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Nutritional concerns of survivors of childhood cancer: A "First World" perspective

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Abstract
Childhood cancer survivor (CCS) numbers are increasing as a result of advances in both treatment and supportive care. This positive outcome is tempered by the recognition of a high burden of chronic health conditions. Here, we review the nutritional concerns of CCS, including dietary habits after treatment and the factors during treatment that may contribute to chronic health conditions. Dietary interventions that have been conducted in CCS will be summarized along with focused goals of these interventions. We will also address the need to leverage these interventions to reduce the risk of chronic disease in CCS.

KEYWORDS
childhood cancer, dietary intake, late effects, nutrition, pediatric oncology, quality of life, survivorship

1 | INTRODUCTION

Over the past three decade, the numbers of childhood cancer survivors (CCS) have increased as a consequence of improved therapy and supportive care.[1] Despite this success, long-term health outcomes for CCS are compromised.[2] Among the most common treatment-related late effects in CCS are endocrinopathies, which include diabetes mellitus and metabolic syndrome, both of which are associated, after a variable latent period, with life-altering and life-threatening complications in CCS.[3,4] Diabetes mellitus and metabolic syndrome are known to be associated with an increased risk of cardiovascular disease, the second leading cause of late mortality in CCS,[5] and detection through surveillance and intervention at an early stage is advised to reduce the risk of cardiovascular disease. Survivors who have received abdominal irradiation are at a 3.4-fold increased risk of developing diabetes and those who have received total body irradiation during childhood are at 12.6-fold greater risk than siblings of developing diabetes.[6–8]

Diet and nutrition habits are major contributors to lifestyle diseases such as the metabolic syndrome and cardiovascular disease. Nutrition and diet are modifiable and therefore have the potential to prevent or delay onset of these chronic diseases in CCS. Both pediatric cancer patients undergoing therapy and CCS report poor dietary quality[9,10] and unhealthy lifestyles.[11] The Children's Oncology Group long-term follow-up guidelines recommend strategies to decrease the risk of these late complications including lifestyle modifications, healthier eating behaviors, encouragement of physical activity, and management of hypertension and dyslipidaemia.[12–14] Cancer type and stage, modality of treatment, and socioeconomic status are significant determinants of diet. Diversity in these variables across pediatric oncology patients and CCS is frequently cited as a barrier to implementing effective nutritional interventions.[15] In low- and middle-income countries

Abbreviations: ALL, acute lymphoblastic leukemia; BCM, body cell mass; BIA, bioelectrical impedance analysis; BMI, body mass index; CCS, childhood cancer survivors; CRT, cranial radiotherapy; DXA, dual-energy X-ray absorptiometry; FM, fat mass; HEI, healthy eating index; HIC, high-income countries; LMIC, low- and middle-income countries; MUAC, mid-upper arm circumference; QoL, quality of life; SMN, second malignant neoplasms; TBI, total body irradiation; TSFT, triceps skinfold thickness.

(LMICs), underweight and malnourishment are generally more problematic at diagnosis and during childhood cancer treatment, whereas in high-income countries (HICs) overweight and obesity are being seen at diagnosis.[16] In both scenarios (underweight and overweight) micronutrient deficiencies have been documented, which may further predispose CCS to chronic health conditions such as poor bone health and cardiovascular disease.

In this commentary, we review the nutritional concerns of CCS, including dietary habits posttreatment and the factors during treatment, such as such as health-related quality of life, taste and smell changes, and appetite regulation, that may contribute to chronic health conditions. Dietary interventions that have been conducted in CCS are summarized along with focused goals of some of these interventions. We also address the need to leverage these interventions to ultimately reduce the risk of metabolic syndrome and cardiovascular disease, which are some of the most serious threats to the long-term health of CCS. Considerable information is available on nutrition in survivors of cancer in childhood in HICs and will be reviewed here. However, almost 90% of children with cancer live in LMICs [17] where studies of those who have completed treatment, especially in the long term, are decidedly limited. Whether these survivors will experience the same spectrum of nutritional morbidity, as is evident in those in HICs, is largely unknown but an important target for research.

2 | OBESITY IN CHILDHOOD CANCER SURVIVORS

CCS have been shown to have an increased risk of obesity both during and after treatment.[18–20] Overweight (body mass index [BMI]: 85–95th percentile) and obesity (BMI >95th percentile) are reported to range from 40% to 50% after completion of treatment in CCS, especially those treated for acute lymphoblastic leukemia (ALL), lymphomas, some sarcomas, and central nervous system cancers.[19] Several longitudinal studies in childhood ALL have identified a significant increase in the rate of overweight or obesity from diagnosis to end of treatment with rapid weight gain noted during induction and early maintenance therapy.[18,21,22] Potential mechanisms for the observed increased obesity risk in CCS include the use of cranial radiotherapy (CRT) or high-dose steroids during treatment,[23] pancreatic insufficiency, poor dietary habits, sedentary lifestyle, changes in the gut microbiota and altered secretions of leptin, adiponectin, and ghrelin.[24,25] Obesity is prevalent in young pediatric ALL survivors (<10 years off treatment), regardless of CRT, gender, or age at diagnosis.[26]

The risk of treatment-related late effects, such as cardiovascular disease, metabolic syndrome, diabetes, and poor bone health, is higher in CCS who are overweight or obese.[27] For many children, obesity and obesity-related complications are manifesting during treatment and early after treatment completion. In adults, obesity is associated with a risk of breast, colorectal, endometrial, pancreatic, and renal cancers.[28] Second malignant neoplasms (SMN) become the most common cause of death beyond 30 years after diagnosis in CCS.[29] In a recent case-control study of CCS treated at the Children's Hospital of Los Angeles, there is a suggestion that obesity at diagnosis and end of treatment might be associated with an increased risk of SMN.[30] This study supports obesity being a risk factor for SMN. As obesity is a modifiable risk factor, the need for further research on the relationship between obesity and SMN is essential and gives good reason for strategies to reduce obesity after diagnosis and even during cancer treatment. Future interventions to reduce obesity in CCS should focus on modifiable risk factors such as dietary habits and sedentary lifestyles.[25]

3 | HEALTH-RELATED QUALITY OF LIFE IN CHILDHOOD CANCER SURVIVORS

CCS have poorer quality of life (QoL) than their peers. Reasons are multifactorial but may include poor mental health, limited education, immobility, and/or infertility.[31,32] Although there is information on treatment-related side effects impacting nutritional status during treatment (such as nausea, vomiting, and anorexia), it is unclear how these symptoms affect health behaviors in CCS. Symptoms such as pain, anxiety, and depression have been reported in survivors of childhood cancer.[33,34] In adults with cancer, there is a suggestion of a relationship between nutrition and health-related QoL.[35] Research is required in CCS to determine whether treatment-related side effects impacting nutritional status are affecting their QoL. In the non-cancer population, children with severe obesity are likely to have worse QoL than their peers.[36] Survivors of childhood cancer have also been shown to be less physically active than their peers[37] related to a reduction in mobility and muscle strength,[38] as a result of treatment. Participation in organized sports has been shown to be related to QoL in children in the general population.[39] A reduction in weight in CCS may also improve physical functioning and QoL. Although less commonly discussed, undernutrition is of concern in CCS,[40] which may also be associated with a poorer QoL.[39]

There is emerging evidence that certain dietary patterns may improve symptoms of depression and anxiety in the general population.[41,42] In children, dietary patterns of poor quality are associated with a higher risk of depression and poor mental health.[43] Changing to a healthy dietary pattern (such as the Mediterranean diet) can improve mental health in adults in the general population.[44] This is a potential target for future research. There are also reported issues with body dissatisfaction in CCS, although it is unknown whether rates of body dissatisfaction are higher than in the general population.[45] Structured nutritional interventions with psychosocial support have been shown to improve the QoL, the burden of body dissatisfaction and eating disorder risk in children with obesity in the general population.[46,47] Although there is a dearth of literature assessing dietary intake and mental health in CCS, we hypothesize that improving the nutritional intake and dietary quality of CCS may improve not only metabolic and cardiovascular health, but mental health and other domains of QoL in this population.

