Frailty and sarcopenia within the earliest national Dutch childhood cancer survivor cohort (DCCSS-LATER): a cross-sectional study

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Summary

Background Childhood cancer survivors appear to be at increased risk of frailty and sarcopenia, but evidence on the occurrence of and high-risk groups for these aging phenotypes is scarce, especially in European survivors. The aim of this cross-sectional study was to assess the prevalence of and explore risk factors for pre-frailty, frailty, and sarcopenia in a national cohort of Dutch childhood cancer survivors diagnosed between 1963 and 2001.

Methods Eligible individuals (alive at the time of study, living in the Netherlands, age 18–45 years, and had not previously declined to participate in a late-effects study) from the Dutch Childhood Cancer Survivor Study (DCCSS-LATER) cohort were invited to take part in this cross-sectional study. We defined pre-frailty and frailty according to modified Fried criteria, and sarcopenia according to the European Working Group on Sarcopenia in Older People 2 definition. Associations between these conditions and demographic and treatment-related as well as endocrine and lifestyle-related factors were estimated with two separate multivariable logistic regression models in survivors with any frailty measurement or complete sarcopenia measurements.

Findings 3996 adult survivors of the DCCSS-LATER cohort were invited to participate in this cross-sectional study. 1993 non-participants were excluded due to lack of response or a decline to participate and 2003 (50·1%) childhood cancer survivors aged 18–45 years were included. 1114 (55·6%) participants had complete frailty measurements and 1472 (73·5%) participants had complete sarcopenia measurements. Mean age at participation was 33·1 years (SD 7·2). 1037 (51·8%) participants were male, 966 (48·2%) were female, and none were transgender. In survivors with complete frailty measurements or complete sarcopenia measurements, the percentage of pre-frailty was 20·3% (95% CI 18·0–22·7), frailty was 7·4% (6·0–9·0), and sarcopenia was 4·4% (3·5–5·6). In the models for pre-frailty, underweight (odds ratio [OR] 3·38 [95% CI 1·92–5·95]) and obesity (OR 1·67 [1·14–2·43]), cranial irradiation (OR 2·07 [1·47–2·93]), total body irradiation (OR 3·17 [1·77–5·70]), cisplatin dose of at least 600 mg/m² (OR 3·75 [1·82–7·74]), growth hormone deficiency (OR 2·25 [1·23–4·09]), hyperthyroidism (OR 3·72 [1·63–8·47]), bone mineral density (Z score ≤–1 and >–2, OR 1·80 [95% CI 1·31–2·47]; Z score ≤–2, OR 3·37 [2·20–5·15]), and folic acid deficiency (OR 1·87 [1·31–2·68]) were considered significant. For frailty, associated factors included age at diagnosis between 10–18 years (OR 1·94 [95% CI 1·19–3·16]), underweight (OR 3·09 [1·42–6·69]), cranial irradiation (OR 2·65 [1·59–4·34]), total body irradiation (OR 3·28 [1·48–7·28]), cisplatin dose of at least 600 mg/m² (OR 3·93 [1·45–10·67]), higher carboplatin doses (per g/m²; OR 1·15 [1·02–1·31]), cyclophosphamide equivalent dose of at least 20 g/m² (OR 3·90 [1·65–9·24]), hyperthyroidism (OR 2·87 [1·06–7·76]), bone mineral density Z score ≤–2 (OR 2·85 [1·54–5·29]), and folic acid deficiency (OR 2·04 [1·20–3·46]). Male sex (OR 4·56 [95%CI 2·26–9·17]), lower BMI (continuous, OR 0·52 [0·45–0·60]), cranial irradiation (OR 3·87 [1·80–8·31]), total body irradiation (OR 4·52 [1·67–12·20]), hypogonadism (OR 3·96 [1·40–11·18]), growth hormone deficiency (OR 4·66 [1·44–15·15]), and vitamin B12 deficiency (OR 6·26 [2·17–1·81]) were significantly associated with sarcopenia.

Interpretation Our findings show that frailty and sarcopenia occur already at a mean age of 33 years in childhood cancer survivors. Early recognition and interventions for endocrine disorders and dietary deficiencies could be important in minimising the risk of pre-frailty, frailty, and sarcopenia in this population.

