Critical Reviews in Oncology / Hematology 142 (2019) 94–118

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Is health status impaired in childhood cancer survivors? A systematic review and meta-analysis

Javier S. Morales[a,1], Pedro L. Valenzuela[b,c,1], Cecilia Rincón-Castanedo[a], Alejandro Santos-Lozano[d,e], Carmen Fiuza-Luces[e,*], Alejandro Lucia[a,e]

[a] Universidad Europea de Madrid, Faculty of Sport Sciences, Madrid, Spain
[b] Department of Systems Byology, University of Alcalá, Madrid, Spain
[c] Department of Sport and Health, Spanish Agency for Health Protection in Sport (AEPSAD), Madrid, Spain
[d] i+HeALTH, Department of Health Science, European University Miguel de Cervantes, Valladolid, Spain
[e] Research Institute of the Hospital 12 de Octubre (i+12), Madrid, Spain

ARTICLE INFO

Keywords:
Cardiotoxicity
Cardiometabolic health
Anthracyclines
Physical activity
Mortality

ABSTRACT

Background: : An increase in survival rates of childhood cancer is associated with long-term health issues in survivors.
Methods: : We conducted a systematic review and meta-analysis comparing health status-related endpoints in childhood cancer survivors (CCS) *versus* controls.
Results: : Eighty-six studies (n = 98,480 participants, 62% CCS) were included in the review. Of these, 73 studies (n = 96,550, 63% CCS) could be meta-analyzed. CCS showed a lower left ventricular ejection and fractional shortening (SMD = -0.59 and -0.55, respectively, both $p < 0.01$ [n = 1,824 and 1,880]), a lower HDL-cholesterol concentration (SMD = -0.48, $p < 0.001$, n = 1,378) and a higher waist-to-hip ratio (SMD = 0.61, $p < 0.01$, n = 229) than their healthy peers. No significant differences were found for the remaining endpoints.
Conclusions: : CCS is associated with a lower left ventricular function and HDL-cholesterol level, and a higher waist-to-hip ratio than healthy controls. These findings support the need to closely monitor the cardiometabolic health status of CCS and to implement preventive lifestyle interventions for this population.

1. Introduction

Treatment advances for childhood cancer have improved considerably over the last decades, with an overall 5-year survival of ˜80% (Ward et al., 2014). The prevalence of childhood cancer survivors (CCS) is therefore increasing, with the total number of CCS estimated to reach 500,000 in the United States by 2020 (Robison and Hudson, 2014). However, the increase in survival rates is not necessarily associated with a good health status after disease recovery, and can impose significant medical burdens. Indeed, conventional anti-cancer treatments (chemotherapy and/or radiotherapy) can induce late effects in adult survivors of childhood cancer and thus be associated with long-term health issues (Lipshultz et al., 1991; Oeffinger et al., 2000), which need to be monitored (Ward et al., 2014). Further, intensification of traditional treatments is likely to induce marginal benefits while further aggravating adverse effects, which drives the development of new targeted therapy strategies (*e.g.*, immunotherapy) (Burdach et al., 2018).

Approximately 62% of CCS will have at least one chronic disease 30 years after the first diagnosis (Oeffinger et al., 2006), and a higher incidence of a severe, disabling, life-threatening, or fatal health condition has been reported in CCS as compared with their siblings (Armstrong et al., 2014). Notably, cardiac abnormalities (Adams et al., 2004; Landy et al., 2013; Lipshultz et al., 2012), pulmonary complications (Dietz et al., 2016), diabetes (Meacham et al., 2009; van Nimwegen et al., 2014), obesity,(Guler et al., 2018; Nam et al., 2015), poor bone health (Gilsanz et al., 1990; Mostoufi-Moab et al., 2012; Petryk et al., 2006), impaired muscular and cardiorespiratory fitness (CRF) (Söntgerath and Eckert, 2015; van Brussel et al., 2005), or mental disorders, especially depression (Brinkman et al., 2016), have all been found to be higher among CCS than among healthy peers. However, no meta-analysis has yet compared the global health status of CCS and their controls.

Our objective was to conduct a systematic review and meta-analysis of case (CCS)-control studies to compare, from an integrative perspective, the health status of cancer-free CCS with their healthy

* Corresponding author: Instituto de Investigación Hospital 12 de Octubre ('i+12), Av. Cordoba, s/n, 28041 Madrid, Spain.
E-mail address: cfiuza.imas12@h12o.es (C. Fiuza-Luces).
[1] These two authors have contributed equally to this work.

https://doi.org/10.1016/j.critrevonc.2019.07.008
Received 27 February 2019; Received in revised form 5 July 2019; Accepted 9 July 2019

counterparts. To this end, we studied those health-related parameters likely to be most affected by disease or its treatment considering the aforementioned health conditions more prevalent in CCS, including cardiovascular and pulmonary function, body composition, metabolic and inflammatory markers, physical capacity phenotypes (*e.g.,* CRF, muscular strength), physical activity levels, fatigue, and mental health.

2. Patients and methods

This review is registered in PROSPERO (CRD42018108643). We followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (Moher et al., 2009) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) (Stroup et al., 2000) statements (see the checklists in Supplementary Files 1 and 2, respectively).

2.1. Systematic search

Two researchers (P.L.V. and J.S.M.) independently performed the systematic search for relevant articles in the electronic database PubMed (from inception to September 12th, 2018, search strategy specified in Supplementary File 3). Disagreements were resolved through discussion with a third researcher (A.S.L.). The electronic search was supplemented with a manual review of reference lists from relevant publications and reviews to locate additional publications on the subject. Gray literature (*e.g.*, abstracts, conference proceedings and editorials) and reviews were excluded.

2.2. Study selection and data extraction

Citations initially selected by systematic search were first retrieved and preliminarily screened by title and abstract. Studies were eligible for inclusion if they met the following criteria: *a)* included one group of cancer-free CCS; *b)* had a control group without prior history of cancer; and *c)* reported the differences between CCS and controls for at least one of the endpoints analyzed in this review. Studies that compared the results with reference values or with data obtained from other studies were excluded. Two authors (P.L.V. and J.S.M.) independently extracted the following data from each study, if available: number, sex and age of participants within each group, main cancer characteristics, cancer treatment characteristics (number of CCS receiving anthracyclines, radiation or hematopoietic stem cell transplantation, and type/dose of these treatments), and endpoints assessed in both CCS and controls. Disagreements were resolved through discussion with a third reviewer (A.S.L.). Main endpoints' data were extracted as mean and standard deviation (SD), or in a manner allowing their transformation into mean and SD. In studies where the median and range were provided instead of the mean and SD (Akyay et al., 2014; Alehan et al., 2012; Follin et al., 2011; Jarfelt et al., 2007; Link et al., 2004; Lipshultz et al., 2012; Warner et al., 1998, 2002), these were calculated with the formula of Hozo et al (Hozo et al., 2005). When the standard error (SE) was reported instead of the SD (Gilsanz et al., 1990; Hoffman et al., 2013; Papadia et al., 2007; Slater et al., 2015a, b; Steinberger et al., 2012; Wright et al., 1999, 1998), the latter was obtained through the formula of Altman & Bland (Altman and Bland, 2005). Finally, in those studies which followed normal distribution and provided the mean and confidence interval (Jenney et al., 1995; Zeltzer et al., 2008), we transformed the confidence interval into SE and then calculated the SD (Altman and Bland, 2005) according to Cochrane recommendations (Handbook for Systematic Reviews of Interventions of Cochrane, 2011). We contacted the authors when necessary to clarify any uncertainty or to request additional data. In this regard, six authors provided the required specific data upon request: Jarvela et al (Järvelä et al., 2013, 2010; Järvelä et al., 2016), Beulertz et al (Beulertz et al., 2016), Ruble et al (Ruble et al., 2015), Genberg et al (Genberg et al., 2015; Öberg et al., 2018), Yu et al (H.K. Yu et al., 2013; W. Yu et al., 2013), and Frisk et al (Frisk et al., 2012a, b; Frisk et al., 2012c, 2011).

2.3. Endpoints

The endpoints assessed in the present study were the following:

- Cardiovascular function: left ventricular systolic function (*i.e.,* echocardiography-assessed ejection [LVEF] and fractional shortening [FS]), resting heart rate, and resting systolic and diastolic blood pressure [BP]).
- Pulmonary function: forced expiratory volume in 1 s and forced vital capacity.
- Metabolic and inflammatory markers: fasting blood glucose and insulin levels, homeostasis model assessment-insulin resistance index (HOMA-IR), lipid profile (*i.e.,* total, high-density lipoprotein [HDL] and low-density lipoprotein [LDL], cholesterol, and triglycerides), and C-reactive protein [CRP]).
- Body composition: dual-energy X-ray absorptiometry (DXA)-assessed lean body mass, body fat, body mineral content and density, body mass index (BMI), waist and hip circumference, and waist-to-hip ratio (*i.e.*, circumference of the waist divided by that of the hip).
- Physical capacity (muscle strength assessed by means of isometric handgrip dynamometry, CRF directly assessed with a maximal exercise test [*i.e.*, through peak oxygen uptake measurement], functional mobility assessed by means of the timed up-and-go [TUG] and the timed up and down stairs tests, range of movement or flexibility), and objectively-assessed physical activity levels (*i.e.*, with accelerometer).
- Psychological status: fatigue assessed by means of Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) or Multidimensional Fatigue Inventory (MFI-20) (Cella et al., 2002; Smets et al., 1998), and depression, through Brief Symptom Inventory (BSI) (Recklitis et al., 2017, 2006).

2.4. Quality assessment

Two authors (P.L.V and J.S.M.) independently evaluated the methodological quality of the included studies with the Quality In Prognostic Studies tool (QUIPS) (Hayden et al., 2013). This tool assesses the following six areas: participation, attrition, prognostic factor measurement, confounding measurement and account, outcome measurement, and analysis and reporting. Each potential bias domain was rated as having high, moderate, or low risk of bias. The last item, rating, represents the overall rating of the study. Disagreements were resolved through discussion with a third reviewer (A.S.L.). All studies were included in the review independently of their quality.

2.5. Statistical analysis

We performed a meta-analysis to estimate the overall differences between cancer-free CCS and their healthy counterparts when a minimum of three studies analyzed a given endpoint using the same assessment method. We also performed a meta-analysis of studies reporting the odds ratio of having depression or obesity in each group (or providing enough information to calculate it). When sufficient data were available, we performed subanalyses to determine the differences between CCS and controls attending to whether the former had received a specific treatment (*i.e.*, anthracyclines or radiotherapy) or not. Pooled effect sizes (ES, Cohen´s d) were computed using a random effects model. Begg´s test was used to determine the presence of publication bias, and the Q and I^2 statistics were used to assess heterogeneity among studies. The level of significance was set at $p \leq 0.05$. All statistical analyses were performed using MIX 2.0 Pro for Excel software (Bax et al., 2006).

3. Results

From the retrieved articles, 86 (Akyay et al., 2014; Al-Tawil et al., 2015; Alehan et al., 2012; Bell et al., 2006; Beulertz et al., 2016; Bianco et al., 2014; Brennan et al., 2005; Cantrell and Posner, 2014; Christiansen et al., 2014, 2016a; Christiansen et al., 2016b; De Caro et al., 2006, 2011; Elbl et al., 2003, 2006; Esbenshade et al., 2014; Follin et al., 2011; Frisk et al., 2012a, b; Frisk et al., 2012c, 2011; Ganame et al., 2007; Garmey et al., 2008; Genberg et al., 2015; Gilsanz et al., 1990; Hartman et al., 2018; Hauser et al., 2001; Heikens et al., 2000; Hoffman et al., 2013; Hudson et al., 2015; Jain et al., 2017; Jarfelt et al., 2016, 2007; Järvelä et al., 2013, 2010; Järvelä et al., 2016; Jenney et al., 1995; Johnson et al., 1997; Karakurt et al., 2008; Kazak et al., 2010; Kenney et al., 2010; Klewer et al., 1992; Lanfranconi et al., 2014; Langeveld et al., 2003; Laufer et al., 2012; Li et al., 2017; Link et al., 2004; Lipshultz et al., 2012; Matthys et al., 1993; McKenzie et al., 2000; Mendonça Monteiro de Barros et al., 2016; Miller et al., 2010; Mulrooney et al., 2008; Ness et al., 2015, 2009; Öberg et al., 2018; Oeffinger et al., 2003; Papadia et al., 2007; Prasad et al., 2015; Ruble et al., 2015; Slater et al., 2015a, b; Steinberger et al., 2012; Sung et al., 1997; Talvensaari et al., 1996; Terlou et al., 2007; Tillmann et al., 2002; Toro-Salazar et al., 2013; Turner-Gomes et al., 1996; Vatanen et al., 2015; Warner et al., 1997a, 1998; Warner et al., 1997b, 1999; Warner et al., 2002, 2004; Wilson et al., 2018; Wright et al., 1999, 1998; Yildirim et al., 2010; H.K. Yu et al., 2013; W. Yu et al., 2013; Zebrack et al., 2004, 2002; Zebrack et al., 2007; Zeltzer et al., 2008) met all inclusion criteria and were included in the systematic review (Fig. 1). A total of 98,480 participants (of whom 62% were CCS) were included. We confirmed that some studies [(Christiansen et al., 2014, 2016a; Christiansen et al., 2016b), (Järvelä et al., 2013, 2010; Järvelä et al., 2016), (Slater et al., 2015a; Steinberger et al., 2012), (Frisk et al., 2012a, b; Frisk et al., 2012c, 2011; Genberg et al., 2015; Öberg et al., 2018), (H.K. Yu et al., 2013; W. Yu et al., 2013), (Warner et al., 1997a, 1998; Warner et al., 1997b, 1999; Warner et al., 2002, 2004)], shared the same sample, and thus we used only one to calculate the total number of subjects. Further, in Wilson et al (Wilson et al., 2018), we analyzed data of subgroups of general health (CCS and controls with poor or good general health). In Garmey et al (Garmey et al., 2008), we chose only data of follow-up.

3.1. Quality assessment and publication bias

The methodological quality of the included articles is summarized in Supplementary File 4. The risk of bias was overall low. Of the 86 included articles, 41 had a low risk of bias, 27 had a moderate risk, and the remaining 18 had a high risk of bias, which was in most cases due to unclear attrition.

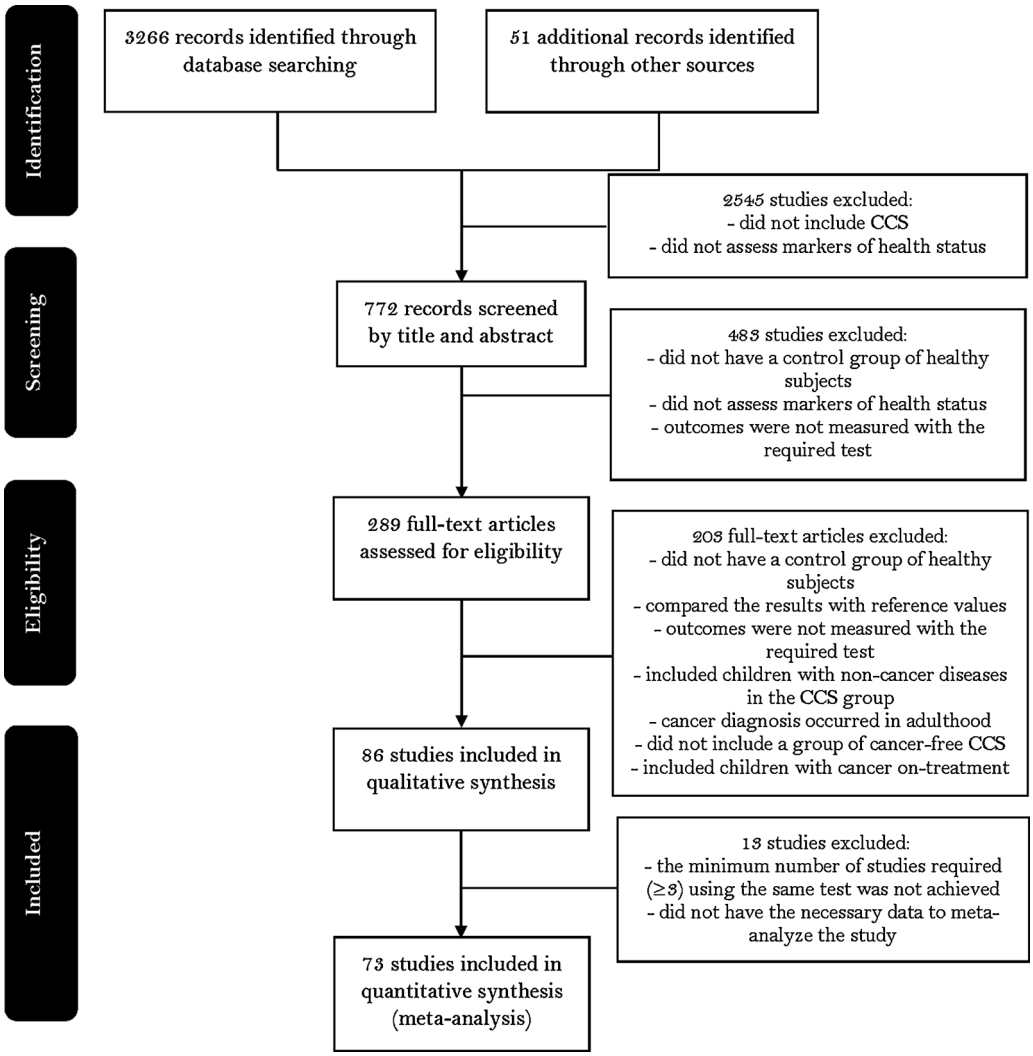

Fig. 1. PRISMA flow diagram detailing the search strategy. Abbreviations: CCS, childhood cancer survivors.

Table 1
Main characteristics of the studies included in the systematic review and meta-analysis.