4 | NUTRITIONAL ASSESSMENT IN SURVIVORS

Determining the most appropriate measure of nutritional status in survivors of childhood cancer is challenging as both undernutrition and overnutrition can present. BMI has been the standard measure of nutritional status in survivors of childhood cancer. BMI does not differentiate between muscle and adipose tissue, thereby missing the "obesity paradox," which occurs when fat mass is increased in the presence of reduced lean mass.[48] In a study of 75 ALL CCS, assessing BMI and arm anthropometry using triceps skinfold test (TSFT), BMI only classified 8% as obese, but this increased to 20% with TSFT.[49] The St. Jude Lifetime Cohort Study also observed similar results of BMI being less sensitive with obesity rates of 40% by BMI, 62% with three site TSFT.[50] The results of these studies highlight discrepancies between BMI and other measures of body composition.[40] Measures of adiposity may better correlate with waist-to-height ratio as a surrogate parameter for visceral obesity than BMI.[51]

More accurate measures of body composition available in the clinical setting include dual-energy X-ray absorptiometry (DXA) and bioelectrical impedance analysis (BIA).[40] The former is limited by its portability, and the latter by body water fluctuations. DXA has been termed the clinical "gold standard" for measuring body composition, providing measures for fat mass (FM), lean body mass (LBM), and bone mineral content. Arm anthropometry as validated by DXA[52] provides an estimate of LBM using mid-upper arm circumference (MUAC) and FM using TSFT. BMI is an inadequate measure of body composition, whereas arm anthropometry detects a higher prevalence of malnutrition and sarcopenic obesity. The majority of research has focused on assessing the relationship between obesity, as measured by BMI, and predicting treatment-related toxicities and other clinical outcomes in CCS.[53] It is important that future studies assessing the nutritional status of CCS use measures of nutritional status such as waist-to-height ratio or triceps skinfold.

4.1 | Diet and nutrient intake

4.1.1 | Young survivors

There have been an increasing number of studies assessing the dietary intake of young CCS early after treatment (Table 1). Several studies have shown that young CCS (< 18 years of age) are consuming an inadequate intake of specific micronutrients. Between 30% and 68% of young survivors have an inadequate calcium intake[54–58] and up to 95% have been shown to have an inadequate vitamin D intake.[57] Since reduced bone mineral density and frank osteoporosis are serious late effects in adult survivors of childhood cancer,[59,60] inadequate intake of calcium and vitamin D may exacerbate the risk of early fractures in survivors.[61] Between 30% and 60% of CCS have been shown to have inadequate folate intake. Cardiovascular disease has been associated with early mortality in survivors.[62] The role of folate and homocysteine levels in cardiovascular disease in the non-cancer population remains controversial.[63] Despite this controversy, an inadequate folate intake and the need for folate supplementation[64] in CCS may be one of the many factors increasing the risk of early mortality and a target for interventions.[54]

Other micronutrients that have been shown to be deficient in young CCS include vitamins B6, B12, and E, as well as iron, copper, iodine, selenium, potassium, magnesium, and choline.[54–57] Chronic micronutrient deficiency has the potential to lead to wasting syndrome in children, leading to developmental delay, reduction in immune function, and diminution in cognitive function.[65] Inadequate intake of iron, folate, and vitamin B12 can also lead to anemia in children on maintenance therapy for ALL.[66] Chronic anemia can increase a child's risk of growth retardation, while reducing cognitive development and cardiac function.[67] Supplementation of deficient nutrients has been reported to reverse the signs of anemia in CCS.[66]

Up to 50% of young CCS have excessive energy intake.[54–56,68] This, combined with low energy expenditure,[69] especially in those who received cranial radiation,[70] may be contributing to higher rates of overweight and obesity in young survivors. As for macronutrients, up to 85% of young CCS have excessive fat intake,[56–58,68] though the source of fat intake from these studies was not analyzed. For young CCS, especially those treated for ALL or lymphoma, with an excessive energy and fat intake, this may be from the consumption of non-core foods or "junk food."[71,72] Although not routinely reported, it appears young CCS have adequate intake of protein and carbohydrates.[55] When comparing CCS with obesity to those without obesity, it appears that CCS with obesity may have lower intakes of fat, carbohydrate, and energy, but this observation may reflect underreporting of calorie intake by the CCS.[73]

Recent studies have focused on diet quality in young CCS. Measuring dietary quality and dietary patterns is important as people do not consume single nutrients.[74] Assessing the dietary quality and dietary patterns in CCS will provide targets for nutritional interventions. Two recent studies assessed the overall dietary quality score of young CCS and found a moderate adherence to dietary recommendations (Healthy Eating Index [HEI] score of 50 [range, 0-100]), with a poor intake of green leafy vegetables, whole fruits, whole grains, and plant-derived protein.[57,68] There appeared to be no difference in dietary quality when compared with age-matched controls.[68] When assessing individual food groups, up to 80% of young CCS had an inadequate intake of fruit and vegetables,[58,71,75,76] and almost no survivors consumed an adequate fiber intake.[55,57,75]

4.1.2 | Adult survivors

Poor dietary habits seen in young CCS appear to continue into adulthood (Table 1). Adult CCS (>18 years of age) have inadequate intake of several micronutrients. Between 50% and 80% have inadequate vitamin E intake,[77,78] and up to 80% have inadequate vitamin A intake.[79] Magnesium and potassium have also been shown to be inadequate in adult CCS.[77] The calcium and vitamin D intake in adult CCS is also inadequate.[77,79] Between 65% and 70% of adult CCS also have excessive sodium intakes.[9,80] The overall dietary quality of adult CCS is poor, with dietary quality scores of 57 (out of a possible 100) using the HEI and 48 (out of a possible 110) using the alternate HEI,[77,79] though these scores do not differ from those who have not been treated for

TABLE 1 Dietary intake and diet quality of childhood cancer survivors

Authors	Participants	Setting	Dietary method	Diet intake	Notes
Young survivors of childhood cancer					
Cohen et al, 2012	50 survivors < 5 years off treatment <13 years of age All diagnosis	Australia	3-day estimated food diary	54% consuming > 110% of requirements 50% not meeting folate requirements 32% not meeting calcium requirements 44% not meeting iron requirements	Parents monitored and restricted intake
Teixeira et al, 2018	79 survivors > 2 years off treatment 0-18 years of age All diagnosis	Brazil	24-hour dietary recall	44% excessive energy intake Adequate protein and carbohydrate Inadequate consumption of polyunsaturated and monounsaturated fats Inadequate intake of fiber, vitamin D, E, B6, B12, calcium, copper, iodine, folate, selenium, and potassium	
Alford et al, 2018	74 survivors > 3 years off treatment 5-25 years of age All diagnosis	Australia	3-day food diary	38% lower intake of carbohydrates 48% had excessive fat intake 20% inadequate energy intake 20% excessive energy intake 77% above upper limit of sodium intake 61% inadequate calcium intake 46% inadequate magnesium intake 38% inadequate iodine intake 38% inadequate folate intake	59% considered undernourished measured by body cell mass with a significantly higher fat mass than controls 64% spent > 2 hours on screen time
Landy et al, 2013	93 survivors > 3 years off treatment and 30 sibling controls <18 years of age All diagnosis	USA	3-day food record	30% excessive energy intake (no difference to controls) Excessive fat intake Mean HEI score was 55.5 with a moderate adherent to recommendations (no difference to controls) Diets low in dark green and leafy vegetables, whole fruits, and whole grains	Low HEI scores associated with increased body fat and those with cranial irradiation Survivors with obesity had poorer quality diets
Hansen et al, 2014	98 survivors > 12 months off treatment 12-19 years of age ALL or brain tumor	USA	Three-Factor Eating Questionnaire-R18	Higher frequency of emotional eating in females Higher cognitive restraint the further off treatment	
Shams-White, 2017	22 survivors < 15 years off treatment 3-25 years of age ALL or lymphoma	USA	Modified Food Craving Inventory (FCI)	Significantly more frequent cravings for fast food than cravings for sweets, carbohydrates, and fats. Individual foods that survivors craved were chips, pizza, French fries, pasta, and ice cream	Less cravings in those who received cranial radiation Older age at diagnosis associated with greater cravings
Badr et al, 2013	170 survivors <17 years off treatment 3-30 years of age Leukemia, lymphoma, sarcoma, or a cancer of the central nervous system (CNS)	USA	17-item National Cancer Institute Multifactor Screener	76% not meeting fruit and vegetable recommendations 96% not meeting fiber recommendations Female survivors had poorer intake of fruit, vegetables, and fiber compared with males	
Zhang et al, 2015	22 survivors 24.1 years (± SD 8.1 y) off treatment 3-25 years All of lymphoma	USA	24-hour recall	The mean healthy eating index (HEI) total score was 52.7 Whole fruit, total vegetables, greens and beans, seafood, plant protein, fatty acids, and sodium achieved less than 50% of the maximum scores. 0% met fiber recommendations 71% excessive saturated fat intake 77% above upper limit of sodium intake 61% inadequate calcium intake 46% inadequate magnesium intake 38% inadequate iodine intake 38% inadequate folate intake 95% inadequate in vitamin D 81% inadequate in vitamin E 71% inadequate Choline	

(Continues)

TABLE 1 (Continued)

