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ORIGINAL ARTICLE

Unhealthy lifestyle behaviors, overweight, and obesity among childhood cancer survivors in the Netherlands: A DCCSS LATER study

Eline Bouwman PhD[1] | Adriaan Penson MSc[1] | Maud de Valk BSc[2] | Selina R. van den Oever MSc[2] | Helena J. H. van der Pal MD, PhD[2,3] | Eline van Dulmen-den Broeder PhD[4] | Nicole M. A. Blijlevens MD, PhD[1] | Dorine Bresters MD, PhD[2] | Elizabeth A. M. Feijen PhD[2] | Marry M. van den Heuvel-Eibrink MD, PhD[2,5,6] | Margriet van der Heiden-van der Loo PhD[7] | Gisela Michel PhD[8] | Cécile M. Ronckers PhD[2,9] | Jop C. Teepen PhD[2] | Wim J. E. Tissing MD, PhD[2,10] | Birgitta A. B. Versluys MD, PhD[2] | Leontien C. M. Kremer MD, PhD[2,6,11] | Saskia M. F. Pluijm PhD[2] | Jacqueline J. Loonen MD, PhD[1] | on behalf of the Dutch LATER Study Group and the PanCareFollowUp Consortium

[1]Radboud University Medical Center, Nijmegen, The Netherlands

[2]Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands

[3]PanCare, Bussum, The Netherlands

[4]Amsterdam University Medical Center, Amsterdam, The Netherlands

[5]Erasmus Medical Center–Sophia Children's Hospital, Rotterdam, The Netherlands

[6]Utrecht University and Utrecht Medical Center, Utrecht, The Netherlands

[7]Dutch Childhood Oncology Group-Late Effects After Childhood Cancer (LATER) Registry, Utrecht, The Netherlands

[8]Faculty of Health Sciences and Medicine, University of Lucerne, Lucerne, Switzerland

[9]Division of Childhood Cancer Epidemiology, Institute of Medical Biostatistics, Epidemiology and Informatics, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany

[10]University Medical Center Groningen, Groningen, The Netherlands

[11]Amsterdam University Medical Center, Amsterdam, The Netherlands

Correspondence
Eline Bouwman, Department of Hematology, Radboud University Medical Center, Reinier Postlaan (Post 942), Nijmegen 6525 GC, The Netherlands.
Email: eline.bouwman@radboudumc.nl

Abstract

Background: The objective of this study was to examine the prevalence of unhealthy lifestyle behaviors, overweight, and obesity in Dutch childhood cancer survivors (CCSs) compared with sibling controls and the Dutch general population. Other aims

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were to assess associated factors of unhealthy lifestyle behaviors, overweight, and obesity and to identify subgroups of CCSs at risk for these unhealthy statuses.

Methods: The authors included 2253 CCSs and 906 siblings from the Dutch Childhood Cancer Survivor Study-Late Effects After Childhood Cancer cohort, part 1, and added data from the Dutch general population. Questionnaire data were collected on overweight and obesity (body mass index >25.0 kg/m^2), meeting physical activity guidelines (>150 minutes per week of moderate or vigorous exercises), excessive alcohol consumption (>14 and >21 alcoholic consumptions per week for women and men, respectively), daily smoking, and monthly drug use. Multivariable logistic regression analyses and two-step cluster analyses were performed to examine sociodemographic-related, health-related, cancer-related, and treatment-related associated factors of unhealthy lifestyle behaviors and to identify subgroups of CCSs at risk for multiple unhealthy behaviors.

Results: CCSs more often did not meet physical activity guidelines than their siblings (30.0% vs. 19.3%; $p < .001$). Married as marital status, lower education level, nonstudent status, and comorbidities were common associated factors for a body mass index ≥25.0 kg/m^2 and insufficient physical activity, whereas male sex and lower education were shared associated factors for excessive alcohol consumption, daily smoking, and monthly drug use. A subgroup of CCSs was identified as excessive alcohol consumers, daily smokers, and monthly drug users.

Conclusions: The current results emphasize the factors associated with unhealthy behaviors and the potential identification of CCSs who exhibit multiple unhealthy lifestyle behaviors.

KEYWORDS
cancer survivorship, cluster analysis, late effects, lifestyle behaviors, pediatric cancer, secondary prevention, tertiary prevention

INTRODUCTION

The past 40 years have witnessed increasing advances in the field of childhood cancer cure rates attributed to improvements in childhood cancer treatment.[1–5] Unfortunately, specific treatments may be accompanied by an elevated risk for long-term childhood cancer survivors (CCSs) to develop adverse health outcomes later in life; i.e., late effects. These late effects can have a severe impact and can lead to impaired quality of life and premature mortality.[6–14]

Overweight and obesity (body mass index [BMI] ≥25.0 kg/m^2), along with unhealthy lifestyle behaviors, such as low physical activity levels, smoking, excessive alcohol consumption, and drug use, are primarily modifiable risk factors recognized for their significance in the etiology of several chronic disorders in the general population.[15–17] However, given the already increased risk for developing late effects, unhealthy lifestyle behaviors may have a particular detrimental impact on the health of CCSs.[18–20] Therefore, to facilitate secondary and tertiary prevention of late effects among CCSs, cancer organizations and guidelines stress the importance of adhering to healthy lifestyle behaviors and a healthy weight status in CCSs (BMI 18.5–24.9 kg/m^2).[18,21,22] Although obesity can be viewed as a chronic condition requiring lifelong management, potentially through intensive lifestyle interventions, a high BMI might be linked to or arise from unhealthy behaviors like poor dietary choices and/or insufficient physical activity, which can be effectively addressed. Several studies have demonstrated the beneficial effects of healthy lifestyle behaviors and weight status among CCSs.[23–29] For instance, Dixon et al. demonstrated that a healthy lifestyle (defined as never smoked, nonheavy or nonrisky drinker, a healthy weight, and sufficient physical activity) was associated with a 20% reduced risk of health-related mortality independent of traditional cardiovascular risk factors.[29] Furthermore, additional studies have indicated that maintaining a normal weight (BMI ≥25.0 kg/m^2) and engaging in sufficient physical activity are associated with improved cardiometabolic outcomes among CCSs.[24,26–28]

However, as observed in the general population, some CCSs fail to adhere to healthy lifestyle behaviors and/or a healthy weight status.[30–35] In addition, to support CCSs in adopting a healthy lifestyle, it is essential to identify those individuals who are at increased risk for engaging in unhealthy lifestyle behaviors or having an

unhealthy BMI. This identification can help determine who could benefit from health behavior interventions and the approach needed to offer these interventions. For this reason, assessing subgroups of CCSs with unhealthy lifestyle behaviors and an unhealthy BMI, along with their associated characteristics, can yield valuable information for use in survivorship care.

Therefore, the objective of the current study was to examine the prevalence of unhealthy lifestyle behaviors, overweight, and obesity in Dutch CCSs compared with siblings and the general population in the Netherlands. In addition, we aimed to assess sociodemographic and clinical-associated factors associated with unhealthy lifestyle behaviors, overweight, and obesity and to identify clusters of CCSs at risk for having multiple unhealthy lifestyle behaviors and/or an unhealthy BMI.

MATERIALS AND METHODS

Study design and study population

A cross-sectional study design was used along with data from the Dutch Childhood Cancer Survivor Study-Late Effects After Childhood Cancer (DCCSS LATER) cohort. This cohort included survivors of all types of childhood malignancies, classified according to the *International Classification of Childhood Cancer*,[36] and their siblings. The CCSs were diagnosed before age 18 years, were at least 5 years post-diagnosis, and were treated in one of the seven Dutch pediatric oncology centers between 1963 and 2001. Details about the DCCSS LATER cohort and data collection were described elsewhere.[37] Of the entire cohort of 6165 CCSs, 963 were deemed ineligible for participation, resulting in 5202 eligible CCSs who were approached to take part in the DCCSS LATER study. Among these, 1455 CCSs did not respond to the invitation, 380 actively declined participation through written or verbal communication, and 200 consented only to the use of their medical records without further involvement in research activities. Consequently, 353 of the 3167 study participants were excluded because of age criteria, and 561 CCSs lacked complete data on health behaviors and weight status. Thus the final study cohort included 2253 CCSs, and the sibling control group comprised 906 siblings (Figure 1).

Data collection and outcomes

DCCSS LATER 1 questionnaire and cancer diagnosis-related and treatment-related data

Between 2013 and 2015, all eligible CCSs and siblings were asked to complete the DCCSS LATER 1 questionnaire. This questionnaire assessed BMI, physical activity, alcohol consumption, smoking, and drug use as proxies for weight status and healthy behaviors. The questionnaire also inquired about sociodemographic characteristics (e.g., marital status, educational level, employment status,), self-reported comorbidities (i.e., present or past medical conditions), and limb amputations. Further details regarding the questionnaire are described by Teepen et al.[37] Information on prior cancer diagnoses and the treatment of survivors was obtained from the centers' medical records.

Unhealthy lifestyle behaviors in the Dutch general population: Dutch Health Survey 2014

The prevalence of unhealthy behaviors was compared with data from the Dutch Health Survey 2014, an annual questionnaire distributed among the Dutch population to assess health, medical contacts, health behaviors, and preventive behavior.[35] Considering the mean age of participating survivors and siblings, we used stratified prevalence rates of Dutch Health Survey participants aged 30–35 years. Specific questions on the Dutch Health Survey 2014 used for this study are listed in Table S1.