Authors (year)	Sample demographics (n, sex, age)	Main cancer characteristics	Anthracyclines/radiation/ HSCT (% of survivors)	Endpoints	Main results
Akyay et al. (2012)	Survivors: n = 18 (8 female), 13 ± 5 years (5–21)	Type of cancer: ALL	Anthracyclines: N/R	**TUG**	Lower performance in TUG in survivors *vs* controls
		Age at diagnosis: N/R			
	Controls (matched by sex and age): n = 18 (8 female), 13 ± 5 years (5–21)	Time since diagnosis: N/R	CRT: 39%	**Muscle strength** (hand dynamometer)	No differences in muscle strength
		Time since treatment: 1 ± 1 years (0–5)			
		Time of remission: N/R	HSCT: N/R		
Alehan et al. (2012)	Survivors: n = 72 (21 female), 17 years (7–27)	Type of cancer: HL	Anthracyclines: 86% (doxorubicin, dose: 150 mg/m^2 [50–410])	**LVEF** and **FS** (echocardiography)	Lower LVEF and SF in survivors *vs* controls
		Age at diagnosis: 7 years (2–16)			
	Controls (matched by sex): n = 33 (16 female), 15 years (11–26)	Time since diagnosis: N/R	Radiation: 46% (mediastinal radiation)		
		Time since treatment: N/R			
		Time of remission: 9 years (2–20)	HSCT: N/R		
Al-Tawil et al. (2015)	Survivors: n = 36 (16 female), 13 ± 4 years	Type of cancer: leukemia and lymphoma	Anthracyclines: N/R	**BMI**	Lower total and LDL-cholesterol, and triglycerides in survivors *vs* controls
		Age at diagnosis: N/R			
	Controls: n = 30 (12 female), 11 ± 4 years	Time since diagnosis: N/R	Radiation: N/R	**Total**, **LDL-** and **HDL-cholesterol** and **triglycerides** (blood assays)	No differences in BMI and HDL-cholesterol
		Time since treatment: > 2 years			
		Time of remission: N/R	HSCT: N/R		
Bell et al. (2006)	Survivors: n = 35 (21 female),	Type of cancer: ALL	Anthracyclines: N/R	**CRF** (maximal treadmill exercise test)	Lower CRF in survivors *vs* controls
	12 ± 3 years (male), 12 ± 4 years (female)	Age at diagnosis: N/R			
		Time since diagnosis: N/R	Radiation: 100% (CRT)	**%body fat** (DXA)	Higher %body fat in female survivors *vs* female controls
	Controls (patients' siblings): n = 32 (14 female), 13 ± 3 years (male), 12 ± 3 years (female)	Time since treatment: > 2 years			
		Time of remission: N/R	HSCT: N/R		No differences in %body fat between male survivors and male controls
Beulertz et al. (2016)	Survivors: n = 13 (8 female), 11 ± 3 years (male), 12 years (female)	Type of cancer: different types	Anthracyclines: N/R	**Active ankle dorsiflexion ROM** (goniometer)	Lower ROM in survivors *vs* controls
		Age at diagnosis: 9 ± 4 years			
	Controls: n = 13 (8 female), 11 ± 3 years (male), 13 years (female)	Time since diagnosis: 2 ± 1 years	Radiation: 31%		
		Time since treatment: 1 ± 1 years			
		Time of remission: N/R	HSCT: N/R		
Brennan et al. (2005)	Survivors: n = 53 (31 female), 11* years (6–18)	Type of cancer: ALL	Anthracyclines: N/R	**BMI**, **lean body mass**, **total bone mineral density** and **content** (DXA)	Higher BMI and lean body mass in survivors *vs* controls
		Age at diagnosis: N/R			
	Controls: n = 187 (101 female), 5–19 years	Time since diagnosis: N/R	Radiation: 0% (CRT)		No differences in total bone mineral density and content
		Time since treatment: > 1 year			
		Time of remission: in first remission	HSCT: N/R		
Bianco et al. (2014)	Survivors: n = 18 (N/R female), 8 ± 2 years	Type of cancer: ALL and lymphoma	Anthracyclines: N/R	**Muscle strength** (hand dynamometer)	Lower muscle strength in survivors *vs* controls
		Age at diagnosis: N/R			
	Controls (matched by age and anthropometric characteristics): n = 40 (N/R female), 8 ± 2 years	Time since diagnosis: N/R	Radiation: N/R		
		Time since treatment: N/R			
		Time of remission: 1–2 years	HSCT: 100% (type: autologous)		

(*continued on next page*)

Table 1 (*continued*)

Authors (year)	Sample demographics (n, sex, age)	Main cancer characteristics	Anthracyclines/radiation/ HSCT (% of survivors)	Endpoints	Main results
Cantrell et al. (2014)	Survivors: n = 66 (66 female), 29 ± 2 years	Type of cancer: N/R	Anthracyclines: N/R	**Depression** (BSI-18)	Higher depression in survivors *vs* controls
		Age at diagnosis: N/R			
	Controls: n = 8186 (8186 female), 29 ± 2 years	Time since diagnosis: N/R	Radiation: N/R		
		Time since treatment: N/R			
		Time of remission: N/R	HSCT: N/R		
Christiansen et al. (2014)	Survivors: n = 125 (58 female), 33 years (26–39)	Type of cancer: HL and NHL	Anthracyclines: 74% (dose: 160* mg/m^2 [102–214])	**LVEF** and **FS** (echocardiography)	Lower SF in survivors (except in those who did not receive cardiotoxic treatment) *vs* controls
		Age at diagnosis: 14 years (10–16)			
	Controls (matched by sex, age and body weight): n = 125 (58 female), 33 years	Time since diagnosis: 20 ± 8 years	Radiation: 53% (mediastinal radiation)		
		Time since treatment: N/R			No differences in LVEF
		Time of remission: N/R	HSCT: N/R		
Christiansen et al. (2016a)	Survivors: n = 246 (116 female), 31 ± 8 years	Type of cancer: ALL, HL, NHL	Anthracyclines: 77% (dose: 150* mg/m^2 [40–485])	**HR** and **systolic BP**	Higher HR in survivors *vs* controls
		Age at diagnosis: 9 ± 5			
	Controls (matched for sex, age, body weight, and systolic BP): n = 211 (109 female), 32 ± 9 years	Time since diagnosis: N/R	Radiation: 24% (mediastinal radiation)		No differences in systolic BP
		Time since treatment: N/R			
		Time of remission: N/R	HSCT: N/R		
Christiansen et al. (2016b)	Survivors: n = 231 (113 female), 32 ± 8 years	Type of cancer: ALL, HL, NHL	Anthracyclines: 77% (dose: 150* mg/m^2 [40–485])	**HR** and **systolic BP**	Higher HR in survivors *vs* controls
		Age at diagnosis: 9 ± 5			
	Controls (matched for sex, age, body weight, and systolic BP): n = 180 (94 female), 32 ± 8 years	Time since diagnosis: N/R	Radiation: 29% (mediastinal radiation)		No differences in systolic BP
		Time since treatment: N/R			
		Time of remission: N/R	HSCT: N/R		
De Caro et al. (2006)	Survivors: n = 84 (26 female), 7–21 years	Type of cancer: different types	Anthracyclines: 100% (dose: 212 ± 100 mg/m^2 [64–545])	**CRF** (maximal treadmill exercise test)	Lower CRF in male survivors < 13 years *vs* male controls of the same age.
		Age at diagnosis: 6 ± 4 (0–16)			
	Controls (matched by sex and age): n = 79 (26 female), 14–21 years	Time since diagnosis: N/R	Radiation: 38% (chest radiation)		No differences in CRF for the remainder groups
		Time since treatment: 6 ± 3 (1-15)			
		Time of remission: N/R	HSCT: N/R		
De Caro et al. (2011)	Survivors: n = 55 (16 female), 14 ± 3 years	Type of cancer: different types	Anthracyclines: 100% (dose: 240* mg/m^2 [100–490])	**FS** (echocardiography)	Lower SF in survivors *vs* controls
		Age at diagnosis: 7 ± 5 years			
	Controls (matched by sex): n = 63 (19 female), 14 ± 3 years	Time since diagnosis: N/R	Radiation: 38% (chest radiation)	**CRF** (maximal treadmill exercise test)	Lower SF in survivors with subclinical cardiac dysfunction *vs* those without this condition
		Time since treatment: 6 ± 3 years			
		Time of remission: N/R	HSCT: 27% (type: autologous: 40% and allogenic: 60%)	**BMI**	Lower CRF in survivors Higher BMI in survivors
Elbl et al. (2003)	Survivors: n = 36 (16 female), 14 ± 4 years	Type of cancer: N/R	Anthracyclines: 100% (doxorubicin, dose: 226 ± 106 mg/m^2)	**LVEF** and **FS** (echocardiography)	No differences
		Age at diagnosis: 9 ± 4 years			
	Controls (matched by sex and age): n = 20 (8 female), 12 ± 5 years	Time since diagnosis: 5 ± 2 years	Radiation: 22% (mediastinal radiation)		
		Time since treatment: N/R			
		Time of remission: N/R	HSCT: N/R		

(*continued on next page*)

Table 1 (*continued*)

Authors (year)	Sample demographics (n, sex, age)	Main cancer characteristics	Anthracyclines/radiation/ HSCT (% of survivors)	Endpoints	Main results
Elbl et al. (2006)	Survivors: n = 108 (45 female), 15 ± 5 years (5–29)	Type of cancer: different types	Anthracyclines: 33% (doxorubicin or daunorubicin, dose: 250 ± 131 mg/m^2 [(50–1200])	**LVEF** and **FS** (echocardiography)	Lower LVEF and SF in survivors in the no–dexrazoxane group *vs* controls
		Age at diagnosis: 8 ± 5 years (1–18)			
	Controls: n = 32 (sex N/R), 13 ± 7 years	Time since diagnosis: 7 ± 4 years (2–20)	Mediastinal radiation: 19%		No differences in LVEF and SF between the dexrazoxane-treated group and controls
		Time since treatment: N/R			
		Time of remission: > 2 years	HSCT: N/R		
Esbenshade et al. (2014)	Survivors: n = 171 (75 female), 12* years (4–22)	Type of cancer: different types	Anthracyclines: N/R	**BMI**	Higher BMI in survivors *vs* controls
		Age at diagnosis: < 23 years			
	Controls: n = 97 (62 female), 11* years (1–19)	Time since diagnosis: N/R	Radiation: N/R		
		Time since treatment: 3* years (0–11)			
		Time of remission: N/R	HSCT: N/R		
Follin et al. (2011)	Survivors: n = 44 (21 female), 26* years (19–32)	Type of cancer: ALL	Anthracyclines: 100% (dose: 120* [40–540])	**BMI**, **%body fat** and **lean body mass** (DXA)	Higher BMI and % body fat in survivors *vs* controls
		Age at diagnosis: 1–17 years			
	Controls (matched by age, residence, smoking habits and sex): n = 44 (21 female), 25* years (20–32)	Time since diagnosis: N/R	Radiation: 100% (CRT)		Lower lean body mass in survivors *vs* controls
		Time since treatment: N/R			
		Time of remission: N/R	HSCT: N/R		
Frisk et al. (2011)	Survivors: n = 18 (8 female), 28* years (17–37)	Type of cancer: ALL and LBL	Anthracyclines: N/R	**BMI**, **waist circumference**, **%body fat** and **lean body mass** (DXA)	Higher HOMA-IR, insulin and % body fat in survivors *vs* controls
		Age at diagnosis: N/R			
	Controls (matched by sex and age): n = 18 (8 female), 27* years (19–39)	Time since diagnosis: N/R	Radiation: 100% (TBI), 39% (CRT), 17% (testes)	**HOMA-IR**, **glucose** and **insulin** (blood assays)	Lower lean body mass in survivors *vs* controls
		Time since HSCT: 18* years (10–22)			
		Time of remission: N/R	HSCT: 100% (type: autologous: 83% and allogenic: 17%)		No differences in BMI, waist circumference and glucose
Frisk et al. (2012a)	Survivors: n = 18 (8 female), 28* years (17–37)	Type of cancer: ALL and LBL	Anthracyclines: 100% (dose: 225–600 mg/m^2)	**FEV1** and **FVC** (spirometry)	Lower FEV1 and FVC in survivors *vs* controls
		Age at diagnosis: N/R			
	Controls (matched by sex and age): n = 18 (8 female), 27* years (19–38)	Time since diagnosis: N/R	Radiation: 100% (TBI), 39% (CRT), 17% (testes)		
		Time since HSCT: 18* years (10–22)			
		Time of remission: N/R	HSCT: 100% (type: autologous: 83% and allogenic: 17%)		
Frisk et al. (2012b)	Survivors: n = 18 (8 female), 28* years (17–37)	Type of cancer: ALL and LBL	Anthracyclines: 100% (dose: 225–600 mg/m^2)	**Systolic** and **diastolic BP**	Higher diastolic BP, triglycerides, insulin, total and LDL-cholesterol in survivors *vs* controls
		Age at diagnosis: N/R			
	Controls (matched by sex and age): n = 18 (8 female), 27* years (19–38)	Time since diagnosis: N/R	Radiation: 100% (TBI), 39% (CRT), 17% (testes)	**BMI** and **waist circumference**	No differences in BMI, waist circumference, systolic BP, glucose and HDL-cholesterol
		Time since HSCT: 18* years (10–22)			
		Time of remission: N/R	HSCT: 100% (type: autologous: 83% and allogenic: 17%)	**Glucose**, **insulin**, **total**, **LDL-** and **HDL-cholesterol** and **triglycerides** (blood assays)	

(*continued on next page*)

Table 1 (*continued*)

Authors (year)	Sample demographics (n, sex, age)	Main cancer characteristics	Anthracyclines/radiation/ HSCT (% of survivors)	Endpoints	Main results
Frisk et al. (2012c)	Survivors: n = 18 (8 female), 28* years (17–37)	Type of cancer: ALL and LBL	Anthracyclines: N/R	**BMI, % body fat and total bone mineral density** (DXA)	Lower bone mineral density in survivors *vs* controls
		Age at diagnosis: N/R			
	Controls (matched by sex and age): n = 18 (8 female), 27* years (19–39)	Time since diagnosis: N/R	Radiation: 100% (TBI), 39% (CRT), 17% (testes)		No differences in BMI and % body fat
		Time since HSCT: 18* years (10–22)			
		Time of remission: N/R	HSCT: 100% (type: autologous: 83% and allogenic: 17%)		
Ganame et al. (2007)	Survivors: n = 56 (34 female), 12 ± 5 years (4–28)	Type of cancer: different types	Anthracyclines: 100% (dose: 240 mg/m^2 [90–300])	**LVEF** and **FS** (echocardiography)	No differences
		Age at diagnosis: N/R			
	Controls (matched by age): n = 41 (22 female), 16 ± 7 years	Time since diagnosis: N/R	Radiation: N/R	**HR** and **systolic BP**	
		Time since anthracyclines: 5 years (2–15)			
		Time of remission: N/R	HSCT: N/R		
Garmey et al. (2008)	Survivors: n = 1451 (742 female), 32 ± 5 years (22–50)	Type of cancer: ALL	Anthracyclines: 28% (doxorubicin, dose: N/R), daunorubicin: 25% (dose: N/R)	**BMI**	Higher BMI in survivors treated with CRT *vs* controls
		Age at diagnosis: 8 ± 5 years (0–20)			
	Controls (patients' siblings): n = 2167 (1164 female), 36 ± 7 years (21–57)	Time since diagnosis: 25 ± 4 years (16–34)	Radiation: 77% (CRT), 2% (TBI)		No differences in BMI between survivors treated with chemotherapy alone and controls
		Time since treatment: N/R			
		Time of remission: N/R	HSCT: N/R		
Genberg et al. (2015)	Survivors: n = 18 (8 female), 27* years (17–38)	Type of cancer: ALL and LBL	Anthracyclines: 100% (dose: 225–600 mg/m^2)	**LVEF** and **FS** (echocardiography)	Lower lean body mass and SF in survivors *vs* controls
		Age at diagnosis: N/R			
	Controls (matched by sex and age): n = 18 (8 female), 27* years (17–38)	Time since diagnosis: N/R	Radiation: 100% (TBI)	**HR**, **systolic** and **diastolic BP**	Higher HR and diastolic BP in survivors *vs* controls
		Time since HSCT: 18* years (10–22)			
		Time of remission: N/R	HSCT: 100% (type: autologous 83% and allogenic 17%)	**BMI** and **lean body mass** (DXA)	No differences in BMI, systolic BP and LVEF
Gilsanz et al. (1990)	Survivors: n = 42 (23 female), 12 ± 1 years	Type of cancer: ALL	Anthracyclines: N/R	**BMI**	No differences
		Age at diagnosis: 0-15 years			
	Controls (matched by age, sex and race): n = 43 (23 female), 12 ± 1 years	Time since diagnosis: N/R	Radiation: 69% (CRT)		
		Time since treatment: 4 ± 0 years (1–11)			
		Time of remission: N/R	HSCT: N/R		
Hartman et al. (2018)	Survivors: n = 71 (31 female), 19–63 years	Type of cancer: AML, neuroblastoma and Wilms' tumor	Anthracyclines: 100% (dose: 225–600 mg/m^2)	**BMI**	Higher BMI in survivors *vs* controls
		Age at diagnosis: 0–15 years			
	Controls (patients' siblings and others): n = 75 (39 female), 27* years (18–62)	Time since diagnosis: 25* years (7–44)	Radiation: 38%	**Muscle strength** (hand dynamometer)	No differences in muscle strength and flexibility
		Time since treatment: > 10 years			
		Time of remission: N/R	HSCT: 5% (type: allogenic: 100%)	**Flexibility** (sit and reach)	
Hauser et al. (2001)	Survivors: n = 38 (sex N/R per group), 6 ± 2 years	Type of cancer: ALL	Anthracyclines: 100% (doxorubicin)	**LVEF** and **FS** (echocardiography)	Lower CRF in survivors, with decreased LVEF and SF after exercise, *vs* controls
		Age at diagnosis: N/R			
	Controls (matched by body surface area and age): n = 38 (16 female), 6 ± 2 years	Time since diagnosis: N/R	Radiation: N/R	**CRF** (maximal treadmill exercise test)	No differences in CRF in survivors with normal ventricular function and controls
		Time since doxorubicin: > 6 months			
		Time of remission: N/R	HSCT: N/R		No differences in LVEF and SF

(*continued on next page*)

Table 1 (*continued*)

