertens AC, et al. Non-cancer Related Mortality Risks in Adult Survivors of Pediatric Malignancies: The Childhood Cancer Survivor Study. Journal of cancer survivorship : research and practice. 2014;8:460-71.
[52] Zhang FF, Saltzman E, Must A, Parsons SK. Do childhood cancer survivors meet the diet and physical activity guidelines? A review of guidelines and literature. International Journal of Child Health and Nutrition. 2012;1:44-58.
[53] Ladas E. Nutritional Counseling in Survivors of Childhood Cancer: An Essential Component of Survivorship Care. Children. 2014;1:107.
[54] Children's Oncology Group (COG). Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancer, Staying healthy through diet and physical activity. Version 4 – October 2013.
[55] Rebholz CE, von der Weid NX, Michel G, Niggli FK, Kuehni CE. Follow-up care amongst long-term childhood cancer survivors: A report from the Swiss Childhood Cancer Survivor Study. European Journal of Cancer. 2011;47:221-9.
[56] Willet W. Nutritional Epidemiology, Monographs in epidemiology and biostatistics. 2nd ed: Oxford University Press; 1998.

Chapter 9

Summary

SUMMARY

Late effects like cardiovascular and endocrine disorders secondary to childhood cancer or its treatment are frequently reported in childhood cancer survivors (CCS) (**Chapter 1**). Health promoting lifestyles, including improved diet and a healthy body weight could modify the morbidity and mortality trajectory that CCS experience due to their earlier cancer treatment. Therefore, the aims of this thesis were to get a better understanding of the dietary intake of Swiss CCS and to gain insights in the potential risk factors for being overweight during and long after treatment (**Chapter 1**).

In **chapter 2** we compared adherence to national dietary recommendations between 1864 CCS, 698 siblings, and 8258 participants in the Swiss Health Survey (SHS), a representative survey of the general population, identified determinants of adherence, and assessed the association of adherence with cardiovascular disease (CVD) risk profiles. We found that only 43% of the CCS met the recommended dietary intakes for meat, 34% for fruit, 30% for fish, 18% for dairy products, 11% for vegetables, and 7% for combined fruit and vegetables. Results were similar for both control groups. In all groups, dietary adherence was associated with gender, parental education, migration background, language region in Switzerland, smoking, alcohol consumption, and sport participation. CCS with a higher CVD risk profile because of cardiotoxic treatment had no better adherence. Therefore, based on this research we conclude that CCS have similar food patterns as their siblings and the general population, and poorly adhere to current recommendations. Awareness of the importance of a healthy diet should be raised among CCS, to prevent chronic diseases like CVD.

In **chapter 3** we assessed dietary intake with a food frequency questionnaire (FFQ). We assessed dietary intake and quality of 878 CCS in comparison to three random samples of the general Swiss population represented by data from 9216 participants of Bus Santé, 1311 participants of CoLaus, and 1189 participants of the Swiss National Nutrition Survey. We also identified whether clinical characteristics had an impact on CCS long-term dietary intake.

A multicentre validation study has been set up in order to investigate the relation between the self-reported FFQ (**Chapter 3**) and the objective biochemical indicators obtained from urine spots. CCS who had filled in the FFQ during the follow-up study of the SCCSS were invited to collect a first morning urine spot at home and send it to CHUV. Hospitalised childhood cancer patients (CCP) were asked to collect an urine spot sample during their stay at CHUV or HUG. These samples were used to control the quality of the urine samples that were send by post mail by the CCS. The design, current status, and the study setup are discussed in **chapter 4**.

In **chapter 5, 6, and 7** we showed results of studies that investigated the socio-demographic, lifestyle, and clinical risk factors to develop overweight during and long after

treatment. Being overweight or obese is a modifiable risk factor to develop chronic health conditions like diabetes, dyslipidaemia, hypertension, and cardiovascular disease. Since CCS are more susceptible to develop these chronic health conditions due to their cancer treatment, it is important to prevent an early onset of excessive weight gain and keep a healthy weight throughout life.

In **chapter 5** we assessed prevalence of overweight in CCP at diagnosis and at the end of treatment, determined risk factors, and identified weight change during treatment by type of cancer. We performed a multicentre cohort study in which we collected height and weight measurements of 327 CCP at diagnosis and repeatedly during treatment. We found that at diagnosis 8% of the CCP were overweight versus 13% at end of treatment. Risk factors for weight gain during treatment were being a boy and having been diagnosed with ALL or lymphoma. During the first half of treatment, BMI Z-scores increased in ALL and lymphoma patients, whereas for patients with CNS tumours, sarcoma, or other types of cancer BMI Z-scores tended to drop initially. During the second half of treatment BMI Z-scores of all patients tended to increase. Based on these findings, we concluded that CCP diagnosed with ALL or lymphoma are at increased risk of weight gain during treatment, and might particularly benefit from early lifestyle interventions.

In **chapter 6** we assessed the prevalence of overweight in 2365 CCS, with a focus on leukaemia survivors, compared it with their peers (819 siblings, and 9591 SHS participants), and determined potential risk factors. We found that the prevalence of and risk factors for being overweight are similar in long-term CCS and their peers. Therefore, it is suggested that prevention methods can be the same as in the general population. An important exception are CCS treated with cranial radiotherapy (CRT) ≥20 gray who may need extra attention during follow-up care.

In **chapter 7** we investigated if overweight in long-term CCS was associated with the cumulative glucocorticoid dose received, if there was a dose-response relationship between cumulative glucocorticoid dose and BMI, and if the respective effects of prednisone and dexamethasone differed. We studied the entire group of 1936 CCS, and separately 546 ALL, 114 NHL, and 195 HL survivors. Prevalence of overweight was 24% in CCS treated with glucocorticoids only, 37% in those with CRT, and 49% in those with both glucocorticoids and CRT. We found no evidence for a dose-response relationship between cumulative glucocorticoid doses and overweight and no evidence that CRT modified the effect of cumulative glucocorticoid dose treatment on overweight. This study suggested that glucocorticoids used for the treatment of childhood cancer are not associated with long-term risk of overweight.

Concluding, our studies show that CCS equally poor adhere to dietary guidelines as the general population. In addition, overweight prevalence and risk factors for being overweight

are similar as to the general population. This suggests that prevention methods can be the same as in the general population. An important exception are survivors treated with cranial radiotherapy of 20 gray or more who may need extra attention during follow-up care. Besides, patients diagnosed with ALL or lymphoma might benefit from early lifestyle interventions.