Authors	Participants	Setting	Dietary method	Diet intake	Notes
Mayer et al, 2000	39 survivors < 14.6 years off treatment 10-20 years of age ALL	USA	24-hour recall	Adequate energy intake	No significant difference in energy intake between children who had cranial radiation and those who didn't
Denmark-Wahnefried et al, 2005	380 survivors off treatment at 1-28 years after diagnosis 11-33 years of age ALL, lymphoma or CNS tumors	USA	Self-reported serve sizes	84% excessive fat intake 79% inadequate fruit and vegetable intake 68% inadequate calcium intake	A significant barrier to increasing consumption of fruits and vegetables was confidence in one's ability to adopt healthier behaviors
Love et al, 2011	102 survivors off treatment at 5-15 years after diagnosis 8-19 years of age ALL	USA	2 × 24-hour recalls	The overweight group consumed less total energy, fat, and carbohydrates compared with normal weight group	
Fisher et al, 2018	82 survivors off treatment three years after diagnosis 5-17 years of age All diagnosis	USA	Self-reported diet intake	Two years after diagnosis: Did not meet recommendations for fruit and vegetable intake or dairy. Met guidelines for junk food intake Five years after diagnosis: Did not meet recommendations for fruit and vegetable intake or dairy. Met guidelines for junk food intake	Those with a higher socioeconomic status had reduced junk food intake over time and those families from a lower socioeconomic status had increasing junk food intake over time
Cohen et al, 2015	18 survivors <5 years off treatment <13 years of age All diagnosis	Australia	Qualitative interviews with parent report	Compared with before diagnosis: 1. Decreased fruit and vegetable intake. 2. Increased consumption of "junk food" 3. Increased portion sizes	
Adult survivors of childhood cancer					
Zhang et al, 2016	2570 survivors 32.3 (± SD 8.3) years of age All diagnosis	USA (St. Jude Lifetime Cohort)	Block FFQ HEI-2010	Mean HEI-2010 score was 57.9 27% inadequate vit D intake 54% inadequate vit E intake 58% inadequate potassium intake 59% inadequate fiber intake 84% inadequate magnesium intake 90% inadequate calcium intake Excessive sodium intake and saturated fat Age at diagnosis (<5) = lower HEI-2010 index score (poor diet quality)	CCS have poor dietary quality compared with 2010 Dietary Guidelines for Americans
Tonorezos et al, 2013	117 survivors 24.3 (± SD 4.9) years of age ALL	USA (ALLIFE study)	Harvard FFQ Mediterranean diet index (0-8 score)	Improved anthropometric and metabolic measures with greater adherence to Mediterranean diet = lower visceral and subcutaneous adiposity = lower waist circumference = lower BMI Metabolic syndrome risk decreased by 31% for each point higher on the Mediterranean diet score	Mediterranean diet consists of high intake of fruit, veg, fish and legumes, and low intake of meat and dairy
Robien et al, 2008	72 survivors 19-45 years of age ALL	USA	NCI Diet History Questionnaire (DHQ) - The 2007 WCRF/AICR Cancer Prevention Diet Recommendations - The DASH diet - The USDA food guide score	Poor adherence to recommended guidelines (all three dietary index scores being < half the possible points) 50% inadequate intake of fruit and vegetables per day 50% excess fat intake Inadequate wholegrain intake 90% inadequate fiber intake 65% excessive intake of sodium Added sugar intake was > double over the recommended (16.6% of energy)	Poor adherence to recommended guidelines (all three dietary index scores being < half the possible points)

(Continues)

TABLE 1 (Continued)

Authors	Participants	Setting	Dietary method	Diet intake	Notes
Tylavsky et al, 2010	164 survivors 19-47 years of age ALL	USA	110-item FFQ DRIs, USDA pyramid food guide and HEI used to assess diet quality	Food quality (HEI score) was 58.9 (<19 y) and 56.9 (≥19 y) <10% inadequate met protein intake 47% excess fat intake 38% excess carbohydrate 94% had inadequate fiber intake 48% inadequate folate intake 77% inadequate vitamin E intake 37%-51% met their energy requirements	Multivit used in 13.8% (<19 y) and 30.4% (≥19 y)
Belle et al, 2017	1864 survivors 16-45 years of age All diagnosis	Switzerland (SCCSS)	FFQ	43% inadequate meat intake 34% inadequate fruit intake 30% inadequate fish intake 18% inadequate fish intake 11% inadequate for vegetables	Survivors had similarly poor diet patterns and adherence to recommendations as siblings and general population
Arroyave et al, 2008	118 survivors 13-35 years of age leukemia, lymphoma, or CNS cancers			More barriers to following a low-fat diet then consuming fruit and vegetables and calcium foods Barriers include: taste preferences, availability when dining out, lack of education for food choices, peers eating high fat foods and commercial appeal	Examine barriers to consuming less fat, more fruit and vegetables, whole grains, and calcium-rich foods
Badr et al, 2011	170 survivors 17.8 (± SD 8.3) years of age; 32% were ≥ 21 years of age leukemia, lymphoma, sarcoma, or CNS cancers	USA	17-item NCI multifactor screener	36 excessive fat intakes 96% inadequate fiber intake 76% inadequate fruit and vegetable intake	45% of survivors overweight or obese
Rebholz et al, 2012	835 survivors 20-35 years of age All diagnosis	Switzerland	SHS questionnaire	72% of survivors and 68% of controls eat ≥ 1 portion/day of fruit and vegetables	
Belle et al, 2019	774 survivors 29-40 years of age All diagnosis	Switzerland	FFQ and 24 diet-recall AHEI (diet quality)	121% inadequate vit D 41% inadequate in fiber 72% inadequate in carbohydrate 72% inadequate in iron 79% inadequate in vitamin A 89% inadequate in calcium Excess intake of saturated fat, protein, cholesterol, and total fat The mean alternate healthy eating index (AHEI) score was low (48.0)	The AHEI for general population scored lower overall than CCS (41.5)
Arroyave et al, 2008	118 survivors 13-35 years of age Leukemia, lymphoma, CNS cancers	USA		Barriers to following a healthy diet: – taste preferences – availability when dining out – lack of education for food choices – peers eating high-fat foods – commercial appeal	
Butterfield et al, 2004	541 survivors Mean age 30.7 y	USA		67% excessive meat intake	32% consumed a multivitamin
Smith et al, 2014	1598 survivors 18-59 years of age All diagnosis	USA		74% inadequate intake of fruit and vegetables 52% inadequate intake in complex carbohydrates 90% excessive meat intake 70% excessive sodium intake	Metabolic syndrome was present in 32.5% of males and 31.0% of females Survivors who did not meet the dietary guidelines were two times more likely to have the metabolic syndrome

ALL, acute lymphoblastic leukemia; CNS, central nervous system.

cancer.[79] Up to 75% of adult survivors appear to have inadequate fruit and vegetable intake,[9,80–83] up to 96% of survivors have an inadequate intake of fiber and whole grains,[9,77–79] and 67% have an excessive meat intake.[84]

Several studies analyzed the adherence of adult CCS to dietary guidelines and the association with a reduction in the risk of metabolic syndrome. Adult CCS who consume a Mediterranean diet appear to reduce the risk of the metabolic syndrome by up to 30%.[85] Adult survivors who do not meet the dietary guidelines for fruit and vegetable intake are two times more likely to have the metabolic syndrome than CCS who do meet the dietary guidelines.[80] Recent literature on the general population shows that diets low in whole grains,[86] fiber, fruit[87] and processed foods[88] are associated with an increased risk of mortality from cardiovascular disease. The dietary patterns we are seeing in survivors of childhood cancer are likely exacerbating their risk of late effects such as cardiovascular disease.

5 | ETIOLOGY OF EATING HABITS AMONG CHILDHOOD CANCER SURVIVORS

5.1 | Taste and smell dysfunction

Dysfunction of taste and smell may be one of the contributing factors to poor dietary intake in CCS. Taste and smell are linked strongly with food choice[89] and a person's experience of eating,[90] and a dysfunction in taste and/or smell may contribute to poor dietary habits seen in CCS. Taste and smell dysfunction is common during cancer treatment.[91] A recent qualitative study of children during treatment found that 50% of childhood cancer patients self-reported dysfunction of taste during treatment.[92] What is unclear is whether cancer therapy causes permanent damage with loss of smell and taste receptors once treatment is completed.[93]

In children, the literature on taste and smell in survivorship is limited. One study of long-term survivors of childhood cancer found a higher incidence of dysfunction than we would see in the general population.[94] The same results were not replicated in a study of 71 survivors of childhood cancer, though a different methodology was applied to assess chemosensory dysfunction.[95] It is not clear from the literature whether dysfunction of taste and smell contributes to poor dietary habits in CCS. For those who report dysfunction of taste after cancer therapy, this may not necessarily affect oral intake.[96] Some people who experience permanent loss of taste may overcompensate by consuming large amounts of food or foods of poor quality and for others such dysfunction may reduce oral intake significantly.[97] Dysfunction of taste and smell in survivors of childhood cancer needs further exploration and is a potential target for future interventions.