Authors (year)	Sample demographics (n, sex, age)	Main cancer characteristics	Anthracyclines/radiation/ HSCT (% of survivors)	Endpoints	Main results
Heikens et al. (2000)	Survivors: n = 26 (12 female), 26 ± 5 years	Type of cancer: brain cancer	Anthracyclines: N/R	**Systolic** and **diastolic BP**	Higher systolic BP, waist-to-hip ratio, and LDL-cholesterol in survivors *vs* controls
		Age at diagnosis: 10 ± 4			
	Controls (college students or patients' siblings): n = 29 (19 female), 28 ± 4 years	Time since diagnosis: N/R	Radiation: 100% (CRT)	**BMI** and **waist-to-hip ratio**	Lower HDL-cholesterol in survivors *vs* controls
		Time since treatment: 16 ± 5			
		Time of remission: N/R	HSCT: N/R	**Total**, **LDL-** and **HDL-cholesterol** and **triglycerides** (blood assays)	No differences in diastolic BP, BMI, total cholesterol and triglycerides
Hoffman et al. (2013)	Survivors: n = 183 (86 female), 14 ± 3 years	Type of cancer: different types	Anthracyclines: 45% (dose N/R)	**BMI**	Lower performance in TUG in survivors *vs* controls
		Age at diagnosis: 4 ± 3			
	Controls (patients' siblings): n = 147 (73 female), 13 ± 2 years	Time since diagnosis: 9 ± 3	Radiation: 34%	**Muscle strength** (hand dynamometer)	No differences in BMI and muscle strength
		Time since treatment: N/R			
		Time of remission: N/R		**TUG**	
			HSCT: N/R		
Hudson et al. (2015)	Survivors: n = 22568 (10855 female), > 18 years	Type of cancer: different types	Anthracyclines: 27% (dose: N/R)	**BMI**	Higher levels of BMI and depression in survivors *vs* controls
		Age at diagnosis: 10 ± 6 years (0–20)			
	Controls (patients' siblings): n = 7504 (4022 female), > 18 years	Time since diagnosis: 22 ± 7 years (6–39)	Radiation: 33% (CRT), 28% (chest), 26% (abdominal), 20% (pelvic)	**Depression** (BSI-18)	
		Time since treatment: N/R			
		Time of remission: N/R	HSCT: N/R		
Jain et al. (2017)	Survivors: n = 65 (13 female), 15* years (8–28)	Type of cancer: ALL	Anthracyclines: N/R	**BMI**, **total bone mineral density** and **content** (DXA)	Higher BMI in survivors *vs* controls
		Age at diagnosis: 6* years (1–19)			
	Controls (patients' siblings): n = 50 (11 female), 15* years (7–27)	Time since diagnosis: 7* years (5–17)	Radiation: 48% (CRT), 3% (testes)		No differences in total bone mineral density and content
		Time since treatment: N/R			
		Time of remission: N/R	HSCT: N/R		
Jarfelt et al. (2007)	Survivors: n = 23 (11 female), 27* years (20–31)	Type of cancer: ALL	Anthracyclines: 100% (dose: 120* mg/m^2 [120–400])	**LVEF** and **FS** (echocardiography)	Lower LVEF and CRF in survivors *vs* controls
		Age at diagnosis: 5 years (1–8)			
	Controls: n = 12 (6 female), 27* years (20–32)	Time since diagnosis: N/R	Radiation: 48% (CRT)	**CRF** (maximal treadmill/ cycle- ergometer exercise test)	No differences in SF and BMI
		Time since doxorubicin: N/R			
		Time of remission: 21* years (17–27)	HSCT: N/R	**BMI**	
Jarfelt et al. (2016)	Survivors: n = 98 (55 female), 17* years (5–36)	Type of cancer: AML	Anthracyclines: 100% (doxorubicin: 99%, dose: 150 mg/m^2 [75–235]); (mitoxantrone: 90%, dose: 30 mg/m^2 [20–90])	**LVEF** and **FS** (echocardiography)	Lower LVEF and SF in survivors *vs* controls
		Age at diagnosis: 3* years (0–15)			
	Controls (matched by sex and age): n = 30 (sex N/R), age N/R	Time since diagnosis: 11* years (4–25)	Radiation: N/R	**HR**	No differences in HR
		Time since treatment: N/R			
		Time of remission: N/R	HSCT: N/R		

(*continued on next page*)

Table 1 (*continued*)

Authors (year)	Sample demographics (n, sex, age)	Main cancer characteristics	Anthracyclines/radiation/ HSCT (% of survivors)	Endpoints	Main results
Jarvela et al. (2010)	Survivors: n = 21 (11 female), 22 years (16–30)	Type of cancer: ALL	Anthracyclines: 100% (dose: 240 mg/m^2 [120–370])	**LVEF** and **FS** (echocardiography)	Lower CRF in survivors *vs* controls
		Age at diagnosis: 6 ± 4 years (1–13)			
	Controls (matched by sex and age): n = 21 (11 female), 21 years (16–28)	Time since diagnosis: 16 ± 3 years (11–21)	Radiation: 24% (CRT)	**CRF** (maximal cycle-ergometer exercise test)	No differences in the remainder measurements
		Time since treatment: N/R			
		Time of remission: N/R	HSCT: N/R	**Muscle strength** (hand dynamometer)	
				BMI, **waist** and **hip circumference** and **waist-to-hip ratio**	
				Systolic and **diastolic BP**	
Jarvela et al. (2013)	Survivors: n = 21 (11 female), 22 years (16–30)	Type of cancer: ALL	Anthracyclines: 100% (dose: 240 mg/m^2 [120–370])	**HOMA-IR**, **glucose**, **insulin**, **total**, **LDL-** and **HDL-cholesterol** and **triglycerides** (blood assays)	No differences
		Age at diagnosis: N/R			
	Controls (matched by sex and age): n = 21 (11 female), 21 years (16–28)	Time since diagnosis: 16 years (11–21)	Radiation: 24% (CRT)		
		Time since treatment: N/R			
		Time of remission: N/R	HSCT: N/R		
Jarvela et al. (2016)	Survivors: n = 21 (11 female), 22 years (16–30)	Type of cancer: ALL	Anthracyclines: 100% (dose: 240 mg/m^2 [120–370])	**LVEF** and **FS** (echocardiography)	No differences
		Age at diagnosis: 5 years (1–13)			
	Controls (matched by sex and age): n = 21 (11 female), 21 years (16–28)	Time since diagnosis: 16 ± 3 years (11–21)	Radiation: 24% (CRT)		
		Time since treatment: N/R			
		Time of remission: N/R	HSCT: N/R		
Jenney et al. (1995)	Survivors: n = 70 (28 female), 14 years (13–16)	Type of cancer: ALL, ANLL	Anthracyclines: N/R	**LVEF** and **FS** (echocardiography)	Lower LVEF, SF, CRF, FEV1 and FVC in survivors *vs* controls
		Age at diagnosis: 5 years (1–15)			
	Controls (matched by sex and age): n = 146 (62 female), 14 years (13–16)	Time since diagnosis: N/R	Radiation: 59% (CRT),	**CRF** (maximal cycle-ergometer exercise test)	
		Time since chemotherapy: 4 years (1–18)	14% (craniospinal),		
		Time of remission: N/R	20% (TBI)	**FEV1** and **FVC** (spirometry)	
			HSCT: N/R		
Johnson et al. (1997)	Survivors: n = 13 (6 female), 13 ± 4 years	Type of cancer: N/R	Anthracyclines : 100% (doxorubicin, dose: 293 ± 119 mg/m^2 [76–500])	**CRF** (maximal cycle-ergometer exercise test)	Lower CRF in survivors *vs* controls
		Age at diagnosis: N/R			
	Controls (matched by age): n = 15 (7 female), 14 ± 2 years	Time since diagnosis: N/R	Radiation: N/R	**HR**, **systolic** and **diastolic BP**	No differences in HR, systolic and diastolic BP
		Time since treatment: 5 ± 2 years (2–9)			
		Time of remission: N/R	HSCT: N/R		
Karakurt et al. (2008)	Survivors: n = 32 (17 female), 9 ± 5 years	Type of cancer: ALL, AML, NHL, neuroblastoma	Anthracyclines: 100% (daunorubicin: 86%, dose: 163 ± 83 mg/m^2 [100–300]); (doxorubicin: 94%, dose: 82 ± 34 mg/m^2 [50–240]);	**LVEF** and **FS** (echocardiography)	No differences
		Age at diagnosis: N/R	(mitoxantrone: 3%, dose: 50 mg/m^2)		
	Controls: n = 22 (9 female), 10 ± 3 years	Time since diagnosis: N/R			
		Time since anthracyclines: 2 ± 2 years (0–7)	Radiation: N/R		
		Time of remission: N/R			
			HSCT: N/R		

(*continued on next page*)

Table 1 (*continued*)

Authors (year)	Sample demographics (n, sex, age)	Main cancer characteristics	Anthracyclines/radiation/ HSCT (% of survivors)	Endpoints	Main results
Kazak et al. (2010)	Survivors: n = 167 (88 female), 20 ± 3 years (16–30)	Type of cancer: different types	Anthracyclines: N/R	**Depression** (BSI-18)	No differences
		Age at diagnosis: < 21 years			
	Controls (matched by sex, age and race/ethnicity): n = 170 (87 female), 22 ± 3 years	Time since diagnosis: > 5 years	Radiation: N/R		
		Time since treatment: N/R			
		Time of remission: N/R	HSCT: N/R		
Kenney et al. (2010)	Survivors: n = 50 (32 female), 56* years (51–71)	Type of cancer: different types	Anthracyclines: N/R	**Fatigue** (FACIT-Fatigue)	Higher fatigue in survivors *vs* controls
		Age at diagnosis: 8* years (0–17)			
	Controls (patients' siblings): n = 32 (23 female), 58* years (48–70)	Time since diagnosis: 48* years (36–65)	Radiation: 74%		
		Time since treatment: N/R			
		Time of remission: N/R	HSCT: N/R		
Klewer et al. (1992)	Survivors: n = 21 (9 female), 16 ± 5 years (9–27)	Type of cancer: different types	Anthracyclines : 100% (doxorubicin dose: 196 ± 137 mg/m^2 [27–532])	**FS** (echocardiography)	No differences
		Age at diagnosis: N/R			
	Controls (matched by age): n = 12 (3 female), 18 ± 4 years (10–22)	Time since diagnosis: 3 years (3–4)	Radiation: N/R	**HR**	
		Time since doxorubicin: 6 ± 4 years (1–14)			
		Time of remission: N/R	HSCT: N/R		
Lanfranconi et al. (2014)	Survivors: n = 10 (3 female), 7 ± 1 years	Type of cancer: ALL	Anthracyclines: 100% (dose: < 300 mg/m^2)	**CRF** (maximal treadmill exercise test)	No differences in CRF and BMI
		Age at diagnosis: N/R			
	Controls (matched by sexual maturity, sex and age): n = 10 (4 female), 8 ± 2 years	Time since diagnosis: 3 years (3–4)	Radiation: 0% (thoracic radiation)	**BMI**	
		Time since treatment: 1 year			
		Time of remission: N/R	HSCT: N/R		
Langeveld et al. (2003)	Survivors: n = 416 (200 female), 24 ± 5 years (16–49)	Type of cancer: different types	Anthracyclines: N/R	**Fatigue** (MFI-20)	Lower general fatigue in survivors *vs* controls
		Age at diagnosis: 8 ± 5 years (0–18)			
	Controls: n = 1026 (564 female), 26 ± 5 years (16–53)	Time since diagnosis: N/R	Radiation: 53%		Higher mental fatigue in survivors *vs* controls
		Time since treatment: 15 ± 6 years			
		Time of remission: N/R	HSCT: N/R		No differences in physical fatigue
Laufer et al. (2012)	Survivors: n = 25 (13 female), 25 ± 5 years (18–39)	Type of cancer: different types	Anthracyclines: N/R	**BMI**	No differences
		Age at diagnosis: 9 years			
	Controls: n = 28 (15 female), 30 ± 9 years (18–39)	Time since diagnosis: N/R	Radiation: 0% (CRT)		
		Time since treatment: 15 years			
		Time of remission: N/R	HSCT: 8% (type: allogeneic)		
Li et al. (2017)	Survivors: n = 94 (41 female), 22 ± 6 years	Type of cancer: ALL and AML	Anthracyclines: 100% (dose: 227 ± 100 mg/m^2)	**BMI**	No differences
		Age at diagnosis: 13 ± 7			
	Controls: n = 66 (30 female), 23 ± 7 years	Time since diagnosis: N/R	Radiation: 12% (TBI)		
		Time since treatment: 15 ± 6			
		Time of remission: N/R	HSCT: 12%		

(*continued on next page*)

Table 1 (*continued*)

Authors (year)	Sample demographics (n, sex, age)	Main cancer characteristics	Anthracyclines/radiation/ HSCT (% of survivors)	Endpoints	Main results
Link et al. (2004)	Survivors: n = 44 (21 female), 25* years (20–31)	Type of cancer: ALL	Anthracyclines: 100% (dose: 120* [40–540])	**LVEF** and **FS** (echocardiography)	Higher HR, BMI, waist circumference, waist-to-hip ratio, glucose, insulin and LDL-cholesterol in survivors *vs* controls
		Age at diagnosis: 4* (1–17)			
		Time since diagnosis: N/R			
	Controls (matched by age, sex and residence): n = 44 (sex N/R), age N/R	Time since treatment: 17* (6–24)	Radiation: 100% (CRT)	**HR, systolic** and **diastolic BP**	Lower EF, SF, lean body mass, HDL-cholesterol and triglycerides in survivors *vs* controls
		Time of remission: N/R			
			HSCT: N/R	**BMI**, **waist** and **hip circumference**, **waist–to–hip ratio**, **lean body mass** (DXA) **Glucose**, **insulin**, **total**, **LDL-** and **HDL-cholesterol** and **triglycerides** (blood assays	No differences in systolic and diastolic BP, hip circumference and total cholesterol
Lipshultz et al. (2012)	Survivors: n = 201 (101 female). 156 subjects exposed to cardiotoxic treatment, 17* years (6–39). 45 subjects unexposed to cardiotoxic treatment, 23* years (8–32)	Type of cancer: different types	Anthracyclines: 67% (dose N/R)	**FS** (echocardiography)	Lower SF in exposed survivors *vs* controls
		Age at diagnosis: 6* (0–24) (exposure to cardiotoxic treatment), 6* (0–17) (unexposed to cardiotoxic treatment)			
	Controls (patients' siblings): n = 76 (35 female), 15* years (5–45)	Time since diagnosis: 10* (3–31) (exposure to cardiotoxic treatment), 15* (5–25) (unexposed to cardiotoxic treatment)	Radiation: 19% (cardiac radiation)	**HR**, **systolic** and **diastolic BP**	No differences in SF between unexposed survivors and controls
		Time since treatment: N/R			
		Time of remission: N/R	HSCT: N/R	**BMI**	Higher HR in exposed survivors *vs* controls
				Insulin, LDL- and **HDL-cholesterol** and **CRP** (blood assays)	No differences in HR between unexposed survivors and controls
					Lower systolic BP in exposed survivors *vs* controls
					No differences in systolic BP between unexposed survivors and controls
					No differences in diastolic BP
					Higher BMI in unexposed survivors *vs* controls
					No differences in BMI between exposed survivors and controls
					Higher insulin, LDL-cholesterol and CRP in survivors *vs* controls
					No differences in HDL-cholesterol
Matthys et al. (1993)	Survivors: n = 35 (17 female), 14 ± 2 years (11–19) (male), 14 ± 3 years (10–18) (female)	Type of cancer: different types	Anthracyclines: 31% in male and 31% in female (dose: 275 mg/m^2 (180–480) (male), 330 mg/m^2 (150–500) (female)	**CRF** (maximal cycle-ergometer exercise test)	Lower CRF in female survivors *vs* female controls
		Age at diagnosis: 6 ± 3 (male) and 5 ± 3 (female) years			
	Controls (matched by age): n = 50 (25 female), 14 ± 1 years (male), 14 ± 1 years (female)	Time since diagnosis: N/R	Radiation: 40% (CRT)	**HR**	No differences in CRF between male survivors and male controls
		Time since treatment: 7 ± 3 (male) and 7 ± 4 (female) years			
		Time of remission: N/R	HSCT: N/R		Higher HR in survivors *vs* controls

(*continued on next page*)

Table 1 (*continued*)