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Research in context

Evidence before this study

We searched PubMed from database inception on March 14, 2022, using the search terms "frailty" OR "sarcopenia" AND "childhood cancer survivors" and all synonyms for articles published in English. Several high-quality studies in two large American childhood cancer survivors cohorts (the St Jude Lifetime Cohort Study and the Childhood Cancer Survivor Study) were identified. Childhood cancer survivors seem to be at increased risk of frailty and sarcopenia, two partly overlapping ageing phenotypes. Frailty has been associated with adverse health outcomes such as excess morbidity and mortality in the general population and in survivors. However, the prevalence of and risk factors for frailty might be different for European survivors, as certain lifestyle factors such as diet and physical activity differ between Americans and Europeans.

Added value of this study

In this study, we established the prevalence of pre-frailty, frailty, and sarcopenia in European childhood cancer survivors. Our findings help to better identify individuals at high-risk of pre-frailty, frailty, and sarcopenia, and provide insights into novel targeted opportunities to potentially prevent them in upfront treatment but also during adult survivorship.

Implications of all the available evidence

The evidence provides a clear risk profile for those childhood cancer survivors who are at risk of developing pre-frailty, frailty, and sarcopenia, which aids in clinical case-finding. Additionally, rationale for interventions that could be beneficial for all survivors have been established by the identification of modifiable risk factors. Early identification and adequate counselling for endocrine disorders, as well as supplementation of vitamin deficiencies, might be relatively simple interventions to minimise the risk of pre-frailty, frailty, and sarcopenia for these childhood cancer survivors. Future studies are needed to assess the effect of these interventions.

Introduction

The improving survival of children with cancer leads to a continuously growing population of childhood cancer survivors.[1] These survivors are at increased risk of developing several conditions that appear to be related to ageing in the general population, such as metabolic syndrome and low bone mineral density (BMD).[2] Increasing evidence suggests that a process of accelerated ageing occurs in long-term survivors,[3] which includes frailty and sarcopenia as important clinical components. According to the phenotype approach (first established by Fried and colleagues[4]), frailty is characterised by a reduction in two (pre-frailty) or three (frailty) physical ability measurements. Frailty and sarcopenia have been associated with a marked susceptibility to adverse health outcomes such as neurocognitive decline and death in the general population,[4,5] as well as in childhood cancer survivors for frailty.[6,7]

Studies in two American childhood cancer survivor cohorts have shown that 6–8% of survivors (mean age, 30–37 years; mean time since cancer diagnosis, 25–30 years) were frail,[6,8] and that 3·5% of survivors had sarcopenia.[9] Additionally, several demographic, disease-related and treatment-related, endocrine, and lifestyle-related factors were shown to be associated with frailty or pre-frailty in these cohorts.[6,8,10–12] However, the prevalence of and risk factors for frailty might be different for European survivors, as certain lifestyle factors such as diet and physical activity differ between Americans and Europeans.[13] The aim of this cross-sectional study was to assess the prevalence of and explore risk factors for pre-frailty, frailty, and sarcopenia, in a national cohort of Dutch childhood cancer survivors diagnosed between 1963 and 2001.

Methods

Study design and participants

This cross-sectional study is part of the Dutch Childhood Cancer Survivor Study-LATER cohort.[14] This cohort consists of 6165 individuals who were: (1) survivors at least 5 years after a childhood cancer diagnosis; (2) diagnosed in a Dutch paediatric oncology centre between 1963 and 2001; (3) 0–19 years of age at cancer diagnosis; and (4) alive at cohort formation in 2008. Adult survivors (alive at the time of the study, living in the Netherlands, age 18–45 years, and who had not previously declined to participate in a late-effects study) who were eligible were invited to partake in this cross-sectional study. Survivors older than 45 years were excluded to minimise the effect of physiological menopause. The study was approved by the Institutional Review Board of the Amsterdam University Medical Center, the Netherlands (2011/116). Written informed consent was obtained from all participants.

Procedures

All data were collected using standardised methods during a single late-effects clinic visit between June 28, 2016, and Feb 28, 2020.

Although there is overlap between frailty and sarcopenia, we analysed both phenotypes separately. Sarcopenia is the physical substrate of frailty,[15] and certain cancer treatments such as corticosteroids lead specifically to myopathy during administration.[16] Additionally, sarcopenia has been associated with a range of conditions earlier in life, as opposed to age-related frailty.[15] Therefore, sarcopenia in addition to frailty might be a relevant condition in young adult survivors (age 18–45 years). According to modified Fried criteria,[4] pre-frailty and frailty were defined as the

presence of at least two (pre-frailty) or three (frailty) of the following criteria: low appendicular lean mass, low muscle strength, exhaustion, slowness, or low physical activity. We defined sarcopenia as the presence of both low appendicular lean mass and low muscle strength as proposed by the European Working Group on Sarcopenia in Older People 2.[15] We aligned the definitions and thresholds of each component to a large extent with those in previous childhood cancer survivor studies[6,10] to be able to compare our data with previously published results. However, we chose to use age-specific and sex-specific normative values for each component.