5.1.1 | Altered appetite regulation

Ghrelin and leptin are hormones that are involved in the regulation of food intake and consequently body weight. Ghrelin is a peptide hormone that regulates food intake directly and has a strong orexigenic effect.[98] Disruption to ghrelin signaling impairs satiety, causing hyperphagia leading to obesity.[99] Leptin is an adipokine that plays a role in appetite regulation, body weight, and insulin sensitivity. It promotes satiety and energy use. Leptin's effects on the hypothalamic arc circuitry are counter to those of ghrelin's.[100,101] CCS have exhibited variability in ghrelin and leptin levels.[102] These levels are different compared with those in children who did not have treatment for cancer.[103]

It has been suggested that the increased risk of obesity, metabolic syndrome, and cardiovascular disease in CCS is likely due to damage in the hypothalamic-pituitary axis from cancer treatment, including CRT, intrathecal chemotherapy, or the tumor location.[25,104]Damage to the hypothalamic-pituitary region potentially impairs hormone signaling from ghrelin and leptin, altering the regulation of appetite, hunger, and body fat.[101] Several studies show a link between altered appetite regulation and late effects in CCS. Elevated leptin levels were found in CCS with obesity,[105] and decreased ghrelin levels were found in CCS who were treated for craniopharyngioma and had metabolic syndrome.[106] Evidence suggests that survivors who received CRT, are female, and diagnosed at young age are at increased risk of hyperleptinemia and increased body fatness.[107] Hypoleptinemia was noted in association with cancer cachexia and was associated directly with appetite and insulin resistance.[108] Use of corticosteroids during treatment has also been suggested to alter appetite hormone regulation. Treatment with high-dose steroids such as methylprednisolone has been shown to cause elevated leptin levels, initially during cancer treatment, but a reduction was noted after the induction phase.[102] What remains unknown is the long-term impact of the use of corticosteroids during treatment and its impact on appetite regulation in CCS and requires further investigation.

5.1.2 | Health behaviors/eating habits

Children learn their eating habits from a young age. The dietary habits and food preferences of children are usually established within the first five years of life.[109,110] Constant and repeated exposure to new foods in young children is one of the keys to forming good dietary habits when older.[111] Treatment-related side effects such as nausea, vomiting, and diarrhea can lead to poor oral intake.[112,113] Many children are unable to consume adequate energy from food during treatment and require intensive nutritional support.[114] For those who can tolerate an oral diet, many food choices tend to be of poor quality.[115,116] During treatment, children tend to increase their intake of salty snacks and carbohydrate, and reduce their intake of nutritious foods such as fruit and vegetables.[71] The lack of exposure to a variety of nutritious foods during treatment may be contributing to the poor dietary intake we are seeing early after treatment completion in young childhood cancer patients.[116]

In the general population, children's fussy/picky eating can be influenced by other factors beyond early exposure.[117] Parental factors also play a role in shaping a child's long-term eating habits. Pressuring a child to eat or providing food rewards for good eating or behavior are associated with higher rates of fussy/picky eating.[118] Parents view diet and nutrition as one of the only elements of their child's cancer treatment that they can control, and research has shown that parents tend to use negative feeding practices, such as pushing the child to eat and using food rewards as a way to get a child to eat.[119] These

TABLE 2 Nutrition and dietary interventions for childhood cancer survivors

First author (year) Country	Sample characteristics: Intervention: *N* (state of treatment)	Sample characteristics: Intervention: Cancer type (age)	Sample characteristics: Control: *N* (state of treatment)	Randomized	Intervention: Description (duration)	Intervention: Primary outcome	Intervention: Follow-up measuring time point	Results: Primary outcomes: Study group means	Results: Primary outcomes: Between-group differences	Results: Secondary outcomes: Reported diet and health status Secondary outcomes
Two-armed nutritional interventions										
Kaste et al. (2014) USA	141 (ccs +5 y follow-up)	ALL (9-36.1 y)	134 (ccs +5 y follow-up)	Yes	Nutritional counseling with calcium and vitamin D supplement vs without it (24 months)	Change in bone mineral density (LS-BMD)	At time points 12 months and 24 months	Not reported	*Coefficient (95% CI)* LS-BMD-z: 0.008 (−0.15, 0.16), $P = 0.92$. LS-BMD change: 0.03 (−0.13, 0.19), $P = 0.70$	Supplements did not increase intake nor LS-BMD in addition to nutritional counseling. Higher frequency of hypothyroidism with supplements ($P = 0.003$)
Blair et al. (2014) USA	12 + 12 (ccs)	Mixed, 50% hematopoietic (13.7-17.2 y)	*Same as intervention in cross-over design*	Yes	*Pilot study.* Cross-over: effect of grape juice (intervention) vs apple juice (control) on markers for metabolic syndrome (16 weeks)	Endothelial and vascular functions	4 weeks run-in 4 weeks juice 4 weeks washout 4 weeks juice	Grape juice: cholesterol changes +5.0, HDL −1.0, LDL +4.0 Apple juice: cholesterol changes −6.0, HDL −5.0 ($P = 0.001$), LDL −2.0	HDL: $P = 0.04$ Total cholesterol: $P = 0.03$	Reactive hyperemia index (RHI) increased more, but not significant, with apple juice
Two-armed nutritional counselling interventions										
Cox et al. (2005) USA	132 (ccs)	Mixed (mean 15.09 ± SD 1.90 y)	125 (ccs)	Yes	Multicomponent risk counselling vs standard care (1 year)	Knowledge and perception of health risks, and frequency of health behavior	1 year	Not reported Scores were positively skewed toward lower end of scale (better performance)	*P* value of differences: Knowledge: ≤0.05 Need to change: ≤0.005.	Junk food: Intervention: T0: 2.45 (0.670) T1: 2.32 (0.643) Control: T0: 2.48 (0.668) T1: 2.49 (0.710) *P* value of difference = 0.052
Moyer-Mileur et al. (2009) USA	6 (maintenance)	Standard-risk ALL (4-10 y)	7 (maintenance)	Yes	*Pilot study.* Home-based nutrition and exercise program vs standard care (12 months)	Cardiovascular fitness, flexibility, and strength	6 months 12 months	Results shown in graph only, exact values not reported	Activity minutes higher in intervention group: $P = 0.05$ Not reported. *P* value = 0.11	No between-group differences found on nutrient intake, muscle mass, or BMI

(Continues)

TABLE 2 (Continued)

	Sample characteristics				Intervention			Results		
	Intervention		Control					Primary outcomes		Secondary outcomes
First author (year) Country	*N* (state of treatment)	Cancer type (age)	*N* (state of treatment)	Randomized	Description (duration)	Primary outcome	Follow-up measuring time point	Study group means	Between-group differences	Reported diet and health status Secondary outcomes
Mays et al. (2011) USA	38 (ccs +1 y)	Mixed, 55.3 % leukemia (11-21 y)	37 (ccs +1 y)	Yes	SHARE (bone health behavior change) program vs standard care waitlist (½ day)	Intake of milk and calcium	1 month	Milk intake: *Mean (SD)* 3.36 (0.72) vs 2.93 (0.88), P value = 0.03	Not reported. Intervention group increased calcium intake more than controls $P = 0.02$.	–
Huang et al. (2014) USA	13 (ccs, BMI ≥ 85 %)	ALL (10-16 y)	13 (ccs, BMI ≥ 85 %)	Yes	*Pilot study.* Web, phone, and text message delivered weight-maintenance program vs standard care (4 months)	Weight status	4 months	Intervention: *Mean (SD)* 65.5 (18.8) Control: 71.4 (18.1)	Intervention: −0.1 kg control: +1.4 kg ($P = 0.06$ for entire study $P = 0.05$ for ccs >14-y-old)	No within- or between-group effect found on BMI, blood glucose, or total kcal intake
Two-armed parent-focused interventions										
Stern et al. (2018) USA	27 (obese ccs, ½-4 y off treatment)	Mixed (5-13 y)	26 (obese ccs, ½-4 y off treatment)	Yes	*Pilot study.* Parent focused counselling vs standard care for improved eating behavior in ccs (6 weeks, one session/week)	BMI, pressure to eat, daily steps count	6 weeks 4 months	Means not reported Intervention: Decrease in BMI ($P < 0.001$), pressure to eat ($P < 0.001$), and family eating together ($P < 0.001$), increase in step count ($P < 0.001$) Control: No changes	Not reported	–
One-armed interventions										
Blair et al. (2013) USA	8 (adult survivors) 4 (ccs)	Mixed (adults: (10-57 y)	–	–	*Pilot study.* Vegetable gardening for fruit and vegetable intake (1 year)	Fitness, grip strength, physical activity	6 months 1 year	No significant differences before and after trial reported	–	No difference on fruit and vegetable intake, vitamin D status, or BMI found

negative feeding practices may also be contributing to poor dietary intake in CCS off treatment. Although rates of fussy and picky eating have not been studied specifically in survivors of childhood cancer, studies have shown that female adolescent survivors of childhood cancer show high rates of emotional eating after treatment completion.[120] To improve the dietary intake of survivors, the dietary behaviors, dietary quality, and food exposures during treatment may be a target for future interventions.[116,121–123]

5.2 | Nutrition and health interventions in survivors

It is becoming clear that CCS consume diets of poor quality, which may be increasing their risk of chronic diseases such as obesity, cardiovascular disease and type II diabetes, and early mortality. A focus is now needed on effective nutritional interventions for survivors of childhood cancer. A systematic search of intervention studies including diet or health behavior in combination with cancer survivorship in childhood or young adults was conducted. Studies of CCS, who had completed treatment for cancer or were on maintenance therapy of any age, were included. Outcomes of interest were dietary intake, eating behavior or any marker for metabolic syndrome (blood glucose, blood pressure, waist circumference, cholesterol, or blood lipids) before and after an intervention.