Authors (year)	Sample demographics (n, sex, age)	Main cancer characteristics	Anthracyclines/radiation/ HSCT (% of survivors)	Endpoints	Main results
McKenzie et al. (2002)	Survivors: n = 34 (12 female), 13 years (8–18)	Type of cancer: solid tumors	Anthracyclines: 47% (doxorubicin, dose: 255 mg/m^2 (male), 282 mg/m^2 (female)	**CRF** (maximal cycle-ergometer exercise test)	Lower CRF in female survivors *vs* female controls
	Controls: n = 15 (6 female), 13 years	Age at diagnosis: N/R Time since diagnosis: N/R	Radiation: 56%		No differences in CRF between male survivors and male controls.
		Time since treatment: 4 years (1–13)			
		Time of remission: N/R	HSCT: N/R		
Mendonça Monteiro de Barros et al. (2016)	Survivors: n = 17 (15 female), 27 ± 6 years (20–42)	Type of cancer: thyroid carcinoma	Anthracyclines: N/R	**BMI**	No differences
	Controls (matched by age, sex and BMI): n = 34 (31 female), 30 ± 6 years (20–43)	Age at diagnosis: N/R Time since diagnosis: N/R	Radiation: N/R		
		Time since treatment: N/R			
		Time of remission: N/R	HSCT: N/R		
Miller et al. (2010)	Survivors: n = 170 (83 female), 19 years (6–40)	Type of cancer: different types Age at diagnosis: 8 years (0–24)	Anthracyclines: 66% (dose: N/R)	**BMI** and **%body fat** (DXA)	Higher %body fat in survivors *vs* controls
	Controls (patients' siblings): n = 71 (33 female), 16 years (5–46)	Time since diagnosis: 12 years (4–32)	Radiation: 48% (CRT)		No differences in BMI
		Time since treatment: N/R			
		Time of remission: N/R	HSCT: N/R		
Mulrooney et al. (2008)	Survivors: n = 1897 (964 female), > 18 years	Type of cancer: different types Age at diagnosis: 0–21 years	Anthracyclines: N/R	**Fatigue** (FACIT-Fatigue)	Higher fatigue and depression in survivors *vs* controls
	Controls (patients' siblings): n = 369 (193 female), > 18 years	Time since diagnosis: > 15 years	Radiation: 70%	**Depression** (BSI-18)	
		Time since treatment: N/R			
		Time of remission: N/R	HSCT: N/R		
Ness et al. (2009)	Survivors: n = 9301 (4586 female), ≥18 years	Type of cancer: different types Age at diagnosis: N/R	Anthracyclines: N/R	**BMI**	Higher BMI and depression in survivors *vs* controls
	Controls (patient' siblings): n = 2886 (1548 female), ≥18 years	Time since diagnosis: N/R	Radiation: N/R	**Depression** (BSI-18)	
		Time since treatment: N/R			
		Time of remission: N/R	HSCT: N/R		
Ness et al. (2015a)	Survivors: n = 365 (174 female), 29 ± 6 years (18–45)	Type of cancer: ALL	Anthracyclines: (daunorubicin: 66%, dose: 75* mg/m^2 [24-451]), (doxorubicin: 11%, dose: 179* mg/m^2 [25-324])	**HR**, **systolic** and **diastolic BP**	Lower flexibility and ROM in survivors *vs* controls
	Controls (matched by age, sex and race): n = 365 (174 female), 30 ± 8 years (18–45)	Age at diagnosis: 5 (1–19) Time since diagnosis: 21.9 (11–31)	Radiation: 41% (CRT)	**Muscle strength** (hand dynamometer)	Lower muscle strength, HR, and diastolic BP in CRT-exposed survivors *vs* controls
		Time since treatment: N/R			
		Time of remission: N/R	HSCT: N/R	**Flexibility** (sit and reach)	No differences in muscle strength, HR and diastolic BP between CRT-unexposed survivors and controls
				Passive ankle dorsiflexion ROM (goniometer)	No differences in systolic BP between survivors and controls
				BMI and waist circumference	Higher BMI in survivors *vs* controls
				% body fat and **lean body mass** (DXA)	Higher waist circumference and % body fat in male survivors *vs* male controls
				PA level (accelerometer)	Higher waist circumference and % body fat in CRT-exposed female survivors *vs* female controls

(*continued on next page*)

Table 1 (*continued*)

Authors (year)	Sample demographics (n, sex, age)	Main cancer characteristics	Anthracyclines/radiation/ HSCT (% of survivors)	Endpoints	Main results
					No differences in waist circumference between CRT-unexposed female survivors and female controls Lower lean body mass in CRT-exposed male survivors *vs* male controls No differences in lean body mass between CRT-unexposed male survivors and male controls No differences in lean body mass between female survivors and female controls Higher BMI and % body fat in CRT-exposed female survivors *vs* those survivors not exposed to CRT Lower PA level in survivors *vs* controls Higher diastolic BP in CRT-exposed survivors *vs* controls No differences in body composition variables between female survivors not exposed to CRT and female controls No difference in HR, systolic and diastolic BP, muscle strength, flexibility and passive ankle dorsiflexion ROM between CRT-exposed survivors and those survivors not exposed to CRT No difference in systolic BP between survivors and controls
Oberg et al. (2018)	Survivors: n = 17 (17 female), 27* years (17–37)	Type of cancer: ALL and LBL Age at diagnosis: N/R	Anthracyclines: 100% (daunorubicin, dose: 30 mg/m^2)	**FS** (echocardiography)	Lower SF, lean body mass and FEV1 in survivors *vs* controls
	Controls: n = 17 (7 female), 26* years (19–39)	Time since diagnosis: N/R Time since HSCT: 18* years (10–22)	Radiation: 100% (TBI)	**BMI**, **% body fat** and **lean body mass** (DXA)	Higher % body fat in survivors *vs* controls
		Time of remission: N/R	HSCT: 100% (type: N/R)	**FEV1** (spirometry)	No differences in BMI
Oeffinger et al. (2003)	Survivors: n = 1765 (870 female), 24 ± 5 years (18–42)	Type of cancer: ALL Age at diagnosis: 8 ± 5 years (0–21)	Anthracyclines: (doxorubicin: 28%, dose: N/R), (daunorubicin: 24%, dose: N/R)	**BMI**	Higher BMI in survivors treated with higher-dose CRT *vs* controls
	Controls (patients' siblings): n = 2565 (1357 female), 29 ± 7 years (18–56)	Time since diagnosis: 17 ± 4 years (7–28)	Radiation: 76% (CRT)		No differences in BMI between survivors treated with chemotherapy and CRT at moderate dose and controls
		Time since treatment: N/R Time of remission: N/R	HSCT: N/R		No differences in BMI between survivors treated with chemotherapy alone and controls
Papadia et al. (2007)	Survivors: n = 27 (12 female), 14 ± 1 years (6–21)	Type of cancer: ALL Age at diagnosis: 6 ± 1 years (1–14)	Anthracyclines: N/R	**BMI**, **waist** and **hip circumference** and **waist-to-hip ratio**	Higher waist circumference in survivors *vs* controls
	Controls: n = 17 (11 female), 13 ± 1 years (8–21)	Time since diagnosis: N/R Time since treatment: 9 ± 1 years (2–14)	Radiation: 100% (CRT)	**Insulin** (blood assays)	No differences in BMI, hip circumference, waist to hip ratio and insulin
		Time of remission: > 2 years	HSCT: 0%		
Prasad et al. (2015)	Survivors: n = 2589 (1305 female), > 25 years	Type of cancer: different types Age at diagnosis: 11–21 years	Anthracyclines: N/R	**Depression** (BSI-18)	Higher depression in survivors *vs* controls

(*continued on next page*)

Table 1 (*continued*)

Authors (year)	Sample demographics (n, sex, age)	Main cancer characteristics	Anthracyclines/radiation/ HSCT (% of survivors)	Endpoints	Main results
	Controls (patients' siblings): n = 390 (204 female), > 15 years	Time since diagnosis: N/R Time since treatment: N/R Time of remission: N/R	Radiation: 40% (26% CRT) HSCT: N/R		
Ruble et al. (2015)	Survivors: n = 16 (8 female), 13 ± 1 years	Type of cancer: ALL Age at diagnosis: N/R	Anthracyclines: 94% (dose: 148 ± 85 mg/m^2)	**Systolic** and **diastolic BP**	No differences
	Controls (patients' siblings): n = 16 (6 female), 14 ± 1 years	Time since diagnosis: N/R Time since treatment: 4 ± 2 years (1–10) Time of remission: N/R	Radiation: 31% (CRT) HSCT: N/R	**BMI**	
Slater et al. (2015a)	Survivors: n = 319 (148 female), 15 ± 0 years	Type of cancer: different types Age at diagnosis: N/R	Anthracyclines: N/R	**Systolic** and **diastolic BP**	Higher waist circumference, % body fat, LDL-cholesterol and triglycerides in survivors *vs* controls
	Controls (patient's siblings): n = 208 (96 female), 14 ± 0 years	Time since diagnosis: 10 (5–17) Time since treatment: N/R Time of remission: > 5 years	Radiation: 12% (CRT) HSCT: N/R	**BMI**, **waist circumference**, **% body fat** and **lean body mass** (DXA) **HOMA-IR, LDL-** and **HDL-cholesterol** and **triglycerides** (blood assays)	Lower lean body mass in survivors *vs* controls No differences in systolic and diastolic BP, BMI, HOMA-IR and HDL-cholesterol
Slater et al. (2015b)	Survivors: n = 119 (52 female), 27 ± 1 years	Type of cancer: different types Age at diagnosis: N/R	Anthracyclines: N/R	**Muscle strength** (hand dynamometer)	Higher % body fat, HOMA-IR, LDL-cholesterol and triglycerides in survivors *vs* controls
	Controls (patient's siblings): n = 66 (30 female), 25 ± 1 years	Time since diagnosis: N/R Time since treatment: N/R Time of remission: in remission	Radiation: 20% (CRT); 72% (TBI) HSCT: 100% (type: autologous 27%, allogenic 73%)	**Systolic** and **diastolic BP** **BMI**, **waist circumference**, **% body fat** and **lean body mass** (DXA) **HOMA-IR, LDL-** and **HDL-cholesterol** and **triglycerides** (blood assays)	Lower lean body mass in survivors *vs* controls No differences in muscle strength, systolic and diastolic BP, BMI, waist circumference and HDL-cholesterol
Steinberger et al. (2012)	Survivors: n = 319 (148 female), 15 ± 0 years	Type of cancer: different types Age at diagnosis: N/R	Anthracyclines: N/R	**Systolic** and **diastolic BP**	Higher waist circumference, % body fat, total and LDL-cholesterol and triglycerides in survivors *vs* controls
	Controls (patient's siblings): n = 208 (96 female), 14 ± 0 years	Time since diagnosis: 10 (5–17) Time since treatment: N/R Time of remission: > 5 years	Radiation: N/R HSCT: N/R	**BMI**, **waist circumference**, **% body fat** and **lean body mass** (DXA) **HOMA-IR**, **glucose**, **insulin**, **total**, **LDL-** and **HDL-cholesterol** and **triglycerides** (blood assays)	Lower lean body mass in survivors *vs* controls No differences in systolic and diastolic BP, BMI, HOMA-IR, glucose, insulin and HDL-cholesterol
Sung et al. (1997)	Survivors who received anthracyclines: n = 110 (39 female), 11 ± 4 years Survivors who did not receive anthracyclines: n = 76 (25 female), 12 ± 5 years	Type of cancer: different types Age at diagnosis: 5 ± 4 years	Anthracyclines: 100% (dose: 219 ± 95 mg/m^2 [19–600]).	**LVEF** and **FS** (echocardiography)	Higher HR in survivors *vs* controls
		Time since diagnosis: N/R	Radiation: N/R	**HR**, **systolic** and **diastolic BP**	Lower LVEF and SF in the group of survivors who received anthracyclines *vs* those who did not receive anthracyclines
	Controls: n = 124 (52 female), 11 ± 5 years	Time since anthracyclines: 5 ± 3 years (0–16) Time of remission: N/R	HSCT: N/R		Higher LVEF and SF in the group of survivors who received anthracyclines *vs* controls No differences in LVEF and SF between survivors who did not receive anthracyclines and controls No differences in systolic and diastolic BP

(*continued on next page*)

Table 1 (*continued*)

Authors (year)	Sample demographics (n, sex, age)	Main cancer characteristics	Anthracyclines/radiation/ HSCT (% of survivors)	Endpoints	Main results
Talvensaari et al. (1996)	Survivors: n = 50 (27 female), 18* years (11–31)	Type of cancer: different types Age at diagnosis: 4* years (0–15)	Anthracyclines: N/R	**Systolic** and **diastolic BP**	Lower total and HDL-cholesterol in survivors *vs* controls
	Controls (matched by age and sex): n = 50 (27 female), age N/R	Time since diagnosis: 13* years (8–21)	Radiation: 56% (CRT)	**Glucose**, **insulin**, **total**, **LDL-** and **HDL-cholesterol** and **triglycerides** (blood assays)	Higher glucose and insulin in survivors *vs* controls
		Time since treatment: N/R Time of remission: N/R	HSCT: N/R		No differences in systolic and diastolic BP, LDL-cholesterol and triglycerides
Terlou et al. (2007)	Survivors: n = 39 (23 female), 19 ± 7 (12–42) years	Type of cancer: different types Age at diagnosis: 9 ± 6 (0–17)	Anthracyclines: 56% (doxorubicin, dose N/R)	**HR**, **systolic** and **diastolic BP**	Higher HR in survivors *vs* controls
	Controls: n = 56 (21 female), 23 ± 5 years	Time since diagnosis: N/R Time since treatment: : 9 ± 7 (1–38)	Radiation: 49%		Lower diastolic BP in survivors *vs* controls
		Time of remission: N/R	HSCT: 13%		No differences in systolic BP
Tillmann et al. (2002)	Survivors: n = 28 (11 female), 11 ± 2 years (5–14)	Type of cancer: ALL Age at diagnosis: N/R	Anthracyclines: sample N/R (daunorubicin, dose: 180 mg/m^2)	**BMI**, **% body fat**, **total bone mineral density** and **content** (DXA)	No differences
	Controls (matched by age and sex): n = 28 (11 female), 10 ± 3 years (5–15)	Time since diagnosis: N/R Time since treatment: 5 years (2–7)	Radiation: 0%		
		Time of remission: in first clinical remission	HSCT: N/R		
Toro–Salazar et al. (2013)	Survivors: n = 46 (13 female), 22 ± 6 years	Type of cancer: different types Age at diagnosis: 11 ± 5 years	Anthracyclines: 100% (dose: 328 mg/m^2 [200–600]).	**LVEF** (echocardiography)	Lower LVEF in survivors *vs* controls
	Controls: n = 18 (sex N/R), 20 ± 9 years	Time since diagnosis: N/R Time since anthracyclines: N/R	Radiation: 9% (chest radiation)		
		Time of remission: N/R	HSCT: N/R		
Turner-Gomes et al. (1996)	Survivors: n = 14† (sex per group N/R), 13 ± 5 years (8–24)	Type of cancer: ALL Age at diagnosis: 6 ± 4 years (2–18)	Anthracyclines: 100% (doxorubicin, dose: 37% 50 ± 21 mg/m^2, 63% 349 ± 16 mg/m^2)	**BMI**	No differences
	Controls: n = 14 (sex N/R), age N/R	Time since diagnosis: N/R Time since treatment: 5 ± 2 years (1–7)	Radiation: 0% (mediastinal radiation)		
		Time of remission: N/R	HSCT: N/R		
Vatanen et al. (2015)	Survivors: n = 19 (11 female), 23 ± 5 years	Type of cancer: neuroblastoma Age at diagnosis: 3 ± 1 years (1–4)	Anthracyclines: 100% (doxorubicin, dose: 88 ± 68 mg/m^2)	**BMI**	Lower BMI in survivors *vs* controls
	Controls (matched by age and sex): n = 20 (11 female), 22 ± 5 years	Time since diagnosis: 20 ± 5 years (13–27)	Radiation: 53% (TBI)	**Glucose**, **total**, **LDL-** and **HDL-cholesterol**, **triglycerides** and **CRP** (blood assays)	Higher total cholesterol, triglycerides and CRP in survivors *vs* controls
		Time since treatment: N/R Time of remission: N/R	HSCT: 100% (type: autologous)		No differences in glucose, LDL- and HDL-cholesterol
Warner et al. (1997a)	Survivors: n = 56 (31 female), 12 ± 3 years (male with ALL), 11 ± 4 years (male with other tumors), 12 ± 4 years (female with ALL), 12 ± 3 years (female with other tumors)	Type of cancer: different types Age at diagnosis: 3 ± 1 years (ALL), 4 ± 3 (other tumors)	Anthracyclines: % N/R (dose: 0–330 in ALL, and 0–450 in other tumors)	**CRF** (maximal cycle-ergometer exercise test)	Lower CRF in ALL group *vs* controls

(*continued on next page*)

Table 1 (*continued*)

Authors (year)	Sample demographics (n, sex, age)	Main cancer characteristics	Anthracyclines/radiation/ HSCT (% of survivors)	Endpoints	Main results
	Controls (patients' siblings): n = 32 (14 female), 13 ± 3 years (male), 12 ± 3 years (female)	Time since diagnosis: N/R Time since treatment: 7 ± 3 years (in both groups) Time of remission: in first remission	Radiation: 63% (CRT) HSCT: N/R	**BMI** and **% body fat** (DXA) **FEV1** and **FVC** (spirometry)	No differences in CRF between the other tumors group and controls Higher BMI and % body fat in ALL group *vs* controls No differences in BMI and % body fat between other tumors group and controls No differences in FEV1 and FVC
Warner et al. (1997b)	Survivors: n = 43 (25 female), 12 ± 4 years Controls (patients' siblings and others): n = 40 (17 female), 12 ± 3 years	Type of cancer: N/R Age at diagnosis: N/R Time since diagnosis: N/R Time since treatment: N/R Time of remission: N/R	Anthracyclines: N/R Radiation: N/R HSCT: N/R	**BMI** and **% body fat** (DXA)	Higher BMI and % body fat in survivors *vs* controls
Warner et al. (1998)	Survivors: n = 55 (30 female), 10* years (7–18) Controls (patients' siblings): n = 32 (14 female), 12* years (8–17)	Type of cancer: different types Age at diagnosis: N/R Time since diagnosis: N/R Time since treatment: 6* years (3–13) (ALL), 6* years (2–12) (other tumors) Time of remission: N/R	Anthracyclines: % N/R (dose: 0-330 mg/m^2) Radiation: 64% (CRT) HSCT: N/R	**HR** **BMI** and **% body fat** (DXA)	No differences in HR Higher BMI and % body fat in ALL group *vs* controls No differences in BMI and % body fat between other tumors group and controls
Warner et al. (1999)	Survivors: n = 55 (31 female), 12 ± 4 years (ALL), 11 ± 4 years (with other tumors) Controls (patients' siblings): n = 31 (14 female), 12 ± 3 years	Type of cancer: different types Age at diagnosis: 3 years (1–6 for (ALL), 4 years (1–15 for other tumors) Time since diagnosis: N/R Time since treatment: 7 years (3–13) for ALL and 7 years (2–12) for other tumors Time of remission: in continuous first remission	Anthracyclines: % N/R (daunorubicin, dose: N/R) Radiation: 64% (CRT) HSCT: N/R	**Total bone mineral content** (DXA)	No differences
Warner et al. (2002)	Survivors: n = 56 (35 female), 12* years (8–17) (male with ALL), 9* years (7–18) (male with other tumors), 12* years (7–18) (female with ALL), 10* years (8–18) (female with other tumors) Controls (patients' siblings): n = 32 (14 female), 13* years (8–17) (male), 12* years (8–17) (female)	Type of cancer: different types Age at diagnosis: 3 ± 1 years (ALL), 4 ± 3 years (other tumors) Time since diagnosis: N/R Time since treatment: 7 ± 3 years (ALL), 7 ± 3 years (other tumors) Time of remission: N/R	Anthracyclines: N/R Radiation: 100% (CRT) HSCT: N/R	**BMI**, **% body fat** and **lean body mass** (DXA)	Higher BMI and % body fat in female ALL group *vs* female other tumors group Higher BMI and % body fat in female ALL group *vs* controls No differences in BMI and % body fat between male other tumors group and male controls Lower lean body mass in male other tumors group *vs* male controls No differences in lean body mass between male ALL group and male controls No differences in lean body mass in female