Outcome definitions for unhealthy lifestyle behaviors and weight status

Table 1 provides details on questionnaire items and outcome categorization. BMI was classified according to the World Health Organization classifications, with a BMI of 25.0–29.9 kg/m^2 indicating moderate overweight and a BMI ≥30 kg/m^2 indicating obesity.[38] In this study, both overweight and obesity were considered unhealthy. Physical activity was determined using constructs of the European Prospective Investigation into Cancer and Nutrition study Physical Activity Questionnaire (short version).[39] Participants were categorized as either meeting or not meeting the physical activity guidelines based on norms set by the Health Council of the Netherlands. People meet these guidelines when they performed at least 150 minutes per week of physical activity, spread over several days, combined with at least activities twice a week that strengthen muscles and bones.[40] Because of the lack of data on whether activities were spread over multiple days and data on muscle and bone strengthening activities, this study focuses only on meeting the moderate or vigorous activity guideline. To be able to categorize participants into meeting or not meeting the physical activities guidelines, first, activities were subdivided into moderate-intensity or vigorous-intensity exercises, based on the *Compendium of Physical Activities* by Ainsworth et al.[42] Activities were classified into two categories based on their intensity: moderate-intensity exercises, which included activities like cycling and biking, with a metabolic equivalent of task value between 4.0 and <6.5; and vigorous-intensity exercises, such as running and playing singles tennis, with a metabolic equivalent of task value ≥6.5.[43] Alcohol consumption was categorized as excessive drinking (yes/no) when men and women consumed more than 21 and 14 alcoholic consumptions per week, respectively.[41] In current study, daily smoking (yes/no) was defined smoking more than seven cigarettes per week, given the assumption that people divide smoking cigarettes

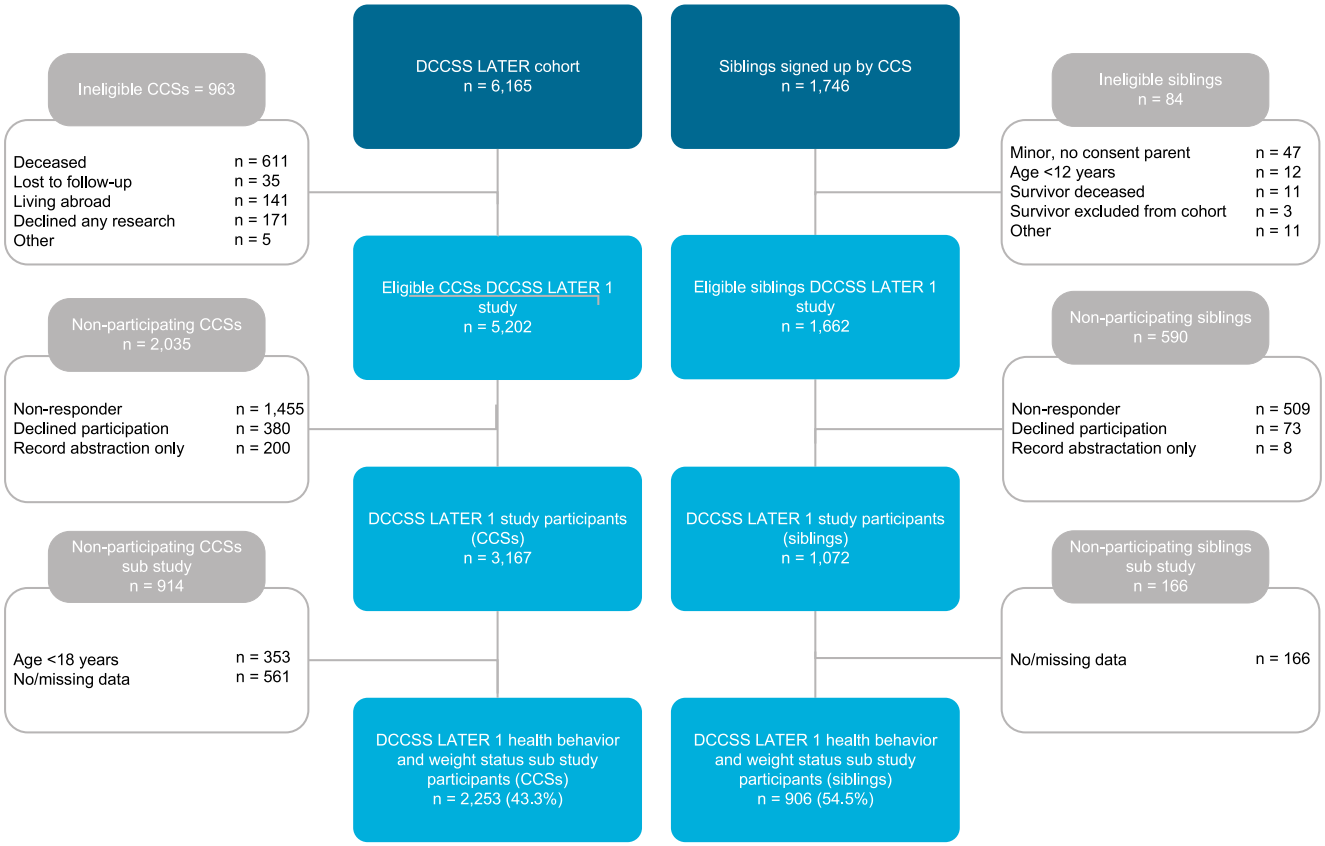

FIGURE 1 Flowchart of participants in the DCCSS LATER 1 health behavior and weight status substudy. CCSs, childhood cancer survivors; DCCSS, Dutch Childhood Cancer Survivor Study; LATER, Late Effects After Childhood Cancer.

over multiple days. Finally, monthly drug use was defined as using drugs (i.e., hashish, weed, cocaine, heroin, ecstasy, or other drugs) at least once a month in the past year (yes/no).

Definitions of sociodemographic and health-related variables

In this study, being married included all living situations in which a CCS or a sibling lives together with a partner. Educational levels were categorized according to the Dutch educational system. A *low educational level* encompassed primary education, technical and vocational education and training (i.e., education that prepares people for a skilled craft), or special education (i.e., education for individuals who need specialized or intensive support). A *middle educational level* encompassed preparatory secondary vocational education (i.e., preparation for vocational training as part of secondary education), secondary vocational education (i.e., vocational training after secondary education), higher general secondary education, and preuniversity education. A *higher education level* included higher vocational education and university after secondary education. Employment status was defined as either *employed* (i.e., those employed at time of study), *student* (i.e., those who were students and employed for a maximum of 12 hours/week), *unemployed* (i.e., those unemployed by choice or looking for a job at time of the study), or *incapacitated* (i.e., those physically or mentally unable to work). Comorbidities were categorized as either *zero*, *one or two*, or *more than two* health problems, as defined by Streefkerk et al.[44] Finally, amputations included those who had at least one limb amputated.

Statistical analysis

Statistical analyses were performed using IBM SPSS software (version 25; IBM Corporation). Descriptive data included raw numbers, percentages (prevalence), means, and standard deviations. All p values $< .05$ were considered statistically significant. The χ^2 test was used to compare sex, age at diagnosis, primary childhood cancer diagnosis, and treatment of participants and nonparticipants. Sociodemographic differences between survivors and siblings were examined using independent t-tests (for continuous variables) and χ^2 tests (for categorical variables). Multiple imputation was performed to handle missing data of independent variables regarding the sociodemographic characteristics of participating CCSs and siblings. Missing values were assumed to be at random because no pattern in the missing data was observed. Twenty data sets were imputed, and Rubin's rules were used to pool the results.[45,46]

TABLE 1 Data collected in the Dutch Childhood Cancer Survivor Study Late Effects After Childhood Cancer 1 health behavior and weight status substudy: Outcome measures and classifications of unhealthy lifestyle behaviors and weight status.

Health behavior/ weight status	Validated questionnaire used	Specific question in the DCCSS LATER 1 questionnaire	Definitions used in current study	Classification of unhealthy lifestyle behavior in the current study
BMI	NA	What is your current weight (kg)? How tall are you at the moment (cm)?	BMI was calculated as kg/m^2 and further categorized in WHO 2010[38]: Underweight (BMI <18.5 kg/m^2; yes/no) Healthy weight (BMI 18.5–24.9 kg/m^2; yes/no) Overweight (BMI 25.0–29.9 kg/m^2; yes/no) Obesity (BMI ≥30.0 kg/m^2; yes/no)	Overweight (WHO 2010[38]) BMI 25.0–29.9 kg/m^2 Obesity (WHO 2010[38]) BMI ≥30 kg/m^2
Physical activity	European Prospective Investigation into Cancer and Nutrition study (EPIC; Wareham 2003[39])	Can you indicate how many hours you spent, approximately, during last summer and winter, per week on the following activities (number of hours): walking, cycling, gardening, do-it-yourself activities, sport activities and other physical activities, and household activities?	The Compendium of Physical Activities was used to categorize activities in moderate or vigorous intensity exercises. Meeting physical activity guidelines was defined as ≥150 minutes of moderate or vigorous intensity physical activity per week (Gezondheidsraad 2017[40]): Meeting guidelines (yes/no) Hours of physical active per week (number of hours)	Physical activity guidelines (Gezondheidsraad 2017[40]) Meeting guidelines (no)
Alcohol consumption	NA	How many glasses of alcoholic beverages do you currently drink on average per day during the week? (number of glasses) How many glasses of alcoholic beverage do you currently drink on average per day during the weekend (number of glasses)?	Excessive alcohol consumption was defined as >21 alcoholic drinks per week for men and >14 alcoholic drinks per week for women (Trimbos-Institute 2018[41]): Excessive (yes/no) Not excessive (yes/no) Alcoholic drinks per week (n)	Excessive alcohol consumption (yes; Trimbos-Institute 2018[41])
Smoking	NA	Are you currently smoking more than one cigarette per week? (yes [number of cigarettes per week], but I used to smoke; no, I have never smoked)	Daily smoking was defined as smoking seven or more cigarettes per week: Daily (yes/no) Nondaily (yes/no)	Daily smoking (yes)
Drug use	NA	How many times, did you use drugs during the last month (such as hashish, weed, cocaine, heroin, ecstasy or other drugs)? (number of times) What was the name of the drug used during the past month (e.g., cannabis, ecstasy, or heroin)	Monthly drug use was defined as using drugs one or more times time during the last month: Monthly (yes/no) Not monthly (yes/no)	Monthly drug use (yes)

Abbreviations: BMI, body mass index; DCCSS, Dutch Childhood Cancer Survivor Study; LATER, Late Effects After Childhood Cancer; NA, not applicable.