5.2.1 | Nutrient intake

There are currently only a few interventions aiming to improve the diet of survivors of childhood cancer (Table 2).[124] One intervention focused on improving bone mineral density of CCS (9-35 years) uses calcium and vitamin D supplementation. There appeared to be no improvement in bone mineral density and total calcium intake from two years of calcium and vitamin D supplements.[125] At baseline, participants had low bone mineral density, but adequate calcium intake. The latter might explain why they did not increase calcium intake significantly. An intervention that included one year of counseling, and guided participants to set their own health goals, reported an increase in milk and calcium intake.[126] A half-day workshop included teaching and motivational exercises for adolescent survivors to maintain a healthy lifestyle. At one-month follow-up, the intervention arm had higher milk intake and calcium intake than controls. However, the metabolic and bone-related effects were not measured.[126] Another study investigated potential protective effects of flavonoids on vascular function in adolescent survivors in a cross-over design using two juices with differing flavonoid content. The study found no improvement with supplementation.[127] Further research is needed to establish potential beneficial effects of specific dietary interventions in survivors.

5.2.2 | Health behaviors

Two interventions delivered regular online and physical teaching materials for diet and exercise programs for young survivors (<14 years of age) and phone-based follow-ups and reminders for 12 months (Fit4Life)[128] and four months,[129] respectively. Both interventions reported no effect on dietary intake, BMI, and muscle mass. The Fit4Life program did, however, find improved weight maintenance in adolescent participants over 14 years of age.[129] One intervention was a pilot study that included one year of personal gardening mentoring for survivors to improve their fruit and vegetable intake (Harvest for Health).[130] The Harvest for Health program showed no effect on intake. One parent-targeted intervention in young CCS used one-on-one sessions and group learning focusing on healthy lifestyle for young survivors with obesity (Nourish-T).[131] The Nourish-T program improved BMI and waist circumference significantly in both parents and children. This study also reported more frequent family dinners and less pressure on the child to eat after the intervention.[131] However, whether this approach affects children's long-term health behavior remains unknown.

Another intervention used motivational counseling in adolescent survivors and found an increase in health knowledge and increased perceived need to change health behavior.[132]

It is clear from a review of the current literature that there remains a dearth of effective nutritional interventions for CCS. Many of the published interventions have small sample sizes, and there is inadequate detail on their long-term effectiveness. These programs are heterogeneous in nature, and although not assessed in this paper, a recent Cochrane review of nutritional interventions in CCS notes many current published interventions are of low quality.[124] It is also unclear whether these nutritional interventions could be implemented into routine clinical care. There appear to be several new interventions under way, aiming to improve the dietary intake of survivors of childhood cancer, though the results of these interventions are yet to be published. One intervention is a parent-led behavioral intervention to improve the fruit and vegetable intake in young survivors, called Reboot-Kids.[133] Programs targeting healthy cooking practices at summer camps for CCS have also been described as a potential venue for intervention delivery.[134] We recommend that a systematic review is undertaken of nutritional interventions in CCS. A major evidence gap/limitation in the field of nutrition in survivorship is a lack of understanding of whether specific subsets of survivors require tailored interventions. It is unclear whether interventions should be designed based on the age of the patient at time of treatment, intensity of therapy, or specific diagnoses, or whether there are common nutritional deficiencies spanning these variables seen in survivors of all ages which could be targeted using a uniform strategy. The latter scenario seems unlikely, but will require more focused study.

6 | CONCLUSION

Although improved interventions focusing on nutrition are needed for CCS, key questions about where, when, and how to deliver these interventions remain unclear. Benefits of delivering interventions during treatment include reinforcement of healthy dietary principles and leveraging health awareness as a "teachable moment."[76] However, interventions delivered during treatment must accommodate symptoms that arise due to chemotherapy and radiation therapy. This type of focused symptom management is challenging to deliver in person due to limited services in clinical nutrition in most pediatric cancer treatment settings. Directing patients and parents to electronic resources that highlight healthy foods and accommodate symptoms, such as the "@TheTable" website,[135] could potentially aid these efforts. However, reserving time for meal planning and preparation are major obstacles for families dealing with a cancer diagnosis. Once treatment is completed, similar challenges exist, yet there are ample data indicating that improvement in diet is needed in survivors. In addition to the late effects described above that are particularly problematic in CCS such as cardio-metabolic disease, the risk of second cancers may also be diminished by improving diet. It is well documented that the incidence of colorectal cancer is rising in adolescents and young adults.[136] Possible acquired risk factors include diet, obesity, diabetes, changes in gut microbiome, and infectious agents. One can speculate that CCS may also be at increased risk, and this suggests that dietary interventions and effective screening at a younger age in CCS is also needed to reduce the incidence of colorectal cancer.

Another area for development in the field of nutrition research for pediatric cancer survivorship is to view the known macro- and micronutrient deficiencies seen from a biochemical and cell biological lens in order to define molecular aspects of these deficiencies and predisposition to late effects. This is an ambitious goal, since biomarkers of dietary change is an evolving field of study and are also dependent upon host genetic factors. However, many of the late effects seen in survivors that are associated with poor health behaviors (such as cardiac ill-health and diabetes) have known etiologies that can be followed in dietary interventions to assess efficacy.[137] Incorporation of biomarkers of dietary change with relevance to late effects seen in survivorship in tandem with interventions will further this goal.

The development of dedicated survivorship clinics for surveillance and early detection of late effects is an ideal setting for revisiting health behavioral practices and encouraging improvement through interventional strategies. However, a barrier to in-person interventions is the distance of survivors from urban centers where these clinics frequently exist.[138,139] Digital interventions that incorporate video calls or geotracking hold great potential for populations for whom distance and access to survivor clinics are challenging. Moreover, the psychosocial underpinnings of dietary behaviors in CCS of various ages are complex, and changing these habits may require therapy, adding an additional component needed in designing novel interventions. Local and international consortia will be critical for the development and implementation of interventions. Establishment of guidelines for monitoring of dietary intake, and assessment of body composition and weight should be developed and standardized. Once these guidelines become broadly disseminated, coordinated intervention development and efficacy trials with multiple sites could be encouraged. This requires personnel and nutrition resources that may be challenging to provide in developing countries, and for children from areas of social disadvantage. However, in general, dietary interventions that focus on whole foods are relatively accessible globally. Progress in this field will rely on coordinated, yet multifaceted, multidimensional interventions with broad reach that share a long-term goal of preventing late effects in CCS associated with poor nutrition.

