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Original Research

Prevalence, risk factors, and optimal way to determine overweight, obesity, and morbid obesity in the first Dutch cohort of 2338 long-term survivors of childhood cancer: a DCCSS-LATER study

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Abstract

Background: Overweight and obesity are common challenges among childhood cancer survivors. Overweight may be disguised, as survivors can have normal weight but high fat percentage (fat%) on dual-energy X-ray absorptiometry (DXA). We aimed to assess prevalence, identify determinants and biomarkers, and assess which method captures overweight best, in a nationwide cohort.

Methods: The prevalence of overweight and obesity, primarily defined by body mass index (BMI), was assessed in the DCCSS-LATER cohort of adult survivors treated from 1963-2002, with the LifeLines cohort as reference. The associations between risk factors and overweight metrics were investigated using logistic regression. Additional overweight metrics included DXA fat%, waist circumference (WC), waist/hip ratio (WHR), waist/height ratio (WHtR), and high-molecular-weight (HMW) adiponectin.

Results: A total of 2338 (mean age 35.5 years, follow-up 28.3 years) survivors participated. The overweight prevalence was 46.3% in men and 44.3% in women (obesity 11.2% and 15.9%, morbid obesity 2.4% and 5.4%), with highest rates among brain tumor survivors. Compared to controls, there was no overall increased overweight rate, but this was higher in women > 50 years, morbid obesity in men > 50 years. Overweight at cancer diagnosis (adjusted odds ratio [aOR] = 3.83, 95% CI 2.19-6.69), cranial radiotherapy (aOR = 3.21, 95% CI 1.99-5.18), and growth hormone deficiency (separate model, aOR = 1.61, 95% CI 1.00-2.59) were associated with overweight. Using BMI, WC, WHR, and WHtR, overweight prevalence was similar. Low HMW adiponectin, present in only 4.5% of survivors, was an insensitive overweight marker. Dual-energy X-ray absorptiometry–based classification identified overweight in an additional 30%, particularly after abdominal radiotherapy, total body irradiation, anthracyclines, and platinum.

Conclusions: Overweight occurs in almost half of long-term survivors. There was no overall increased incidence of overweight compared to controls. We identified factors associated with overweight, as well as subgroups of survivors in whom DXA can more reliably assess overweight.

Keywords: dual-energy X-ray absorptiometry, obesity, overweight, childhood cancer survivors, national cohort

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Significance

In the DCCSS-LATER cohort of 2338 adult survivors of childhood cancer, there was no overall increased overweight incidence compared to controls, but it was higher in women aged 50 years and older, as was morbid obesity incidence in men aged 50 years and older. Overweight at cancer diagnosis, cranial radiotherapy, and growth hormone deficiency were associated with overweight. Dual-energy X-ray absorptiometry–based classification identified overweight in an additional 30%, particularly after abdominal radiotherapy, total body irradiation, anthracyclines, and platinum.

Introduction

Although childhood cancer survival rates have increased impressively, excess treatment-related morbidity and mortality among childhood cancer survivors are observed.[1-3] Overweight and obesity are examples of long-term morbidity after treatment. These are components of metabolic syndrome and risk factors for diabetes mellitus, atherosclerotic disease, and consequent mortality.

While in the general population overweight is a common problem, among survivors, it is even more frequent. The reported prevalence of overweight (8.5%-40.7%) and obesity (1.4%-42%) in survivors varies due to different follow-up times, size, and selection of cohorts.[4-16] Except for Switzerland,[8] overweight prevalence has so far not been assessed in a nationwide, unselected cohort of survivors.

Risk factors for overweight in the general population are related to lifestyle (unhealthy diet, lack of exercise, and smoking) and genetic susceptibility.[17,18] Additionally, in survivors, increased overweight risk can be of endocrine origin: cranial and abdominal radiotherapy and alkylating chemotherapy can cause growth hormone deficiency (GHD), hypogonadism, and hypothyroidism.[4,7-10,19-22] Also, abdominal radiotherapy and stem cell transplantation (SCT) have been shown to be associated with an altered body composition, ie, increased abdominal fat.[23,24] For other potential risk factors, eg, corticosteroid use, study results are conflicting.[5,9,10,16] Lastly, survivors may experience visual, neurologic, or orthopedic problems causing decreased ability to exercise.

Overweight and obesity are mostly reported as high body mass index (BMI).[25] Body mass index can however underestimate the true adiposity status, or overestimate overweight in muscular people. Other overweight measurements include waist circumference (WC),[26-28] the ratio of waist to hip circumference (WHR),[28] and the ratio of waist to height (WHtR).[29] These methods involve easily performed assessments that are specifically directed at measuring abdominal fat, which in the general population correlates better with fat% than BMI.[26-28] Still, these methods are not ideal, and can be more challenging in survivors treated with abdominal radiotherapy, in whom due to tissue damage waist circumference does not reflect the total fat%.[23,30,31] Fat percentage (fat %) on dual-energy X-ray absorptiometry (DXA) is regarded as a more accurate method for overweight assessment,[32,33] but performing it as standard of care can be a logistic and financial challenge. Therefore, BMI is still the primary method to measure overweight in the current Dutch surveillance guideline for survivors. Serum adiponectin might serve as another overweight diagnostic. Low adiponectin is associated with overweight and higher intra-abdominal fat in the general population,[34] but studies on its diagnostic value for assessing overweight in survivors are lacking.[35] The underestimation of overweight in survivors who in fact may have an increased risk of developing subsequent health problems is a major challenge in surveillance of survivors and prohibits adequate counseling.

We studied overweight in the first treated Dutch national cohort of long-term survivors of childhood cancer, aiming to assess prevalence based on a nationwide survivor cohort and compare this to the general population, to further clarify risk factors for developing overweight, and to assess optimal overweight measurement methods for future survivor surveillance.

Methods

Study cohort

This study is part of the nationwide Dutch Childhood Cancer Survivor Study—Long Term Effects (DCCSS-LATER) study.[36,37] The national cohort of all adult survivors treated in a pediatric oncology center in The Netherlands between 1963 and 2002 was invited ($n = 4671$, Figure 1). This study was approved by the Amsterdam UMC Medical Research Ethics Committee, The Netherlands (toetsingonline.nl, NL32117.018.10). Written informed consent was obtained from all participants according to the declaration of Helsinki.

Reference cohort

Data on BMI from the Dutch LifeLines study cohort served as reference population.[38] This is a large 3-generational cohort of which we included all members aged between 18 and 65 years, without a history of cancer.