Dual-energy X-ray absorptiometry (DXA; Hologic Discovery A and Horizon A, Marlborough, MA, USA) was performed to assess lean mass of the arms and legs (not including bone mass) divided by height squared (kg/m²). Normative values from the DXA manufacturer (ie, the National Health and Nutrition Examination Survey Body Composition Analysis) were used to calculate appendicular lean mass Z scores.[17] Appendicular lean mass was classified as low in cases of an age-specific and sex-specific Z score of –1·5 or less.

Muscle strength was measured with a hand-held dynamometer (Jamar, Sammons Preston Rolyan, Bolingbrook, IL, USA) using a standardised procedure. We calculated the mean of two measurements to determine muscle strength for each side. A Z score of –1·5 or less at one or both sides was considered low (appendix pp 2–4). Age-specific and sex-specific normative values from the dynamometer manufacturer were used.

The subscale vitality of the Dutch version of the Medical Outcome Study-Short Form-36 (MOS-SF-36) Health Survey[18] was used as proxy measure for exhaustion. Age-specific and sex-specific normative values from the general Dutch population were available.[18] We classified scores of 1·5 SD below the Dutch mean as low vitality, which indicates exhaustion (appendix pp 2–4).

The subscale physical function of the Dutch version of the MOS-SF-36 Health Survey[18] was used as proxy measure for slowness. Age-specific and sex-specific normative values from the general Dutch population were available.[18] We classified scores of 1·5 SD below the Dutch mean as low physical functioning, which indicates slowness (appendix pp 2–4). Additionally, we performed a 6-min walking test in a sub-cohort of survivors that had previously been treated in Rotterdam or Utrecht to assess the correlation between survey results and distance covered during the 6-min walking test.

The validated Short QUestionnaire to ASsess Health enhancing physical activity, also termed SQUASH, questionnaire was used to assess regular physical activity (including commuting, household, work or school, and leisure-time activities).[19] We converted each activity to a metabolic equivalent of task value to determine activity intensity using the 2011 compendium by Ainsworth and colleagues.[20] The number of minutes spent on moderate-to-vigorous physical activity per week was compared with that in age-matched and sex-matched young adults from the general Dutch population (Lifelines cohort).[21] Values below the 20th percentile were considered low (appendix pp 2–4).

For all eligible survivors, we retrieved sex, age at cancer diagnosis, attained age, and disease-related and all treatment-related data from historical individual medical records. The disease-related and treatment-related data included cancer diagnosis, chemotherapy regimens and total cumulative doses, radiotherapy fields and fractionated dose, haematopoietic stem cell transplantation, and amputation surgery for primary diagnoses as well as recurrences. Intention-to-treat cumulative corticosteroid doses were determined on the basis of treatment protocols and converted to prednisone equivalent doses.[22] If the treatment protocol was missing, it was estimated based on disease type and treatment decade. Height and weight were obtained to calculate BMI (weight/height²), which was adjusted for amputation using estimated total body weight percentages of the amputated limb (appendix pp 2–4). Amputation was defined as any amputation surgery (excluding the fingers or toes) using the Dutch Classification of Operations codes (appendix pp 2–4). We measured bone mineral density and fat mass using DXA. A medical history was taken to assess fractures that occurred from 5 years after cancer diagnosis onwards. Additionally, we registered whether survivors had ever been diagnosed with endocrine disorders based on data in the medical records. Survivors completed various questionnaires, including questionnaires regarding individual health behaviours. Furthermore, blood samples were obtained after an overnight fast and stored at –80°C in a central biobank. When the study inclusion was finalised, we assessed free thyroxine, thyroid stimulating hormone, insulin-like growth factor 1 (IGF-1), 25-hydroxyvitamin D, vitamin B12, homocysteine, and folic acid concentrations for all survivors with available blood samples in one centre at the same time point (appendix pp 2–4).