Prevalence of unhealthy lifestyle behaviors, overweight, and obesity

Logistic regression analyses, adjusted for confounding (sociodemographic) factors and after multiple imputation, assessed differences in the prevalence of health behavior variables and weight status between survivors and siblings. Adjustments were made for sex and age, and in the case of BMI, an additional adjustment was made for amputation status. Sensitivity analyses using generalized estimating equations were conducted to correct for unmeasured correlations between survivors and their siblings. Comparisons with the Dutch Health Survey 2014 regarding overweight, obesity, excessive alcohol consumption, and smoking were made descriptively (no statistical comparisons).

Analysis to examine associated factors of unhealthy lifestyle behaviors, overweight, and obesity in CCSs

To examine associated factors of unhealthy lifestyle behaviors, overweight, and obesity, odds ratios (ORs) and 95% confidence intervals (CIs) were computed using multivariable logistic regression analyses for each unhealthy lifestyle behavior (i.e., not meeting the physical activity guidelines, excessive alcohol consumption, daily smoking, and any drug use in the past month), and a BMI ≥25.0 kg/m^2 served as a dependent variable. Sex, age at questionnaire completion, marital status, educational level, employment status, comorbidities (zero, one or two, or two or more health issues[44]), amputation of one or more limb(s) (yes/no), cancer diagnosis, cancer treatment, radiotherapy to the head/cranium, radiotherapy to the abdomen, total body irradiation, and stem cell transplantation (yes/no) were included in the model as independent variables. Variance inflation factors were calculated for all associated factors with a threshold of >5 to test for problematic multicollinearity.[47] An additional sensitivity analysis was performed using two separate models (i.e., one model with diagnosis only and one with treatment only) to determine whether separate models would present major different outcomes.

Cluster analysis for unhealthy lifestyle behaviors, overweight, and obesity

To identify subgroups (clusters) of CCSs that had similar patterns of unhealthy lifestyle behaviors, overweight, obesity, and associated factors, a two-step cluster analysis was performed, which used both distance measures and probability measures to separate subgroups.[48] Two-step cluster analysis is considered a reliable technique to identify subgroups in large data sets.[48,49] For this analysis, the number of alcoholic consumptions and cigarettes per week, the hours spent cycling/participating in sports per week, and BMI were used as continuous variables; and monthly drug use (yes/no) was used as a categorical variable. Log-likelihood was used as a distance measure to identify clusters, and the optimal number of clusters was determined using the Schwarz Bayesian information criterion. The silhouette measure of cohesion and separation was used as a measure of goodness-of-fit of the cluster structure, with a value of ≥0.5 considered acceptable.[50] After conducting the cluster analysis, we conducted univariable logistic regression analysis to investigate variations between the clusters in terms of sociodemographic and medical characteristics.

RESULTS

Participants versus nonparticipants

Characteristics of participants versus nonparticipants are displayed in Table S2. Compared with nonparticipating CCSs, participating CCSs were more often male, were older at diagnosis, and were survivors of non-Hodgkin lymphoma, Hodgkin lymphoma, or bone tumors. Participating CCSs also were more likely to have received a combination of radiotherapy and chemotherapy as treatment than nonparticipating CCSs.

Study sample

Table 2 presents the characteristics of participating survivors and siblings. CCSs were predominantly male, slightly younger at the time they completed the questionnaire, less likely to be married or living together with a partner, and more likely to have lower educational attainment compared with sibling controls. Incapacity for work was observed in nearly one of six survivors versus one of 50 siblings, whereas comorbidities (one or more) were more prevalent in CCSs than in siblings. Among CCSs, 2.6% had at least one limb amputated versus 0.1% of siblings. Leukemia was the most common childhood cancer diagnosis (32.6%). Overall, the average age at diagnosis was 7.2 years. Finaly, more than five of six CCSs had received chemotherapy exclusively or had received a combination of radiotherapy and chemotherapy, and 3.2% of survivors had undergone a stem cell transplantation.

Unhealthy lifestyle behaviors, overweight, and obesity in CCSs, siblings, and the Dutch general population

Figure 2 presents the prevalence of unhealthy lifestyle behaviors, overweight, and obesity in CCSs, siblings, and the Dutch general population. Logistic regression analyses, adjusted for confounding sociodemographic factors, showed that, compared with siblings, CCSs had a higher likelihood of not meeting physical activity guidelines (30.0% vs. 19.3%; OR, 1.92; 95% CI, 1.58–2.32). Prevalence rates for overweight (26.4% vs. 27.4%; OR, 1.05; 95% CI, 0.88–1.27), obesity (9.5% vs. 9.4%; OR, 1.23; 95% CI, 0.93–1.62), excessive alcohol consumption (7.1% vs. 8.8%; OR, 0.77; 95% CI, 0.58–1.03), daily smoking (12.6% vs. 13.4%; OR, 0.89; 95% CI, 0.70–1.12), and monthly

TABLE 2 Characteristics of participating childhood cancer survivors and siblings.

	CCSs, *n* = 2253		Siblings, *n* = 906		
Characteristic	**No.**	**%**	**No.**	**%**	***p*[a]**
Sex					< .001
Male	1162	51.6	377	41.6	
Female	1091	48.4	529	58.4	
Age at completion questionnaire, years					
Mean ± SD	32.1 ± 8.8	45.2	33.7 ± 9.8	40.3	< .001
18–29	1081	35.1	365	35.0	.004
30–39	791	19.7	317	24.7	
≥40	444		224		
Marital status[b]					< .001
Married	1163	51.9	580	64.4	
Unmarried	1078	48.1	321	35.6	
Missing	12	–	5	–	
Level of education[c]					< .001
Low	426	19.0	69	7.6	
Middle	1057	47.2	405	44.9	
High	755	33.7	429	47.5	
Missing	15	–	3	–	
Employment status					< .001
Employed	1476	66.3	709	78.6	
Student	303	13.6	123	13.6	
Unemployed	124	5.6	53	5.9	
Incapacitated	323	14.5	17	1.9	
Missing	27	–	4	–	
Comorbidities					< .001
0	1252	56.3	675	77.9	
1–2	798	35.9	185	21.3	
>2	173	7.8	7	0.8	
Missing	30	–	39	–	
Amputation					< .001
No	2172	97.4	902	99.9	
Yes	81	2.6	1	0.1	
Missing	–	–	3	–	
Primary childhood cancer diagnosis[d]					
Leukemia	734	32.6			
Non-Hodgkin lymphoma[e]	278	12.3			
Hodgkin lymphoma	162	7.2			
CNS	265	11.8			
Neuroblastoma	116	5.1			
Retinoblastoma	12	0.5			

TABLE 2 (Continued)

Characteristic	CCSs, $n = 2253$		Siblings, $n = 906$		p[a]
	No.	%	No.	%	
Renal tumors	243	10.8			
Hepatic tumors	18	0.8			
Bone tumors	146	6.5			
Soft tissue tumors	163	7.2			
Germ cell tumors	81	3.6			
Other and unspecified[f]	35	1.6			
Age at diagnosis, years					
Mean ± SD	7.2 ± 4.7				
Childhood cancer treatment[g]					
Surgery only	191	8.5			
Chemotherapy, no radiotherapy	1133	50.3			
Radiotherapy, no chemotherapy	169	7.5			
Radiotherapy and chemotherapy	753	33.4			
No treatment/treatment unknown	7	0.3			
Stem cell transplantation					
No	2180	96.8			
Yes	173	3.2			

Abbreviations: CNS, central nervous system; CSSs, childhood cancer survivors; SD, standard deviation.

[a]The χ^2 test was used for categorical variables, and an independent *t*-test was used for continuous variables.

[b]Married as marital status includes all situations in which a CCS lives together with a partner.

[c]*Low*: primary education, technical and vocational education and training, special school; *middle*: preparatory secondary vocational education, secondary vocational education, higher general secondary education, preuniversity education; *high*: higher vocational education, university.

[d]Not applicable because of the influence of amputation of a limb on BMI. Diagnostic groups included all malignancies covered by the third edition of the *International Classification of Childhood Cancer* (ICCC-3) as well as multifocal Langerhans cell histiocytosis.