Data collection and definitions of overweight

An overview of definitions of outcomes and covariates is provided in Table S1. During a late effects clinic visit (2016-2020), height, weight (adjusted for amputation when applicable), and waist and hip circumference were measured. From this data, BMI, WHR, and WHtR were calculated. Total body DXA scans were performed in survivors < 40 years to measure fat% (converted to Hologic values when applicable). Overweight, obesity, and morbid obesity, as primarily defined by BMI, were defined as ≥25, ≥30, and ≥35 kg/m^2, respectively.[25] Thresholds for overweight for the other modalities were (in men/women) WC ≥ 94/≥80 cm[26] and ≥102/88 cm,[27] WHR ≥ 0.90/0.85,[28] WHtR ≥ 0.50/0.50,[29] and DXA fat% ≥ 25/30%.[39,40] During outpatient clinic visit, venous samples were drawn after overnight fasting, for assessment of high-molecular-weight (HMW) adiponectin and insulin-like growth factor 1 (IGF-1) levels. Smoking habits were collected in a questionnaire, and physical activity information was acquired with the SQUASH questionnaire. From the medical records, we extracted height and weight at cancer diagnosis to calculate BMI at diagnosis. If present, we also extracted data on GHD tests and treatment. Growth hormone deficiency was defined as either low IGF-1 and having had a brain tumor, cranial radiotherapy (CrRT), or total body irradiation

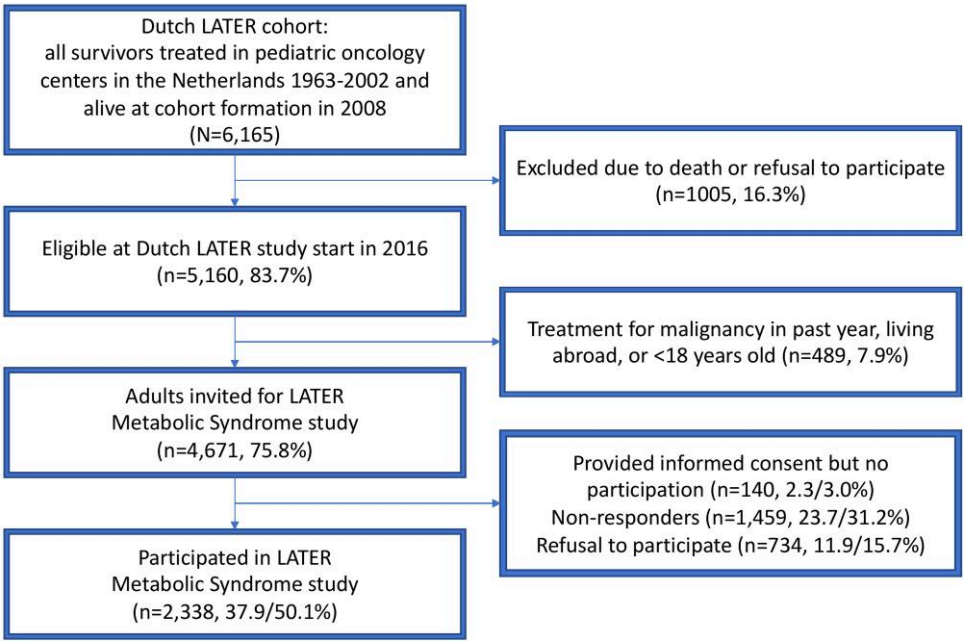

Figure 1. Flow chart of study participants. The current study used the cohort of the Metabolic Syndrome sub-study of the DCCSS-LATER study. This flow chart shows the number of participants in the current study and how they are embedded in the overall cohort. Percentages indicate the proportion of the overall cohort ($n = 6165$). In the lower 2 blocks, there are 2 percentages: the first indicates the proportion of the overall cohort, the second is the proportion of the invited survivors, indicating the (non-)participation rate. At formation in 2008, the entire survivors cohort contained 6165 eligible survivors. By mail, survivors were provided the option to opt-out of future study participation. At the start of the DCCSS-LATER study, the cleaned cohort was frozen in 2016, leaving 5160 subjects eligible. For the Metabolic Syndrome sub-study, only adults ($n = 4671$) were invited.

(TBI), or as diagnosed based on results of dynamic GHD tests in the past or treatment with growth hormone. Childhood cancer treatment data were collected on a national level in our central database.[41]

Statistical analysis

Analyses were conducted in R version 3.6.3 (R Foundation, Vienna, Austria).[42] Demographic and treatment characteristics were compared between participants and non-participants. Sex-specific prevalence of overweight, obesity, and morbid obesity in men and women was compared to that in the LifeLines reference population using (unadjusted) chi-squared or Fisher's exact test. Risk factors for these outcomes were assessed using logistic regression. Significant variables ($P < .05$) in univariable analysis and patient factors known to be relevant from literature (age, sex, smoking, physical activity) were included in the multivariable model. Multicollinearity was inspected with the variance inflation factor. As GHD is a potential mechanism for overweight caused by therapies, it was analyzed in a separate model. Sensitivity analyses were performed to inspect the role of missing data. The influence of overweight measurement methods was evaluated by assessing overweight prevalence according to each, and discrepancies were calculated with BMI < 25 kg/m^2 and high fat% as references. We studied what factors were associated with disguised overweight, in logistic regression models with all treatment groups as predictors.

Results

Study cohort description

In total, 2338 long-term survivors (52.1% male) participated (50.1% participation rate) (Figure 1, Table 1). Mean age was 35.5 (SD ±9.3) years, and mean follow-up time was 28.3 (±8.4) years. The most common childhood cancer diagnosis groups had been leukemias (35.5%), lymphomas (19.2%), renal tumors (11.5%), and central nervous system (CNS) tumors (9.1%). Participants had more often received cranial and abdominal radiotherapy, alkylating agents, anthracyclines, platinum derivatives, and vinca alkaloids (compared to non-responders ($n = 1599$) only, these data were unavailable for survivors who declined participation), but did not differ regarding age at diagnosis, treatment period, age at invitation, and follow-up time (Table S2).

The LifeLines reference cohort consisted of 132 150 subjects (58.6% female), with mean age of 42.0, SD ±11.0 years (Table S3).

Prevalence of overweight, obesity, and morbid obesity

Based on BMI values, overweight prevalence was 46.3% (males) and 44.3% (females), while in the LifeLines cohort, this was 60.8% and 47.4%, respectively (Table 1 and Table S3). For obesity, this was 11.2% and 15.9%, and for morbid obesity 2.4% and 5.4%, respectively. Compared to LifeLines, there was a higher overweight rate among women aged 50+ (68.7 vs 57.0%, $P = .032$) and a higher morbid obesity rate among men aged 50+ (6.7 vs 2.5%, $P = .040$) (Figure 2). Lower rates were observed for overweight in male survivors aged 30-40 (44.0 vs 56.3%, $P < .001$) and 40-50 (59.7 vs 66.9%, $P = .012$) and for obesity in male survivors aged 30-40 (8.5 vs 12.2%, $P = .019$).

Overweight was most common in survivors of a CNS tumor (52.3%), retinoblastoma (50.0%), and lymphomas (49.4%) (Figure S1). Obesity and morbid obesity rates were

Table 1. Baseline characteristics of the study cohort.