Appendices

Future projects
Acknowledgements
About the author

FUTURE PROJECTS I

Childhood Cancer Survivor Study
Analysis Concept Proposal

STUDY TITLE

Risk factors for overweight and obesity in childhood acute lymphoblastic leukemia survivors in the US and Switzerland: A comparison of two cohort studies

WORKING GROUP

Primary: Chronic Disease Working Group

Secondary: Epidemiology/Biostatistics and Psychology Working Groups

INVESTIGATORS

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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 rates exceed 80% leading 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]. Therefore, it is important to identify additional, preventable risk factors such as overweight and obesity to reduce the already elevated burden of chronic diseases. Overweight and obesity are reported frequently in pediatric ALL survivors (6-8). Multiple risk factors seem to contribute to the development of overweight and obesity in pediatric ALL survivors:

- Age at survey influences overweight and obesity prevalence. In the Swiss Childhood Cancer Survivor Study (SCCSS), risk factors for overweight and obesity were both young (5-14 years) and older (25-29 years) age in childhood cancer survivors including ALL survivors [9]. Children and adolescent ALL survivors were also at higher risk for obesity in a meta-analysis including studies from several countries [8].
- Conflicting results have been described for gender; female ALL survivors were more overweight or obese in the US Childhood Cancer Survivor Study (CCSS) [10-12], whereas male ALL survivors were more overweight in the SCCSS [9].
- Other socio-demographic factors potentially also increase the risk for overweight and obesity, e.g. race/ethnicity, migration background, lower education status [13, 14].
- Lifestyle factors including physical inactivity and an unhealthy diet may increase the risk for overweight and obesity like in the general population [15]
- Age at diagnosis; children diagnosed at a young age (<5 years) [7, 8].

- A clear association between cranial radiation therapy (CRT) and increased BMI has been found in the CCSS [10-12] and the SCCSS [13, 16]. In contrast, a systematic review by Zhang et al. described conflicting results for this association. In the meta-analysis that they performed they found a high prevalence of obesity in ALL survivors regardless of CRT therapy [17].

The prevalence of overweight and obesity varies across studies and countries. In a systematic review including US and European studies, the prevalence of overweight and obesity ranged from 34 to 46% for long-term (≥10 years off treatment) pediatric ALL survivors of whom the majority were adults [8]. A US study reported a prevalence of overweight and obesity of up to 60% in long-term adult pediatric ALL survivors [6]. In contrast, the prevalence of overweight and obesity was only 26% in Swiss adult survivors 16 years after treatment for pediatric leukemia, of whom 88% had ALL [13]. But the US and Swiss study populations differed in terms of socio-demographic (age at survey, time since diagnosis, race/ethnicity, migration background, living situation), socio-economic (health insurance, education level), lifestyle (smoking, physical activity, diet), and clinical factors (treatment protocol, frequency and dose of CRT, chemotherapy). This may have influenced the observed overweight and obesity prevalence. Therefore it is difficult to conclude the reasons of the observed differences.

We propose a de novo analysis of the CCSS and SCCSS datasets that allows a direct comparison between results from the US and Swiss datasets, by:

- Applying the same inclusion criteria for the US and Swiss study population, so that we have a broad overlap between the two populations regarding age at diagnosis, age at study, and treatment era.
- Adjusting the dataset and the analysis for important confounding factors (gender, age at diagnosis, age at study)
- Using the same analytical approach.

This method will give better insights into the risk factors and might help to understand why prevalence of overweight and obesity differs between the two countries.

AIMS & OBJECTIVES

We aim

1) To compare the overweight and obesity prevalence between pediatric ALL survivors and their siblings in the US and Switzerland.

Hypothesis: We hypothesize that the absolute prevalence of overweight and obesity in ALL survivors and their siblings is higher in the US than in Switzerland. But we hypothesize that the association between cancer survivorship and overweight and obesity is similar.

2) To identify socio-demographic (gender, age at survey, race/ethnicity, migration background, living situation), socio-economic (health insurance, education level), lifestyle (smoking, physical activity, diet), and clinical (year of diagnosis, age at diagnosis, radiation, chemotherapy) risk factors for overweight and obesity and investigate whether the direction and strength of the effects are similar in the US and Switzerland.

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

ANALYSES FRAMEWORK

Outcome of interest

Overweight and obesity (body mass index [BMI] as continuous variable)

Study population

Inclusion criteria

1) All CCSS survivors diagnosed with ALL (diagnosed 1976-2010) 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).

Potential explanatory risk factors (Figure 1)

• Sociodemographic risk factors

- Age at survey; young and older age [9, 17]
- Gender; contradicting associations [6, 7, 9, 17]
- Race/ethnicity; Hispanic ethnicity [14]
- Migration background [13]
- Living situation; living alone

• Socioeconomic risk factors

- Health insurance: health care access
- Socio-economic status/education level; low education level [9]

• Lifestyle factors

- Smoking
- Physical activity/sports; physical inactivity [9]
- Diet; unhealthy diet

• Clinical factors

- Year of diagnosis,
- Age at diagnosis; younger age [7, 8, 18, 19]
- Radiation

  - Cranial [6-9, 16, 20]

  - Total body irradiation: proxy for more severe disease, involvement of cranial field [21]
- Chemotherapy, Glucocorticoids (prednisone, dexamethasone [yes/no]): no long-term association [16], short-term [15, 22-25]

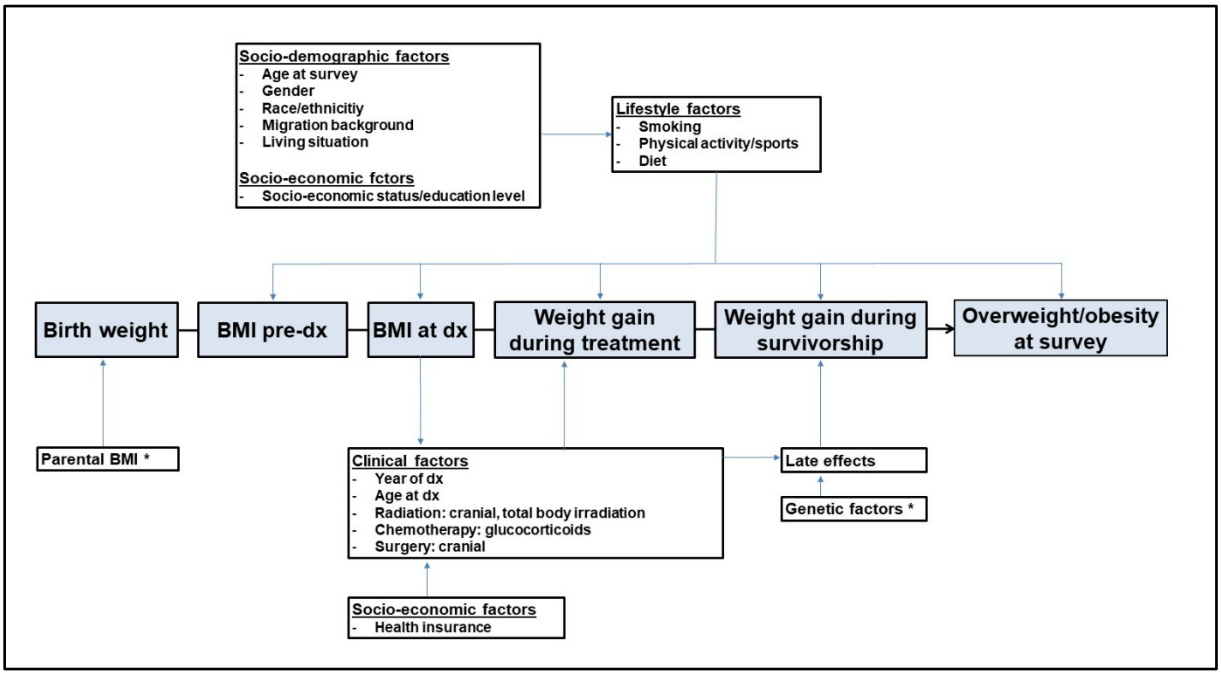

Figure 1. "Lifetime causal diagram" of overweight and obesity at survey
BMI, body mass index; dx, diagnosis