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REFERENCES

1. Ward E, DeSantis C, Robbins A, Kohler B, Jemal A. Childhood and adolescent cancer statistics, 2014. *CA Cancer J Clin*. 2014;64(2):83-103.
2. Bhakta N, Liu Q, Ness KK, et al. The cumulative burden of surviving childhood cancer: an initial report from the St Jude Lifetime Cohort Study (SJLIFE). *Lancet*. 2017;390(10112):2569-2582.
3. Chemaitilly W, Cohen LE, Mostoufi-Moab S, et al. Endocrine late effects in childhood cancer survivors. *J Clin Oncol*. 2018;36(21):2153-2159.
4. 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.
5. Armstrong GT, Chen Y, Yasui Y, et al. Reduction in late mortality among 5-year survivors of childhood cancer. *N Engl J Med* 2016;374(9):833-842.
6. Meacham LR, Sklar CA, Li S, et al. Diabetes mellitus in long-term survivors of childhood cancer. Increased risk associated with radiation therapy: a report for the childhood cancer survivor study. *Arch Intern Med*. 2009;169(15):1381-1388.
7. Friedman DN, Moskowitz CS, Hilden P, et al. Radiation Dose and volume to the pancreas and subsequent risk of diabetes mellitus. *J Natl Cancer Inst*. 2019. pii: djz152.
8. Friedman DN, Tonorezos ES, Cohen P. Diabetes and metabolic syndrome in survivors of childhood cancer. *Horm Res Paediatr*. 2019;91(2):118-127.
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(11):815-822.
10. Cohen J, Wakefield C, Fleming C, Gawthorne R, Tapsell L, Cohn R. Dietary intake after treatment in child cancer survivors. *Pediatr Blood Cancer*. 2012;58(5):752-757.
11. Vetsch J, Wakefield CE, Robertson EG, et al. Health-related quality of life of survivors of childhood acute lymphoblastic leukemia: a systematic review. *Qual Life Res*. 2018;27(6):1431-1443.
12. Zabih V, Kahane A, O'Neill NE, Ivers N, Nathan PC. Interventions to improve adherence to surveillance guidelines in survivors of childhood cancer: a systematic review. *J Cancer Surviv*. 2019;13(5):713-729
13. Group CsO. *Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers*. 25th October 2019.
14. Landier W, Bhatia S, Eshelman DA, et al. Development of risk-based guidelines for pediatric cancer survivors: the Children's Oncology Group long-term follow-up guidelines from the Children's Oncology Group Late Effects Committee and Nursing Discipline. *J Clin Oncol* 2004;22(24):4979-4990.
15. Dixon SB, Li N, Yasui Y, et al. Racial and ethnic disparities in neurocognitive, emotional, and quality-of-life outcomes in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Cancer*. 2019;125(20):3666-3677.
16. Barr RD, Mosby TT. Nutritional status in children and adolescents with leukemia: an emphasis on clinical outcomes in low and middle income countries. *Hematology*. 2016;21(4):199-205.
17. Barr R. Pediatric oncology in countries with limited resources. In: Lippincott Williams & Wilkins, ed. *Principles and Practice of Pediatric Oncology*. Philadelphia, United States; 2002:1541-1552.

18. Touyz LM, Cohen J, Neville KA, 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. *Pediatr Blood Cancer*. 2017;64(4):e26344.
19. Zhang FF, Parsons SK. Obesity in childhood cancer survivors: call for early weight management. *Adv Nutr* 2015;6(5):611-619.
20. 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):1452-1460.
21. Zhang F, 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;61:1263-1269.
22. Withycombe JS, Smith LM, Meza JL, et al. Weight change during childhood acute lymphoblastic leukemia induction therapy predicts obesity: a report from the Children's Oncology Group. *Pediatr Blood Cancer*. 2015;62(3):434-439.
23. 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(13):2262-2270.
24. Srivastava R, Batra A, Tyagi A, Dhawan D, Ramakrishnan L, Bakhshi S. Adiponectin correlates with obesity: a study of 159 childhood acute leukemia survivors from India. *Indian J Cancer*. 2015;52(2):195.
25. Barnea D, Raghunathan N, Friedman DN, Tonorezos ES. Obesity and metabolic disease after childhood cancer. *Oncology (Williston Park, NY)*. 2015;29(11):849.
26. 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-e715.
27. Carneiro JT, Maia-Lemos P, Cypriano M, Pellegrini LP. Obesity in survivors of childhood cancer: a review. *Pediatr Endocrinol Rev*. 2017;15(1):33-39.
28. Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K. Body fatness and cancer—viewpoint of the IARC Working Group. *N Engl J Med* 2016;375(8):794-798.
29. Armstrong GT, Liu Q, Yasui Y, et al. Late mortality among 5-year survivors of childhood cancer: a summary from the Childhood Cancer Survivor Study. *J Clin Oncol* 2009;27(14):2328.
30. Moke DJ, Hamilton AS, Chehab L, Deapen D, Freyer DR. Obesity and risk for second malignant neoplasms in childhood cancer survivors: a case-control study utilizing the California Cancer Registry. *Cancer Epidemiol Biomarkers Prev*. 2019;28(10):1612-1620.
31. Quinn GP, Gonçalves V, Sehovic I, Bowman ML, Reed DR. Quality of life in adolescent and young adult cancer patients: a systematic review of the literature. *Patient Relat Outcome Meas*. 2015;6:19.
32. Bitsko MJ, Cohen D, Dillon R, Harvey J, Krull K, Klosky JL. Psychosocial late effects in pediatric cancer survivors: a report from the Children's Oncology Group. *Pediatr Blood Cancer*. 2016;63(2):337-343.
33. Huang I-C, Brinkman TM, Kenzik K, et al. Association between the prevalence of symptoms and health-related quality of life in adult survivors of childhood cancer: a report from the St Jude Lifetime Cohort study. *J Clin Oncol* 2013;31(33):4242.
34. Zebrack BJ, Chesler MA. Quality of life in childhood cancer survivors. *Psychooncology*. 2002;11(2):132-141.
35. Kassianos AP, Raats MM, Gage H, Peacock M. Quality of life and dietary changes among cancer patients: a systematic review. *Qual Life Res* 2015;24(3):705-719.
36. Buttitta M, Iliescu C, Rousseau A, Guerrien A. Quality of life in overweight and obese children and adolescents: a literature review. *Qual Life Res* 2014;23(4):1117-1139.
37. van Brussel M, Takken T, Lucia A, van der Net J, Helders PJ. Is physical fitness decreased in survivors of childhood leukemia? A systematic review. *Leukemia*. 2005;19(1):13.
38. Ness KK, Baker KS, Dengel DR, et al. Body composition, muscle strength deficits and mobility limitations in adult survivors of childhood acute lymphoblastic leukemia. *Pediatr Blood Cancer*. 2007;49(7):975-981.
39. Vella SA, Magee CA, Cliff DP. Trajectories and predictors of health-related quality of life during childhood. *J Pediatr* 2015;167(2):422-427.
40. Murphy AJ, White M, Elliott SA, Lockwood L, Hallahan A, Davies PS. Body composition of children with cancer during treatment and in survivorship. *Am J Clin Nutr* 2015;102(4):891-896.
41. Jacka FN. Nutritional psychiatry: where to next? *EBioMedicine*. 2017;17:24-29.
42. Sarris J, Logan AC, Akbaraly TN, et al. Nutritional medicine as mainstream in psychiatry. *Lancet Psychiatry*. 2015;2(3):271-274.
43. Khalid S, Williams CM, Reynolds SA. Is there an association between diet and depression in children and adolescents? A systematic review. *Br J Nutr* 2016;116(12):2097-2108.
44. Jacka FN, O'Neil A, Opie R, et al. A randomised controlled trial of dietary improvement for adults with major depression (the 'SMILES' trial). *BMC Med*. 2017;15(1):23.
45. Zucchetti G, Bellini S, Bertolotti M, et al. Body image discomfort of adolescent and young adult hematologic cancer survivors. *J Adolesc Young Adult Oncol*. 2017;6(2):377-380.
46. Steele RG, Gayes LA, Dalton III WT, Smith C, Maphis L, Conway-Williams E. Change in health-related quality of life in the context of pediatric obesity interventions: a meta-analytic review. *Health Psychol* 2016;35(10):1097.
47. Jebeile H, Gow ML, Baur LA, Garnett SP, Paxton SJ, Lister NB. Treatment of obesity, with a dietary component, and eating disorder risk in children and adolescents: a systematic review with meta-analysis. *Obes Rev* 2019;20(9):1287-1298.
48. Gonzalez MC, Pastore CA, Orlandi SP, Heymsfield SB. Obesity paradox in cancer: new insights provided by body composition. *Am J Clin Nutr* 2014;99(5):999-1005.
49. Collins L, Beaumont L, Cranston A, Savoie S, Nayiager T, Barr R. Anthropometry in long-term survivors of acute lymphoblastic leukemia in childhood and adolescence. *J Adolesc Young Adult Oncol*. 2017;6(2):294-298.
50. Karlage RE, Wilson CL, Zhang N, et al. Validity of anthropometric measurements for characterizing obesity among adult survivors of childhood cancer: a report from the St. Jude Lifetime Cohort Study. *Cancer*. 2015;121(12):2036-2043.
51. Neville KA, Cohn RJ, Steinbeck KS, Johnston K, Walker JL. Hyperinsulinemia, impaired glucose tolerance, and diabetes mellitus in survivors of childhood cancer: prevalence and risk factors. *J Clin Endocrinol Metab* 2006;91(11):4401-4407.
52. Barr R, Collins L, Nayiager T, et al. Nutritional status at diagnosis in children with cancer. 2.: An assessment by arm anthropometry. *J Pediatr Hematol Oncol* 2011;33(3):e101-e104.
53. Barr RD, Gomez-Almaguer D, Jaime-Perez JC, Ruiz-Argüelles GJ. Importance of nutrition in the treatment of leukemia in children and adolescents. *Arch Med Res* 2016;47(8):585-592.
54. Cohen J, Wakefield CE, Fleming CAK, Gawthorne R, Tapsell LC, Cohn RJ. Dietary intake after treatment in child cancer survivors. *Pediatr Blood Cancer*. 2012;58(5):752-757.
55. Teixeira JFC, Maia-Lemos PdS, Pisani LP. Nutritional Characteristics of the diets of child and adolescent cancer survivors. *J Adolesc Young Adult Oncol*. 2018;7(2):230-237.
56. Murphy-Alford AJ, White M, Lockwood L, Hallahan A, Davies PS. Body composition, dietary intake and physical activity of young survivors of childhood cancer. *Clin Nutr* 2019;38(2):842-847.
57. Zhang FF, Saltzman E, Kelly MJ, et al. Comparison of childhood cancer survivors' nutritional intake with US dietary guidelines. *Pediatr Blood Cancer*. 2015;62(8):1461-1467.
58. Demark-Wahnefried W, Werner C, Clipp EC, et al. Survivors of childhood cancer and their guardians. *Cancer*. 2005;103(10):2171-2180.