	Entire cohort	Male	Female	Comparison male vs female
Number of participants	2338	1198 (51.2%)	1140 (48.8%)	
–*Patient, cancer, and treatment characteristics*				
Age and follow-up time				
Age at clinic visit (years) (mean [SD])	35.5 (9.3)	35.5 (9.0)	35.5 (9.5)	0.87
Age at clinic visit categorized (years) (%)				0.77
18/30	728 (31.3)	371 (31.0)	357 (31.6)	
30/39	883 (38.0)	462 (38.7)	421 (37.2)	
40+	715 (30.7)	362 (30.3)	353 (31.2)	
Follow-up time (years) (mean [SD])	28.3 (8.4)	28.0 (8.2)	28.5 (8.7)	0.17
Follow-up time categorized (years) (%)				0.63
10/19	472 (20.2)	241 (20.1)	231 (20.3)	
20/29	928 (39.7)	489 (40.8)	439 (38.5)	
30/39	693 (29.6)	352 (29.4)	341 (29.9)	
40/49	220 (9.4)	103 (8.6)	117 (10.3)	
50/59	25 (1.1)	13 (1.1)	12 (1.1)	
Childhood cancer characteristics				**<0.001**
Childhood cancer diagnosis per ICCC-3 site group (%)				
1 Leukemias, myeloproliferative diseases, and myelodysplastic diseases	831 (35.5)	437 (36.5)	394 (34.6)	
2 Lymphomas and reticuloendothelial neoplasms	448 (19.2)	288 (24.0)	160 (14.0)	
3 CNS and miscellaneous intracranial and intraspinal neoplasms	213 (9.1)	107 (8.9)	106 (9.3)	
4 Neuroblastoma and other peripheral nervous cell tumors	135 (5.8)	44 (3.7)	91 (8.0)	
5 Retinoblastoma	11 (0.5)	5 (0.4)	6 (0.5)	
6 Renal tumors	269 (11.5)	111 (9.3)	158 (13.9)	
7 Hepatic tumors	18 (0.8)	9 (0.8)	9 (0.8)	
8 Bone tumors	136 (5.8)	63 (5.3)	73 (6.4)	
9 Soft tissue and other extraosseous sarcomas	167 (7.1)	93 (7.8)	74 (6.5)	
10 Germ cell tumors, trophoblastic tumors, and neoplasms of gonads	76 (3.3)	28 (2.3)	48 (4.2)	
11 Other malignant epithelial neoplasms and malignant melanomas	31 (1.3)	12 (1.0)	19 (1.7)	
12 Other and unspecified malignant neoplasms	3 (0.1)	1 (0.1)	2 (0.2)	
Age at diagnosis (years) (mean [SD])	6.71 (4.69)	6.90 (4.63)	6.51 (4.74)	**0.045**
Age at diagnosis categorized (years) (%)				0.14
0/5	1071 (45.8)	525 (43.8)	546 (47.9)	
5/10	651 (27.8)	347 (29.0)	304 (26.7)	
10/15	481 (20.6)	261 (21.8)	220 (19.3)	
15/18	135 (5.8)	65 (5.4)	70 (6.1)	
Treatment period (%)				0.15
1960/69	33 (1.4)	15 (1.3)	18 (1.6)	
1970/79	317 (13.6)	142 (11.9)	175 (15.4)	
1980/89	732 (31.3)	386 (32.2)	346 (30.4)	
1990/99	1013 (43.3)	528 (44.1)	485 (42.5)	
2000/09	243 (10.4)	127 (10.6)	116 (10.2)	
Height at cancer diagnosis (cm) (mean [SD])	120.4 (30.6)	122.0 (30.5)	118.6 (30.7)	**0.016**
Weight at cancer diagnosis (kg) (mean [SD])	25.6 (15.4)	26.1 (15.2)	25.1 (15.7)	0.16
BMI at cancer diagnosis (kg/m^2) (mean [SD])	16.22 (2.88)	16.14 (2.90)	16.30 (2.85)	0.26
Overweight at cancer diagnosis	116 (6.1)	51 (5.1)	65 (6.8)	0.11
Obesity at cancer diagnosis	22 (1.1)	12 (1.2)	10 (1.1)	0.75
Cancer treatment characteristics	432 (18.5)	239 (20.1)	193 (16.9)	0.053
Cranial radiotherapy (%)				
Cranial radiotherapy categorized (%)				**0.008**
No	1898 (81.6)	952 (80.1)	946 (83.2)	
1-25 Gy	204 (8.8)	100 (8.4)	104 (9.1)	
25+ Gy	223 (9.6)	136 (11.4)	87 (7.7)	
Total body irradiation	88 (3.8)	63 (5.3)	25 (2.2)	**<0.001**
Abdominal/pelvic radiotherapy (%)	201 (8.6)	84 (7.1)	117 (10.3)	**0.006**
Abdominal/pelvic radiotherapy categorized (%)				**0.006**
No	2126 (91.4)	1104 (93.0)	1022 (89.8)	
1-29 Gy	112 (4.8)	41 (3.5)	71 (6.2)	
30+ Gy	87 (3.7)	42 (3.5)	45 (4.0)	
Alkylating agents (CED) (%)	1175 (55.3)	648 (59.0)	527 (51.3)	**<0.001**
Cyclophosphamide equivalent dose categorized (%)				**0.001**
No	951 (44.7)	451 (41.0)	500 (48.7)	
1-4000 mg/m^2	445 (20.9)	229 (20.8)	216 (21.0)	

(*continued*)