[e]Includes all morphology codes specified in the ICCC-3 under lymphomas and reticuloendothelial neoplasms, except for Hodgkin lymphomas. Also includes multifocal Langerhans cell histiocytosis.

[f]Includes all morphology codes specified in the ICCC-3 under other malignant epithelial neoplasms and malignant melanomas and other and unspecified malignant neoplasms.

[g]Treatment data included primary treatment and all recurrences.

drug use (3.6% vs. 3.6%; OR, 0.77; 95% CI, 0.50–1.17) were similar among CCSs and siblings. Generalized estimating equation analyses did not result in significant different results.

Compared with the Dutch general population, obesity was similar in CCSs (9.5% vs. 9.3%), whereas overweight (26.4% vs. 28.4%), excessive alcohol consumption (7.4% vs. 9.2%), and daily smoking (12.6% vs. 22.4%) appeared to be less prevalent in CCSs. The same trends could be observed in other age ranges (see Figure S1).

Associated factors and clusters of unhealthy lifestyle behaviors, overweight, and obesity

Table 3 displays the associations between unhealthy lifestyle behaviors, overweight, and obesity in CCSs and sociodemographic or medical factors. The variance inflation factors were <2.7 for all factors, indicating no problematic multicollinearity. CCSs with overweight or obesity (i.e., BMI ≥25.0 kg/m^2) were more likely to be aged 30–39 years or 40 years or older, to be married, to have lower educational attainment, to be a nonstudent, to have one or two or two or more comorbidities, and to have a history of stem cell transplantation compared with CCSs who had a BMI <25.0 kg/m^2. Moreover, overweight or obese CCSs were less often diagnosed with germ cell tumors or other unspecified tumors compared with leukemia. Physically inactive CCSs had higher odds of being married, having a low education level, being a nonstudent, and having two or more comorbidities than those who participated in sufficient physical activity according to the guidelines. CCSs who excessively consumed alcohol (i.e., for men and women, >21 and > 14 alcoholic drinks per week, respectively) were more often male, had a low education level, were incapacitated for work, and had higher odds of having two or more comorbidities than nonexcessive alcohol consumers. In

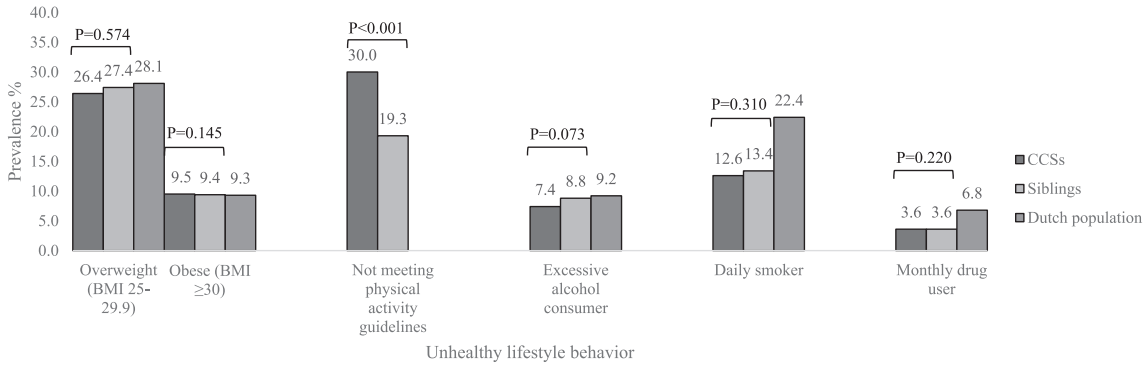

FIGURE 2 The prevalence (%) unhealthy lifestyle behaviors, overweight, and obesity in CCSs, siblings, and the general Dutch population after multiple imputation and adjustment for confounders. Because of a lack of access to original data from the 2014 Dutch Health Survey, statistical testing to examine differences in the prevalence of *not meeting physical activity guidelines* and *monthly drug use* with CCSs was not possible. Univariate logistic regression analysis (categorical BMI) after multiple imputation was adjusted for sex, age, and amputation (only for BMI). Because of differences in physical activity guideline definitions, data from the 2014 Dutch Health Survey on *not meeting physical activity guidelines* were not included. The ORs (95% CIs) indicating statistical differences between CCSs and siblings regarding unhealthy behaviors, overweight, and obesity were as follows: *overweight* (BMI, 25.0–29.9 kg/m^2): OR, 1.05 (95% CI, 0.88–1.27); *obese* (BMI ≥30 kg/m^2): OR, 1.28 (95% CI, 0.93–1.62); *not meeting physical activity guidelines:* OR, 1.92 (95% CI, 1.58–2.32); *excessive alcohol consumer:* OR, 0.77 (95% CI, 0.58–1.03); *daily smoker:* OR, 0.89 (95% CI, 0.70–1.12); *monthly drug user:* OR, 0.77 (95% CI, 0.50–1.17). BMI indicates body mass index; CCSs, childhood cancer survivors; CI, confidence interval; OR, odds ratio.

addition, those CCSs more often had at least one limb amputated. Regarding daily smokers, it was observed that CCSs who were smokers were more often male and had a low education level compared with nonsmokers. Smokers were less often students, more often unemployed, and more often were incapacitated for work compared with nonsmokers. Daily smokers among CCSs were also less often diagnosed with central nervous system (CNS) tumors, and received treatment for childhood cancer radiotherapy exclusively or in combination with chemotherapy compared with CCSs who were nonsmokers. Finally, the analysis indicated that monthly drug-using CCSs more often were male, unmarried, had a low education level, and were diagnosed between ages 10 and 15 years with childhood cancer versus nonmonthly drug users. In addition, monthly drug users also less frequently received radiotherapy exclusively. A sensitivity analysis with two separate models (i.e., one model with diagnosis only and one with treatment only) revealed no major differences in the results compared with the model displayed in this article, including both diagnosis and treatment variables (results not shown).

The results of the cluster analysis are presented in Table 4. Two distinct subgroups of CCSs were identified (cluster 1, n = 1911; cluster 2, n = 342) in 20 datasets, with a silhouette measure of cohesion and separation ≥0.5 in 19 imputed data sets. These clusters were primarily characterized by differences in alcohol consumption, smoking habits, and drug use. In cluster 2, a higher percentage of CCSs consumed alcohol excessively (41.8% vs. 1.3% in cluster 1; OR, 56.5; 95% CI, 35.8–89.2), smoked cigarettes daily (62.0% vs. 3.8% in cluster 1; OR, 41.7; 95% CI, 30.2–57.4), and used drugs monthly (23.4% vs. 0.0% in cluster 1). Clusters did not differ on BMI or physical activity. Compared with CCSs in cluster 1, CCSs in cluster 2 were more likely to be male, unmarried, to have a low education level, and to be survivors of non-Hodgkin lymphoma. Those in cluster 2 were also less likely to be currently aged 40 years or older, to have one or two or more than two comorbidities, to be ages 10–14 years at the time of cancer diagnosis, and to be survivors of Hodgkin lymphoma CNS tumors compared with CCSs in cluster 1.

DISCUSSION

This study demonstrates a higher prevalence of physical inactivity in CCSs compared with their siblings and the Dutch population. Furthermore, the results indicate that male sex, a low or middle educational level, marital status, employment status, and comorbidities are associated with unhealthy behaviors in CCSs. Notably, this is the first Dutch study to report the prevalence of unhealthy lifestyle behaviors, overweight, and obesity of CCSs compared with both their siblings (using data from the Dutch national cohort) and age-matched Dutch peers. Moreover, the study also offers unique insights by examining associations and identifying clusters of multiple unhealthy lifestyle behaviors in CCSs.

In our study, more than one third of CCSs were overweight or obese, similar to their siblings and the Dutch general population, but the proportion was slightly higher than that reported in other studies conducted among European CCSs, possibly attributed to cultural differences in dietary patterns.[51,52] Given the increased susceptibility of CCSs for late effects as an inevitable consequence of cancer treatment, the presence of overweight and obesity as additional risk factors for developing these conditions are concerning. Therefore, to potentially achieve secondary and tertiary prevention of late effects, it is crucial to address the unhealthy behaviors in survivorship care that can result in an elevated BMI, namely, poor dietary choices and/or insufficient physical activity.