(*continued on next page*)

Table 1 (*continued*)

Authors (year)	Sample demographics (n, sex, age)	Main cancer characteristics	Anthracyclines/radiation/ HSCT (% of survivors)	Endpoints	Main results
Warner et al. (2004)	Survivors: n = 56 (sex N/R), 12 ± 4 years (ALL), 11 ± 4 years (with other tumors)	Type of cancer: different types	Anthracyclines: N/R	**BMI**, **% body fat** and **lean body mass** (DXA)	Higher BMI and % body fat in ALL group *vs* other tumors group
		Age at diagnosis: N/R			
	Controls (patients' siblings): n = 21 (sex N/R), 13 ± 3 years	Time since diagnosis: N/R	Radiation: 0%		No differences in BMI and % body fat between other tumors group and controls
		Time since treatment: N/R			
		Time of remission: N/R	HSCT: N/R		No differences in lean body mass
Wilson et al. (2018)	Survivors: n = 365 (174 female), 29 ± 6 years (18–45)	Type of cancer: ALL	Anthracyclines: N/R	**HR**	Lower flexibility in survivors *vs* controls
		Age at diagnosis: 7 ± 5 years (1–19)			
	Controls (matched by sex, age and race): n = 365 (174 female), 29 ± 8 years (18–51)	Time since diagnosis: 22 ± 5 years (11–31)	Radiation: N/R	**% body fat** (DXA)	No differences in HR and % body fat
		Time since treatment: N/R			
		Time of remission: N/R	HSCT: N/R	**Flexibility** (sit and reach)	
Wright et al. (1998)	Survivors: n = 36 (11 female), 9* years (5–14)	Type of cancer: ALL	Anthracyclines: N/R	**Muscle strength** (hand dynamometer)	Lower muscle strength and passive ankle dorsiflexion ROM in survivors *vs* controls
		Age at diagnosis: 4* years (0–9)			
	Controls (matched by age and sex): n = 36 (11 female), age N/R	Time since diagnosis: N/R	Radiation: 80% (CRT)	**Passive ankle dorsiflexion ROM** (goniometer)	
		Time since treatment: 3* years			
		Time of remission: N/R	HSCT: N/R		
Wright et al. (1999)	Survivors: n = 54 (19 female), 10 years (3–21)	Type of cancer: ALL	Anthracyclines: N/R	**Passive and active ankle dorsiflexion ROM** (goniometer)	Lower passive and active ankle dorsiflexion ROM in survivors *vs* controls
		Age at diagnosis: 5 years (0–17)			
	Controls (matched by age and sex): n = 54 (19 female), age N/R	Time since diagnosis: N/R	Radiation: 85% (CRT)		
		Time since treatment: 3 years			
		Time of remission: N/R	HSCT: N/R		
Yildirim et al. (2010)	Survivors: n = 20 (6 female), 18 ± 3 years (13–26)	Type of cancer: different types	Anthracyclines: 100% (dose: 282 ± 126 mg/m^2 [90–480]).	**LVEF** and **FS** (echocardiography)	No differences
		Age at diagnosis: 7 ± 4 years (4–15)			
	Controls: 18 (4 female), 19 ± 4 years (14–26)	Time since diagnosis: N/R	Radiation: 5% (mediastinal radiation)	**HR**, **systolic** and **diastolic BP**	
		Time since anthracyclines: 10 ± 4 years			
		Time of remission: N/R	HSCT: N/R		
H.K. Yu et al., 2013; W. Yu et al., 2013a)	Survivors: n = 53 (16 female), 19 ± 5 years	Type of cancer: different types	Anthracyclines: 100% (dose: 229* mg/m^2 [40–644])	**LVEF** (echocardiography)	Lower LVEF in survivors *vs* controls
		Age at diagnosis: N/R			
	Controls (patients' siblings): n = 38 (15 female), 20 ± 6 years	Time since diagnosis: N/R	Radiation: N/R	**BMI**	No differences in BMI
		Time since treatment: 7* years (2–16)			
		Time of remission: N/R	HSCT: N/R		
H.K. Yu et al., 2013; W. Yu et al., 2013b)	Survivors: n = 32 (11 female), 19 ± 5 years	Type of cancer: different types	Anthracyclines: 100% (dose: 220* mg/m^2 [120–470])	**LVEF** and **FS** (echocardiography)	Lower LVEF in survivors *vs* controls
		Age at diagnosis: N/R			
	Controls (matched by age): n = 28 (12 female), 20 ± 7 years	Time since diagnosis: N/R	Radiation: N/R	**BMI**	No differences in SF and BMI
		Time since treatment: 7* years (2–14)			
		Time of remission: N/R	HSCT: N/R		

(*continued on next page*)

Table 1 (*continued*)

Authors (year)	Sample demographics (n, sex, age)	Main cancer characteristics	Anthracyclines/radiation/ HSCT (% of survivors)	Endpoints	Main results
Zebrack et al. (2002)	Survivors: n = 5736 (2561 female), 27 ± 6 years (18–48) Controls (patients' siblings): n = 2565 (1357 female), 29 ± 7 years (18–45)	Type of cancer: leukemia, HL and NHL Age at diagnosis: 10 ± 6 years (0–20) Time since diagnosis: 16 ± 5 years (5–29) Time since treatment: N/R Time of remission: N/R	Anthracyclines: N/R Radiation: 30% (CRT) HSCT: N/R	**Depression** (BSI-18)	Higher depression in survivors *vs* controls
Zebrack et al. (2004)	Survivors: n = 1101 (507 female), 27 ± 6 years (18–44) Controls (patients' siblings): n = 2817 (1503 female), 29 ± 7 years (18–56)	Type of cancer: CNS tumors Age at diagnosis: N/R Time since diagnosis: > 5 years Time since treatment: N/R Time of remission: N/R	Anthracyclines: N/R Radiation: 52% (CRT) HSCT: N/R	**Depression** (BSI-18)	Higher depression in survivors *vs* controls
Zebrack et al. (2007)	Survivors: n = 2778 (sex N/R), 27 ± 6 years (18–56) Controls (patients' siblings): n = 2925 (sex N/R), 30 ± 7 years (18–56)	Type of cancer: solid tumors Age at diagnosis: N/R Time since diagnosis: N/R Time since treatment: N/R Time of remission: N/R	Anthracyclines: 37% (dose: N/R) Radiation: 55% HSCT: N/R	**Depression** (BSI-18)	Higher depression in survivors *vs* controls
Zeltzer et al. (2008)	Survivors: n = 7147 (3666 female), 32* years (18–54) Controls (patients' siblings): n = 2925 (sex N/R), 33V years (18–58)	Type of cancer: different types Age at diagnosis: 7* years (0–20) Time since diagnosis: 23* years (15–34) Time since treatment: N/R Time of remission: N/R	Anthracyclines: 37% (dose: N/R) Radiation: 29% (CRT); 34% (other) HSCT: N/R	**Depression** (BSI-18)	Higher depression in survivors *vs* controls

Endpoints were assessed in both survivors and controls. Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; ANLL, acute non-lymphoblastic leukemia; BMI, body mass index; BP, blood pressure; BSI-18, Brief Symptom Inventory-18; CNS, central nervous system; CRF, cardiorespiratory fitness; CRP, C-reactive protein; CRT, cranial radiation therapy; DXA, dual-energy X-ray absorptiometry; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue; FEV1, forced expiratory volume in 1 s; FS, fractional shortening; FVC, forced vital capacity; HDL, high density lipoprotein; HL, Hodgkin lymphoma; HOMA-IR, homeostasis model assessment insulin resistance index; HR, heart rate; HSCT, hematopoietic stem cell transplantation; LBL, lymphoblastic lymphoma; LDL, low density lipoprotein; LVEF, left ventricular ejection fraction; MFI-20, Multidimensional Fatigue Inventory; NHL, non-Hodgkin lymphoma; N/R, not reported; PA, physical activity; ROM, range of movement; TBI, total body irradiation; TUG, timed up-and-go test.

* Data are expressed as median.

† Data are referred to an initial sample of 19 survivors.

3.2. Participants' and cancer characteristics

The details of the included studies are summarized in Table 1. The age at study ranged from 3 (Wright et al., 1999) to 71 (Kenney et al., 2010) years and from 5 (Akyay et al., 2014; Brennan et al., 2005; Lipshultz et al., 2012; Tillmann et al., 2002) to 70 (Kenney et al., 2010) years in the CCS and control group, respectively. The age at diagnosis, the time since diagnosis, and the time since end of treatment ranged from 0 (Garmey et al., 2008; Hudson et al., 2015; Jarfelt et al., 2016; Kenney et al., 2010; Langeveld et al., 2003; Lipshultz et al., 2012; Miller et al., 2010; Mulrooney et al., 2008; Oeffinger et al., 2003; Talvensaari et al., 1996; Terlou et al., 2007; Wright et al., 1999, 1998; Zebrack et al., 2002; Zeltzer et al., 2008) to 24 (Lipshultz et al., 2012) years, from 1 (Elbl et al., 2006) to 65 (Kenney et al., 2010) years, and from 0 (Akyay et al., 2014) to 38 (Terlou et al., 2007) years, respectively. Thirty-nine, 66 and 41% of the included studies did not report the age at diagnosis, time since diagnosis and time since end of treatment, respectively. The studies included children/adolescents and adult survivors with different types of childhood cancer, with the most common being hematological malignancies (leukemia and lymphoma), solid tumors (bone tumors, neuroblastoma, Wilms' tumors) and central nervous system tumors. Controls were mainly matched by sex, age and race, and were in some cases the patients' siblings.

3.3. Endpoints

The endpoints assessed in the present systematic review and meta-analysis that yielded significant differences between CCS and controls are shown in Table 2 whereas those showing no between-group differences are shown in Supplementary File 5.

3.3.1. Cardiovascular function

CCS presented with a lower LVEF than controls (weighted mean ± SD of 64% ± 5% *vs* 67% ± 7%, respectively; Fig. 2, panel A), with no evidence of publication bias (Begg´s test, $p = 0.34$) but heterogeneity between studies ($I^2 = 99\%$, $Q = 245$). Moreover, CCS patients showed lower FS compared with controls (35% ± 5% *vs* 37% ± 5%; Fig. 3, panel A), with no evidence of publication bias ($p = 0.48$) but heterogeneity among studies ($I^2 = 98\%$, $Q = 930$). These differences between CCS and controls remained significant for both LVEF (63% ± 6% *vs* 65% ± 5%; ES = -0.35, 95% confidence interval [CI] = -0.55, -0.14; $p < 0.01$; Begg´s test $p = 0.67$; $I^2 = 98\%$, $Q = 528$) and FS (35% ± 5% *vs* 37% ± 5%; ES = -0.51, 95% CI = -0.66, -0.36; $p < 0.01$; Begg´s test $p = 0.58$; $I^2 = 98\%$, $Q = 803$) when analyzing only those patients who had received anthracyclines (Fig. 2, panel B and Fig. 3, panel B, respectively). No differences were observed between CCS and controls for BP (diastolic or systolic) or resting heart

Table 2
Endpoints showing significant differences between childhood cancer survivors (CCS) and their controls.

Endpoint	Assessment method	Number of studies in the systematic review	Number of participants in the systematic review		Risk of bias[a]	Number of studies in the meta-analysis	Number of participants in the meta-analysis		Meta-analysis results
			CCS	Controls			CCS	Controls	
LVEF	Echocardiography	19	1045*	795*		17	1045	779*	− 0.59 (-0.89; -0.29); $P < 0.01$; $I^2 = 99\%$; Q = 245; $P = 0.34$
FS	Echocardiography	21	1238*	903*		18	1054	826*	− 0.55 (-0.70; -0.40); $P < 0.01$; $I^2 = 98\%$; Q = 930; $P = 0.48$
Waist-to-hip ratio		4	118	111		4	118	111	0.61 (0.23; 0.99); $P < 0.01$; $I^2 = 96\%$; Q = 79; $P = 0.73$
HDL-cholesterol	Blood assays	11	853*	562*		9	834	544*	− 0.48 (-0.85; 0.10); $P < 0.001$; $I^2 = 51\%$; Q = 16; $P = 0.62$

Pooled effect sizes (ES, Cohen´s d) were computed using a random effects model. The Begg´s test was used to determine the presence of publication bias, and the Q and I^2 statistics were used to assess heterogeneity among studies. Abbreviations: FS, fractional shortening (of the left ventricle); HDL, high density lipoprotein; LVEF, left ventricular ejection fraction.

[a] Indicates the percentage of studies for each outcome with high (red), moderate (yellow) and low (green) risk of bias.

* Several studies shared the same sample, and thus only one was used to count the total number of subjects.

rate (Supplementary File 5). Similarly, there were no differences between CCS and controls in these endpoints when analyzing only those patients who had received anthracyclines or radiotherapy (Supplementary File 6).

3.3.2. Pulmonary function

There were no differences between CCS and controls for pulmonary function (Supplementary File 5). No subanalyses could be performed attending to the specific treatment received.

3.3.3. Metabolic and inflammatory markers

CCS presented with lower levels of HDL-cholesterol than controls (49 ± 12 mg/dL *vs* 55 ± 13 mg/dL, respectively; Fig. 4), with no evidence of publication bias ($p = 0.62$) or heterogeneity between studies ($I^2 = 51\%$, Q = 16). No differences were found for total cholesterol, LDL-cholesterol, fasting blood glucose or insulin, or HOMA-IR (Supplementary File 5). Two studies (Lipshultz et al., 2012; Vatanen et al., 2015) analyzed the levels of CRP and both reported significantly higher levels in CCS than in controls (data not meta-analyzed).

3.3.4. Body composition

Although no differences were observed between CCS and controls for waist or hip circumference when these outcomes were analyzed independently (Supplementary File 5), CCS showed a higher waist-to-hip ratio (0.85 ± 0.08 *vs* 0.80 ± 0.06; Fig. 5), with no evidence of publication bias ($p = 0.73$), but with heterogeneity between studies ($I^2 = 96\%$, Q = 76).

No differences were observed between CCS and controls for BMI when analyzing the former irrespective of the treatment received (Supplementary File 5) or in subgroup analyses attending to whether they had been treated with anthracyclines (Supplementary File 6). Similarly, no differences were observed between CCS and controls for body fat or lean body mass when analyzing all CCS together (Supplementary File 5), or when attending to the treatment received (Supplementary File 6). No differences were observed for bone mineral content or density (Supplementary File 5).

3.3.5. Physical capacity

No significant differences were observed between CCS and controls for CRF (Supplementary File 5), a finding that remained unchanged after attending to whether CCS had been treated with anthracyclines (Supplementary File 6). Similarly, no differences were observed between CCS and controls for handgrip strength or range of movement/flexibility (Supplementary File 5). Two studies (Akyay et al., 2014; Hoffman et al., 2013) assessed functional mobility by means of the TUG, and both reported significantly lower values in CCS than in controls (data not meta-analyzed). Physical activity levels were analyzed in one study (Ness et al., 2015), which reported lower levels in CCS than in controls.

3.3.6. Psychological status

There were no differences in depression symptoms between CCS and controls (Supplementary File 5). Two studies (Kenney et al., 2010; Mulrooney et al., 2008) observed higher overall fatigue in CCS compared with controls (data not meta-analyzed). One further study (Langeveld et al., 2003) reported the specific score in different dimensions of fatigue, finding a lower general fatigue and a higher mental fatigue in CCS compared with controls, but no differences in physical fatigue.

4. Discussion

Our results indicate that CCS have lower left ventricular function (lower LVEF and FS), higher levels of a central adiposity indicator (waist-to-hip ratio) and lower HDL-cholesterol levels when compared with their healthy counterparts with no prior history of cancer. To the

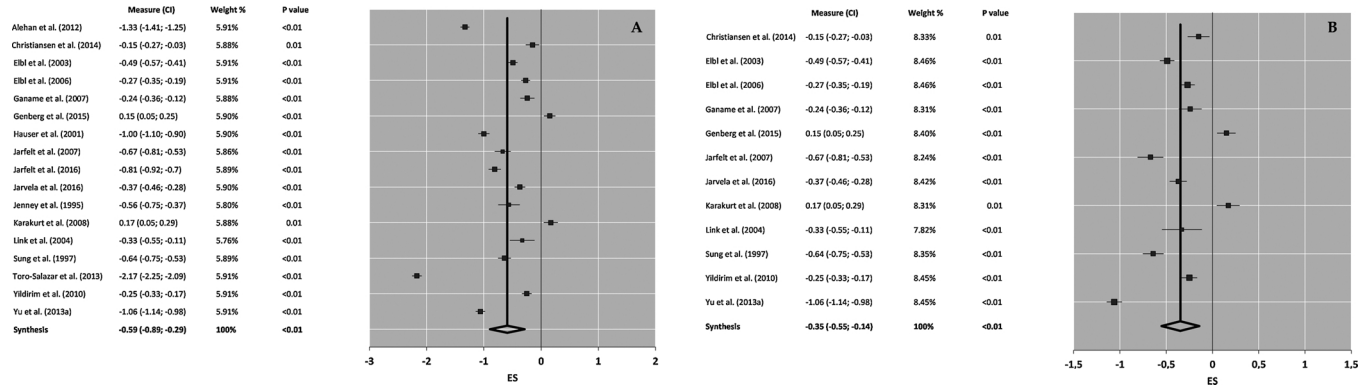

Fig. 2. Differences between childhood cancer survivors (CCS) and controls for left ventricular ejection fraction irrespective of the treatment received (panel **A**) or when including only those CCS who had received anthracyclines (panel **B**).