Table 1. Continued

	Entire cohort	Male	Female	Comparison male vs female
4000-8000 mg/m^2	340 (16.0)	201 (18.3)	139 (13.5)	
8000+ mg/m^2	390 (18.3)	218 (19.8)	172 (16.7)	
Anthracyclines (DED) (%)	1172 (53.2)	635 (55.7)	537 (50.5)	**0.014**
Doxorubicin equivalent dose categorized (%)				**0.041**
No	1032 (46.8)	505 (44.3)	527 (49.5)	
Tertile 1 (range 9-138 mg/m^2)	391 (17.7)	200 (17.5)	191 (18.0)	
Tertile 2 (range 139-273 mg/m^2)	391 (17.7)	216 (18.9)	175 (16.4)	
Tertile 3 (range 275-1764 mg/m^2)	390 (17.7)	219 (19.2)	171 (16.1)	
Corticosteroids (SED) (%)	1190 (50.9)	675 (56.3)	515 (45.2)	**<0.001**
Steroid equivalent dose categorized (%)				**<0.001**
No	1148 (49.1)	523 (43.7)	625 (54.8)	
1-10 g/m^2	1083 (46.3)	598 (49.9)	485 (42.5)	
10+ g/m^2	107 (4.6)	77 (6.4)	30 (2.6)	
Asparaginase (%)	584 (25.0)	316 (26.4)	268 (23.6)	0.11
Platinum derivatives (%)	311 (13.3)	142 (11.9)	169 (14.9)	**0.03**
Vinca alkaloids (%)	1829 (78.3)	966 (80.7)	863 (75.8)	**0.004**
Amputation (%)	67 (2.9)	24 (2.0)	43 (3.8)	**0.010**
Amputation type				0.084
Elbow/upper arm	3 (0.1)	1 (0.1)	2 (0.2)	
Shoulder/scapula	4 (0.2)	3 (0.3)	1 (0.1)	
Ankle/lower leg	9 (0.4)	3 (0.3)	6 (0.5)	
Knee/upper leg	42 (1.8)	13 (1.1)	29 (2.5)	
Hip/pelvis	9 (0.4)	4 (0.3)	5 (0.4)	
Allogeneic SCT (%)	99 (4.3)	65 (5.4)	34 (3.0)	**0.004**
–Measurements assessed at clinic visit	173.6 (10.1)	179.5 (8.8)	167.2 (7.2)	**<0.001**
Physical examination				
Height (cm) (mean [SD])				
Weight (kg) (mean [SD])	76.1 (16.0)	81.1 (15.3)	70.8 (15.0)	**<0.001**
BMI (kg/m^2) (mean [SD])	25.20 (4.65)	25.10 (4.15)	25.30 (5.12)	0.33
BMI > 25 kg/m^2	1020 (45.3)	535 (46.3)	485 (44.3)	0.33
BMI > 30 kg/m^2	303 (13.5)	129 (11.2)	174 (15.9)	**0.001**
BMI > 35 kg/m^2	87 (3.9)	28 (2.4)	59 (5.4)	**<0.001**
Waist circumference (cm) (mean [SD])	87.2 (12.7)	89.8 (11.6)	84.5 (13.3)	**<0.001**
Hip circumference (cm) (mean [SD])	99.2 (10.3)	98.5 (8.8)	99.9 (11.7)	**0.001**
High waist circumference JIS	1040 (46.8)	382 (33.6)	658 (60.8)	**<0.001**
High waist circumference NCEP	543 (24.5)	159 (14.0)	384 (35.5)	**<0.001**
Waist hip ratio (mean [SD])	0.88 (0.09)	0.91 (0.07)	0.85 (0.09)	**<0.001**
High waist hip ratio	1082 (49.0)	608 (53.8)	474 (43.9)	**<0.001**
Waist height ratio (mean [SD])	0.50 (0.07)	0.50 (0.06)	0.51 (0.08)	0.087
High waist height ratio	1042 (47.0)	524 (46.1)	518 (47.9)	0.41
Mean systolic blood pressure (mmHg) (mean [SD])	124 (16)	126 (15)	121 (16)	**<0.001**
Mean diastolic blood pressure (mmHg) (mean [SD])	76 (10)	77 (11)	75 (10)	**<0.001**
Hypertension (%)	806 (36.1)	470 (41.2)	336 (30.8)	**<0.001**
DXA scan, laboratory, and questionnaire data	31.1 (7.7)	26.3 (5.3)	36.4 (6.2)	**<0.001**
Fat% on DXA scan (mean [SD])				
High fat% on DXA 25/30% (%)	1150 (70.4)	503 (58.4)	647 (83.7)	**<0.001**
High fat% on DXA Gallagher (%)	649 (39.7)	395 (45.9)	254 (32.9)	**<0.001**
High fat% on DXA Heo	346 (21.2)	206 (23.9)	140 (18.1)	**0.004**
Adiponectin (µg/mL) (mean [SD])	3.96 (2.31)	3.17 (1.78)	4.79 (2.50)	**<0.001**
Low adiponectin (%)	106 (4.5)	57 (4.8)	49 (4.3)	0.59
IGF-1 (nmol/L) (mean [SD])	24.40 (8.04)	24.86 (7.66)	23.91 (8.41)	**0.006**
Low IGF-1 (%)	27 (1.2)	15 (1.3)	12 (1.1)	0.67
Growth hormone deficiency (%)	116 (5.0)	55 (4.6)	61 (5.4)	0.40
Smoking (current or former) (%)	665 (32.5)	372 (35.4)	293 (29.4)	**0.003**
Minutes per week of moderate activity (median [IQR])	390 [135, 960]	450 [180, 1132.5]	352.50 [120, 845]	**<0.001**
Low physical activity (%)	436 (25.5)	191 (21.6)	245 (29.8)	**<0.001**

BMI was available for 2252 (96.3%) survivors, WC for 2220 (95.0%), WHR for 2210 (94.5%), and WHtR for 2218 (94.9%), a DXA scan was performed in 1652 (70.7%), and adiponectin was measured in 2219 (94.9%) survivors. Significant *P*-values (<0.05) are marked in bold.
Abbreviations: BMI, body mass index; IGF-1, insulin-like growth factor 1; ICCC-3, International Classification of Childhood Cancer, Third edition; CNS, central nervous system; SCT, stem cell transplantation; DXA, dual-energy X-ray absorptiometry.

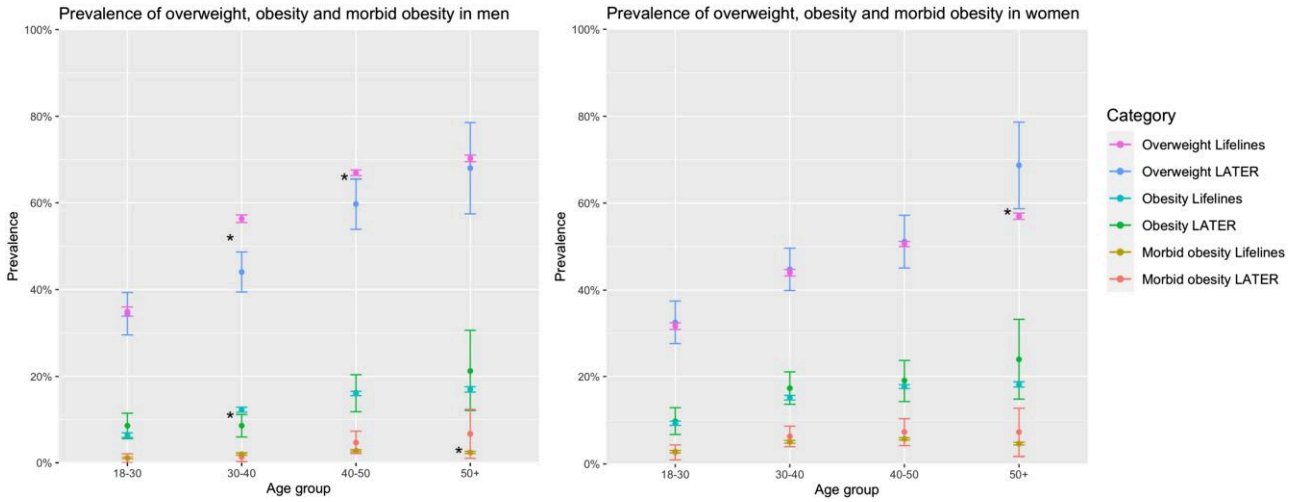

Figure 2. Comparison of overweight, obesity, and morbid obesity between our survivor cohort and the LifeLines control cohort. Prevalence of overweight (BMI > 25 kg/m^2), obesity (>30 kg/m^2), and morbid obesity (>35 kg/m^2) in the LATER study cohort and LifeLines control cohort in men and women. Significantly different proportions are indicated by an asterisk.

particularly high after CNS tumor (22.1% and 10.8%, respectively) and retinoblastoma (30.0% and 10.0%).