*: not available information

Statistical plan

Direct comparisons between the populations of interest (survivors versus siblings, US versus Swiss populations) are problematic because these populations may differ in many aspects which may confound associations assessed. For comparisons between survivors with siblings **(aim 1)**, we will attempt to correct for this using weighted analyses. Siblings will be weighted such that they become representative of survivors regarding the distribution of key socio-demographic variables (gender, age at survey, 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. We will not pool the data from the CCSS and SCCSS since the study populations differ in overweight and obesity prevalence, study design, and data collection. We will rather run the same analysis in both populations and qualitatively compare results.

For better comparison between ALL survivors and siblings, we will weight siblings for gender and age at survey (inverse probability weighting). Standardization will be performed for the US and Swiss population separately. Furthermore, we will match Swiss with US ALL survivors based on gender, year of diagnosis, and age at survey on a 1:3 ratio or with frequency matching.

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.

To evaluate the difference in overweight and obesity prevalence between ALL survivors and siblings **(aim 1)**, 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 run models for both the US and the Swiss population.

We will use multinomial logistic regressions [BMI categories] to determine risk factors associated with overweight and obesity at survey in pediatric ALL survivors **(aim 2)**. Regressions will be run separately for US and Swiss pediatric ALL survivors. We will select potential risk factors a priori based on a literature review, e.g. gender, age at diagnosis, age at survey, physical activity, cumulative CRT, steroid usage. Variables with p-values <0.01 in univariable models will be jointly included in a multivariable model.

REFERENCES

[1] Swiss Childhood Cancer Regsitry Annual Report 2015/2016. Bern: Bern Swiss Childhood Cancer Registry, 2017.
[2] American Cancer Society, Cancer Facts & Figures 2014 2014.
[3] Schindler M, Belle FN, Grotzer MA, von der Weid NX, Kuehni CE, Swiss Paediatric Oncology G. Childhood cancer survival in Switzerland (1976-2013): Time-trends and predictors. Int J Cancer. 2017;140(1):62-74.
[4] Mody R, Li S, Dover DC, Sallan S, Leisenring W, Oeffinger KC, et al. Twenty-five-year follow-up among survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. Blood. 2008;111(12):5515-23.
[5] Oeffinger KC, Mertens AC, Sklar CA, Kawashima T, Hudson MM, Meadows AT, et al. Chronic health conditions in adult survivors of childhood cancer. The New England journal of medicine. 2006;355(15):1572-82.
[6] Garmey EG, Liu Q, Sklar CA, Meacham LR, Mertens AC, Stovall MA, et al. Longitudinal changes in obesity and body mass index among adult survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2008;26(28):4639-45.
[7] Oeffinger KC, Mertens AC, Sklar CA, Yasui Y, Fears T, Stovall M, et al. Obesity in adult survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2003;21(7):1359-65.
[8] Zhang FF, Kelly MJ, Saltzman E, Must A, Roberts SB, Parsons SK. Obesity in pediatric ALL survivors: a meta-analysis. Pediatrics. 2014;133(3):e704-15.
[9] Belle FN, Weiss A, Schindler M, Goutaki M, Bochud M, Zimmermann K, et al. Overweight in childhood cancer survivors: the Swiss Childhood Cancer Survivor Study. Am J Clin Nutr. 2018;107(1):3-11.
[10] Garmey EG, Liu Q, Sklar CA, Meacham LR, Mertens AC, Stovall MA, et al. Longitudinal Changes in Obesity and Body Mass Index Among Adult Survivors of Childhood Acute Lymphoblastic Leukemia: A Report From the Childhood Cancer Survivor Study. Journal of Clinical Oncology. 2008;26(28):4639-45.
[11] Oeffinger KC, Mertens AC, Sklar CA, Yasui Y, Fears T, Stovall M, et al. Obesity in Adult Survivors of Childhood Acute Lymphoblastic Leukemia: A Report from the Childhood Cancer Survivor Study. Journal of Clinical Oncology. 2003;21(7):1359-65.
[12] Meacham LR, Gurney JG, Mertens AC, Ness KK, Sklar CA, Robison LL, et al. Body mass index in long-term adult survivors of childhood cancer. Cancer. 2005;103(8):1730-9.
[13] Belle FN, Weiss A, Schindler M, Sommer G, Goutaki M, Bochud M, et al. Overweight in childhood cancer survivors: the Swiss Childhood Cancer Survivor Study. American Journal of Clinical Nutrition. 2018;107(1):3-11.
[14] Brown AL, Lupo PJ, Danysh HE, Okcu MF, Scheurer ME, Kamdar KY. Prevalence and Predictors of Overweight and Obesity Among a Multiethnic Population of Pediatric Acute Lymphoblastic Leukemia Survivors: A Cross-Sectional Assessment. Journal of pediatric hematology/oncology. 2016;38(6):429-36.
[15] Jansen H, Postma A, Stolk RP, Kamps WA. Acute lymphoblastic leukemia and obesity: increased energy intake or decreased physical activity? Supportive Care in Cancer. 2009;17(1):103-6.
[16] Belle FN, Kasteler R, Schindera C, Bochud M, Ammann RA, von der Weid N, et al. No evidence for overweight in long-term childhood cancer survivors after glucocorticoid treatment. Cancer. 2018, doi: 10.1002/cncr.31599
[17] Zhang FF, Kelly MJ, Saltzman E, Must A, Roberts SB, Parsons SK. Obesity in Pediatric ALL Survivors: A Meta-Analysis. Pediatrics. 2014;133(3):e704-e15.
[18] Razzouk BI, Rose SR, Hongeng S, Wallace D, Smeltzer MP, Zacher M, et al. Obesity in Survivors of Childhood Acute Lymphoblastic Leukemia and Lymphoma. Journal of Clinical Oncology. 2007;25(10):1183-9.
[19] Withycombe JS, Post-White JE, Meza JL, Hawks RG, Smith LM, Sacks N, et al. Weight Patterns in Children With Higher Risk ALL: A Report From the Children's Oncology Group (COG) for CCG 1961. Pediatric blood & cancer. 2009;53(7):1249-54.
[20] Meacham LR, Gurney JG, Mertens AC, Ness KK, Sklar CA, Robison LL, et al. Body mass index in long-term adult survivors of childhood cancer: a report of the Childhood Cancer Survivor Study. Cancer. 2005;103(8):1730-9.