TABLE 3 Associated factors of individual unhealthy lifestyle behaviors, overweight, and obesity in childhood cancer survivors.[a]

Characteristic	BMI: Overweight and obesity, OR (95% CI)	Physical activity: Not meeting the guidelines, OR (95% CI)	Alcohol: Excessive, OR (95% CI)	Smoking: Daily, OR (95% CI)	Drug use: Monthly, OR (95% CI)
Sex					
Male	Ref	Ref	Ref	Ref	Ref
Female	0.91 (0.75–1.10)	0.99 (0.81–1.20)	0.60 (0.43–0.85)[b]	0.74 (0.56–0.98)[b]	0.18 (0.09–0.34)[b]
Age at completion questionnaire, years					
18–29	Ref	Ref	Ref	Ref	Ref
30–39	1.47 (1.15–1.87)[b]	1.16 (0.91–1.48)	0.77 (0.50–1.19)	1.18 (0.84–1.65)	0.58 (0.31–1.10)
≥40	1.59 (1.16–2.17)[b]	1.31 (0.96–1.78)	0.86 (0.49–1.49)	0.86 (0.54–1.39)	0.46 (0.17–1.22)
Marital status[c]					
Married	Ref	Ref	Ref	Ref	Ref
Unmarried	0.79 (0.63–0.98)[b]	0.72 (0.58–0.91)[b]	1.27 (0.87–1.85)	1.38 (1.02–1.88)b	1.94 (1.07–3.52)b
Level of education[d]					
Low	Ref	Ref	Ref	Ref	Ref
Middle	0.63 (0.49–0.81)[b]	0.68 (0.52–0.88)[b]	0.75 (0.49–1.16)	0.54 (0.39–0.74)[b]	0.68 (0.44–1.64)
High	0.38 (0.29–0.51)[b]	0.49 (0.37–0.65)[b]	0.59 (0.36–0.96)[b]	0.16 (0.10–0.25)[b]	0.36 (0.17–0.77)[b]
Employment status					
Employed	Ref	Ref	Ref	Ref	Ref
Student	0.67 (0.47–0.95)[b]	0.31 (0.20–0.47)[b]	0.62 (0.37–1.05)	0.32 (0.19–0.52)[b]	0.85 (0.44–1.64)
Unemployed	0.90 (0.60–1.34)	0.76 (0.50–1.15)	1.32 (0.68–2.54)	1.92 (1.17–3.13)[b]	1.09 (0.31–3.81)
Incapacitated	0.85 (0.62–1.15)	1.31 (0.97–1.77)	0.52 (0.27–1.00)[b]	0.60 (0.38–0.95)[b]	1.30 (0.60–2.81)
Comorbidities					
0	Ref	Ref	Ref	Ref	Ref
1–2	2.10 (1.69–2.61)[b]	0.96 (0.77–1.21)	0.92 (0.62–1.35)	0.84 (0.61–1.15)	0.97 (0.55–1.73)
>2	3.52 (2.37–5.25)[b]	1.58 (1.07–2.31)[b]	0.33 (0.11–0.96)[b]	0.87 (0.47–1.59)	0.45 (0.10–2.11)
Amputation					
No		Ref	Ref	Ref	Ref
Yes	NA[e]	1.35 (0.71–2.58)	3.43 (1.01–11.17)[b]	1.09 (0.36–3.29)	1.38 (0.21–9.06)
Age at diagnosis, years					
Birth to 5	Ref	Ref	Ref	Ref	Ref
5–10	1.01 (0.80–1.29)	0.98 (0.77–1.26)	0.94 (0.63–1.41)	1.15 (0.83–1.59)	0.94 (0.51–1.73)
10–15	1.15 (0.87–1.52)	1.04 (0.78–1.38)	0.85 (0.52–1.39)	0.85 (0.57–1.28)	1.99 (1.01–3.92)[b]
15–18	1.28 (0.84–1.96)	1.22 (0.80–1.86)	1.09 (0.51–2.31)	0.97 (0.51–1.84	0.73 (0.16–3.41)
Primary childhood cancer diagnosis[f]					
Leukemia	Ref	Ref	Ref	Ref	Ref
Non-Hodgkin lymphoma[g]	1.24 (0.91–1.71)	0.81 (0.57–1.13)	1.33 (0.80–2.19)	1.28 (0.85–1.92)	1.37 (0.71–2.65)
Hodgkin lymphoma	0.80 (0.51–1.24)	0.76 (0.48–1.20)	0.69 (0.28–1.68)	0.46 (0.21–1.02)	0.55 (0.14–2.15)
CNS	0.96 (0.64–1.43)	1.17 (0.78–1.76)	0.59 (0.26–1.31)	0.53 (0.29–0.97)[b]	0.52 (0.15–1.76)
Neuroblastoma	0.76 (0.46–1.26)	0.96 (0.58–1.61)	0.93 (0.39–2.22)	1.75 (0.94–3.24)	1.41 (0.43–4.64)
Retinoblastoma	1.25 (0.37–4.23)	0.62 (0.13–3.03)	1.31 (0.15–11.4)	0.71 (0.08–6.18)	5.49 (0.52–58.1)
Renal tumors	0.94 (0.64–1.38)	1.16 (0.78–1.71)	0.95 (0.50–1.80)	0.70 (0.41–1.21)	0.88 (0.34–2.29)

(Continues)

TABLE 3 (Continued)

Characteristic	BMI: Overweight and obesity, OR (95% CI)	Physical activity: Not meeting the guidelines, OR (95% CI)	Alcohol: Excessive, OR (95% CI)	Smoking: Daily, OR (95% CI)	Drug use: Monthly, OR (95% CI)
Hepatic tumors	0.67 (0.22–2.02)	NA[h]	0.72 (0.09–5.68)	0.59 (0.13–2.74)	1.27 (0.15–10.7)
Bone tumors	0.66 (0.38–1.15)	1.10 (0.64–1.91)	0.54 (0.17–1.77)	0.71 (0.29–1.74)	0.66 (0.13–3.23)
Soft tissue tumors	0.86 (0.58–1.27)	1.24 (0.84–1.84)	1.27 (0.69–2.40)	0.90 (0.51–1.58)	0.69 (0.22–2.17)
Germ cell tumors	0.56 (0.32–0.97)[b]	1.14 (0.66–1.95)	1.50 (0.64–3.48)	0.71 (0.33–1.56)	1.51 (0.44–5.14)
Other and unspecified[i]	0.29 (0.12–0.73)[b]	0.96 (0.40–2.29)	2.60 (0.85–7.94)	1.72 (0.62–4.76)	1.28 (0.14–11.9)
Treatment[j]					
Surgery only	Ref	Ref	Ref	Ref	Ref
Chemotherapy, no radiotherapy	0.88 (0.58–1.35)	1.34 (0.86–2.10)	0.83 (0.41–1.68)	0.76 (0.43–1.34)	0.87 (0.31–2.46)
Radiotherapy, no chemotherapy	0.98 (0.55–1.74)	0.91 (0.50–1.66)	0.50 (0.17–1.48)	0.54 (0.22–1.31)[b]	0.78 (0.14–4.39)[b]
Radiotherapy and chemotherapy	0.83 (0.48–1.44)	1.65 (0.94–2.89)	0.59 (0.22–1.62)	0.52 (0.23–1.18)[b]	0.82 (0.19–3.65)
No treatment/ treatment unknown	0.27 (0.03–2.47)	2.02 (0.41–9.96)	1.98 (0.21–18.9)	1.41 (0.22–8.93)[b]	2.73 (0.21–35.3)
Radiotherapy to head/cranium					
No	Ref	Ref	Ref	Ref	Ref
Yes	1.44 (0.93–2.22)	1.06 (0.69–1.64)	1.44 (0.63–3.35)	1.03 (0.51–2.08)	0.44 (0.11–1.77)
Radiotherapy to abdomen					
No	Ref	Ref	Ref	Ref	Ref
Yes	0.83 (0.52–1.35)	0.88 (0.55–1.42)	2.04 (0.83–5.00)	1.55 (0.72–3.35)	1.32 (0.31–5.55)
Total body irradiation					
No	Ref	Ref	Ref	Ref	Ref
Yes	1.65 (0.52–5.28)	0.68 (0.26–1.79)	1.46 (0.28–7.70)	2.10 (0.53–8.40)	1.09 (0.17–7.13)
SCT					
No	Ref	Ref	Ref	Ref	Ref
Yes	0.29 (0.18–0.48)[b]	0.66 (0.41–1.04)	(0.46–2.19)	1.28 (0.69–2.37)	2.13 (0.88–5.11)

Abbreviations: BMI, body mass index; CI, confidence interval; CNS, central nervous system; NA, not applicable; OR, odds ratio; Ref, reference category; SCT, stem cell transplantation.

[a]Multivariate logistic regression after multiple imputation for independent variables.

[b]These ORs and 95% CIs indicate statistical significance.

[c]Married as marital status includes all situations in which a CCS lives together with a partner.

[d]*Low* indicates primary education, technical and vocational education and training, special school; *middle*, preparatory secondary vocational education, secondary vocational education, higher general secondary education, preuniversity education; *high:* higher vocational education, university.

[e]Not applicable because of the influence of amputation of a limb on BMI.

[f]Diagnostic groups included all malignancies covered by the third edition of the International Classification of Childhood Cancer (ICCC-3) as well as multifocal Langerhans cell histiocytosis.

[g]Includes all morphology codes specified in the ICCC-3 under *lymphomas and reticuloendothelial neoplasms*, except for Hodgkin lymphomas. Also includes multifocal Langerhans cell histiocytosis.

[h]There were too few cases to calculate the OR.

[i]Includes all morphology codes specified in the ICCC-3 under *other malignant epithelial neoplasms* and *malignant melanomas and other and unspecified malignant neoplasms*.

[j]Treatment data included primary treatment and all recurrences.