Risk factors for overweight, obesity, and morbid obesity

The strongest risk factor for overweight in univariable analysis was overweight at cancer diagnosis (odds ratio [OR] 3.16, 95% CI 2.08-4.79) (Table S4). CrRT was another risk factor, with stronger association for lower dose CrRT (OR for 1-25 Gy 3.58 [95% CI 2.60-4.94], for >25 Gy 1.75 [95% CI 1.31-2.34]) as was for GHD (OR 2.28, 95% CI 1.59-3.27). Corticosteroid use was not associated with overweight. In a sex-stratified analysis, we observed that treatment-related risk estimates were similar in men and women (data not shown).

In multivariable analysis, as shown in Table 2, risk factors for overweight were overweight at diagnosis (OR 3.83, 95% CI 2.19-6.69), CrRT 1-25 Gy (OR 3.21, 95% CI 1.99-5.18), and older age at clinic visit (OR 1.03, 95% CI 1.01-1.05 per year). In the separate model, GHD was also associated with overweight (OR 1.61, 95% CI 1.00-2.59).

Female sex, CrRT, and GHD were identified as independent risk factors for obesity and morbid obesity (Table S5). Inspection of variance inflation in all multivariable models suggested that multicollinearity was not present. Sensitivity analyses showed similar results (data not shown).

Assessment of overweight using different methods

In the overall cohort, BMI, WC (≥94/80 cm), WHR, and WHtR revealed an overweight prevalence in the range 45.3%-49.0% (Table S6). When stratified by sex, high WC was observed less in men (33.6%) and more in women (60.8%). High fat% on DXA identified overweight in 83.7% of women and 58.4% of men as well as in 77.7% of abdominally irradiated survivors. When using Gallagher's threshold for high fat%, higher prevalence was observed particularly in men (82.3%, and 66.1% in women). When using Heo's threshold, prevalence remained similar to BMI, WHR, and WHtR.

There were differences in the classification of overweight according to different methods. High WC was observed in 11.2% of survivors with normal BMI, high WHR in 18.8%, and high WHtR in 9.3%. Dual-energy X-ray absorptiometry identified an additional 31.6% survivors with normal BMI as overweight, and this was 39.3% in the abdominally irradiated group.

When compared to fat% on DXA scan, underestimation of overweight was comparable with BMI, WC, WHR, and WHtR for the whole cohort (range 29.9%-32.9%) (Figure 3). The BMI, WHR, and WHtR underestimated overweight more often in women (up to 47.4%). After abdominal irradiation, the percentage of underestimation of overweight was highest for the methods that use waist circumference (range 45.9%-63.1%).

Consequently, in the regression model with outcome underestimation of overweight with BMI (Table 3, Table S7), female sex was a strong risk factor (OR 3.02, 95% CI 2.27-4.03). Therapies significantly associated with underestimation were total body irradiation (TBI, OR 9.06, 95% CI 2.41-34.04) and anthracyclines (second tertile OR 1.57 [95% CI 1.02-2.24], a trend for the highest tertile 1.48 [95% CI 0.99-2.23]). Abdominal radiotherapy was a major risk factor for misclassification with the methods that use WC (for WC OR up to 3.06 [95% CI 1.64-5.72], data for WHR and WHtR were similar [data not shown]). In this model, anthracyclines (OR highest tertile 1.58, 95% CI 1.12-2.23) and platinum (OR 1.66, 95% CI 1.21-2.29) also emerged as independent risk factors.

Adiponectin as marker for overweight

Low HMW adiponectin was present in only 4.5% of survivors. Consequently, only 1.9% of survivors with normal BMI were additionally diagnosed as overweight (Table S6). Also, when compared to fat%, low adiponectin underestimated overweight in 66.1% of survivors, with higher rates in women (78.9%) and abdominally irradiated survivors (72.3%). Sensitivity and specificity for low adiponectin compared to high BMI were 6.2% and 96.5%, respectively. When compared to high fat% on DXA, sensitivity was 6.1% and specificity 97.1%.

Table 2. Multivariable logistic regression analysis of variables associated with overweight (body mass index ≥ 25 kg/m^2).

	Frequency of high BMI (*n* [%])	Multivariable model 1			Multivariable model 2		
		OR	95% CI	*P*-value	OR	95% CI	*P*-value
–*Patient characteristics*							
Age at clinic visit		1.03	1.01-1.05	**.006**	1.04	1.02-1.06	**<.001**
First tertile	258 (34.1%)						
Second tertile	326 (43.8%)						
Third tertile	435 (58.1%)						
Sex		0.88	0.69-1.13	.32	0.96	0.76-1.20	.70
Female	485 (44.3%)						
Male	535 (46.3%)						
Age at diagnosis		1.02	0.99-1.05	.27	1.00	0.98-1.03	.77
First tertile	299 (40.0%)						
Second tertile	340 (45.0%)						
Third tertile	381 (50.9%)						
Overweight at cancer diagnosis		3.83	2.19-6.69	**<.001**	3.44	2.04-5.78	**<.001**
Yes	80 (70.8%)						
No	782 (43.4%)						
Smoking (current or former)		1.26	0.97-1.63	.079	1.24	0.97-1.58	.086
Yes	338 (52.7%)						
No	590 (44.2%)						
Low physical activity		1.12	0.85-1.47	.42	1.14	0.88-1.48	.31
Yes	188 (44.8%)						
No	500 (40.3%)						
–*Treatment characteristics*							
Cranial radiotherapy							
Yes	260 (63.1%)						
No	755 (41.2%)						
Cranial radiotherapy categorized				**<.001**			
No	755 (41.2%)	Ref					
1-25 Gy	143 (71.5%)	3.21	1.99-5.18				
25+ Gy	114 (55.1%)	1.67	0.98-2.87				
Total body irradiation		0.39	0.12-1.31	.13			
Yes	12 (13.8%)						
No	1001 (46.5%)						
Abdominal/pelvic radiotherapy							
Yes	89 (44.5%)						
No	924 (45.2%)						
Abdominal/pelvic radiotherapy categorized							
No	924 (45.2%)						
1-29 Gy	52 (46.4%)						
30+ Gy	35 (41.4%)						
Alkylating agents (CED)							
Yes	477 (41.7%)						
No	431 (47.3%)						
Cyclophosphamide equivalent dose categorized				**.050**			
No	431 (47.3%)	Ref					
1-4000 mg/m^2	183 (42.3%)	0.99	0.73-1.35				
4000-8000 mg/m^2	140 (42.9%)	0.92	0.65-1.32				
8000+ mg/m^2	154 (40.1%)	0.62	0.44-0.88				
Corticosteroids							
Yes	536 (46.7%)						
No	484 (43.8%)						
Corticosteroids categorized							
No	484 (43.8%)						
0-10 g/m^2	490 (46.9%)						
10+ g/m^2	46 (44.2%)						
Allogeneic SCT		0.56	0.16-1.91	.35			
Yes	17 (17.7%)						
No	996 (46.5%)						
–*Comorbidity*							
Growth hormone deficiency					1.61	1.00-2.59	**.048**
Yes	88 (64.2%)						
No	932 (44.1%)						