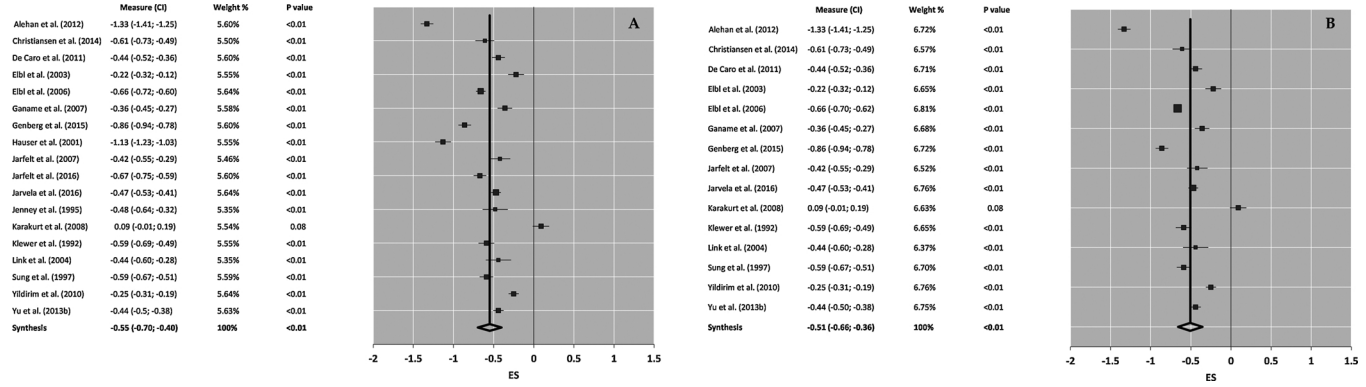

Fig. 3. Differences between childhood cancer survivors (CCS) and controls for left ventricular fractional shortening irrespective of the treatment received (panel **A**) or when including only those CCS who had received anthracyclines (panel **B**).'.

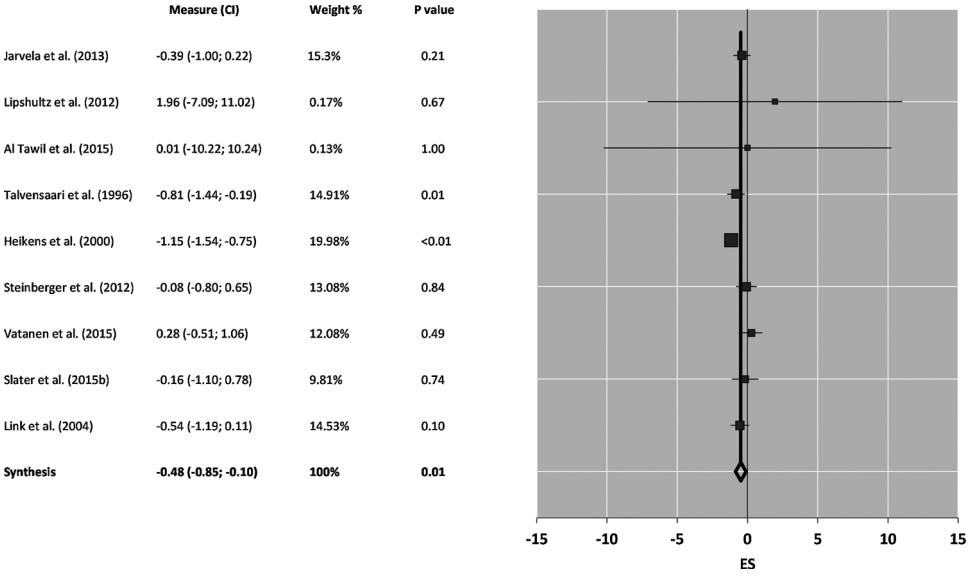

Fig. 4. Differences between childhood cancer survivors and controls for HDL-cholesterol. Abbreviation: HDL, high-density lipoprotein.

best of our knowledge, this is the first meta-analysis compiling CCS data for different health-related endpoints, including cardiac and pulmonary function, body composition, metabolic syndrome indicators, biochemical parameters, fatigue, mental health, and physical capacity-related variables.

Anti-cancer treatments are associated with long-term health complications known as late effects (Lipshultz et al., 1991; Oeffinger et al., 2000). For instance, anthracycline-based chemotherapy is a major cause of cardiotoxicity even years after the end of treatment (Christiansen et al., 2016a; Toro-Salazar et al., 2013), and treatment-related cardiac death is the leading non-malignant cause of death among CCS (Mertens et al., 2008). In this regard, our results show that CCS have a lower LVEF and FS as compared with their healthy peers, whether or not the former had received anthracyclines. Further, these patients present a higher waist-to-hip ratio, which has been identified as a surrogate marker of central fat in children (Santos et al., 2018), and

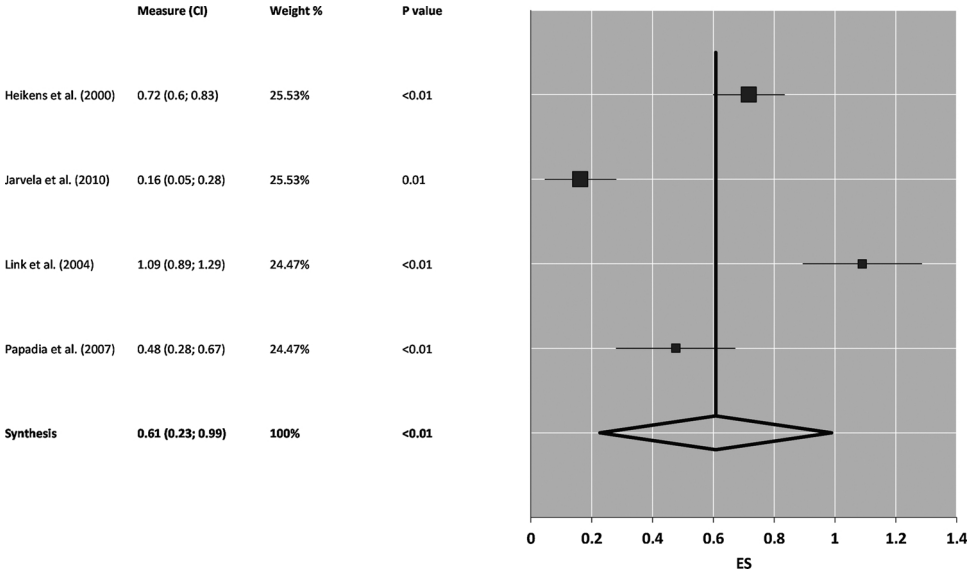

Fig. 5. Differences between childhood cancer survivors and controls for waist-to-hip ratio.

is related to a higher risk of cardiac events and mortality (Rost et al., 2018; Streng et al., 2018). We also found lower levels of HDL-cholesterol in the CCS group, which is a strong and independent risk factor for cardiovascular disease (Orozco-Beltran et al., 2017) due in part to the atheroprotective function of HDL particles (Kontush, 2014). Overall, our results suggest that CCS have a worse cardiometabolic health status than their healthy peers with no history of cancer, which highlights the importance of long-term monitoring (*i.e.*, not only during treatment but also after the end of it) in this patient population. In this regard, current clinical practice includes echocardiographic screening after treatment completion. The Children's Oncology Group Long-Term Follow-up Guidelines recommend lifelong cardiac screening for CCS to identify anthracycline-related cardiotoxicity (Landier et al., 2004), which should be performed once every 1–5 years depending on several risk factors such as treatment, age, lifetime anthracycline dose, and radiotherapy exposure (Childrenös Oncology Group, 2013).

It is important to note, however, that although cardiometabolic health was poorer in CCS, the mean values for the related endpoints in the meta-analysed studies were within non-pathological limits (*i.e.*, above the lower reference limits in the general population for LVEF [55%], FS [27%] and HDL-cholesterol [40 mg/dL], and below those for waist-to-hip ratio [94 for men and 80 for women, respectively]). This might reflect the progresses made in cancer treatments, not only with regard to improved survival, but also attending to the severity of late adverse effects. Still, our findings reinforce the need for implementing preventive interventions to reduce cardiovascular morbimortality risk in CCS.

In this context, data from preclinical models have demonstrated the cardioprotective effects of exercise against anthracycline-induced cardiotoxicity (Ascensão et al., 2005; Chicco et al., 2005; Parry and Hayward, 2015), but the evidence in humans after cancer diagnosis remains sparse (Scott et al., 2018). However, there is meta-analytic evidence showing that physical exercise exerts a beneficial effect on CRF in CCS (Bourdon et al., 2018), which is a valid predictor of overall mortality and cardiovascular risk (Kodama et al., 2009). Moreover, exercise interventions have been proven to increase HDL-cholesterol levels and to decrease the waist-to-hip ratio in both children and adults (Eddolls et al., 2017; Friedenreich et al., 2015; Lin et al., 2015; van Biljon et al., 2018). Accordingly, regular physical exercise is a potential lifestyle intervention in this population.

Although the risk of bias of the included studies was overall low, a limitation of the present work is the heterogeneity in the characteristics of the populations included (different ages, cancer types, treatments and times since diagnosis and since end of treatment). In this regard, differences in age and stage of disease at diagnosis, as well as in race and cancer type are associated with the prognosis of the disease (Kahn et al., 2016; La Quaglia et al., 1994; Perkins et al., 2014; Tai et al., 2010; Wang et al., 2016; Youlden et al., 2019). Thus, the meta-analytical approach used here did not allow for the precise assessment of exposures. However, we compared CCS who had received anthracyclines (for seven variables [LVEF, FS, systolic and diastolic BP, resting heart rate, BMI and CRF]) or radiotherapy (for four variables [systolic and diastolic BP, resting heart rate and lean body mass]) *versus* their controls when possible. Likewise, we compared CCS who had received anthracyclines or not (for a variable [BMI]) or radiotherapy or not (for two variables [BMI and fat mass, with the latter being cranial radiotherapy in all CCS who had been treated with radiotherapy]) *versus* their controls when possible. On the other hand, the design of the vast majority of included studies did not allow for a separate outcome analysis by cancer type as they usually assessed CCS of different types of cancer with no specific analysis by tumor type. Further, one of the greatest difficulties we found is that several studies did not report the data needed to be included in the meta-analysis, and although we contacted the authors to solve this problem, not all of them answered. In turn, a major strength of our meta-analysis is that it is the first to analyze the health status of CCS from an integrative perspective, combining numerous health indicators (including cardiometabolic, body composition, physical capacity or mental outcomes among others). Further, this is the first meta-analysis showing that CCS present with an altered lipid profile (at least in part, *i.e.,* lower HDL-cholesterol levels) and greater central obesity compared with their healthy counterparts with no prior history of cancer. In addition, we did not include studies in which CCS were compared to normative reference values (obtained from other studies and in some cases with different assessment techniques), which we also consider a methodological strength of our study.

In conclusion, CCS present with a lower LVEF, higher levels of a central adiposity indicator and lower HDL-cholesterol values compared with their healthy counterparts, all of which are potentially associated with a worse cardiovascular risk. These results reinforce the need to implement preventive lifestyle interventions (particularly physical activity) and to develop long-term monitoring units to detect late complications in this patient population.

Funding source

This work was supported by the Spanish Ministry of Education, Culture and Sport (contract number FPU14/03435 and FPU16/03956 to JSM and CRC, respectively); University of Alcalá (contract number FPI2016to PLV]; Universidad Europea de Madrid [2017/UEM14 and 2018/UEM02); Cátedra Real Madrid–Universidad Europea (2017/RM05); the Spanish Ministry of Economy and Competitiveness (Fondo de Investigaciones Sanitarias and Fondos FEDER, grant numbers PI15/00558 and PI18/00139 to Lucia), the Spanish Ministry of Economy and Competitiveness (Miguel Servet research contract [ref. # CP18/00034 to Fiuza-Luces], 'Fundación Unoentrecienmil' and 'Fundación MAPFRE' (Convocatoria Ignacio H. de Larramendi).

Declaration of Competing Interest

The authors report no conflict of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.critrevonc.2019.07.008.

References

Adams, M.J., Lipsitz, S.R., Colan, S.D., Tarbell, N.J., Treves, S.T., Diller, L., Greenbaum, N., Mauch, P., Lipshultz, S.E., 2004. Cardiovascular status in long-term survivors of Hodgkin's disease treated with chest radiotherapy. J Clin. Oncol. 22 (15), 3139–3148.

Akyay, A., Olcay, L., Sezer, N., Atay Sönmez, Ç., 2014. Muscle strength, motor performance, cardiac and muscle biomarkers in detection of muscle side effects during and after acute lymphoblastic leukemia treatment in children. J Pediatr Hematol Oncol. 36 (8), 594–598.

Alehan, D., Sahin, M., Varan, A., Yıldırım, I., Küpeli, S., Büyükpamukçu, M., 2012. Tissue Doppler evaluation of systolic and diastolic cardiac functions in long-term survivors of Hodgkin lymphoma. Pediatr Blood Cancer 58 (2), 250–255.

Al-Tawil, M.M., Shoeeb, A.S., Abbas, A., El-Tawil, A., El-Sayed, M.H., 2015. Lipid profile and hepatic steatosis in hepatitis C infected egyptian survivors of childhood cancer. Pediatr Hematol Oncol. 32 (1), 70–77.

Altman, D., Bland, J., 2005. Stand. Deviations Stand. Errors. BMJ 331 (7521), 903.

Armstrong, G.T., Kawashima, T., Leisenring, W., Stratton, K., Stovall, M., Hudson, M.M., Sklar, C.A., Robison, L.L., Oeffinger, K.C., 2014. Aging and risk of severe, disabling, life-threatening, and fatal events in the childhood cancer survivor study. J Clin. Oncol. 32 (12), 1218–1227.

Ascensão, A., Magalhães, J., Soares, J., Ferreira, R., Neuparth, M., Marques, F., Oliveira, J., Duarte, J., 2005. Endurance training attenuates doxorubicin-induced cardiac oxidative damage in mice. Int. J Cardiol. 100 (3), 451–460.

Bax, L., Yu, L.M., Ikeda, N., Tsuruta, H., Moons, K.G., 2006. Development and validation of MIX: comprehensive free software for meta-analysis of causal research data. BMC Med. Res. Methodol. 6, 50.

Bell, W., Warner, J.T., Evans, W.D., Webb, D.K., Mullen, R.H., Gregory, J.W., 2006. Perception of effort at low and moderate intensity exercise in survivors of childhood acute lymphoblastic leukaemia. Ann. Hum. Biol 33 (3), 357–371.

Beulertz, J., Bloch, W., Prokop, A., Rustler, V., Fitzen, C., Herich, L., Streckmann, F., Baumann, F.T., 2016. Limitations in ankle dorsiflexion range of motion, gait, and walking efficiency in childhood cancer survivors. Cancer Nurs. 39 (2), 117–124.

Bianco, A., Patti, A., Thomas, E., Palma, R., Maggio, M.C., Paoli, A., Palma, A., 2014. Evaluation of fitness levels of children with a diagnosis of acute leukemia and lymphoma after completion of chemotherapy and autologous hematopoietic stem cell transplantation. Cancer Med. 3 (2), 385–389.

Bourdon, A., Grandy, S.A., Keats, M.R., 2018. Aerobic exercise and cardiopulmonary fitness in childhood cancer survivors treated with a cardiotoxic agent: a meta-analysis. Support Care Cancer 26 (7), 2113–2123.

Brennan, B.M., Mughal, Z., Roberts, S.A., Ward, K., Shalet, S.M., Eden, T.O., Will, A.M., Stevens, R.F., Adams, J.E., 2005. Bone mineral density in childhood survivors of acute lymphoblastic leukemia treated without cranial irradiation. J Clin. Endocrinol. Metab. 90 (2), 689–694.

Brinkman, T.M., Li, C., Vannatta, K., Marchak, J.G., Lai, J.S., Prasad, P.K., Kimberg, C., Vuotto, S., Di, C., Srivastava, D., Robison, L.L., Armstrong, G.T., Krull, K.R., 2016. Behavioral, social, and emotional symptom comorbidities and profiles in adolescent survivors of childhood cancer: A report from the childhood cancer survivor study. J Clin. Oncol. 34 (28), 3417–3425.

Burdach, S.E.G., Westhoff, M.A., Steinhauser, M.F., Debatin, K.M., 2018. Precision medicine in pediatric oncology. Mol. Cell. Pediatr 5 (1), 6.

Cantrell, M.A., Posner, M.A., 2014. Psychological distress between young adult female survivors of childhood cancer and matched female cohorts surveyed in the adolescent health study. Cancer Nurs. 37 (4), 271–277.

Cella, D., Lai, J.S., Chang, C.H., Peterman, A., Slavin, M., 2002. Fatigue in cancer patients compared with fatigue in the general United States population. Cancer 94 (2), 528–538.

Chicco, A.J., Schneider, C.M., Hayward, R., 2005. Voluntary exercise protects against acute doxorubicin cardiotoxicity in the isolated perfused rat heart. Am J Physiol Regul. Integr. Comp. Physiol 289 (2), R424–R431.

Children's Oncology Group, 2013. Long-Term Follow-up Guidelines for Survivors of Childhood, Adolescent and Young Adult Cancers Version 4.0 (Accessed June 29, 2019 2019). http://www.survivorshipguidelines.org/.

Christiansen, J.R., Hamre, H., Massey, R., Dalen, H., Beitnes, J.O., Fosså, S.D., Kiserud, C.E., Aakhus, S., 2014. Left ventricular function in long-term survivors of childhood lymphoma. Am J Cardiol. 114 (3), 483–490.

Christiansen, J.R., Massey, R., Dalen, H., Kanellopoulos, A., Hamre, H., Fosså, S.D., Ruud, E., Kiserud, C.E., Aakhus, S., 2016a. Utility of global longitudinal strain by echocardiography to detect left ventricular dysfunction in Long-term adult survivors of childhood lymphoma and acute lymphoblastic leukemia. Am J Cardiol. 118 (3), 446–452.

Christiansen, J.R., Massey, R., Dalen, H., Kanellopoulos, A., Hamre, H., Ruud, E., Kiserud, C.E., Fosså, S.D., Aakhus, S., 2016b. Right ventricular function in long-term adult survivors of childhood lymphoma and acute lymphoblastic leukaemia. Eur Heart J Cardiovasc. Imaging 17 (7), 735–741.

De Caro, E., Fioredda, F., Calevo, M.G., Smeraldi, A., Saitta, M., Hanau, G., Faraci, M., Grisolia, F., Dini, G., Pongiglione, G., Haupt, R., 2006. Exercise capacity in apparently healthy survivors of cancer. Arch Dis. Child. 91 (1), 47–51.