59. den Hoed MA, Klap BC, te Winkel ML, et al. Bone mineral density after childhood cancer in 346 long-term adult survivors of childhood cancer. *Osteoporos Int* 2015;26(2):521-529.
60. Oskarsson T, Duun-Henriksen A, Harila-Saari A, et al. Osteoporotic fractures in childhood cancer survivors—ALICCS Cohort Study. *Pediatr Blood Cancer*. 2018;65(Suppl. 2):S693-S694.
61. Marcucci G, Beltrami G, Tamburini A, et al. Bone health in childhood cancer: review of the literature and recommendations for the management of bone health in childhood cancer survivors. *Ann Oncol* 2019;30(6):908-920.
62. Faber J, Wingerter A, Neu M-A, et al. Burden of cardiovascular risk factors and cardiovascular disease in childhood cancer survivors: data from the German CVSS-study. *Eur Heart J* 2018;39(17):1555-1562.
63. Chrysant SG, Chrysant GS. The current status of homocysteine as a risk factor for cardiovascular disease: a mini review. *Expert Rev Cardiovasc Ther* 2018;16(8):559-565.
64. Li Y, Huang T, Zheng Y, Muka T, Troup J, Hu FB. Folic acid supplementation and the risk of cardiovascular diseases: a meta-analysis of randomized controlled trials. *J Am Heart Assoc* 2016;5(8):e003768.
65. Chowdhury M, Shill L, Purba N, Rabbi F, Chowdhury M. Adverse effect of micronutrient deficiencies on children's development: the wasting syndrome. *Food Nutr Current Res*. 2019;2(1):136-147.
66. Pattnaik J, Kayal S, Dubashi B, et al. Profile of anemia in acute lymphoblastic leukemia patients on maintenance therapy and the effect of micronutrient supplementation. *Support Care Cancer*. 2019:1-8.
67. Allali S, Brousse V, Sacri A-S, Chalumeau M, de Montalembert M. Anemia in children: prevalence, causes, diagnostic work-up, and long-term consequences. *Expert Rev Hematol*. 2017;10(11):1023-1028.
68. Landy DC, Lipsitz SR, Kurtz JM, 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(4):547-555.
69. Zhang FF, Roberts SB, Parsons SK, et al. Low levels of energy expenditure in childhood cancer survivors: implications for obesity prevention. *J Pediatr Hematol Oncol* 2015;37(3):232.
70. Mayer EI, Reuter M, Dopfer RE, Ranke MB. Energy expenditure, energy intake and prevalence of obesity after therapy for acute lymphoblastic leukemia during childhood. *Horm Res Paediatr*. 2000;53(4):193-199.
71. Cohen J, Wakefield CE, Tapsell LC, Walton K, Fleming CA, Cohn RJ. Exploring the views of parents regarding dietary habits of their young cancer-surviving children. *Support Care Cancer*. 2015;23(2):463-471.
72. Shams-White M, Kelly MJ, Gilhooly C, et al. Food craving and obesity in survivors of pediatric ALL and lymphoma. *Appetite*. 2016;96:1-6.
73. Love E, Schneiderman JE, Stephens D, et al. A cross-sectional study of overweight in pediatric survivors of acute lymphoblastic leukemia (ALL). *Pediatr Blood Cancer*. 2011;57(7):1204-1209.
74. Ocké MC. Evaluation of methodologies for assessing the overall diet: dietary quality scores and dietary pattern analysis. *Proc Nutr Soc* 2013;72(2):191-199.
75. 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.
76. Fisher RS, Rausch JR, Ferrante AC, et al. Trajectories of health behaviors across early childhood cancer survivorship. *Psychooncology*. 2019;28(1):68-75.
77. 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.
78. Tylavsky FA, Smith K, Surprise H, et al. Nutritional intake of long-term survivors of childhood acute lymphoblastic leukemia: Evidence for bone health interventional opportunities. *Pediatr Blood Cancer*. 2010;55(7):1362-1369.
79. Belle FN, Chatelan A, Kasteler R, et al. Dietary intake and diet quality of Swiss adult survivors of childhood cancer compared to the general population. *bioRxiv*. 2019:527424.
80. 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.
81. Badr H, Paxton RJ, Ater JL, Urbauer D, Demark-Wahnefried W. Health behaviors and weight status of childhood cancer survivors and their parents: similarities and opportunities for joint interventions. *J Am Diet Assoc* 2011;111(12):1917-1923.
82. Belle F, Wengenroth L, Weiss A, et al. Low adherence to dietary recommendations in adult childhood cancer survivors. *Clin Nutr* 2017;36(5):1266-1274.
83. Rebholz C, Rüegg CS, Michel G, et al. Clustering of health behaviours in adult survivors of childhood cancer and the general population. *Br J Cancer*. 2012;107(2):234.
84. Butterfield RM, Park ER, Puleo E, et al. Multiple risk behaviors among smokers in the childhood cancer survivors study cohort. *Psychooncology*. 2004;13(9):619-629.
85. Tonorezos ES, Robien K, Eshelman-Kent D, et al. Contribution of diet and physical activity to metabolic parameters among survivors of childhood leukemia. *Cancer Causes Control* 2013;24(2):313-321.
86. Riccardi G, Costabile G. Carbohydrate quality is key for a healthy and sustainable diet. *Nat Rev Endocrinol* 2019;15(5):257.
87. Meier T, Gräfe K, Senn F, et al. Cardiovascular mortality attributable to dietary risk factors in 51 countries in the WHO European Region from 1990 to 2016: a systematic analysis of the Global Burden of Disease Study. *Eur J Epidemiol* 2019;34(1):37-55.
88. Srour B, Fezeu LK, Kesse-Guyot E, et al. Ultra-processed food intake and risk of cardiovascular disease: prospective cohort study (NutriNet-Santé). *BMJ*. 2019;365:l1451.
89. Bilsin E, Bal Yılmaz H. Development and validation of the taste alteration scale for children receiving chemotherapy. *J Res Nurs*. 2018;23(7):568-580.
90. Bernhardson B-M, Olson K, Baracos VE, Wismer WV. Reframing eating during chemotherapy in cancer patients with chemosensory alterations. *Eur J Oncol Nurs* 2012;16(5):483-490.
91. Hovan AJ, Williams PM, Stevenson-Moore P, et al. A systematic review of dysgeusia induced by cancer therapies. *Support Care Cancer*. 2010;18(8):1081-1087.
92. Loves R, Plenert E, Tomlinson V, et al. Changes in taste among pediatric patients with cancer and hematopoietic stem cell transplantation recipients. *Qual Life Res* 2019:1-9.
93. Hong JH, Omur-Ozbek P, Stanek BT, et al. Taste and odor abnormalities in cancer patients. *J Support Oncol* 2009;7(2):58-65.
94. Cohen J, Laing DG, Wilkes FJ. Taste and smell function in pediatric blood and marrow transplant patients. *Support Care Cancer*. 2012;20(11):3019-3023.
95. Nagai A, Kubota M, Adachi S, Watanabe K-i, Takeshita Y. Alteration of taste acuity in pediatric cancer patients after treatment completion: a cross-sectional study using a filter-paper disc method. *Food Nutr Sci*. 2014;5(14):1440.
96. Cohen J, Wakefield CE, Laing DG. Smell and taste disorders resulting from cancer and chemotherapy. *Curr Pharm Des* 2016;22(15):2253-2263.
97. Spotten L, Corish CA, Lorton C, et al. Subjective and objective taste and smell changes in cancer. *Ann Oncol* 2017;28(5):969-984.
98. Pradhan G, Samson SL, Sun Y. Ghrelin: much more than a hunger hormone. *Curr Opin Clin Nutr Metab Care*. 2013;16(6):619.
99. Wang KW, Fleming A, Johnston D, et al. Overweight, obesity and adiposity in survivors of childhood brain tumours: a systematic review and meta-analysis. *Clinical Obesity*. 2018;8(1):55-67.
100. Kojima C, Kubota M, Nagai A, Adachi S, Watanabe KI, Nakahata T. Adipocytokines in childhood cancer survivors and correlation with metabolic syndrome components. *Pediatr Int* 2013;55(4):438-442.