Model 1: patient and cancer treatment characteristics. Model 2: patient characteristics and growth hormone deficiency. For variables with more than 2 categories, the overall *P*-value was calculated with the Wald test. Significant variables in univariable analysis and patient factors known to be relevant from literature (age, sex, smoking, physical activity) were included in the multivariable model. If for a treatment factor both the dichotomous and categorized variable were significant, only the latter was included. Significant *P*-values (<0.05) are marked in bold.
Abbreviations: CI, confidence interval; OR, odds ratio; Ref, reference; SCT, stem cell transplantation; BMI, body mass index.

Table 3. Multivariable logistic regression of factors associated with outcome false-negative classification of overweight based on body mass index and waist circumference, when compared to overweight based on fat% on dual-energy X-ray absorptiometry scan.

Dependent variable	Frequency of false-negative classification with BMI (*n* [%])	Outcome false-negative classification with BMI		
		Multivariable model		
		OR	95% CI	*P*-value
–Patient characteristics				
Age and sex				
Age at clinic visit		1	0.98-1.03	.74
First tertile	203 (32.2%)			
Second tertile	199 (31.9%)			
Third tertile	111 (29.9%)			
Sex		3.02	2.27-4.03	**<.001**
Female	327 (42.4%)			
Male	187 (21.9%)			
Weight at diagnosis		0.57	0.29-1.11	.098
Overweight at cancer diagnosis				
Yes	18 (21.4%)			
No	437 (32.6%)			
Lifestyle		0.95	0.70-1.29	.76
Smoking (current or former)				
Yes	128 (26.8%)			
No	321 (33.4%)			
Low physical activity		1.36	1.00-1.85	.052
Yes	143 (39.7%)			
No	323 (30.0%)			
–Treatment characteristics				
Cranial radiotherapy				
Yes	68 (26.8%)			
No	445 (32.6%)			
Cranial radiotherapy categorized				**.036**
No	445 (32.6%)		Ref	
1-25 Gy	28 (23.5%)		0.47	0.26-0.83
25+ Gy	39 (30.0%)		0.89	0.45-1.76
Total body irradiation		9.06	2.41-34.04	**.001**
Yes	42 (62.7%)			
No	471 (30.4%)			
Cyclophosphamide equivalent dose categorized				.55
No	188 (27.8%)		Ref	
1-4000 mg/m^2	114 (32.7%)		1.13	0.72-1.77
4000-8000 mg/m^2	76 (33.0%)		1.15	0.72-1.84
8000+ mg/m^2	103 (37.7%)		1.36	0.90-2.05
Doxorubicin equivalent dose categorized				.13
No	195 (27.9%)		Ref	
First tertile	86 (28.7%)		1.29	0.80-2.09
Second tertile	110 (35.8%)		1.57	1.02-2.42
Third tertile	100 (38.9%)		1.48	0.99-2.23
Platinum derivatives		1.35	0.89-2.04	.16
Yes	91 (37.6%)			
No	422 (30.5%)			
Allogeneic SCT		0.63	0.16-2.44	.5
Yes	42 (56.0%)			
No	469 (30.4%)			

Dependent variable	Frequency of false-negative classification with WC (*n* [%])	Outcome false-negative classification with WC		
		Multivariable model		
		OR	95% CI	*P*-value
–Patient characteristics				
Age at clinic visit		0.99	0.97-1.01	.28
First tertile	203 (32.2%)			
Second tertile	190 (30.5%)			
Third tertile	94 (25.6%)			
Age at diagnosis		0.97	0.94-1.00	**.023**
First tertile	184 (31.1%)			
Second tertile	179 (31.9%)			
Third tertile	124 (26.6%)			

(*continued*)

Table 3. Continued

Dependent variable	Frequency of false-negative classification with WC (*n* [%])	Outcome false-negative classification with WC		
		Multivariable model		
		OR	95% CI	*P*-value
–*Treatment characteristics*				
Total body irradiation		4.35	1.78-10.67	**<.001**
Yes	38 (56.7%)			
No	448 (29.1%)			
Abdominal/pelvic radiotherapy categorized				**<.001**
No	434 (29.0%)		Ref	
1-29 Gy	28 (43.1%)		2.05	1.17-3.56
30+ Gy	24 (52.2%)		3.06	1.64-5.72
Cyclophosphamide equivalent dose categorized				.71
No	171 (25.5%)		Ref	
1-4000 mg/m^2	106 (30.6%)		1.07	0.74-1.56
4000-8000 mg/m^2	85 (36.8%)		1.25	0.85-1.83
8000+ mg/m^2	94 (34.4%)		1.11	0.79-1.57
Doxorubicin equivalent dose categorized				**.049**
No	177 (25.5%)		Ref	
First tertile	89 (29.7%)		1.33	0.90-1.97
Second tertile	102 (33.7%)		1.43	0.99-2.05
Third tertile	99 (38.5%)		1.58	1.12-2.23
Platinum derivatives		1.66	1.21-2.29	**.002**
Yes	95 (39.4%)			
No	392 (28.5%)			
Allogeneic SCT		1.08	0.46-2.51	.86
Yes	37 (49.3%)			
No	447 (29.1%)			

For variables with more than 2 categories, the overall *P*-value was calculated with the Wald test. Significant variables in univariable analysis were included in the multivariable model. If for a treatment factor both the dichotomous and categorized variable were significant, only the latter was included. Significant *P*-values (<0.05) are marked in bold.
Abbreviations: CI, confidence interval; OR, odds ratio; Ref, reference; BMI, body mass index; SCT, stem cell transplantation; WC, waist circumference.

Discussion

This study shows that overweight (BMI ≥ 25 kg/m^2) occurs in almost half of all adult long-term childhood cancer survivors, and that associated factors include overweight at diagnosis, CrRT, and GHD. We also show that DXA scans identified overweight in an additional 30% of survivors not identified with conventional methods such as BMI and WC.