[21] Chemaitilly W, Boulad F, Oeffinger KC, Sklar CA. Disorders of glucose homeostasis in young adults treated with total body irradiation during childhood: a pilot study. Bone Marrow Transplant. 2009;44(6):339-43.
[22] Arpe M-LH, Rørvig S, Kok K, Mølgaard C, Frandsen TL. The association between glucocorticoid therapy and BMI z-score changes in children with acute lymphoblastic leukemia. Supportive Care in Cancer. 2015;23(12):3573-80.
[23] Chow EJ, Pihoker C, Hunt K, Wilkinson K, Friedman DL. Obesity and hypertension among children after treatment for acute lymphoblastic leukemia. Cancer. 2007;110(10):2313-20.
[24] Collins L, Zarzabal LA, Nayiager T, Pollock BH, Barr RD. Growth in Children With Acute Lymphoblastic Leukemia During Treatment. Journal of Pediatric Hematology/Oncology. 2010;32(8):e304-e7.
[25] Murphy AJ, Wells JC, Williams JE, Fewtrell MS, Davies PS, Webb DK. Body composition in children in remission from acute lymphoblastic leukemia. The American Journal of Clinical Nutrition. 2006;83(1):70-4.

TABLES AND FIGURES

Table I. Sociodemographic and lifestyle characteristics by country population

Characteristics	ALL survivors		Siblings	
	USA *n=….*	**Switzerland** *n=671*	**USA** *n=….*	**Switzerland** *n=678*
Gender, *n (%)*				
Female		319 (48)		402 (59)
Male		352 (52)		276 (42)
Age (years), *n (%)*				
Mean (SD)		23.5 ± 7.8		29.4 ± 8.0
Median (IQR)		21.9 (17.5-28.2)		28.1 (23.0-34.8)
18-24		416 (62)		234 (35)
25-34		190 (28)		281 (41)
35-44		61 (9)		136 (20)
≥45		4 (<1)		27 (4)
Country of birth – Race/ethnicity, *n (%)*				
Non-Hispanic White		660 (98)		676 (100)
Non-Hispanic Black		-		
Hispanic		1 (<1)		
Asian		5 (1)		
Other/Unknown		5 (<1)		2 (<1)
Living situation, *n (%)*				
Alone		90 (13)*		97 (14)
Other		581 (87)		581 (86)
Education level (highest degree), *n (%)*				
Lower than university/ post graduate		572 (85)*		502 (74)
University/post graduate		99 (15)		176 (26)
Current employment, *n (%)*				
No		367 (55)*		236 (35)
Yes		304 (45)		442 (65)
Insurance, *n (%)*				
No		-		-
Yes		671 (100)		678 (100)
Smoking status, *n (%)*				
Never		449 (67)*		423 (62)
Former		76 (11)		124 (18)
Current		146 (22)		131 (19)
Alcohol consumption, *n (%)*				
Never/rarely		382 (57)*		358 (53)
Weekly, ≥1 std drink/week		270 (40)		290 (43)
Daily, 1 std drink/day		16 (2)		18 (3)
Frequently, >1 std drink/day		3 (<1)		12 (2)
Physical activity, *n (%)*				
Inactive		106 (16)*		108 (16)
Active[a]		437 (65)		570 (84)
Missing		128 (19)		
BMI, *n (%)*				
Underweight		51 (8)*		12 (2)
Normal		443 (66)		477 (70)
Overweight		120 (18)		152 (22)
Obese		29 (4)		37 (5)
Missing		28 (4)		

IQR: interquartile range, SD: standard deviation

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

**** Will be updated for Switzerland after follow-up information is available – currently in data entry phase***

Table II. Clinical characteristic of ALL survivors by country

Characteristics	ALL survivors	
	US	**Switzerland**
	n=	***n=671***
Age at diagnosis (years), *n (%)*		
Mean (SD)		6.4 ± 4.2
Median (IQR)		5.1 (3.1-9.1)
<5		331 (49)
6-9		196 (29)
10-14		118 (18)
≥15		26 (4)
Year of diagnosis, *n (%)*		
<1980		63 (9)
1980-1990		219 (33)
1991-2000		267 (40)
2001-2010		122 (18)
Time since diagnosis, *n (%)*		
Mean (SD)		17.1 ± 7.4
Median (IQR)		15.8 (11.0-22.3)
<10		125 (19)
11-14		176 (26)
15-19		149 (22)
≥20		221 (33)
Chemotherapy, *n (%)*		
Any		499 (74)
Prednisone		495 (74)
Dexamethasone		173 (26)
Prednisone and dexamethasone		169 (25)
Missing		***153 (23)***
Cranial radiation therapy (gray), *n (%)*		
None		521 (78)
<18		67 (10)
≥18		83 (12)
Abdominal radiation therapy (gray), *n (%)*		
None		670 (100)
<10		1 (<1)
≥10 to <20		-
≥20		-
Total body radiation, *n (%)*		
No		656 (98)
Yes		15 (2)
Hematopoietic stem cell transplantation, *n (%)*		
No		642 (96)
Yes		29 (4)
Relapse, *n (%)*		
No		590 (88)
Yes		81 (12)

IQR: interquartile range, SD: standard deviation

Table III. Overweight and obesity in ALL survivors compared to siblings by country

	Non overweight/obese OR (95%CI)		Overweight OR (95%CI)		Obese OR (95%CI)	
	Univariable	Multivariable[b]	Univariable	Multivariable[b]	Univariable	Multivariable[b]
US						
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 gender, age at survey… according to ALL survivors
b: adjusted for….

Table IV. Predictors for overweight and obesity in ALL survivors by country (retrieved from multinomial logistic regressions)

	Overweight				Obese			
	US ALL survivors		Swiss ALL survivors		US ALL survivors		Swiss ALL survivors	
	%[a] OR (95%CI)[b]	p-value[c]	%[a] OR (95%CI)[b]	p-value[c]	%[a] OR (95%CI)[b]	p-value[c]	%[a] OR (95%CI)[b]	p-value[c]
Gender								
Female	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
Male								
Age, y								
18-24	1.00 (ref)		1.00 (ref)		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: gender, 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).