TABLE 4 Health behaviors, sociodemographic characteristics, and medical characteristics according to cluster of childhood cancer survivors.[a]

Characteristic	Percentage		
	Cluster 1, $n = 1911$[b]	Cluster 2, $n = 342$[b]	OR (95% CI)
Health behaviors			
BMI			
Overweight: BMI 25.0–29.9 kg/m^2	26.1	27.8	1.05 (0.81–1.37)
Obese: BMI >30.0 kg/m^2	9.7	8.8	0.89 (0.59–1.35)
Physical activity			
Not meeting the physical activity guidelines	29.3	33.9	1.24 (0.97–1.58)
Alcohol consumption			
Excessive	1.3	41.8	56.5 (35.8–89.2)[c]
Smoking			
Daily	3.8	62.0	41.7 (30.2–57.4)[c]
Drugs use			
Monthly	0.0	23.4	NA
Sociodemographic characteristics			
Sex			
Male	48.1	70.8	Ref
Female	51.9	29.2	0.38 (0.30–0.49)[c]
Age at completion questionnaire, years			
Mean ± SE	32.3 ± 0.20	31.1 ± 0.47	Ref
18–29	44.1	51.5	0.79 (0.61–1.02)
30–39	35.5	32.7	0.66 (0.48–0.92)[c]
≥40	20.4	15.8	
Marital status[d]			
Married	53.5	43.2	Ref
Unmarried	46.5	56.8	1.51 (1.20–1.91)[c]
Level of education[e]			
Low	17.7	26.5	Ref
Middle	46.2	53.3	0.77 (0.58–1.02)
High	36.1	20.2	0.37 (0.27–0.53)[c]
Employment status			
Employed	65.7	67.3	Ref
Student	14.1	13.4	0.93 (0.66–1.31)
Unemployed	5.2	7.4	1.37 (0.86–2.17)
Incapacitated	15.0	11.9	0.77 (0.54–1.10)
Medical characteristics			
Comorbidities			
0	54.9	64.4	Ref
1–2	36.8	30.9	0.72 (0.56–0.92)[c]
>2	8.3	4.7	0.49 (0.29–0.83)[c]
Amputation			
No	96.3	97.1	Ref
Yes	3.7	2.9	0.78 (0.40–1.53)

(Continues)

TABLE 4 (Continued)

Characteristic	Percentage		OR (95% CI)
	Cluster 1, $n = 1911$[b]	Cluster 2, $n = 342$[b]	
Age at diagnosis, years			
Mean ± SE	7.4 ± 0.11	6.6 ± 0.25	Ref
Birth to 4	39.4	44.7	0.91 (0.69–1.20)
5–9	29.4	30.4	0.73 (0.54–1.00)[c]
10–14	24.0	19.9	0.61 (0.36–1.03)
15–17	7.2	5.0	
Primary childhood cancer diagnosis[f]			
Leukemia	32.1	35.4	Ref
Non-Hodgkin lymphoma[g]	11.2	18.7	1.52 (1.08–2.13)[c]
Hodgkin lymphoma	7.8	3.8	0.44 (0.24–0.81)[c]
CNS	12.5	7.9	0.58 (0.37–0.90)[c]
Neuroblastoma	5.0	6.1	1.12 (0.67–1.87)
Retinoblastoma	0.5	0.6	1.01 (0.22–4.68)
Renal tumors	10.7	11.1	0.94 (0.63–1.40)
Hepatic tumors	0.8	0.9	1.01 (0.29–3.55)
Bone tumors	6.9	4.4	0.58 (0.33–1.02)
Soft tissue tumors	7.4	6.1	0.75 (0.46–1.68)
Germ cell tumors	3.6	3.5	0.88 (0.46–1.68)
Other and unspecified[h]	1.6	1.5	0.84 (0.32–2.22)
Childhood cancer treatment[i]			
Surgery only	8.6	7.9	Ref
Chemotherapy, no radiotherapy	49.3	55.8	1.23 (0.80–1.90)
Radiotherapy, no chemotherapy	7.8	5.6	0.77 (0.41–1.44)
Radiotherapy and chemotherapy	34.1	29.5	0.94 (0.60–1.49)
No treatment/treatment unknown	0.2	1.2	8.10 (1.72–38.2)[c]
SCT			
No	94.7	93.6	Ref
Yes	5.3	6.4	1.22 (0.76–1.96)

Abbreviations: BMI, body mass index; CI, confidence interval; CNS, central nervous system; NA, not applicable; OR, odds ratio; Ref, reference category; SCT, stem cell transplantation; SE, standard error.

[a]Univariable logistic regression with cluster as a dependent variable and demographic/medical variables as independent variables for categorical variables.

[b]Could not be generated because the prevalence in cluster 1 was 0.0%, but a χ^2 test revealed a statistically significant difference ($p < .001$).

[c]These ORs and 95% CIs indicate statistical significance.

[d]Married as marital status includes all situations in which a CCS lives together with a partner.

[e]Low: primary education, technical and vocational education and training, special school; middle: preparatory secondary vocational education, secondary vocational education, higher general secondary education, preuniversity education; high: higher vocational education, university.

[f]Diagnostic groups included all malignancies covered by the third edition of the International Classification of Childhood Cancer (ICCC-3) as well as multifocal Langerhans cell histiocytosis.

[g]Includes all morphology codes specified in the ICCC-3 under *lymphomas and reticuloendothelial neoplasms*, except for Hodgkin lymphomas. Also includes multifocal Langerhans cell histiocytosis.

[h]Includes all morphology codes specified in the ICCC-3 under *other malignant epithelial neoplasms and malignant melanomas* and *other and unspecified malignant neoplasms*.

[i]Treatment data included primary treatment and all recurrences.

Another worrying finding of our study is that CCSs more often are not meeting physical inactivity guidelines compared with their siblings. The prevalence of physical inactivity (30.0%) was lower than in other CCS populations following similar national physical activity guidelines.[53–56] For instance, Ness et al. reported that more than one half of American adult CCSs did not meet physical activity guidelines. Likewise, in a study by Badr et al., as much as 65% of American CCSs did not adhere to these guidelines. However, it is worth noting that these cohorts consisted of younger CCSs with a shorter time since diagnosis than the CCSs in our cohort. In addition, cultural differences in work and leisure activities between Dutch and American CCSs may contribute to this discrepancy.

It has been recognized that overweight and obesity (BMI ≥25.0 kg/m^2) often coincide with physical inactivity. This study confirms this relationship in both CCSs and their siblings, indicating that individuals not meeting physical activity guidelines were more likely to be overweight or obese (see Table S3). Furthermore, our findings demonstrate that CCSs with BMI ≥25.0 kg/m^2 and those who are insufficiently physically active generally share the same associated factors, such as being married and having lower educational attainment, consistent with findings in other cancer survivor populations.[51,57] Notably, we also observed that CCSs who are students are less likely to be overweight or obese and physically inactive than those who are employed. Regarding overweight and obesity, we also observed that CCSs of germ cell tumors and other and unspecified diagnoses were less often overweight or obese compared with survivors of leukemia. This finding reinforces the hypothesis that survivors of pediatric acute lymphoblastic leukemia face a heightened risk of developing overweight and obesity not only during treatment but also in the posttreatment survivorship phase, and these weight gains can persist well beyond the completion of treatment.[58] However, CCSs who had other diagnoses were not less often overweight or obese compared with CCSs who had leukemia and we hypothesize that a changed treatment regime since the 1980s and 1990s, with less use of prophylactic cranial therapy, potentially could explain the absence of more associations. In the current study, we also identified no other cancer diagnosis-related or treatment-related factors associated with overweight or obesity and physical inactivity, which may suggest that these lifestyle behaviors are predominantly influenced by noncancer (treatment)-related factors. However, comorbidities, which may include late effects impeding physical activity, were associated with an increased vulnerability to overweight and obesity, suggesting that a childhood cancer history could still have a negative impact. Therefore, health-promoting strategies and interventions targeting weight loss and/or physical activity should be personalized to the sociodemographic characteristics and current health status of CCSs.

Regarding the prevalence of substance-use behaviors, it is noteworthy that daily smoking and monthly drug use in both CCSs and siblings was considerably less prevalent than such behaviors in the Dutch general population. In addition, excessive alcohol consumption also seemed to be lower in survivors and siblings compared with their age-matched peers. This aligns with previous studies indicating similar rates of substance-use behaviors in CCSs and siblings.[59–61] The relatively low prevalence of these behaviors in the current study may indicate that most CCSs are health-conscious because of their cancer history and that siblings are potentially influenced by their brother's or sister's illness in substance-use behaviors. Furthermore, patients who attend cancer survivorship care clinics may exhibit an increased reluctance to disclose substance-use behaviors on the questionnaire, possibly because of concerns about their late-effects physician accessing and interpreting the responses.

In accordance with previous studies, cluster analysis revealed one distinct cluster of CCSs with the co-occurrence of excessive alcohol use, smoking, and drug use.[57,62,63] Compared with CCSs who did not exhibit those behaviors, these CCSs were predominantly male, unmarried, had a low education level, and were survivors of non-Hodgkin lymphoma. In addition, they were less likely to have comorbidities or to be survivors of Hodgkin lymphoma or CNS tumors. Similarly, Pinto et al., in a study of French CCSs categorized into a *high-risk behaviors cluster*, observed that individuals in that cluster had the highest probabilities of smoking, cannabis use, and alcohol consumption. They were also more likely to be male, less educated, and/or single.[63] These findings confirm that sociodemographic factors may be associated with unhealthy lifestyle behaviors, overweight, and obesity in CCSs and underscore the necessity for healthy behavior support tailored for these sociodemographic subgroups of CCSs.