There was no overall increased overweight prevalence compared to the reference cohort. This may suggest that other factors, such as lifestyle, contribute to a high overweight prevalence in both cohorts. There was a significantly higher prevalence in our cohort for overweight among women aged 50+ and for morbid obesity among men aged 50+. Our findings may suggest that the increase in prevalence per age category is more pronounced in survivors than in the general population. This was particularly the case in women, among whom we also observed a higher incidence of increased WC. This may be partly attributed to loss of the protective effect against abdominal overweight prior to menopause. So, while aging, prevalence of overweight, obesity, and morbid obesity may be higher in survivors, increasing their risk of overweight-associated comorbidity and mortality. It could also be that this increase slows down later on, as was observed for cardiac disease in survivors.[43] Another potential reason for increased prevalence in the oldest age groups is that younger participants were treated more recently, and may therefore suffer from less treatment-related side effects. ALL is the most prevalent cancer type in this cohort. The use of prophylactic CrRT was reduced in the 1980-1990s with the introduction of the ALL-6 and ALL-9 protocols. Accordingly, ALL survivors who underwent CrRT are overrepresented among the oldest survivors in this study. Longitudinal follow-up is required to elucidate this.

The only other study so far on overweight in a heterogeneous nationwide survivor cohort, the Swiss Childhood Cancer Survivor Study ($n = 2365$), found a prevalence of 26% after 15 years, which was not different from sibling and general population controls.[8] The lower prevalence compared to our study might be due to the shorter follow-up (15 vs 28 years), since overweight prevalence increases with aging. The Childhood Cancer Survivor Study (CCSS)[7] and the St Jude Lifetime Cohort Study (SJLIFE)[9] had a comparable follow-up time (~24 years). Higher overweight rates in these studies seem in part to be due to an already higher general population overweight prevalence. The CCSS found no difference with siblings. In SJLIFE, the general population obesity prevalence was already twice as high as in our control group. Still, the authors observed more obesity among survivors (standardized morbidity ratio 1.14). It is clear that follow-up time and general population risk impede a full comparison between studies.

We observed that overweight prevalence was highest among survivors of CNS tumors, but differences between diagnosis groups were small. Obesity and morbid obesity prevalence was clearly higher after CNS tumors. This is in line with previous findings[8,12,13,44] and likely related to damage to the hypothalamus and pituitary gland due to tumor and treatment. Whereas other studies also observed a higher overweight prevalence after ALL,[5,10] we did not, as there was no excess overweight in ALL survivors unexposed to CrRT.

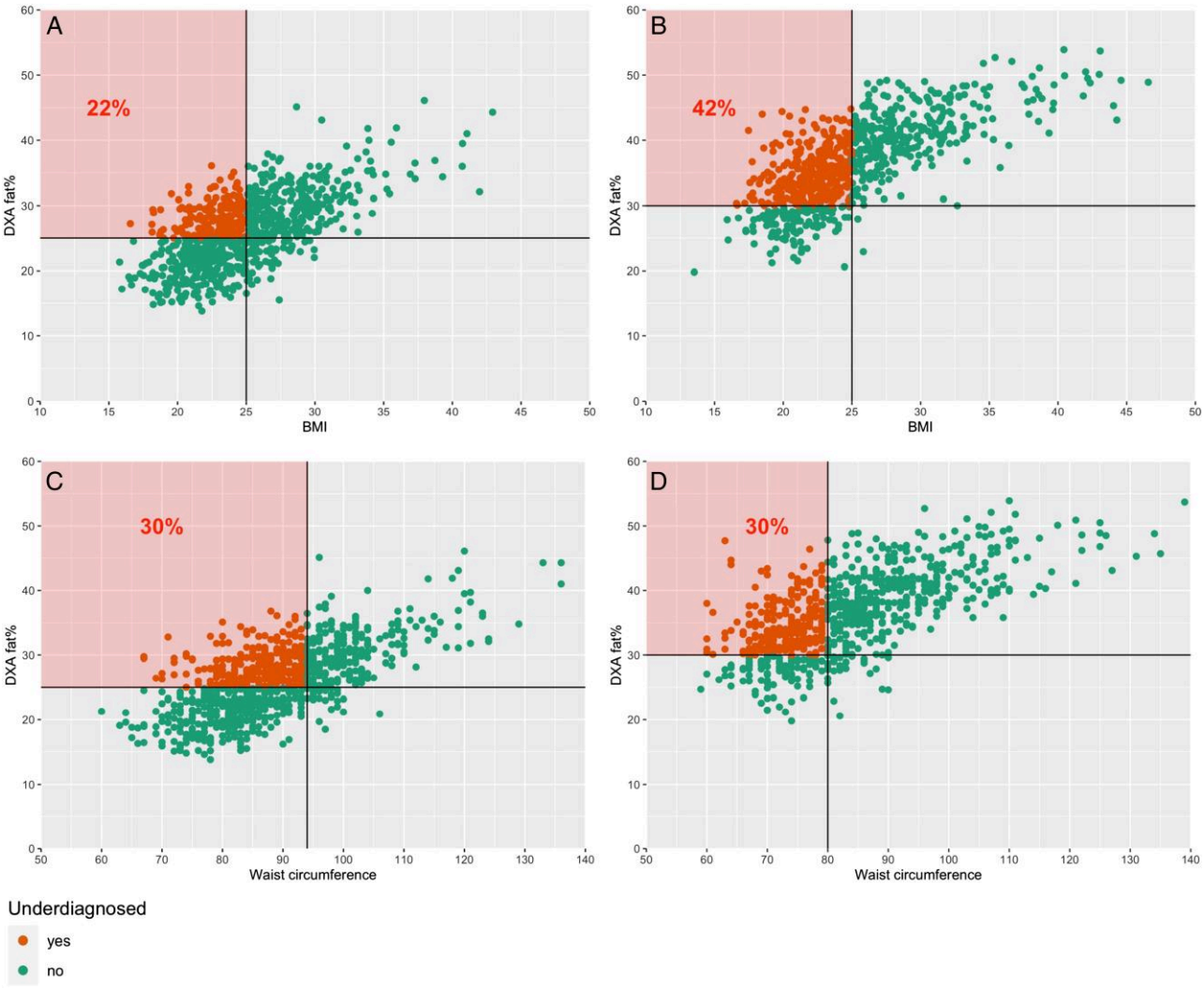

Figure 3. Comparison of overweight classification using BMI and waist circumference vs DXA scan. Underdiagnosis of overweight, when compared to fat percentage on DXA scan, with BMI in men (panel A) and in women (panel B), and with waist circumference in men (panel C) and in women (panel D). The upper-left square and percentage in each figure indicate the survivors with high fat percentage and normal waist circumference or BMI. DXA, dual-energy X-ray absorptiometry; BMI, body mass index.

We further explored the role of CrRT and confirmed the association with overweight, obesity, and morbid obesity, as has been reported multiple times.[7-11] In multivariable analysis, the effect of dosages < 25 Gy on overweight was stronger. This group most likely consists of survivors who received craniospinal radiotherapy. The higher dose group more likely received local radiotherapy to a brain tumor, with the exception of medulloblastoma and a few ALL survivors who received higher dose craniospinal radiation. In the low dose group, the hypothalamus and pituitary may therefore have been in the radiation field more often. Radiotherapy affects the somatotropic axis first, with GHD occurring from 15-20 Gy.[21,45,46] In our regression models, GHD was independently associated with overweight, obesity, and morbid obesity. Another potential mechanism is hypogonadism, which can occur after hypothalamic and gonadal radiation and alkylating chemotherapy.[21,47] Alkylating agents were no independent risk factor in our analysis. Unfortunately, no data were available yet on presence of hypogonadism. This and other potential mechanisms will be further explored in additional studies in this cohort.