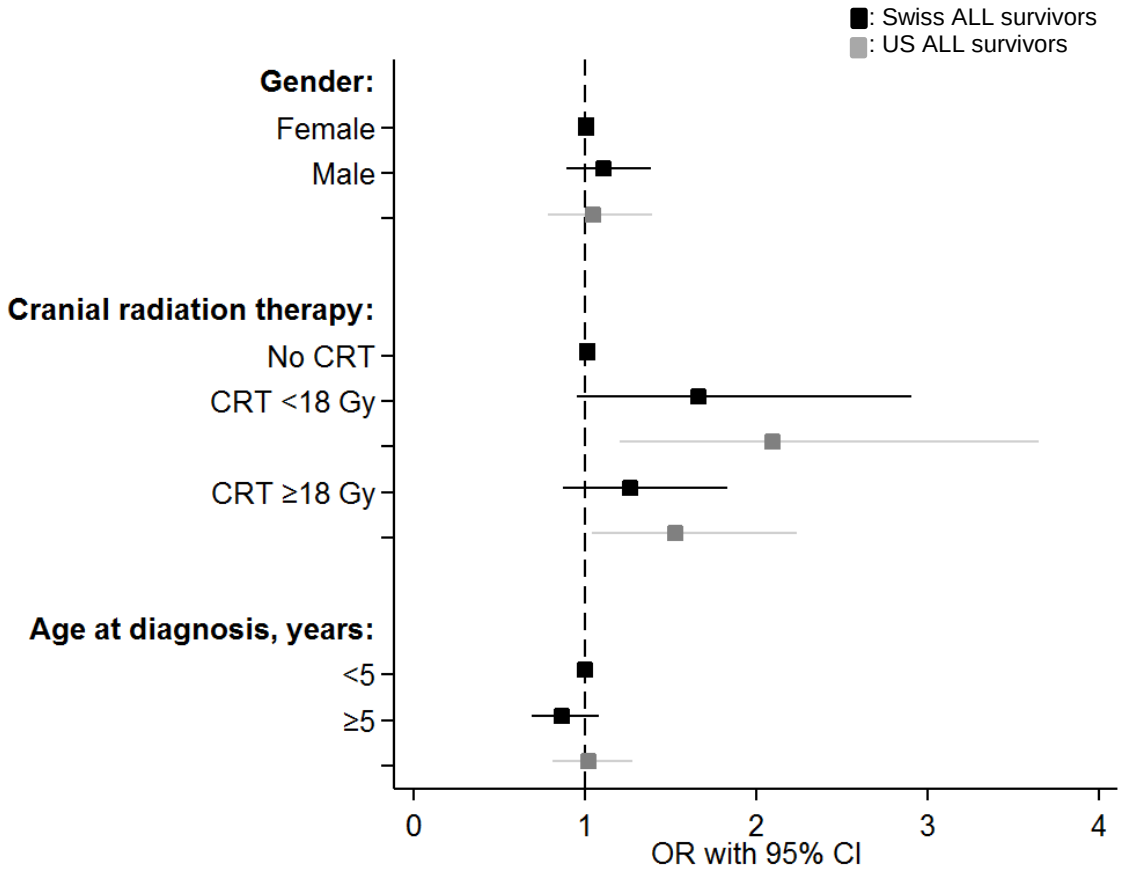

Figure 1 (EXAMPLE). Risk factor specific OR and 95%CI for overweight in Swiss and US pediatric ALL survivors (from multivariable logistic regression[1])
Squares, OR for overweight; whiskers, the respective 95% CI
Abbreviations: CI, confidence interval; CRT, cranial radiation therapy; Gy, gray
[1] Adjusted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

FUTURE PROJECTS II

International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG): Metabolic Syndrome

The IGHG, is a worldwide effort initiated by several national guideline groups and the Cochrane Childhood Cancer Group in partnership with the 'PanCare Childhood and Adolescent Cancer Survivor Care and Follow-up Studies' (PanCareSurFup) Consortium to collaborate in guideline development (www.ighg.org).

Representatives of the North American Children's Oncology Group (COG), the Dutch Childhood Oncology Group (DCOG), the Swiss Childhood Cancer Survivor Study group (SCCSS), and members of other international paediatric oncology groups will work together to develop guidelines for metabolic syndrome surveillance. The members will look for areas of concordance and discordance across existing guidelines. They devised clinical questions to address areas of discordance for surveillance of metabolic syndrome covering obesity, hypertension, diabetes, and hyperlipidaemia and following key issues: who needs surveillance; at what age or time from treatment should screening be initiated; how often, and what surveillance modality should be used (obesity and impaired glucose metabolism/ diabetes mellitus). Please, see below the specific (sub)questions for the obesity work group where I take part in.

Working group obesity

Overweight/Obesity – Who needs surveillance?

Definition: Overweight/Obesity: includes BMI ≥25 kg/m^2, BMI > 95th percentile, increased waist circumference, increased waist-hip ratio, increased body fat mass

Research questions:

1. What is the risk of obesity in childhood, adolescent, and young adult (CAYA) cancer survivors compared to the general population of the same age?
2. Treated with chemotherapy; do risks differ between different agents? What is the risk after higher doses?
3. Treated with radiotherapy
    a. Cranial
    b. Abdominal
    c. Total body irradiation

    d. Other fields
    e. Is dose relevant?
    f. Does fractionation matter?
4. Treated with hormonal therapy
5. Treated with steroids
    a. Is type of steroids, dose or potency relevant?
6. Treated with stem cell transplantation
7. Cranial surgery (hypothalamus)
8. Does the risk of obesity in CAYA cancer survivors differ between sexes?
9. Does the risk of obesity in CAYA cancer survivors differ by races/ethnicities?
10. Does the risk of obesity in CAYA cancer survivors depend on the age at treatment?
11. What is the evidence that endocrine abnormalities affect the risk of obesity in CAYA cancer survivors?
    a. Gonadal hormone status
    b. Thyroid hormone deficiency or excess
    c. Growth hormone or other pituitary hormone deficiencies or excess
    d. Does treatment of these endocrine abnormalities alter the risk?
12. Is the risk of obesity in CAYA cancer survivors associated with lifestyle factors?
    a. Smoking, physical activity, diet?
    b. Are there any lifestyle interventions that alter this risk?
13. Is there a role of pre-treatment factors (e.g. birthweight, body weight status at diagnosis)?
14. Do cancer-unrelated factors modify the risk for obesity in cancer survivors (e.g. weight status of parents, ethnicity, socioeconomic status)?
15. Does the risk for obesity in CAYA cancer survivors differ between different cancer types?
    a. Leukaemia's, lymphomas
    b. Brain tumours
    c. Solid tumours, including musculoskeletal tumours

Obesity – What surveillance modality should be used?

16. What is the value of BMI versus waist circumference vs. measurement of body composition (e.g. waist to height ratio or percent body fat by skin folds or dual energy x-ray absorptiometry) to define obesity in CAYA survivors?

Obesity – At what age or time from exposure should surveillance be initiated? At what frequency should surveillance be performed?