101. Nogueiras R, Tschöp MH, Zigman JM. CNS regulation of energy metabolism: ghrelin versus leptin. *Ann N Y Acad Sci* 2008;1126:14.
102. Fayh APT, de Lima Bezerra AD, Friedman R. Appetite hormones in children and adolescents with cancer: a systematic review of observational studies. *Nutr Hosp* 2018;35(1):201-210.
103. Park SH, Jung MH, Chung NG, Suh B-K, Lee BC. Serum ghrelin and leptin concentrations in children with cancer: comparisons with normal children. *Korean J Pediatr*. 2007;50(9):905-911.
104. Talvensaari K, Knip M. Childhood cancer and later development of the metabolic syndrome. *Ann Med*. 1997;29(5):353-355.
105. Siviero-Miachon AA, Spinola-Castro AM, Guerra-Junior G. Adiposity in childhood cancer survivors: insights into obesity physiopathology. *Arq Bras Endocrinol Metabol*. 2009;53(2):190-200.
106. Trivin C, Busiah K, Mahlaoui N, et al. Childhood craniopharyngioma: greater hypothalamic involvement before surgery is associated with higher homeostasis model insulin resistance index. *BMC Pediatrics*. 2009;9(1):24.
107. Gibson TM, Ehrhardt MJ, Ness KK. Obesity and metabolic syndrome among adult survivors of childhood leukemia. *Curr Treat Options Oncol* 2016;17(4):17.
108. Smiechowska J, Utech A, Taffet G, Hayes T, Marcelli M, Garcia JM. Adipokines in patients with cancer anorexia and cachexia. *J Investig Med* 2010;58(3):554-559.
109. Birch LL. Development of food acceptance patterns in the first years of life. *Proc Nutr Soc* 1998;57(4):617-624.
110. Birch LL, Fisher JO. Development of eating behaviors among children and adolescents. *Pediatrics*. 1998;101(3 Pt 2):539-549.
111. Mura Paroche M, Caton SJ, Vereijken CM, Weenen H, Houston-Price C. How infants and young children learn about food: a systematic review. *Front Psychol*. 2017;8:1046.
112. Baggott C, Dodd M, Kennedy C, Marina N, Miaskowski C. Multiple symptoms in pediatric oncology patients: a systematic review. *J Pediatr Oncol Nurs* 2009;26(6):325-339.
113. Arpaci T, Toruner EK, Altay N. Assessment of nutritional problems in pediatric patients with cancer and the information needs of their parents: a parental perspective. *Asia Pac J Oncol Nurs*. 2018;5(2):231.
114. Ladas EJ, Sacks N, Meacham L, et al. A multidisciplinary review of nutrition considerations in the pediatric oncology population: a perspective from children's oncology group. *Nutr Clin Pract* 2005;20(4):377-393.
115. Ladas EJ, Orjuela M, Stevenson K, et al. Fluctuations in dietary intake during treatment for childhood leukemia: A report from the DALLT cohort. *Clin Nutr* 2019;38(6):2866-2874.
116. Goddard E, Cohen J, Bramley L, Wakefield CE, Beck EJ. Dietary intake and diet quality in children receiving treatment for cancer. *Nutr Rev* 2019;77(5):267-277.
117. Scaglioni S, De Cosmi V, Ciappolino V, Parazzini F, Brambilla P, Agostoni C. Factors influencing children's eating behaviours. *Nutrients*. 2018;10(6):706.
118. Cole NC, An R, Lee S-Y, Donovan SM. Correlates of picky eating and food neophobia in young children: a systematic review and meta-analysis. *Nutr Rev* 2017;75(7):516-532.
119. Fleming CA, Cohen J, Murphy A, Wakefield CE, Cohn RJ, Naumann FL. Parent feeding interactions and practices during childhood cancer treatment. A qualitative investigation. *Appetite*. 2015;89: 219-225.
120. Hansen JA, Stancel HH, Klesges LM, et al. Eating behavior and BMI in adolescent survivors of brain tumor and acute lymphoblastic leukemia. *J Pediatr Oncol Nurs* 2014;31(1):41-50.
121. Hill R, Hamby T, Bashore L, et al. Early nutrition intervention attenuates weight gain for pediatric acute lymphoblastic leukemia patients in maintenance therapy. *J Pediatr Hematol Oncol* 2018;40(2):104-110.
122. Beaulieu-Gagnon S, Bélanger V, Marcil V. Food habits during treatment of childhood cancer: a critical review. *Nutr Res Rev* 2019;32(2):265-281.
123. Schadler KL, Kleinerman ES, Chandra J. Diet and exercise interventions for pediatric cancer patients during therapy: tipping the scales for better outcomes. *Pediatr Res* 2018;83(1-1):50.
124. Cohen JE, Wakefield CE, Cohn RJ. Nutritional interventions for survivors of childhood cancer. *Cochrane Database Syst Rev*. 2016;22(8):CD009678.
125. Kaste S, Qi A, Smith K, et al. Calcium and cholecalciferol supplementation provides no added benefit to nutritional counseling to improve bone mineral density in survivors of childhood acute lymphoblastic leukemia (ALL). *Pediatr Blood Cancer*. 2014;61(5):885-893.
126. Mays D, Black JD, Mosher RB, Heinly A, Shad AT, Tercyak KP. Efficacy of the Survivor Health and Resilience Education (SHARE) program to improve bone health behaviors among adolescent survivors of childhood cancer. *Ann Behav Med* 2011;42(1):91-98.
127. Blair CK, Kelly AS, Steinberger J, et al. Feasibility and preliminary efficacy of the effects of flavanoid-rich purple grape juice on the vascular health of childhood cancer survivors: A randomized, controlled crossover trial. *Pediatr Blood Cancer*. 2014;61(12):2290-2296.
128. Moyer-Mileur LJ, Ransdell L, Bruggers CS. Fitness of children with standard-risk acute lymphoblastic leukemia during maintenance therapy: response to a home-based exercise and nutrition program. *J Pediatr Hematol Oncol* 2009;31(4):259-266.
129. Huang JS, Dillon L, Terrones L, et al. Fit4Life: a weight loss intervention for children who have survived childhood leukemia. *Pediatr Blood Cancer*. 2014;61(5):894-900.
130. Blair CK, Madan-Swain A, Locher JL, et al. Harvest for health gardening intervention feasibility study in cancer survivors. *Acta Oncol (Madr)*. 2013;52(6):1110-1118.
131. Stern M, Bleck J, Ewing LJ, et al. NOURISH-T: targeting caregivers to improve health behaviors in pediatric cancer survivors with obesity. *Pediatr Blood Cancer*. 2018;65(5):e26941.
132. Cox CL, McLaughlin RA, Rai SN, Steen BD, Hudson MM. Adolescent survivors: a secondary analysis of a clinical trial targeting behavior change. *Pediatr Blood Cancer*. 2005;45(2):144-154.
133. Touyz L, Cohen J, Wakefield C, et al. Design and rationale for a parent-led intervention to increase fruit and vegetable intake in young childhood cancer survivors (Reboot): protocol for a pilot study. *JMIR Res Protoc*. 2018;7(5):e129.
134. Raber M, Crawford K, Chandra J. Healthy cooking classes at a children's cancer hospital and patient/survivor summer camps: initial reactions and feasibility. *Public Health Nutr* 2017;20(9):1650-1656.
135. Li R, Raber M, Chandra J. Developing a healthy web-based cookbook for pediatric cancer patients and survivors: rationale and methods. *JMIR Res Protoc*. 2015;4(1):e37.
136. Levine O, Zbuk K. Colorectal cancer in adolescents and young adults: defining a growing threat. *Pediatr Blood Cancer*. 2019:e27941.
137. Saeedi P, Shavandi A, Skidmore PML. What do we know about diet and markers of cardiovascular health in children: a review. *Int J Environ Res Public Health*. 2019;16(4):548.
138. Ou JY, Smits-Seemann RR, Wu YP, Wright J, Kirchhoff AC. An investigation of survivorship clinic attendance among childhood cancer survivors living in a five-state rural region. *J Cancer Surviv*. 2018;12(2):196-205.
139. Kam V, Hendershot E, Anderson L, Marjerrison S. Evaluation of a joint adult and pediatric clinic for cancer survivorship care. *Pediatr Blood Cancer*. 2017;64(9):e26501.

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