In our cohort, corticosteroid use during cancer treatment did not impact overweight or obesity. Apparently, the short-term metabolic side effects of these compounds[48] have not led to overweight on the long-term. Our study is the first to investigate the effect of total cumulative dose steroids on development of overweight, obesity, and morbid obesity in a large, unselected, national cohort of long-term survivors of all types of childhood cancer. Two previous studies among ALL survivors, 10 and 12.7 years after treatment, still observed an association with corticosteroids and overweight.[49,50] In the SJLIFE cohort, the association between glucocorticoid treatment and obesity was significant even after 24.6 years.[9] This difference with our cohort might be explained by environmental and lifestyle factors that make it harder to lose weight after weight gain during adolescence.

Overweight at cancer diagnosis emerged as a strong patient factor associated with overweight and obesity. Other studies have observed similar results.[5,9,10] This may reflect a genetic susceptibility to weight gain, socio-economic status, and associated lifestyle, and for some brain tumors a hypothalamus/pituitary damaging effect prior to diagnosis. Smoking was also an independent risk factor for overweight, as is in the general

population. Our findings show that these patient factors have an additional effect on top of historical treatment and emphasize that they need to be acknowledged in surveillance.

Our third aim was to explore how adequate currently used methods assess overweight in survivors. After abdominal irradiation, WC and WHR do not provide optimal overweight assessment, and that fat% assessment with DXA may be more valuable.[23,30,31] Furthermore, short stature due to GHD, reduced bone mineral density, sarcopenia, and amputations can hinder the estimation of overweight with BMI, WC, WHR, and WHtR. We show that waist circumference–based methods classified a substantial number of survivors with normal BMI as overweight. Moreover, we show that DXA scan measured overweight in an additional 30% of survivors, and even 40% in the subgroup of abdominally irradiated survivors. Underestimation occurred more often in females, which is also observed in the general population.[40] The underestimation rate was similar for all types of childhood cancer except hepatic tumors (Figure S2). Previous studies observed similar underestimation rates when comparing anthropometric measurements to DXA measured fat%.[23,30,31] Karlage et al.[31] used the obesity threshold for BMI, hence, the observed discrepancy was higher. Subsequently, we identified subgroups of survivors that may benefit from assessing overweight with DXA. These include survivors treated with abdominal irradiation and TBI. Altered fat distribution has been described after SCT preconditioned with TBI.[24] Furthermore, for the first time, we identified anthracyclines and platinum chemotherapy to be associated with disguised overweight. How these therapies might lead to an altered body composition is yet unknown. Anthracyclines were associated with low BMI in a previous study in Dutch survivors, but the mechanism, eg, sarcopenia, was not clear.[51] In another study in the DCCSS-LATER cohort, an association between platinum and meningioma appeared to be confounded by medulloblastoma survivors also receiving high dose CrRT,[52] but in a sensitivity analysis excluding these survivors, the effect remained. Hence, survivors with BMI or WC near the upper limit of normal and who received abdominal radiation or TBI, and possibly anthracyclines, and platinum chemotherapy, may benefit from a DXA scan as most reliable diagnostic method.

It was remarkable how our analysis of the 3 previously reported thresholds for high fat% influenced overweight prevalence. The common use of 25% for men and 30% for women may in part be caused by a misinterpretation of a World Health Organization statement on body fat.[53-55] In the 2 other studies we compared, the authors attempted to calibrate BMI values of 25 and 30 kg/m^2 to corresponding DXA fat% values.[56,57] This yields a gray area until 28% in men and 40% in women with somewhat unclear overweight diagnosis.

Low HMW adiponectin could serve as alternative marker for overweight. High-molecular-weight adiponectin is the most biologically active isoform of adiponectin, an adipokine that enhances insulin sensitization and suppresses inflammation and cell death.[58,59] In the general population, low adiponectin is associated with overweight, increased intra-abdominal fat, as well as metabolic syndrome, diabetes, and atherosclerotic disease.[34,60] In our recent systematic literature review, we proposed that it may be used to replace the overweight component of metabolic syndrome in survivors with unreliable WC after abdominal radiotherapy.[35] However, less than 5% of the cohort had low adiponectin, so it was not a sensitive marker for overweight, and particularly compared to DXA, many overweight survivors are missed. An explanation of this finding could be that the study cohort was still relatively young and that as the cohort ages, low adiponectin levels may develop. Alternatively, some underlying mechanisms for overweight development may be different in survivors and less correlated with adiponectin than in the general population.

A few limitations of this study require consideration. First, prescribed radiotherapy dose is not the same as dose received by organs involved in metabolic side effects.[61] For full CrRT, the prescribed dose can be assumed to reflect dose received by the hypothalamus and pituitary, but for other malignancies, such dosimetric data were not available yet. Second, DXA scans were intentionally only performed in survivors < 40 years to avoid bias caused by menopause, but it may limit full generalizability of our DXA related findings. Third, we did not have data on hypogonadism. Fourth, due to historic changes in treatment protocols and the cross-sectional design of this study, treatment exposure is correlated with attained age at study participation, and interpretation of findings regarding the impact of attained age require caution. Fifth, while waist circumference and potentially BMI cutoffs may differ depending on ethnicity, we were unable to incorporate data on ethnicity in our analyses due to legal restrictions in The Netherlands. Therefore, we used the Joint Interim Statement waist circumference cutoff for European men and women, which represent the majority of our cohort, and the general BMI cutoffs of 25 and 30 kg/m^2 as per WHO guideline.

To further deepen our understanding of late effects of childhood cancer, future perspectives may include longitudinal designs shedding more light on potential causative mechanisms, dosimetry for specific organs, and further elucidated pathophysiological mechanisms. Also, obesity is often not a sole side effect, but related to other cardiovascular risk factors—insulin resistance, dyslipidemia, and hypertension—as metabolic syndrome, further increasing the risk of diabetes and cardiovascular disease.[16,26,27,62,63] This will be further explored in our study. Lastly, it is important not only to identify risk factors for overweight and other metabolic sequelae, but also to invest in lifestyle interventions.

In conclusion, in this study in our nationwide Dutch cohort of the first treated (1963-2002) childhood cancer survivors, we show that overweight (BMI ≥ 25 kg/m^2) occurs in almost half of all long-term survivors, which is overall not increased compared to the general population. Overweight at diagnosis, CrRT and GHD, but not corticosteroids, are associated with long-term overweight. Of several assessment methods, DXA was most sensitive, as it identified overweight in an additional 30% of survivors, particularly those treated with abdominal irradiation, TBI, anthracyclines, and platinum chemotherapy. High-molecular-weight adiponectin did not have added diagnostic value.

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Supplementary material

Supplementary material is available at *European Journal of Endocrinology* online.

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