Our large sample size from a nationwide cohort, encompassing CCSs of all types of childhood malignancies and siblings, along with cluster analyses to identify at-risk subgroups for multiple unhealthy lifestyle behaviors, overweight, and obesity, strengthens the clinical significance of the results. Nevertheless, a limitation of this study is its cross-sectional nature, which prevents the establishment of causality between potential associated factors and unhealthy lifestyle behaviors, overweight, and obesity. Prospective longitudinal studies are needed in the future to verify those potential causal relations. Another limitation is the potential for selection bias and its effect on the generalizability of the results, because nonparticipation could introduce differences in sex, age at diagnosis, primary childhood cancer diagnosis, and treatment between participants and nonparticipants that may bias the results. However, when observing the Cramer V effect sizes of the differences between participants and nonparticipants, it could be observed that all effects were little (<0.1) or low (0.1), indicating no potential large influences on the results. Moreover, the use of self-reported data from a questionnaire introduces the risk of social desirability bias and subjective interpretation, which could distort the outcomes. Finally, lacking data on the frequency of the amount of physical activity per week and bone-strengthening exercises meant that it was impossible to make comparisons between the participants of the DCCSS LATER study and the Dutch Health Survey participants.

CONCLUSIONS

Overall, our findings show that, despite the additional health risks, CCSs are less likely to meet physical activity guidelines compared to their siblings. In addition, married as marital status, lower education, non-student status, and comorbidities were common associated factors for a BMI ≥25.0 kg/m^2 and insufficient physical activity, while male sex and lower education were shared associated factors for unhealthy substance-use behaviors such as excessive alcohol consumption, daily smoking, and monthly drug use. These substance-use behaviors also tend to cluster together, meaning a subgroup of CCSs exhibits all three of these unhealthy behaviors. This illustrates the necessity for personalized health behavior interventions in CCSs adapted to sociodemographic factors and health status.

AUTHOR CONTRIBUTIONS

Eline Bouwman: Conceptualization, methodology, visualization, project administration, writing–original draft, and writing–review and editing. **Adriaan Penson**: Formal analysis and writing–review and editing. **Maud de Valk**: Formal analysis and writing–review and editing. **Selina R. van den Oever**: Writing–review and editing. **Helena J. H. van der Pal**: Writing–review and editing. **Eline van Dulmen-den Broeder**: Writing–review and editing. **Nicole M. A. Blijlevens**: Writing–review and editing. **Dorine Bresters**: Writing–review and editing. **Elizabeth A. M. Feijen**: Writing–review and editing. **Marry M. van den Heuvel-Eibrink**: Writing–review and editing. **Margriet van der Heiden-van der Loo**: Software, validation, investigation, resources, data curation, and writing–review and editing. **Gisela Michel**: Writing–review and editing. **Cécile M. Ronckers**: Writing–review and editing. **Jop C. Teepen**: Writing–review and editing. **Wim J. E. Tissing**: Writing–review and editing. **Birgitta A. B. Versluys**: Writing–review and editing. **Leontien C. M. Kremer**: Writing–review and editing. **Saskia M. F. Pluijm**: Conceptualization, methodology, and writing–review and editing. **Jacqueline J. Loonen**: Conceptualization, methodology, supervision, and writing–review and editing. **Dutch Late Effects After Childhood Cancer (LATER) Study Group** and **PanCareFollowUp**: funding acquisition.

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CONFLICT OF INTEREST STATEMENT

The authors disclosed no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data underlying this article were provided by the Dutch Childhood Cancer Survivor Study-Late Effects of Childhood Cancer (LATER) Consortium under license. Data will be shared on request to the corresponding author with permission of the Dutch Childhood Cancer Survivor Study LATER Consortium.

ORCID

Eline Bouwman https://orcid.org/0000-0002-9149-9745
Adriaan Penson https://orcid.org/0000-0001-7558-1637
Selina R. van den Oever https://orcid.org/0000-0002-6227-3472
Helena J. H. van der Pal https://orcid.org/0000-0003-2253-2115
Eline van Dulmen-den Broeder https://orcid.org/0000-0002-8870-6539
Nicole M. A. Blijlevens https://orcid.org/0000-0002-1801-2072
Dorine Bresters https://orcid.org/0000-0002-5417-4159
Elizabeth A. M. Feijen https://orcid.org/0000-0001-8930-3160
Marry M. van den Heuvel-Eibrink https://orcid.org/0000-0002-7760-879X
Margriet van der Heiden-van der Loo https://orcid.org/0000-0001-5767-854X
Gisela Michel https://orcid.org/0000-0002-9589-0928
Cécile M. Ronckers https://orcid.org/0000-0003-3524-4657
Jop C. Teepen https://orcid.org/0000-0002-2647-2677
Wim J. E. Tissing https://orcid.org/0000-0001-9101-507X
Birgitta A. B. Versluys https://orcid.org/0000-0002-4283-5503
Leontien C. M. Kremer https://orcid.org/0000-0001-7422-3248
Saskia M. F. Pluijm https://orcid.org/0000-0002-4459-7799
Jacqueline J. Loonen https://orcid.org/0000-0002-9963-8367

REFERENCES

1. Howlader N, Noone AM, Krapcho M, et al., eds. *SEER Cancer Statistics Review (CSR) 1975–2017*. National Cancer Institute; 2020.
2. Miller KD, Pandey M, Jain R, Mehta R. Cancer survivorship and models of survivorship care: a review. *Am J Clin Oncol*. 2015;38(6):627-633. doi:10.1097/coc.0000000000000153
3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin*. 2018;68(1):7-30. doi:10.3322/caac.21442
4. Phillips SM, Padgett LS, Leisenring WM, et al. Survivors of childhood cancer in the United States: prevalence and burden of morbidity. *Cancer Epidemiol Biomarkers Prev*. 2015;24(4):653-663. doi:10.1158/1055-9965.epi-14-1418