De Caro, E., Smeraldi, A., Trocchio, G., Calevo, M., Hanau, G., Pongiglione, G., 2011. Subclinical cardiac dysfunction and exercise performance in childhood cancer survivors. Pediatr Blood Cancer 56 (1), 122–126.

Dietz, A.C., Chen, Y., Yasui, Y., Ness, K.K., Hagood, J.S., Chow, E.J., Stovall, M., Neglia, J.P., Oeffinger, K.C., Mertens, A.C., Robison, L.L., Armstrong, G.T., Mulrooney, D.A., 2016. Risk and impact of pulmonary complications in survivors of childhood cancer: A report from the childhood cancer survivor study. Cancer 122 (23), 3687–3696.

Eddolls, W.T.B., McNarry, M.A., Stratton, G., Winn, C.O.N., Mackintosh, K.A., 2017. High-intensity interval training interventions in children and adolescents: A systematic review. Sports Med. 47 (11), 2363–2374.

Elbl, L., Hrstkova, H., Chaloupka, V., Novotny, J., Michalek, J., 2003. The evaluation of left ventricular function in childhood cancer survivors by pharmacological stress echocardiography. Neoplasma 50 (3), 191–197.

Elbl, L., Hrstkova, H., Tomaskova, I., Michalek, J., 2006. Late anthracycline cardiotoxicity protection by dexrazoxane (ICRF-187) in pediatric patients: echocardiographic follow-up. Support Care Cancer 14 (2), 128–136.

Esbenshade, A.J., Sopfe, J., Zhao, Z., Li, Z., Campbell, K., Simmons, J.H., Friedman, D.L., 2014. Screening for vitamin D insufficiency in pediatric cancer survivors. Pediatr Blood Cancer 61 (4), 723–728.

Follin, C., Link, K., Wiebe, T., Moëll, C., Björk, J., Erfurth, E.M., 2011. Bone loss after childhood acute lymphoblastic leukaemia: an observational study with and without GH therapy. Eur J Endocrinol. 164 (5), 695–703.

Friedenreich, C.M., Neilson, H.K., O'Reilly, R., Duha, A., Yasui, Y., Morielli, A.R., Adams, S.C., Courneya, K.S., 2015. Effects of a high vs moderate volume of aerobic exercise on adiposity outcomes in postmenopausal women: A randomized clinical trial. JAMA Oncol. 1 (6), 766–776.

Frisk, P., Rössner, S.M., Norgren, S., Arvidson, J., Gustafsson, J., 2011. Glucose metabolism and body composition in young adults treated with TBI during childhood. Bone Marrow Transpl. 46 (10), 1303–1308.

Frisk, P., Arvidson, J., Hedenström, H., 2012a. A longitudinal study of pulmonary function after stem cell transplantation, from childhood to young adulthood. Pediatr Blood Cancer 58 (5), 775–779.

Frisk, P., Arvidson, J., Larsson, M., Naessén, T., 2012b. Risk factors for cardiovascular disease are increased in young adults treated with stem cell transplantation during childhood. Pediatr Transpl. 16 (4), 385–391.

Frisk, P., Arvidson, J., Ljunggren, O., Gustafsson, J., 2012c. Decreased bone mineral density in young adults treated with SCT in childhood: the role of 25-hydroxyvitamin D. Bone Marrow Transpl. 47 (5), 657–662.

Ganame, J., Claus, P., Uyttebroeck, A., Renard, M., D'hooge, J., Bijnens, B., Sutherland, G.R., Eyskens, B., Mertens, L., 2007. Myocardial dysfunction late after low-dose anthracycline treatment in asymptomatic pediatric patients. J Am Soc. Echocardiogr. 20 (12), 1351–1358.

Garmey, E.G., Liu, Q., Sklar, C.A., Meacham, L.R., Mertens, A.C., Stovall, M.A., Yasui, Y., Robison, L.L., Oeffinger, K.C., 2008. Longitudinal changes in obesity and body mass index among adult survivors of childhood acute lymphoblastic leukemia: a report from the childhood cancer survivor study. J Clin. Oncol. 26 (28), 4639–4645.

Genberg, M., Öberg, A., Andrén, B., Hedenström, H., Frisk, P., Flachskampf, F.A., 2015. Cardiac function after hematopoietic cell transplantation: an echocardiographic cross-sectional study in young adults treated in childhood. Pediatr Blood Cancer 62 (1), 143–147.

Gilsanz, V., Carlson, M.E., Roe, T.F., Ortega, J.A., 1990. Osteoporosis after cranial irradiation for acute lymphoblastic leukemia. J Pediatr 117 (2 Pt 1), 238–244.

Guler, E., Col, N., Buyukcelik, M., Balat, A., 2018. Prevalence of hypertension determined by ambulatory blood pressure monitoring (ABPM) and body composition in long-term survivors of childhood cancer. Pediatr Hematol Oncol. 35 (1), 1–10.

Yu, H.K., Yu, W., Cheuk, D.K., Wong, S.J., Chan, G.C., Cheung, Y.F., 2013. New three-

dimensional speckle-tracking echocardiography identifies global impairment of left ventricular mechanics with a high sensitivity in childhood cancer survivors. J Am Soc. Echocardiogr. 26 (8), 846–852.
Hartman, A., Pluijm, S.M.F., Wijnen, M., Neggers, S.J.C.M., Clemens, E., Pieters, R., van den Heuvel-Eibrink, M.M., 2018. Health-related fitness in very long-term survivors of childhood cancer: A cross-sectional study. Pediatr Blood Cancer 65 (4).
Hauser, M., Gibson, B.S., Wilson, N., 2001. Diagnosis of anthracycline-induced late cardiomyopathy by exercise-spiroergometry and stress-echocardiography. Eur J Pediatr 160 (10), 607–610.
Handbook for Systematic Reviews of Interventions of Cochrane, 2011. Obtaining standard errors from confidence intervals and P values: absolute (difference) measures. (Accessed 19 September 2018).
Hayden, J.A., van der Windt, D.A., Cartwright, J.L., Côté, P., Bombardier, C., 2013. Assessing bias in studies of prognostic factors. Ann. Intern. Med. 158 (4), 280–286.
Heikens, J., Ubbink, M.C., van der Pal, H.P., Bakker, P.J., Fliers, E., Smilde, T.J., Kastelein, J.J., Trip, M.D., 2000. Long term survivors of childhood brain cancer have an increased risk for cardiovascular disease. Cancer 88 (9), 2116–2121.
Hoffman, M.C., Mulrooney, D.A., Steinberger, J., Lee, J., Baker, K.S., Ness, K.K., 2013. Deficits in physical function among young childhood cancer survivors. J Clin. Oncol. 31 (22), 2799–2805.
Hozo, S., Djulbegovic, B., Hozo, I., 2005. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med. Res. Methodol. 5 (13).
Hudson, M.M., Oeffinger, K.C., Jones, K., Brinkman, T.M., Krull, K.R., Mulrooney, D.A., Mertens, A., Castellino, S.M., Casillas, J., Gurney, J.G., Nathan, P.C., Leisenring, W., Robison, L.L., Ness, K.K., 2015. Age-dependent changes in health status in the childhood cancer survivor cohort. J Clin. Oncol. 33 (5), 479–491.
Jain, S., Kapoor, G., Virmani, A., Bajpai, R., 2017. No impact of disease and its treatment on bone mineral density in survivors of childhood acute lymphoblastic leukemia. Pediatr Blood Cancer 64 (4).
Jarfelt, M., Kujacic, V., Holmgren, D., Bjarnason, R., Lannering, B., 2007. Exercise echocardiography reveals subclinical cardiac dysfunction in young adult survivors of childhood acute lymphoblastic leukemia. Pediatr Blood Cancer 49 (6), 835–840.
Jarfelt, M., Andersen, N.H., Glosli, H., Jahnukainen, K., Jónmundsson, G.K., Malmros, J., Nysom, K., Hasle, H., (NOPHO), N.S.o.P.H.a.O, 2016. Cardiac function in survivors of childhood acute myeloid leukemia treated with chemotherapy only: a NOPHO-AML study. Eur J Haematol. 97 (1), 55–62.
Järvelä, L.S., Niinikoski, H., Lähteenmäki, P.M., Heinonen, O.J., Kapanen, J., Arola, M., Kemppainen, J., 2010. Physical activity and fitness in adolescent and young adult long-term survivors of childhood acute lymphoblastic leukaemia. J Cancer Surviv. 4 (4), 339–345.
Järvelä, L.S., Niinikoski, H., Heinonen, O.J., Lähteenmäki, P.M., Arola, M., Kemppainen, J., 2013. Endothelial function in long-term survivors of childhood acute lymphoblastic leukemia: effects of a home-based exercise program. Pediatr Blood Cancer 60 (9), 1546–1551.
Järvelä, L.S., Saraste, M., Niinikoski, H., Hannukainen, J.C., Heinonen, O.J., Lähteenmäki, P.M., Arola, M., Kemppainen, J., 2016. Home-based exercise training improves left ventricle diastolic function in survivors of childhood ALL: A tissue doppler and velocity vector imaging study. Pediatr Blood Cancer 63 (9), 1629–1635.
Jenney, M.E., Faragher, E.B., Jones, P.H., Woodcock, A., 1995. Lung function and exercise capacity in survivors of childhood leukaemia. Med. Pediatr Oncol. 24 (4), 222–230.
Johnson, D., Perrault, H., Fournier, A., Leclerc, J.M., Bigras, J.L., Davignon, A., 1997. Cardiovascular responses to dynamic submaximal exercise in children previously treated with anthracycline. Am Heart J 133 (2), 169–173.
Kahn, J.M., Keegan, T.H., Tao, L., Abrahão, R., Bleyer, A., Viny, A.D., 2016. Racial disparities in the survival of American children, adolescents, and young adults with acute lymphoblastic leukemia, acute myelogenous leukemia, and Hodgkin lymphoma. Cancer 122 (17), 2723–2730.
Karakurt, C., Koçak, G., Ozgen, U., 2008. Evaluation of the left ventricular function with tissue tracking and tissue Doppler echocardiography in pediatric malignancy survivors after anthracycline therapy. Echocardiography 25 (8), 880–887.
Kazak, A.E., Derosa, B.W., Schwartz, L.A., Hobbie, W., Carlson, C., Ittenbach, R.F., Mao, J.J., Ginsberg, J.P., 2010. Psychological outcomes and health beliefs in adolescent and young adult survivors of childhood cancer and controls. J Clin Oncol 28 (12), 2002–2007.
Kenney, L.B., Nancarrow, C.M., Najita, J., Vrooman, L.M., Rothwell, M., Recklitis, C., Li, F.P., Diller, L., 2010. Health status of the oldest adult survivors of cancer during childhood. Cancer 116 (2), 497–505.
Klewer, S.E., Goldberg, S.J., Donnerstein, R.L., Berg, R.A., Hutter, J.J., 1992. Dobutamine stress echocardiography: a sensitive indicator of diminished myocardial function in asymptomatic doxorubicin-treated long-term survivors of childhood cancer. J Am Coll. Cardiol. 19 (2), 394–401.
Kodama, S., Saito, K., Tanaka, S., Maki, M., Yachi, Y., Asumi, M., Sugawara, A., Totsuka, K., Shimano, H., Ohashi, Y., Yamada, N., Sone, H., 2009. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. JAMA 301 (19), 2024–2035.
Kontush, A., 2014. HDL-mediated mechanisms of protection in cardiovascular disease. Cardiovasc. Res. 103 (3), 341–349.
La Quaglia, M.P., Heller, G., Ghavimi, F., Casper, E.S., Vlamis, V., Hajdu, S., Brennan, M.F., 1994. The effect of age at diagnosis on outcome in rhabdomyosarcoma. Cancer 73 (1), 109–117.
Landier, W., Bhatia, S., Eshelman, D.A., Forte, K.J., Sweeney, T., Hester, A.L., Darling, J., Armstrong, F.D., Blatt, J., Constine, L.S., Freeman, C.R., Friedman, D.L., Green, D.M., Marina, N., Meadows, A.T., Neglia, J.P., Oeffinger, K.C., Robison, L.L., Ruccione, K.S., Sklar, C.A., Hudson, M.M., 2004. 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. 22 (24), 4979–4990.
Landy, D.C., Miller, T.L., Lipsitz, S.R., Lopez-Mitnik, G., Hinkle, A.S., Constine, L.S., Adams, M.J., Lipshultz, S.E., 2013. Cranial irradiation as an additional risk factor for anthracycline cardiotoxicity in childhood cancer survivors: an analysis from the cardiac risk factors in childhood cancer survivors study. Pediatr Cardiol. 34 (4), 826–834.
Lanfranconi, F., Pollastri, L., Ferri, A., Fraschini, D., Masera, G., Miserocchi, G., 2014. Near infrared spectroscopy (NIRS) as a new non-invasive tool to detect oxidative skeletal muscle impairment in children survived to acute lymphoblastic leukaemia. PLoS One 9 (6), e99282.
Langeveld, N.E., Grootenhuis, M.A., Voûte, P.A., de Haan, R.J., van den Bos, C., 2003. No excess fatigue in young adult survivors of childhood cancer. Eur J Cancer 39 (2), 204–214.
Laufer, D., Ansermet, F., von der Weid, N., Beck Popovic, M., Torrisi, R., Pierrehumbert, B., 2012. Endocrine response and perceived stress test during an experimental challenge task in adult survivors of a childhood cancer. Pediatr Blood Cancer 59 (1), 138–143.
Li, V.W., Cheuk, D.K., Cheng, F.W., Yang, J.Y., Yau, J.P., Ho, K.K., Li, C.K., Li, R.C., Yuen, H.L., Ling, A.S., Chan, G.C., Cheung, Y.F., 2017. Myocardial stiffness as assessed by diastolic wall strain in adult survivors of childhood leukaemias with preserved left ventricular ejection fraction. Eur Heart J Cardiovasc. Imaging 18 (4), 451–458.
Lin, X., Zhang, X., Guo, J., Roberts, C.K., McKenzie, S., Wu, W.C., Liu, S., Song, Y., 2015. Effects of exercise training on cardiorespiratory fitness and biomarkers of cardiometabolic health: a systematic review and meta-analysis of randomized controlled trials. J Am Heart Assoc. 4 (7).
Link, K., Moëll, C., Garwicz, S., Cavallin-Ståhl, E., Björk, J., Thilén, U., Ahrén, B., Erfurth, E.M., 2004. Growth hormone deficiency predicts cardiovascular risk in young adults treated for acute lymphoblastic leukemia in childhood. J Clin. Endocrinol. Metab. 89 (10), 5003–5012.
Lipshultz, S.E., Colan, S.D., Gelber, R.D., Perez-Atayde, A.R., Sallan, S.E., Sanders, S.P., 1991. Late cardiac effects of doxorubicin therapy for acute lymphoblastic leukemia in childhood. N Engl. J Med. 324 (12), 808–815.
Lipshultz, S.E., Landy, D.C., Lopez-Mitnik, G., Lipsitz, S.R., Hinkle, A.S., Constine, L.S., French, C.A., Rovitelli, A.M., Proukou, C., Adams, M.J., Miller, T.L., 2012. Cardiovascular status of childhood cancer survivors exposed and unexposed to cardiotoxic therapy. J Clin. Oncol. 30 (10), 1050–1057.
Matthys, D., Verhaaren, H., Benoit, Y., Laureys, G., De Naeyer, A., Craen, M., 1993. Gender difference in aerobic capacity in adolescents after cure from malignant disease in childhood. Acta Paediatr. 82 (5), 459–462.
McKenzie, D., Coutts, K., Rogers, P., Jespersen, D., Pretula, A., 2000. Aerobic and anaerobic capacities of children and adolescents successfully treated for solid tumors. Clin. Exerc. Physiol 2 (1), 39–42.
Meacham, L.R., Sklar, C.A., Li, S., Liu, Q., Gimpel, N., Yasui, Y., Whitton, J.A., Stovall, M., Robison, L.L., Oeffinger, K.C., 2009. 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. 169 (15), 1381–1388.
Mendonça Monteiro de Barros, G., Madeira, M., Vieira Neto, L., de Paula Paranhos Neto, F., Carvalho Mendonça, L.M., Corrêa Barbosa Lima, I., Corbo, R., Fleiuss Farias, M.L., 2016. Bone mineral density and bone microarchitecture after long-term suppressive levothyroxine treatment of differentiated thyroid carcinoma in young adult patients. J Bone Min. Metab. 34 (4), 417–421.
Mertens, A.C., Liu, Q., Neglia, J.P., Wasilewski, K., Leisenring, W., Armstrong, G.T., Robison, L.L., Yasui, Y., 2008. Cause-specific late mortality among 5-year survivors of childhood cancer: the childhood cancer survivor study. J Natl. Cancer Inst. 100 (19), 1368–1379.
Miller, T.L., Lipsitz, S.R., Lopez-Mitnik, G., Hinkle, A.S., Constine, L.S., Adams, M.J., French, C., Proukou, C., Rovitelli, A., Lipshultz, S.E., 2010. Characteristics and determinants of adiposity in pediatric cancer survivors. Cancer Epidemiol Biomarkers Prev. 19 (8), 2013–2022.
Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., Group, P., 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin. Epidemiol 62 (10), 1006–1012.
Mostoufi-Moab, S., Ginsberg, J.P., Bunin, N., Zemel, B., Shults, J., Leonard, M.B., 2012. Bone density and structure in long-term survivors of pediatric allogeneic hematopoietic stem cell transplantation. J Bone Min. Res. 27 (4), 760–769.
Mulrooney, D.A., Ness, K.K., Neglia, J.P., Whitton, J.A., Green, D.M., Zeltzer, L.K., Robison, L.L., Mertens, A.C., 2008. Fatigue and sleep disturbance in adult survivors of childhood cancer: a report from the childhood cancer survivor study (CCSS). Sleep 31 (2), 271–281.
Nam, G.E., Kaul, S., Wu, Y.P., Nelson, R.E., Wright, J., Fluchel, M.N., Hacking, C.C., Kirchhoff, A.C., 2015. A meta-analysis of body mass index of adolescent and adult survivors of pediatric acute lymphoblastic leukemia. J Cancer Surviv. 9 (3), 412–421.
Ness, K.K., Leisenring, W.M., Huang, S., Hudson, M.M., Gurney, J.G., Whelan, K., Hobbie, W.L., Armstrong, G.T., Robison, L.L., Oeffinger, K.C., 2009. Predictors of inactive lifestyle among adult survivors of childhood cancer: a report from the childhood cancer survivor study. Cancer 115 (9), 1984–1994.
Ness, K.K., DeLany, J.P., Kaste, S.C., Mulrooney, D.A., Pui, C.H., Chemaitilly, W., Karlage, R.E., Lanctot, J.Q., Howell, C.R., Lu, L., Srivastava, D.K., Robison, L.L., Hudson, M.M., 2015. Energy balance and fitness in adult survivors of childhood acute lymphoblastic leukemia. Blood 125 (22), 3411–3419.