See Online for appendix

Statistical analysis

Before the start of this study, a power calculation was done, which showed that about 2500 survivors were needed to build robust models for our outcome. Characteristics of study participants were compared with those of non-participants and the total DCCSS-LATER cohort using a χ^2 test. A Fisher's exact p value was employed when the number of observations was lower than five. The Pearson's correlation coefficient was used to assess the correlation between self-reported physical function (used to indicate slowness) and the distance covered during the 6-min walking test. Risk factors for pre-frailty, frailty, and sarcopenia were first assessed using univariable logistic regression analyses and were presented using odds ratios (ORs), 95% CIs, and p values. Covariates were categorised in a way that translates best to clinical care, and were considered as a continuum

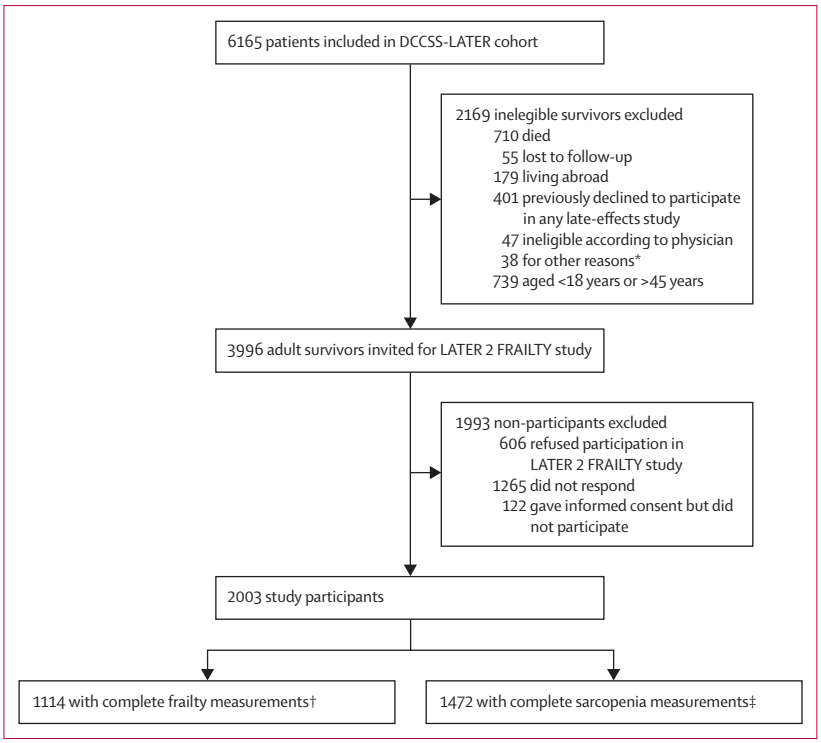

Figure 1: **Study participants**
DCCSS-LATER=Dutch Childhood Cancer Survivor LATER Study. *Including survivors that were not proficient in Dutch or who were pregnant. †Indicating survivors in whom all five frailty components were assessed. ‡Indicating survivors in whom both sarcopenia components were assessed.

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when the number of events did not allow categorisation. Chemotherapy and radiotherapy dose thresholds were chosen on the basis of clinical relevance or previous reports in the literature. We selected potential risk factors identified in univariable analysis (with a p value <0·2) as well as demographic factors known to be associated with pre-frailty, frailty, or sarcopenia from previous literature (ie, sex, attained age, and BMI) for the multivariable models. When two collinear risk factors were identified in univariable analysis (ie, haematopoietic stem cell transplantation and total body irradiation), the risk factor with the largest effect size was included. Case-wise deletion was used when data in covariates were missing, as most covariates were (near) complete. Hence, only survivors with complete values for each covariate were included in our models. We made two separate multivariable models for: (1) potential demographic and treatment-related risk factors, and (2) potential endocrine and lifestyle-related risk factors for pre-frailty, frailty, and sarcopenia, because we suspected that endocrine disorders could mediate the effects of cancer treatment history. Additionally, when interaction was suspected based on literature from the general older population (aged ≥60 years; ie, for the effect of BMI category on our phenotypes for males and females), this was assessed by adding an interaction term. Because survivors with an amputation have per definition lower appendicular lean mass detected by DXA, models were adjusted for amputation surgery when the number of observations was at least five. All analyses were done with R (version 4.0.3; Vienna, Austria).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Of the 6165 participants of the DCCSS-LATER cohort, 2169 survivors were excluded and 3996 adult survivors were eligible and invited to participate in this cross-sectional study. Following exclusion of 1993 non-participants, 2003 (50·1%) of eligible individuals participated in this study. 1114 (55·6%) participants had complete frailty measurements and 1472 (73·5%) participants had complete sarcopenia measurements (figure 1).