5. Gatta G, Botta L, Rossi S, et al. Childhood cancer survival in Europe 1999–2007: results of EUROCARE-5—a population-based study. *Lancet Oncol*. 2014;15(1):35-47. doi:10.1016/s1470-2045(13)70548-5
6. Alvarez JA, Scully RE, Miller TL, et al. Long-term effects of treatments for childhood cancers. *Curr Opin Pediatr*. 2007;19(1):23-31. doi:10.1097/mop.0b013e328013c89e
7. Diller L, Chow EJ, Gurney JG, et al. Chronic disease in the Childhood Cancer Survivor Study cohort: a review of published findings. *J Clin Oncol*. 2009;27(14):2339-2355. doi:10.1200/jco.2008.21.1953
8. Geenen MM, Cardous-Ubbink MC, Kremer LCM, et al. Medical assessment of adverse health outcomes in long-term survivors of childhood cancer. *JAMA*. 2007;297(24):2705-2715. doi:10.1001/jama.297.24.2705
9. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med*. 2006;355(15):1572-1582. doi:10.1056/nejmsa060185
10. Lipshultz ER, Chow EJ, Doody DR, et al. Cardiometabolic risk in childhood cancer survivors: a report from the Children's Oncology Group. *Cancer Epidemiol Biomarkers Prev*. 2022;31(3):536-542. doi:10.1158/1055-9965.epi-21-0360
11. Hudson MM, Ness KK, Gurney JG, et al. Clinical ascertainment of health outcomes among adults treated for childhood cancer. *JAMA*. 2013;309(22):2371-2381. doi:10.1001/jama.2013.6296
12. Woodward E, Jessop M, Glaser A, Stark D. Late effects in survivors of teenage and young adult cancer: does age matter? *Ann Oncol*. 2011;22(12):2561-2568. doi:10.1093/annonc/mdr044
13. Robison LL, Hudson MM. Survivors of childhood and adolescent cancer: life-long risks and responsibilities. *Nat Rev Cancer*. 2014;14(1):61-70. doi:10.1038/nrc3634
14. Teepen JC, van Leeuwen FE, Tissing WJ, et al. Long-term risk of subsequent malignant neoplasms after treatment of childhood cancer in the DCOG LATER study cohort: role of chemotherapy. *J Clin Oncol*. 2017;35(20):2288-2298. doi:10.1200/jco.2016.71.6902
15. Zhang YB, Pan XF, Chen J, et al. Combined lifestyle factors, all-cause mortality and cardiovascular disease: a systematic review and meta-analysis of prospective cohort studies. *J Epidemiol Community Health*. 2021;75(1):92-99. doi:10.1136/jech-2020-214050
16. Zheng HC, Onderko L, Francis SA. Cardiovascular risk in survivors of cancer. *Curr Cardiol Rep*. 2017;19(7):64. doi:10.1007/s11886-017-0873-7
17. Grosso G, Bella F, Godos J, et al. Possible role of diet in cancer: systematic review and multiple meta-analyses of dietary patterns, lifestyle factors, and cancer risk. *Nutr Rev*. 2017;75(6):405-419. doi:10.1093/nutrit/nux012
18. World Cancer Research Fund/American Institute for Cancer Research. *Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective*. American Institute for Cancer Research; 2007.
19. Meacham LR, Chow EJ, Ness KK, et al. Cardiovascular risk factors in adult survivors of pediatric cancer—a report from the Childhood Cancer Survivor Study. *Cancer Epidemiol Biomarkers Prev*. 2010;19(1):170-181. doi:10.1158/1055-9965.epi-09-0555
20. Dixon SB, Bjornard KL, Alberts NM, et al. Factors influencing risk-based care of the childhood cancer survivor in the 21st century. *CA Cancer J Clin*. 2018;68(2):133-152. doi:10.3322/caac.21445
21. van Kalsbeek RJ, van der Pal HJ, Hjorth L, et al. The European multistakeholder PanCareFollowUp project: novel, person-centered survivorship care to improve care quality, effectiveness, cost-effectiveness and accessibility for cancer survivors and caregivers. *Eur J Cancer*. 2021;153:74-85. doi:10.1016/j.ejca.2021.05.030
22. Byrne J, Alessi D, Allodji RS, et al. The PanCareSurFup Consortium: research and guidelines to improve lives for survivors of childhood cancer. *Eur J Cancer*. 2018;103:238-248. doi:10.1016/j.ejca.2018.08.017
23. Cohen K, Weizman A, Weinstein A. Positive and negative effects of cannabis and cannabinoids on health. *Clin Pharmacol Ther*. 2019;105(5):1139-1147. doi:10.1002/cpt.1381
24. Jones LW, Liu Q, Armstrong GT, et al. Exercise and risk of major cardiovascular events in adult survivors of childhood Hodgkin lymphoma: a report from the Childhood Cancer Survivor Study. *J Clin Oncol*. 2014;32(32):3643-3650. doi:10.1200/jco.2014.56.7511
25. Nathan PC, Ford JS, Henderson TO, et al. Health behaviors, medical care, and interventions to promote healthy living in the Childhood Cancer Survivor Study cohort. *J Clin Oncol*. 2009;27(14):2363-2373. doi:10.1200/jco.2008.21.1441
26. Schindera C, Zürcher SJ, Jung R, et al. Physical fitness and modifiable cardiovascular disease risk factors in survivors of childhood cancer: a report from the SURfit study. *Cancer*. 2021;127(10):1690-1698. doi:10.1002/cncr.33351
27. Slater ME, Ross JA, Kelly AS, et al. Physical activity and cardiovascular risk factors in childhood cancer survivors. *Pediatr Blood Cancer*. 2015;62(2):305-310. doi:10.1002/pbc.25276
28. Smith WA, Li C, Nottage KA, 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):2742-2750. doi:10.1002/cncr.28670
29. Dixon SB, Liu Q, Chow EJ, et al. Specific causes of excess late mortality and association with modifiable risk factors among survivors of childhood cancer: a report from the Childhood Cancer Survivor Study cohort. *Lancet*. 2023;401(10386):1447-1457. doi:10.1016/s0140-6736(22)02471-0
30. Zhang FF, Ojha RP, Krull KR, et al. Adult survivors of childhood cancer have poor adherence to dietary guidelines. *J Nutr*. 2016;146(12):2497-2505. doi:10.3945/jn.116.238261
31. Wogksch MD, Goodenough CG, Finch ER, Partin RE, Ness KK. Physical activity and fitness in childhood cancer survivors: a scoping review. *Aging Cancer*. 2021;2(4):112-128. doi:10.1002/aac2.12042
32. Belle FN, Chatelan A, Kasteler R, et al. Dietary intake and diet quality of adult survivors of childhood cancer and the general population: results from the SCCSS-Nutrition study. *Nutrients*. 2021;13(6):1767. doi:10.3390/nu13061767
33. Stival C, Lugo A, Odone A, et al. Prevalence and correlates of overweight and obesity in 12 European countries in 2017–2018. *Obes Facts*. 2022;15(5):655-665. doi:10.1159/000525792
34. Silveira EA, Mendonça CR, Delpino FM, et al. Sedentary behavior, physical inactivity, abdominal obesity and obesity in adults and older adults: a systematic review and meta-analysis. *Clin Nutr ESPEN*. 2022;50:63-73. doi:10.1016/j.clnesp.2022.06.001
35. Centraal Bureau voor de Statistiek (CBS). *Gezondheidsenquête 2014*. CBS; 2014.
36. Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P. International Classification of Childhood Cancer, third edition. *Cancer*. 2005;103(7):1457-1467. doi:10.1002/cncr.20910
37. Teepen JC, Kok JL, Feijen EAM, et al. Questionnaire- and linkage-based outcomes in Dutch childhood cancer survivors: methodology of the DCCSS LATER study part 1. *Cancer Med*. 2022;12(6):7588-7602. doi:10.1002/cam4.5519
38. World Health Organisation (WHO). *A healthy lifestyle—WHO recommendations*. WHO; 2010.
39. Wareham NJ, Jakes RW, Rennie KL, et al. Validity and repeatability of a simple index derived from the short physical activity questionnaire used in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. *Public Health Nutr*. 2003;6(4):407-413. doi:10.1079/phn2002439
40. Gezondheidsraad. *Beweegrichtlijnen 2017 Samenvatting*. Gezondheidsraad; 2017.
41. Trimbos-Institute. *Factsheet riskant alcoholgebruik in Nederland*. Trimbos-Institute; 2018.

42. Ainsworth BE, Haskell WL, Whitt MC, et al. Compendium of Physical Activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc*. 2000;32(9 suppl):S498-S504. doi:10.1097/00005768-200009001-00009
43. Wendel-Vos GC, Schuit AJ, Saris WH, Kromhout D, et al. Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity. *J Clin Epidemiol*. 2003;56(12):1163-1169. doi:10.1016/s0895-4356(03)00220-8
44. Streefkerk N, Tissing WJE, van der Heiden-van der Loo M, et al. The Dutch LATER physical outcomes set for self-reported data in survivors of childhood cancer. *J Cancer Surviv*. 2020;14(5):666-676. doi:10.1007/s11764-020-00880-0
45. Rubin DB. *Multiple Imputation for Nonresponse in Surveys*. John Wiley& Sons, Inc.; 2004.
46. Marshall A, Altman DG, Holder RL, Royston P. Combining estimates of interest in prognostic modelling studies after multiple imputation: current practice and guidelines. *BMC Med Res Methodol*. 2009;9(1):57. doi:10.1186/1471-2288-9-57
47. Akinwande M, Dikko H, Samson A. Variance inflation factor: as a condition for the inclusion of suppressor variable(s) in regression analysis. *Open J Stat*. 2015;5(07):754-767. doi:10.4236/ojs.2015.57075
48. Gelbard R, Goldman O, Spiegler I. Investigating diversity of clustering methods: an empirical comparison. *Data Knowl Eng*. 2007;63(1):155-166. doi:10.1016/j.datak.2007.01.002
49. Kent P, Jensen RK, Kongsted A. A comparison of three clustering methods for finding subgroups in MRI, SMS or clinical data: SPSS TwoStep Cluster analysis, Latent Gold and SNOB. *BMC Med Res Methodol*. 2014;14(1):113. doi:10.1186/1471-2288-14-113
50. Kaufman L, Rousseeuw P. *Finding Groups in Data: An Introduction To Cluster Analysis*. John Wiley & Sons, Inc.; 1990.
51. Belle FN, Weiss A, Schindler M, et al. Overweight in childhood cancer survivors: the Swiss Childhood Cancer Survivor Study. *Am J Clin Nutr*. 2018;107(1):3-11. doi:10.1093/ajcn/nqx006
52. van Santen HM, Geskus RB, Raemaekers S, et al. Changes in body mass index in long-term childhood cancer survivors. *Cancer*. 2015;121(23):4197-4204. doi:10.1002/cncr.29614
53. Badr H, Chandra J, Paxton RJ, et al. Health-related quality of life, lifestyle behaviors, and intervention preferences of survivors of childhood cancer. *J Cancer Surviv*. 2013;7(4):523-534. doi:10.1007/s11764-013-0289-3
54. Florin TA, Fryer GE, Miyoshi T, et al. Physical inactivity in adult survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. *Cancer Epidemiol Biomarkers Prev*. 2007;16(7):1356-1363. doi:10.1158/1055-9965.epi-07-0048
55. Lowe K, Escoffery C, Mertens AC, Berg CJ. Distinct health behavior and psychosocial profiles of young adult survivors of childhood cancers: a mixed methods study. *J Cancer Surviv*. 2016;10(4):619-632. doi:10.1007/s11764-015-0508-1
56. Ness KK, Leisenring WM, Huang S, et al. Predictors of inactive lifestyle among adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Cancer*. 2009;115(9):1984-1994. doi:10.1002/cncr.24209
57. Lown EA, Hijiya N, Zhang N, et al. Patterns and predictors of clustered risky health behaviors among adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Cancer*. 2016;122(17):2747-2756. doi:10.1002/cncr.30106
58. Zhang FF, Parsons SK. Obesity in childhood cancer survivors: call for early weight management. *Adv Nutr*. 2015;6(5):611-619. doi:10.3945/an.115.008946
59. Kahalley LS, Robinson LA, Tyc VL, et al. Risk factors for smoking among adolescent survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Pediatr Blood Cancer*. 2012;58(3):428-434. doi:10.1002/pbc.23139
60. Kasteler R, Belle F, Schindera C, et al. Prevalence and reasons for smoking in adolescent Swiss childhood cancer survivors. *Pediatr Blood Cancer*. 2019;66(1):e27438. doi:10.1002/pbc.27438
61. Klosky JL, Howell CR, Li Z, et al. Risky health behavior among adolescents in the Childhood Cancer Survivor Study cohort. *J Pediatr Psychol*. 2012;37(6):634-646. doi:10.1093/jpepsy/jss046
62. Lown EA, Goldsby R, Mertens AC, et al. Alcohol consumption patterns and risk factors among childhood cancer survivors compared to siblings and general population peers. *Addiction*. 2008;103(7):1139-1148. doi:10.1111/j.1360-0443.2008.02242.x
63. Pinto S, Fresneau B, Hounsossou HC, et al. Identifying clusters of health risk behaviors and their predictors in adult survivors of childhood cancer: a report from the French Childhood Cancer Survivor Study. *Psychooncology*. 2020;29(10):1595-1603. doi:10.1002/pon.5470

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