Öberg, A., Genberg, M., Malinovschi, A., Hedenström, H., Frisk, P., 2018. Exercise capacity in young adults after hematopoietic cell transplantation in childhood. Am J Transpl. 18 (2), 417–423.
Oeffinger, K.C., Eshelman, D.A., Tomlinson, G.E., Buchanan, G.R., Foster, B.M., 2000. Grading of late effects in young adult survivors of childhood cancer followed in an ambulatory adult setting. Cancer 88 (7), 1687–1695.
Oeffinger, K.C., Mertens, A.C., Sklar, C.A., Yasui, Y., Fears, T., Stovall, M., Vik, T.A., Inskip, P.D., Robison, L.L., Study, C.C.S., 2003. Obesity in adult survivors of childhood acute lymphoblastic leukemia: a report from the childhood cancer survivor study. J Clin. Oncol. 21 (7), 1359–1365.
Oeffinger, K.C., Mertens, A.C., Sklar, C.A., Kawashima, T., Hudson, M.M., Meadows, A.T., Friedman, D.L., Marina, N., Hobbie, W., Kadan-Lottick, N.S., Schwartz, C.L., Leisenring, W., Robison, L.L., Study, C.C.S., 2006. Chronic health conditions in adult survivors of childhood cancer. N Engl. J Med. 355 (15), 1572–1582.
Orozco-Beltran, D., Gil-Guillen, V.F., Redon, J., Martin-Moreno, J.M., Pallares-Carratala, V., Navarro-Perez, J., Valls-Roca, F., Sanchis-Domenech, C., Fernandez-Gimenez, A., Perez-Navarro, A., Bertomeu-Martinez, V., Bertomeu-Gonzalez, V., Cordero, A., Pascual de la Torre, M., Trillo, J.L., Carratala-Munuera, C., Pita-Fernandez, S., Uso, R., Durazo-Arvizu, R., Cooper, R., Sanz, G., Castellano, J.M., Ascaso, J.F., Carmena, R., Tellez-Plaza, M., Group, E.S., 2017. Lipid profile, cardiovascular disease and mortality in a mediterranean high-risk population: The ESCARVAL-RISK study. PLoS One 12 (10), e0186196.
Papadia, C., Naves, L.A., Costa, S.S., Vaz, J.A., Domingues, L., Casulari, L.A., 2007. Incidence of obesity does not appear to be increased after treatment of acute lymphoblastic leukemia in Brazilian children: role of leptin, insulin, and IGF-1. Horm Res. 68 (4), 164–170.
Parry, T.L., Hayward, R., 2015. Exercise training does not affect anthracycline antitumor efficacy while attenuating cardiac dysfunction. Am J Physiol Regul. Integr. Comp. Physiol 309 (6), R675–683.
Perkins, S.M., Shinohara, E.T., DeWees, T., Frangoul, H., 2014. Outcome for children with metastatic solid tumors over the last four decades. PLoS One 9 (7), e100396.
Petryk, A., Bergemann, T.L., Polga, K.M., Ulrich, K.J., Raatz, S.K., Brown, D.M., Robison, L.L., Baker, K.S., 2006. Prospective study of changes in bone mineral density and turnover in children after hematopoietic cell transplantation. J Clin. Endocrinol. Metab. 91 (3), 899–905.
Prasad, P.K., Hardy, K.K., Zhang, N., Edelstein, K., Srivastava, D., Zeltzer, L., Stovall, M., Seibel, N.L., Leisenring, W., Armstrong, G.T., Robison, L.L., Krull, K., 2015. Psychosocial and neurocognitive outcomes in adult survivors of adolescent and early Young adult cancer: A report from the childhood cancer survivor study. J Clin. Oncol. 33 (23), 2545–2552.
Recklitis, C.J., Parsons, S.K., Shih, M.C., Mertens, A., Robison, L.L., Zeltzer, L., 2006. Factor structure of the brief symptom inventory–18 in adult survivors of childhood cancer: results from the childhood cancer survivor study. Psychol Assess. 18 (1), 22–32.
Recklitis, C.J., Blackmon, J.E., Chang, G., 2017. Validity of the brief symptom inventory-18 (BSI-18) for identifying depression and anxiety in young adult cancer survivors: comparison with a structured clinical diagnostic interview. Psychol Assess. 29 (10), 1189–1200.
Robison, L.L., Hudson, M.M., 2014. Survivors of childhood and adolescent cancer: life-long risks and responsibilities. Nat. Rev. Cancer 14 (1), 61–70.
Rost, S., Freuer, D., Peters, A., Thorand, B., Holle, R., Linseisen, J., Meisinger, C., 2018. New indexes of body fat distribution and sex-specific risk of total and cause-specific mortality: a prospective cohort study. BMC Public. Health 18 (1), 427.
Ruble, K., Davis, C.L., Han, H.R., 2015. Endothelial health in childhood acute lymphoid leukemia survivors: pilot evaluation with peripheral artery tonometry. J Pediatr Hematol Oncol. 37 (2), 117–120.
Santos, S., Severo, M., Lopes, C., Oliveira, A., 2018. Anthropometric indices based on waist circumference as measures of adiposity in children. Obes. (Silver Spring) 26 (5), 810–813.
Scott, J.M., Nilsen, T.S., Gupta, D., Jones, L.W., 2018. Exercise therapy and cardiovascular toxicity in cancer. Circulation 137 (11), 1176–1191.
Slater, M.E., Ross, J.A., Kelly, A.S., Dengel, D.R., Hodges, J.S., Sinaiko, A.R., Moran, A., Lee, J., Perkins, J.L., Chow, L.S., Baker, K.S., Steinberger, J., 2015a. Physical activity and cardiovascular risk factors in childhood cancer survivors. Pediatr Blood Cancer 62 (2), 305–310.
Slater, M.E., Steinberger, J., Ross, J.A., Kelly, A.S., Chow, E.J., Koves, I.H., Hoffmeister, P., Sinaiko, A.R., Petryk, A., Moran, A., Lee, J., Chow, L.S., Baker, K.S., 2015b. Physical activity, fitness, and cardiometabolic risk factors in adult survivors of childhood cancer with a history of hematopoietic cell transplantation. Biol Blood Marrow Transpl. 21 (7), 1278–1283.
Smets, E.M., Visser, M.R., Willems-Groot, A.F., Garssen, B., Schuster-Uitterhoeve, A.L., de Haes, J.C., 1998. Fatigue and radiotherapy: (B) experience in patients 9 months following treatment. Br J Cancer 78 (7), 907–912.
Söntgerath, R., Eckert, K., 2015. Impairments of Lower extremity muscle strength and balance in childhood cancer patients and survivors: A systematic review. Pediatr Hematol Oncol. 32 (8), 585–612.
Steinberger, J., Sinaiko, A.R., Kelly, A.S., Leisenring, W.M., Steffen, L.M., Goodman, P., Mulrooney, D.A., Dietz, A.C., Moran, A., Perkins, J.L., Baker, K.S., 2012. Cardiovascular risk and insulin resistance in childhood cancer survivors. J Pediatr 160 (3), 494–499.
Streng, K.W., Voors, A.A., Hillege, H.L., Anker, S.D., Cleland, J.G., Dickstein, K., Filippatos, G., Metra, M., Ng, L.L., Ponikowski, P., Samani, N.J., van Veldhuisen, D.J., Zwinderman, A.H., Zannad, F., Damman, K., van der Meer, P., Lang, C.C., 2018. Waist-to-hip ratio and mortality in heart failure. Eur J Heart Fail. 20 (9), 1269–1277.
Stroup, D.F., Berlin, J.A., Morton, S.C., Olkin, I., Williamson, G.D., Rennie, D., Moher, D., Becker, B.J., Sipe, T.A., Thacker, S.B., 2000. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of observational studies in epidemiology (MOOSE) group. JAMA 283 (15), 2008–2012.
Sung, R.Y., Huang, G.Y., Shing, M.K., Oppenheimer, S.J., Li, C.K., Lau, J., Yuen, M.P., 1997. Echocardiographic evaluation of cardiac function in paediatric oncology patients treated with or without anthracycline. Int. J Cardiol. 60 (3), 239–248.
Tai, E., Pollack, L.A., Townsend, J., Li, J., Steele, C.B., Richardson, L.C., 2010. Differences in non-hodgkin lymphoma survival between young adults and children. Arch Pediatr Adolesc. Med. 164 (3), 218–224.
Talvensaari, K.K., Lanning, M., Tapanainen, P., Knip, M., 1996. Long-term survivors of childhood cancer have an increased risk of manifesting the metabolic syndrome. J Clin. Endocrinol. Metab. 81 (8), 3051–3055.
Terlou, A., Ruble, K., Stapert, A.F., Chang, H.C., Rowe, P.C., Schwartz, C.L., 2007. Orthostatic intolerance in survivors of childhood cancer. Eur J Cancer 43 (18), 2685–2690.
Tillmann, V., Darlington, A.S., Eiser, C., Bishop, N.J., Davies, H.A., 2002. Male sex and low physical activity are associated with reduced spine bone mineral density in survivors of childhood acute lymphoblastic leukemia. J Bone Min. Res. 17 (6), 1073–1080.
Toro-Salazar, O.H., Gillan, E., O'Loughlin, M.T., Burke, G.S., Ferranti, J., Stainsby, J., Liang, B., Mazur, W., Raman, S.V., Hor, K.N., 2013. Occult cardiotoxicity in childhood cancer survivors exposed to anthracycline therapy. Circ. Cardiovasc. Imaging 6 (6), 873–880.
Turner-Gomes, S.O., Lands, L.C., Halton, J., Hanning, R.M., Heigenhauser, G.J., Pai, M., Barr, R., 1996. Cardiorespiratory status after treatment for acute lymphoblastic leukemia. Med. Pediatr Oncol. 26 (3), 160–165.
van Biljon, A., McKune, A.J., DuBose, K.D., Kolanisi, U., Semple, S.J., 2018. Do short-term exercise interventions improve cardiometabolic risk factors in children? J Pediatr.
van Brussel, M., Takken, T., Lucia, A., van der Net, J., Helders, P.J., 2005. Is physical fitness decreased in survivors of childhood leukemia? A systematic review. Leukemia 19 (1), 13–17.
van Nimwegen, F.A., Schaapveld, M., Janus, C.P., Krol, A.D., Raemaekers, J.M., Kremer, L.C., Stovall, M., Aleman, B.M., van Leeuwen, F.E., 2014. Risk of diabetes mellitus in long-term survivors of hodgkin lymphoma. J Clin. Oncol. 32 (29), 3257–3263.
Vatanen, A., Sarkola, T., Ojala, T.H., Turanlahti, M., Jahnukainen, T., Saarinen-Pihkala, U.M., Jahnukainen, K., 2015. Radiotherapy-related arterial intima thickening and plaque formation in childhood cancer survivors detected with very-high resolution ultrasound during young adulthood. Pediatr Blood Cancer 62 (11), 2000–2006.
Yu, W., Li, S.N., Chan, G.C., Ha, S.Y., Wong, S.J., Cheung, Y.F., 2013. Transmural strain and rotation gradient in survivors of childhood cancers. Eur Heart J Cardiovasc. Imaging 14 (2), 175–182.
Wang, Y., Huang, J., Rong, L., Wu, P., Kang, M., Zhang, X., Lu, Q., Fang, Y., 2016. Impact of age on the survival of pediatric leukemia: an analysis of 15083 children in the SEER database. Oncotarget 7 (50), 83767–83774.
Ward, E., DeSantis, C., Robbins, A., Kohler, B., Jemal, A., 2014. Childhood and adolescent cancer statistics, 2014. CA Cancer J Clin. 64 (2), 83–103.
Warner, J.T., Bell, W., Webb, D.K., Gregory, J.W., 1997a. Relationship between cardiopulmonary response to exercise and adiposity in survivors of childhood malignancy. Arch Dis. Child. 76 (4), 298–303.
Warner, J.T., Cowan, F.J., Dunstan, F.D., Gregory, J.W., 1997b. The validity of body mass index for the assessment of adiposity in children with disease states. Ann. Hum. Biol 24 (3), 209–215.
Warner, J.T., Bell, W., Webb, D.K., Gregory, J.W., 1998. Daily energy expenditure and physical activity in survivors of childhood malignancy. Pediatr Res. 43 (5), 607–613.
Warner, J.T., Evans, W.D., Webb, D.K., Bell, W., Gregory, J.W., 1999. Relative osteopenia after treatment for acute lymphoblastic leukemia. Pediatr Res. 45 (4 Pt 1), 544–551.
Warner, J.T., Evans, W.D., Webb, D.K., Gregory, J.W., 2002. Body composition of long-term survivors of acute lymphoblastic leukaemia. Med. Pediatr Oncol. 38 (3), 165–172.
Warner, J.T., Evans, W.D., Webb, D.K., Gregory, J.W., 2004. Pitfalls in the assessment of body composition in survivors of acute lymphoblastic leukaemia. Arch Dis. Child. 89 (1), 64–68.
Wilson, C.L., Howell, C.R., Partin, R.E., Lu, L., Kaste, S.C., Mulrooney, D.A., Pui, C.H., Lanctot, J.Q., Srivastava, D.K., Robison, L.L., Hudson, M.M., Ness, K.K., 2018. Influence of fitness on health status among survivors of acute lymphoblastic leukemia. Pediatr Blood Cancer, e27286.
Wright, M.J., Halton, J.M., Martin, R.F., Barr, R.D., 1998. Long-term gross motor performance following treatment for acute lymphoblastic leukemia. Med. Pediatr Oncol. 31 (2), 86–90.
Wright, M.J., Halton, J.M., Barr, R.D., 1999. Limitation of ankle range of motion in survivors of acute lymphoblastic leukemia: a cross-sectional study. Med. Pediatr Oncol. 32 (4), 279–282.
Yildirim, A., Tunaoğlu, F.S., Pinarli, F.G., Ilhan, M., Oğuz, A., Karadeniz, C., Olguntürk, R., Oğuz, D., Kula, S., 2010. Tissue and flow myocardial performance index measurements taken during dobutamine stress echocardiography for early diagnosis of late anthracycline cardiotoxicity. Pediatr Cardiol. 31 (1), 96–105.
Youlden, D.R., Gupta, S., Frazier, A.L., Moore, A.S., Baade, P.D., Valery, P.C., Green, A.C., Aitken, J.F., 2019. stage at diagnosis for children with blood cancers in Australia: application of the Toronto paediatric cancer stage guidelines in a population-based national childhood cancer registry. Pediatr Blood Cancer 66 (6), e27683.
Zebrack, B.J., Zeltzer, L.K., Whitton, J., Mertens, A.C., Odom, L., Berkow, R., Robison,

L.L., 2002. Psychological outcomes in long-term survivors of childhood leukemia, Hodgkin's disease, and non-Hodgkin's lymphoma: a report from the childhood cancer survivor study. Pediatrics 110 (1 Pt 1), 42–52.
Zebrack, B.J., Gurney, J.G., Oeffinger, K., Whitton, J., Packer, R.J., Mertens, A., Turk, N., Castleberry, R., Dreyer, Z., Robison, L.L., Zeltzer, L.K., 2004. Psychological outcomes in long-term survivors of childhood brain cancer: a report from the childhood cancer survivor study. J Clin. Oncol. 22 (6), 999–1006.
Zebrack, B.J., Zevon, M.A., Turk, N., Nagarajan, R., Whitton, J., Robison, L.L., Zeltzer, L.K., 2007. Psychological distress in long-term survivors of solid tumors diagnosed in childhood: a report from the childhood cancer survivor study. Pediatr Blood Cancer 49 (1), 47–51.
Zeltzer, L., Lu, Q., Leisenring, W., Tsao, J., Recklitis, C., Armstrong, G., Mertens, A., Robison, L., Ness, K., 2008. Psychosocial outcomes and health-related quality of life in adult childhood cancer survivors: a report from the childhood cancer survivor study. Cancer Epidemiol Biomarkers Prev. 17 (2), 435–446.

Javier S. Morales, MSc, is a PhD candidate in exercise physiology and researcher at the European University of Madrid (Spain). His main research interest is the application of exercise physiology in cancer research (adults, adolescents and children in general).

Pedro L. Valenzuela, MSc, is a PhD candidate in exercise physiology and researcher in the Physiology Unit of Univerty of Alcalá (Spain). His main research interest is the application of exercise physiology in both clinical populations and athletes.

Cecilia Rincón-Castanedo, MSc, is a PhD candidate in physical activity and exercise and researcher at the European University of Madrid (Spain). His main research interest is the application of exercise physiology in cancer research (both human and childhood cancers in general, including animal models).

Alejandro Santos-Lozano, PhD. is the head of The Department of Health Sciences at European University Miguel de Cervantes, Valladolid, Spain. His main research area (+90 papers in peer-review journals) includes epidemiology and clinical aspects and benefits of physical activity (or 'exercise'); particularly in special population including cancer survivors.

Carmen Fiuza-Luces, PhD, works with a post-doctoral research contract at the Hospital 12 de Octubre ('i+12') Research Institute (Madrid, Spain). She is actively involved in cancer research (both human [leukemia] and childhood cancers in general, including animal models).

Alejandro Lucia, MD, PhD, is a professor in Exercise Physiology and senior researcher at the European University and Hospital 12 de Octubre ('i+12') Research Institute, both in Madrid, (Spain). His main research interests are exercise effects in disease conditions and populations, including childhood cancer survivors.