The mean attained age of participants was 33·1 years (SD 7·2), and the median follow-up time since cancer diagnosis was 25·3 years (IQR 20·3–31·3). Of the 2003 participants, 1037 (51·8%) were male, 966 (48·2%) were female, and none were transgender (table 1). Data on ethnicity and race were not available due to national policies. Compared with non-participants, participants were equally old at cancer diagnosis and study invitation and had a similar follow-up time and surgery frequency (table 1). However, participants were more often female, had a different distribution of cancer diagnoses, and received all evaluated types of cancer treatment more often than did non-participants. The characteristics of the survivors with complete frailty measurements are also compared with those of the non-participants and participants without complete frailty measurements (table 1). The prevalence of pre-frailty and frailty was based on survivors with complete frailty measurements (n=1114), whereas participants with any frailty measurement (n=1962) were included in the regression models.

Low muscle strength was the most prevalent frailty component and was present in 377 (20·6%) of 1830 survivors with muscle strength measurements, and low appendicular lean mass was the least prevalent (185 [12·0%] of 1536 survivors in whom appendicular lean mass was assessed). Slowness was present in 204 (13·7%) of 1485 survivors in whom slowness was assessed (appendix p 5). Self-reported physical function (used to indicate slowness) was significantly correlated with distance covered during the 6-min walking test (n=309; p<0·001); correlation was low to moderate (r=0·39 [95% CI 0·28–0·49]).

In the group of survivors with complete measurements, the prevalence of pre-frailty was 20·3% (95% CI 18·0–22·7; n=226), the prevalence of frailty was 7·4% (6·0–9·0; n=82), and the prevalence of sarcopenia was 4·4% (3·5–5·6; n=65). Overall, the

contribution of each frailty component to frailty scores was similar (appendix p 14), and sarcopenia was found to be a distinct phenotype from frailty (appendix p 15). Pre-frailty and frailty frequencies were higher than the average across all diagnoses among survivors of bone tumour, soft tissue sarcoma, CNS tumour, myeloid leukaemia, and other and unspecified malignant neoplasms, whereas sarcopenia was more frequent among survivors of myeloid leukaemias than other types of cancer (figure 2).