17. What is the latency time (time of onset) to develop obesity in CAYA cancer survivors?
18. What is the likelihood of change (improvement or deterioration) of body weight/waist circumference in CAYA cancer survivors after cancer treatment (chemotherapy, hormonal therapy, radiotherapy and/or stem cell transplantation)
    a. What is the timing of such change?

Team members International Harmonization of Metabolic Syndrome Surveillance Guidelines for Childhood, Adolescent and Young Adult Cancer Survivors

Chairs:

Oeffinger, K.
Gietema, J.
Kremer, L.
Skinner, R.
Hudson, M.

Co-Chairs:

Nuver, J.
Tonorezos, E.

Advisor:

Mulder, R.

Working Group:	Obesity	Hypertension	Diabetes	Hyperlipidaemia	Metabolic syndrome/ CVRF Cluster
Leader:	Kamdar, K.	Armenian, S.	Neville, K.	Fossa, S.	van den Heuvel-Eibrink, M.
Members:	Belle, F.	Steinberger, J.	Friedman, D.	Fullbright, J.	Walwyn, T.
	Lupo, P.	Mulrooney, D.	Chemaitilly, W.	Haupt, R.	Levitt Haworth, G.
	Prasad, P.	van Dalen, E.	Ehrhardt, M.	Morsellino, V.	Rath, S.
	Ness, K.	Haugnes, H.S	Neggers, S.	Feli, F.	Nock, N.
	Denzer, C.	Feldman, D.	Wei, C.		Giwercman, A.
	Schindera, C.				Passmore, J.
	Otth, M.				Bardi, E.
Number of abstracts for review	1562	1160	638	483	371

Cochrane systematic literature search

P (Population)	Childhood, adolescent and young adult cancer survivors
I (Etiologic/risk factor)	Chemotherapy (dose), radiotherapy (dose), hormonal therapy, HSCT, steroids, surgery, gender, race/ethnicity, age, family history, endocrine abnormalities, lifestyle factors, pre-treatment factors
C (Comparison)	General population for Q1, N/A for other questions
O (Outcome)	Obesity

Search 1: ***Childhood cancer***	(leukemia OR hemothe* OR hemother* OR (childhood ALL) OR AML OR lymphoma OR hemothe* OR hemoth OR hemoth* OR T-cell OR B-cell OR non-hodgkin OR sarcoma OR sarcom* OR sarcoma, Ewing's OR Ewing* OR osteosarcoma OR hemotherapy* OR wilms tumor OR wilms* OR nephroblastom* OR neuroblastoma OR neuroblastom* OR rhabdomyosarcoma OR rhabdomyosarcom* OR teratoma OR teratom* OR hepatoma OR hepatom* OR hepatoblastoma OR hepatoblastom* OR PNET OR medulloblastoma OR medulloblastom* OR PNET* OR neuroectodermal tumors, primitive OR retinoblastoma OR hemotherapy* OR meningioma OR hemothera* OR glioma OR gliom*) OR (pediatric oncology OR paediatric oncology) OR (childhood cancer OR childhood tumor OR childhood tumors)) OR (brain tumor* OR brain tumour* OR brain neoplasms OR central nervous system neoplasm OR central nervous system neoplasms OR central nervous system tumor* OR central nervous system tumour* OR brain cancer* OR brain neoplasm* OR intracranial neoplasm*) OR (leukemia, lymphocytic, acute) OR (leukemia, lymphocytic, acute*) OR breast cancer at a young age OR young breast cancer survivor OR testicular cancer OR germ cell cancer OR germ cell tumor OR seminoma OR seminoma* OR non-seminoma OR non-seminom*
Search 2: ***Chemotherapy***	Antineoplastic Protocols OR Antineoplastic Combined Chemotherapy Protocols OR Chemoradiotherapy OR Chemoradiotherapy, Adjuvant OR Chemotherapy, Adjuvant OR Consolidation Chemotherapy OR Induction chemotherapy OR Maintenance chemotherapy OR Chemotherapy, Cancer, Regional Perfusion OR Antineoplastic agents OR hemotherapy* OR high-dose chemotherapy OR chemotherapy dose OR cumulative dose OR cytostatic agents
Search 3: ***Radiotherapy***	Radiotherapy OR radiation OR radiation therapy OR irradiation OR irradiat* OR radiation injuries OR injuries, radiation OR injury, radiation OR radiation injury OR radiation syndrome OR radiation syndromes OR syndrome radiation OR radiation sickness OR radiation sicknesses OR sickness radiation OR radiation* OR irradiation OR radiations OR radiation dose OR radiation volume OR radiotherapy fractionation OR stereotactic RT OR stereotactic radiotherapy[tiab] OR gamma knife OR intensity modulated radiotherapy OR IMRT OR radiotherapy, intensity-modulated[mh] OR (three dimenstional OR 3D OR 3d CRT) OR image guided radiotherapy OR IGRT OR radiotherapy, image-guided[mh] OR photon radiotherapy OR XRT OR "photons/therapeutic use"[Mesh] OR proton radiotherapy OR PRT OR proton therapy OR proton radiation OR proton beam OR carbon ion radiotherapy) AND a. cranial field b. abdominal field c. total body irradiation d. other fields
Search 4: ***Hormonal therapy***	Hormonal therapy OR Endocrine therapy OR tamoxifen OR aromatase inhibitors OR androgen deprivation therapy OR antiandrogens OR hormone therapy OR estrogen/hormone receptor positive OR fulvestrant