	Participants (n=2003)	Complete participants* (n=1114)	Non-participants (n=1993)	Non-participants and incomplete participants (n=2882)	DCCSS-LATER cohort (n=6165)	p value participants *vs* non-participants†
Sex	..	..	..	..	..	<0·0001; 0·021
Male	1037 (51·8%)	596 (53·5%)	1217 (61·1%)	1658 (57·5%)	3433 (55·7%)	..
Female	966 (48·2%)	518 (46·5%)	776 (38·9%)	1224 (42·5%)	2731 (44·3%)	..
Transgender	0	0	0	0	1 (<1%)	..
Primary childhood cancer (International Classification for childhood cancer)	..	..	..	..	..	<0·0001; <0·0001
Leukaemias, myeloproliferative diseases, and myelodysplastic diseases	748 (37·3%)	418 (37·5%)	696 (34·9%)	1026 (35·6%)	2094 (34·0%)	..
Lymphomas and reticulo endothelial neoplasms	373 (18·6%)	210 (18·9%)	349 (17·5%)	512 (17·8%)	1062 (17·2%)	..
CNS and miscellaneous intracranial and intraspinal neoplasms	192 (9·6%)	101 (9·1%)	298 (15·0%)	389 (13·5%)	844 (13·7%)	..
Neuroblastoma and other peripheral nervous cell tumours	119 (5·9%)	73 (6·6%)	94 (4·7%)	140 (4·9%)	324 (5·3%)	..
Retinoblastoma	10 (0·5%)	4 (0·4%)	13 (0·7%)	19 (0·7%)	33 (0·5%)	..
Renal tumours	237 (11·8%)	131 (11·8%)	200 (10·0%)	306 (10·6%)	596 (9·7%)	..
Hepatic tumours	18 (0·9%)	12 (1·1%)	28 (1·4%)	34 (1·2%)	52 (0·8%)	..
Bone tumours	90 (4·5%)	51 (4·6%)	84 (4·2%)	123 (4·3%)	370 (6·0%)	..
Soft tissue and other extraosseous sarcomas	134 (6·7%)	76 (6·8%)	129 (6·5%)	187 (6·5%)	450 (7·3%)	..
Germ cell tumours, trophoblastic tumours, and neoplasms of gonads	60 (3·0%)	25 (2·2%)	78 (3·9%)	113 (3·9%)	232 (3·8%)	..
Other malignant epithelial neoplasms and malignant melanomas	20 (1·0%)	12 (1·1%)	23 (1·2%)	31 (1·1%)	102 (1·7%)	..
Other and unspecified malignant neoplasms	2 (0·1%)	1 (0·1%)	1 (0·1%)	2 (0·1%)	6 (0·1%)	..
Age at diagnosis, years‡	..	..	..	..	..	0·99; 0·60
0–4	998 (49·8%)	553 (49·6%)	994/1989 (50·0%)	1439/2878 (50·0%)	2727/6016 (45·3%)	..
5–9	553 (27·6%)	303 (27·2%)	551/1989 (27·7%)	801/2878 (27·8%)	1628/6016 (27·1%)	..
10–14	366 (18·3%)	215 (19·3%)	359/1989 (18·0%)	510/2878 (17·7%)	1285/6016 (21·4%)	..
15–17	86 (4·3%)	43 (3·9%)	85/1989 (4·3%)	128/2878 (4·4%)	376/6016 (6·3%)	..
Age at invitation, years§	..	..	..	..	..	0·53; 0·80
<18	NA	NA	NA	NA	49/3991 (1·2%)	..
18–29	771 (38·5%)	423 (38·0%)	522/1387 (37·6%)	870/2276 (38·2%)	1313/3991 (32·9%)	..
30–39	871 (43·5%)	488 (43·8%)	629/1387 (45·3%)	1012/2276 (44·5%)	1511/3993 (37·9%)	..
≥40	361 (18·0%)	203 (18·2%)	236/1387 (17·0%)	394/2276 (17·3%)	1118/3991 (28·0%)	..
Follow-up time since childhood cancer diagnosis, years¶	..	..	..	..	..	0·21; 0·98
10–19	466 (23·3%)	255 (22·9%)	432 (21·7%)	643 (22·3%)	981/4811 (20·4%)	..
20–29	916 (45·7%)	519 (46·6%)	956 (48·0%)	1353 (46·9%)	1931/4811 (40·1%)	..
30–39	544 (27·2%)	303 (27·2%)	546 (27·4%)	787 (27·3%)	1393/4811 (29·0%)	..
40–49	77 (3·8%)	37 (3·3%)	59 (3·0%)	99 (3·4%)	460/4811 (9·6%)	..
50–59	0	0	0	0	46/4811 (1·0%)	..

(Table 1 continues on next page)

	Participants (n=2003)	Complete participants* (n=1114)	Non-participants (n=1993)	Non-participants and incomplete participants (n=2882)	DCCSS-LATER cohort (n=6165)	p value participants *vs* non-participants†
(Continued from previous page)						
Radiotherapy‖**						
Any radiotherapy	676 (33·7%)	355 (31·9%)	566/1989 (28·5%)	887/2877 (30·8%)	2527/6135 (41·2%)	<0·0001; 0·53
Cranial††	320/1995 (16·0%)	167/1110 (15·0%)	180/1382 (13·0%)	333/2267 (14·7%)	..	0·015; 0·78
Abdomen or pelvis	148/1992 (7·4%)	71/1108 (6·4%)	63/1382 (4·6%)	140/2266 (6·2%)	..	0·0007; 0·80
Total body	83/1992 (4·2%)	41/1108 (3·7%)	28/1382 (2·0%)	70/2266 (3·1%)	..	0·0006; 0·35
Chemotherapy‖**						
Any chemotherapy	1784 (89·1%)	990 (88·9%)	1603 (80·4%)	2397/2879 (83·3%)	5005/6128 (81·7%)	<0·0001; <0·0001
Alkylating agents	1015/1904 (53·3%)	576/1063 (54·2%)	581/1323 (43·9%)	1020/2164 (47·1%)	..	<0·0001; 0·0002
Anthracyclines	1067/1984 (53·8%)	601/1103 (54·5%)	628/1373 (45·7%)	1094/2254 (48·5%)	..	<0·0001; 0·0012
Platinum	297/2001 (14·8%)	163/1112 (14·7%)	168/1386 (12·1%)	302/2275 (13·3%)	..	0·024; 0·27
Vinca alkaloids	1589/2001 (79·4%)	875/1112 (78·7%)	1015/1386 (73·2%)	1729/2275 (76·0%)	..	<0·0001; 0·082
Methotrexate	939/2001 (46·9%)	522/1112 (46·9%)	588/1386 (42·4%)	1005/2275 (44·2%)	..	0·0096; 0·13
Glucocorticoids	1165 (58·2%)	647 (58·1%)	738/1387 (53·2%)	1256/2276 (55·2%)	..	0·0043; 0·11
Haematopoietic stem cell transplantation‖	..	..	..	..	..	0·0002; 0·83
Autologous	54/1989 (2·7%)	26/1108 (2·3%)	33/1978 (1·7%)	61/2859 (2·1%)	155/5918 (2·6%)	..
Allogeneic	95/1989 (4·8%)	44/1108 (4·0%)	54/1978 (2·7%)	105/2859 (3·7)	231/5918 (3·9%)	..
Surgery‖**						
Any surgery	965/1998 (48·3%)	541/1111 (48·7%)	1003/1981 (50·6%)	1427/2868 (49·8%)	3185/6097 (52·2%)	0·14; 0·55
Amputation	42 (2·1%)	20 (1·8%)	29/1387 (2·1%)	51/2276 (2·2%)	..	0·99; 0·40