Search 5: ***HSCT***	Hematopoietic stem cell transplantation OR HSCT OR stem cell transplantation OR conditioning therapy OR conditioning regimen OR reduced intensity conditioning OR allogeneic transplantation OR autologous transplantation OR reduced intensity transplantation OR graft versus host disease OR graft-versus-host OR GVHD	
Search 6: ***Steroids***	Glucocorticoids OR glucocorticoids therapy OR glucocorticoids administration OR steroids OR steroid hormones OR high dose steroids OR dexamethasone OR prednisone	
Search 7: ***Surgery***	Surgery OR site of syrgery OR surgery, site OR hypothalamic surgery OR pituitary surgery OR cranial surgery OR craniotomy OR surgery, hypothalamic–pituitary axis OR orchidectomy OR hemiorchidectomy OR hemicastration OR ovariectomy OR salpingo-oophorectomy OR surgery, thyroid, OR surgery, testis OR surgery, adrenal	
Search 8: ***Gende*****r**	Sex OR gender OR female sex OR male sex OR female gender OR male gender	
Search 9: ***Race/ethnicity***	Race OR racial difference OR racial influence OR ethnicity OR racial/ethnic groups	
Search 10: ***Age***	Age at diagnosis OR age at treatment OR age at follow-up OR stage of puberty OR age at menarche	
Search 11: ***Endocrine abnormalities***	Endocrine abnormalities OR endocrine effects OR endocrine disorders OR endocrine dysfunction OR endocrine complications OR hormonal abnormalities OR hormonal disorders OR hormonal dysfunction OR endocrine system OR gonadal OR hypogonadism OR gonadotoxicity OR hypogonadal OR testosterone OR hormone supplements OR thyroid hormone deficiency OR thyroid hormone excess OR hyperthyroidism OR hypothyroidism OR thyroid supplements OR growth hormone OR pituitary hormone OR hypopituitarism OR pituitary disorders OR growth hormone deficiency OR hormone supplements OR endocrine deficiency OR endocrine excess OR pituitary-hypothalamus	
Search 12: ***Lifestyle factors***	Lifestyle OR lifestyle factors OR diet OR dietary habits OR healthy diet OR exercise OR sedentary OR physical activity OR physical fitness OR smoking OR cigarette use OR smoking cessation OR lifestyle intervention OR lifestyle program OR weight management OR health behavior OR weight loss	
Search 13: ***Pretreatment factors***	Birthweight OR weight at diagnosis OR comorbid conditions OR comorbidities OR chronic conditions OR parental weight OR maternal weight OR maternal BMI OR maternal body mass index	
Search 14: ***Obesity***	Obesity OR obese OR overweight OR Increased body mass index OR raised body mass index OR increased waist circumference OR increased waist-hip ratio OR increased body fat mass OR percent body fat OR waist to height ratio	
Search 1 AND (2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13) AND 14 **Filters: published since 1990; Humans; English language**		**= … hits**

Obesity – What surveillance modality should be used?

Search 1: ***Childhood cancer***	(leukemia OR hemothe* OR hemother* OR (childhood ALL) OR AML OR lymphoma OR hemothe* OR hemoth OR hemoth* OR T-cell OR B-cell OR non-hodgkin OR sarcoma OR sarcom* OR sarcoma, Ewing's OR Ewing* OR osteosarcoma OR hemotherapy* OR wilms tumor OR wilms* OR nephroblastom* OR neuroblastoma OR neuroblastom* OR rhabdomyosarcoma OR rhabdomyosarcom* OR teratoma OR teratom* OR hepatoma OR hepatom* OR hepatoblastoma OR hepatoblastom* OR PNET OR medulloblastoma OR medulloblastom* OR PNET* OR neuroectodermal tumors, primitive OR retinoblastoma OR hemotherapy* OR meningioma OR hemothera* OR glioma OR gliom*) OR (pediatric oncology OR paediatric oncology) OR (childhood cancer OR childhood tumor OR childhood tumors)) OR (brain tumor* OR brain tumour* OR brain neoplasms OR central nervous system neoplasm OR central nervous system neoplasms OR central nervous system tumor* OR central nervous system tumour* OR brain cancer* OR brain neoplasm* OR intracranial neoplasm*) OR (leukemia, lymphocytic, acute) OR (leukemia, lymphocytic, acute*) OR breast cancer at a young age OR young breast cancer survivor OR testicular cancer OR germ cell cancer OR germ cell tumor OR seminoma OR seminoma* OR non-seminoma OR non-seminom*	
Search 2: ***Obesity***	Obesity OR obese OR overweight OR Increased body mass index OR raised body mass index OR increased waist circumference OR increased waist-hip ratio OR increased body fat mass OR percent body fat OR waist to height ratio	
Search 3: ***Body mass index***	Body mass index	
Search 4: ***Waist circumference***	Waist circumference	
Search 5: ***Waist/height ratio***	Waist-hip ratio OR waist-height ratio	
Search 6: ***DXA***	DXA or dual energy x-ray absorptiometry OR bone densomitry OR DEXA	
Search 7: ***CT, BIA, or MRI for body fat***	BIA OR bioelectrical impedance analysis or body composition or body fat OR percent body fat OR visceral fat OR visceral adiposity	
Search 8: ***Air displacement***	Air displacement plethysmography OR bod pod OR whole-body air displacement OR ADP	
Search 1 AND (3 OR 4 OR 5 OR 6 OR 7 OR 8) AND 2 **Filters: published since 1990; Humans; English language**		**= … hits**

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ABOUT THE AUTHOR

CURRICULUM VITAE

Fabiën Naomi Belle-van Sprundel was born on January 14th 1986 in Zevenaar, The Netherlands. In 2004 she completed secondary school at the "Liemers College" in Zevenaar. Thereafter she moved to Wageningen, to study the Bachelor of Science Nutrition and Health at Wageningen University. She continued to pursue a Master of Science in Nutritional and Public Health Epidemiology. She completed her Master thesis at Wageningen University were she performed analyses in the POLIEP Follow-up Study and set up the DIVA study to gain insight in the dietary supplement use in patients diagnosed with colorectal cancer under supervision of Prof. Dr. Ellen Kampman.

She completed an internship at Fred Hudson Cancer Research Center, Seattle, Washington, USA under supervision of Prof. Dr. Polly Newcomb, Prof. Dr. Marian Neuhouser, and Prof. Dr. Ellen Kampman which resulted in a publication in Cancer Epidemiology Biomarkers & Prevention. After she graduated in 2010, she was employed as scientist clinical nutrition at Danone/Nutricia for almost three years.

In 2014 she moved to Switzerland. She set up her PhD project and submitted successfully two grants to FORCE Foundation and the Swiss Cancer League. In February 2015 she started her PhD at the Division des Maladies Chronique, Institut Universitaire de Médecine Sociale et Préventive (IUMSP), Lausanne University (UNIL). The overall aims of this PhD-project were to assess the dietary intake of Swiss childhood cancer survivors and to gain insights in the potential risk factors for being overweight during and long after childhood cancer treatment. During her PhD she worked closely together with the Swiss Childhood Cancer Survivor Study team at the Institute of Social and Preventive Medicine (ISPM), Bern. The results obtained in this period are described in this thesis. She presented the results on several national and international conferences.