Data are n (%) or n/N (%), unless otherwise specified. NA=not applicable (survivors <18 years or >45 years were excluded). *Participants with complete frailty measurements. †First p value denotes participants versus non-participants, and second p value denotes participants with complete frailty measurements versus non-participants and participants without complete frailty measurements. ‡Not reported for survivors refusing registration. §Not reported for survivors refusing participation. ¶Not reported for survivors refusing registration and those who were ineligible due to reasons such as death, lost to follow-up, or living abroad. ‖For primary cancer and recurrences. **Subgroup data not reported for survivors refusing participation. ††Including cranial irradiation for brain tumours and craniospinal irradiation.

Table 1: **Baseline characteristics of the study cohort**

Risk factors for pre-frailty and frailty estimated from univariable models in the full cohort of 2003 participants are presented in the appendix (pp 6–9).

In the multivariable models for pre-frailty and frailty including demographic and treatment-related factors (n=1802), BMI category was significantly associated with pre-frailty (table 2). Underweight (OR 3·38 [95% CI 1·92–5·95]) as well as obesity (OR 1·67 [1·14–2·43]) were significantly associated with increased odds of pre-frailty, whereas overweight was significantly associated with reduced odds of pre-frailty (OR 0·71 [95% CI 0·52–0·99]) compared with survivors with a normal BMI. A similar pattern was observed for frailty, but only the effect of underweight reached significance (OR 3·09 [95% CI 1·42–6·69]). To investigate the effect of BMI category on pre-frailty for males and females, an interaction term was added to the multivariable model (appendix p 16). This interaction term could not be added to the model for frailty due to small sample size. Age at diagnosis between 10 years and 18 years (OR 1·94 [95% CI 1·19–3·16) was significantly associated with frailty compared with survivors diagnosed at younger than age 10 years (table 2).

Previous treatment with cranial irradiation (OR 2·07 [95% CI 1·47–2·93]), total body irradiation (OR 3·17 [1·77–5·70]), and a total cumulative cisplatin dose of at least 600 mg/m² (OR 3·75 [1·82–7·74]) significantly increased the risk of pre-frailty in a multivariable model that was adjusted for amputation surgery (table 2). Cranial irradiation (OR 2·65 [95% CI 1·59–4·34]), total body irradiation (OR 3·28 [1·48–7·28]), cisplatin dose of at least 600 mg/m² (OR 3·93 [1·45–10·67]), a higher