PUBLICATIONS

Belle FN, Kasteler R, Schindera C, Bochud M, Ammann RA, von der Weid N, Kuehni C. No evidence for overweight in long-term childhood cancer survivors after glucocorticoid treatment. *Cancer. 2018, http://dx.doi.org/10.1002/cncr.31599*

Belle FN, Wenke-Zobler J, Cignacco E, Spycher B, Ammann R, Kuehni C, Zimmermann. Overweight in childhood cancer patients at diagnosis and throughout therapy: A multicentre cohort study. *Clinical Nutrition. 2018, https://doi.org/10.1016/j.clnu.2018.02.022*

Belle FN, Weiss A, Schindler M, Goutaki M, Bochud M, Zimmermann K, von der Weid N, Ammann R, Kuehni C. Overweight in Childhood Leukemia Survivors: the Swiss Childhood Cancer Survival Study. *American Journal of Clinical Nutrition. 2018;107:3-11*

Belle F, Wengenroth L, Weiss A, Sommer G, Beck Popovic M, Ansari M, Bochud M, Kuehni C. Low adherence to dietary recommendations in adult childhood cancer survivors. *Clinical Nutrition. 2017 Oct;36(5):1266-1274.*

Not in this thesis:
Belle FN, Kasteler R. *Letter to the editor,* In response to: Risk factors and the prevention of weight gain during chemotherapy in children with acute lymphoblastic leukemia. *Journal of Pediatric Hematology and Oncology. 2018, JPHO-18-155*

Kasteler R, Belle F, Schindera C, Barben J, Gumy-Pause F, Tinner EM, Kuehni CE. Prevalence and reasons for smoking in adolescent Swiss childhood cancer survivors. *Pediatric Blood & Cancer. 2018, https://doi.org/10.1002/pbc.27438*

Goutaki M, Halbeisen FS, Spycher BD, Maurer E, Belle F, Amirav I, Behan L, Boon M, Carr S, Casaulta C, Clement A, Crowley S, Dell S, Ferkol T, Haarman EG, Karadag B, Knowles M, Koerner-Rettberg C, Leigh MW, Loebinger MR, Mazurek H, Morgan L, Nielsen KG, Phillipsen M, Sagel SD, Santamaria F, Schwerk N, Yiallouros P, Lucas JS, Kuehni CE; PCD Israeli Consortium; Swiss PCD Group; French Reference Centre for Rare Lung Diseases. Growth and nutritional status, and their association with lung function: a study from the international Primary Ciliary Dyskinesia Cohort. *The European Respiratory Journal. 2017 Dec 21;50(6).*

Schindler M, Belle FN, Grotzer MA, von der Weid NX, Kuehni CE. Childhood cancer survival in Switzerland (1976-2013): Time-trends and predictors. *International Journal of Cancer. 2017 Jan 1;140(1):62-74.*

Hartog A, Belle FN, Bastiaans J, de Graaff P, Garssen J, Harthoorn LF, Vos AP. A potential role for regulatory T-cells in the amelioration of DSS induced colitis by dietary non-digestible polysaccharides. *The Journal of Nutritional Biochemistry. 2015 Mar;26(3):227-33.*

Belle FN, Kampman E, McTiernan A, Bernstein L, Baumgartner K, Baumgartner R, Ambs A, Ballard-Barbash R, Neuhouser ML. Dietary fiber, carbohydrates, glycemic index, and glycemic load in relation to breast cancer prognosis in the HEAL cohort. *Cancer Epidemiology Biomarkers Prevention. 2011 May;20(5):890-9.*

ABSTRACTS (during this thesis)

Belle FN, Wenke-Zobler J, Cignacco E, Ammann RA, Kuehni CE, Zimmermann K. Overweight in childhood cancer patients at diagnosis and throughout therapy: a multicentre cohort study. *Clinical Nutrition, Vol 36, S20, OR50, (The European Society for Clinical Nutrition and Metabolism [ESPEN] 2017, oral presentation)*

Belle FN, R. Kasteler R, Schindera C, Bochud M, Ammann RA, Von der Weid NX, Kuehni CE. Steroid Treatment, Cranial Irradiation and Risk of Overweight After Childhood Cancer. *Clinical Nutrition, Vol. 36, S17–S18, OR43, (The European Society for Clinical Nutrition and Metabolism [ESPEN] 2017, oral presentation)*

Kasteler R, Belle F, Gumy-Pause F, Tinner E, Kuehni C. Prevalence and reasons for smoking in adolescent Swiss childhood cancer survivors.
(European respiratory society conference 2017, poster presentation)

Belle FN, Weiss A, Schindler M, Goutaki M, Bochud M, Zimmermann K, Von der Weid NX, Ammann RA, Kuehni CE. Overweight in survivors of childhood cancer.
(Swiss Paediatric Oncology Group Scientific Meeting 2017, oral presentation)

Belle FN, Schindler M, Sommer G, Goutaki M, Kasteler R, Kuonen R, Bochud M, Zimmerman K, Ammann RA, Kuehni CE, Overweight and obesity in Swiss childhood leukaemia survivors. *Clinical Nutrition, Volume 35, S124, SUN-P215, DOI: 10.1016/S0261-5614(16)30558-1*
(The European Society for Clinical Nutrition and Metabolism [ESPEN] 2016, poster presentation)

Belle FN, Wengenroth L, Weiss A, Sommer G, Beck Popovic M, Ansari M. Bochud M, Kuehni CE. Low adherence to dietary recommendations in adult childhood cancer survivors. *Clinical Nutrition, Vol 35, S74-75, SUN-P082, DOI: 10.1016/S0261-5614(16)30425-3*
(The European Society for Clinical Nutrition and Metabolism [ESPEN] 2016, poster presentation)

Belle FN, Schindler M, Sommer G, Goutaki M, Kasteler R, Kuonen R, Bochud M, Zimmerman K, Ammann RA, Kuehni CE, Overweight and obesity in Swiss childhood leukaemia survivors. *(European Symposium on Late Complications after Childhood Cancer [ESLCC] 2016, poster presentation)*

Belle FN, Wengenroth L, Weiss A, Sommer G, Beck Popovic M, Ansari M. Bochud M, Kuehni CE. Low adherence to dietary recommendations in adult childhood cancer survivors. *(European Symposium on Late Complications after Childhood Cancer [ESLCC] 2016, poster presentation)*

Belle FN, Schindler M, Sommer G, Goutaki M, Kasteler R, Kuonen R, Bochud M, Zimmerman K, Ammann RA, Kuehni CE, Overweight and obesity in Swiss childhood leukaemia survivors. *(Clinical Research Day Bern 2016, poster presentation)*

Belle FN, Schindler M, Sommer G, Goutaki M, Kasteler R, Kuonen R, Bochud M, Zimmermann K, Ammann RA, Kuehni CE, Overweight and Obesity in Childhood Leukaemia Survivors: the Swiss Childhood Cancer Survival Study
(Swiss Public Health Conference 2016, poster presentation)

Kasteler R, Belle F, Weiss A, Kuonen R, Von der Weid NX, Ammann RA, Sommer G, Kuehni C, Monitoring of pulmonary health in Swiss childhood cancer survivors: are guidelines necessary?
(Swiss Public Health Conference 2016, poster presentation)

Belle FN, Wengenroth L, Weiss A, Sommer G, Beck Popovic M, Ansari M. Bochud M, Kuehni CE. Low adherence to dietary recommendations in adult childhood cancer survivors. *(Swiss Paediatric Oncology Group annual Scientific Meeting 2016, oral presentation)*

PATENTS

Belle FN, Harthoorn LH, Choi C, Venema P. Induced viscosity fibre system for the treatment or prevention of gastro-oesophageal reflux
EU, PCT/NL2013/050448 – NL, WO2014209106