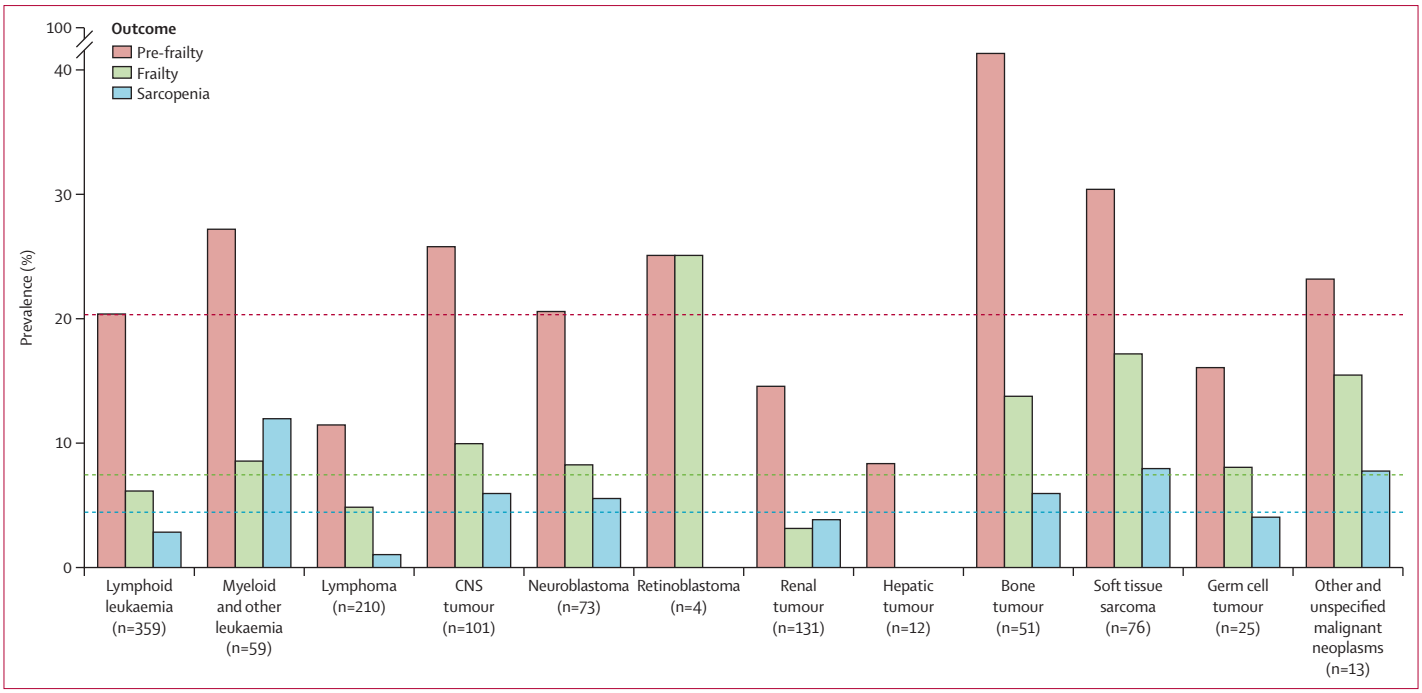

Figure 2: **Frequency of pre-frailty, frailty, and sarcopenia per cancer diagnosis in survivors with complete frailty measurements**
Dashed lines represent average outcome frequencies across all diagnoses.

cumulative dose of carboplatin (per g/m²; OR 1·15 [1·02–1·31]), and a cyclophosphamide equivalent dose of at least 20 g/m² (OR 3·90 [1·65–9·24]) were significantly associated with frailty. In particular, survivors treated with a cranial irradiation dose of at least 25 Gy were at increased risk of pre-frailty (p=0·0010; appendix pp 6–9). A sensitivity analysis only including survivors with complete frailty measurements showed similar results (appendix p 10). However, in this model for pre-frailty, cisplatin dose of at least 600 mg/m² was not significant (OR 1·87 [95% CI 0·71–4·95]).

In the multivariable model for pre-frailty that included endocrine and lifestyle-related factors adjusted for patient characteristics and amputation surgery (n=1512), growth hormone deficiency (OR 2·25 [95% CI 1·23–4·09]), hyperthyroidism (OR 3·72 [1·63–8·47]), bone mineral density Z score ≤–1 and >–2 (OR 1·80 [1·31–2·47]), as well as Z score ≤–2 (OR 3·37 [2·20–5·15]) were all significant and showed a greater risk for pre-frailty (table 3). Hyperthyroidism (OR 2·87 [95% CI 1·06–7·76]) and bone mineral density Z score ≤–2 (OR 2·85 [1·54–5·29]) were significantly associated with frailty. Survivors with hypogonadism also had increased odds of pre-frailty (OR 1·48 [95% CI 0·77–2·83]) and frailty (OR 2·27 [0·98–5·27]), and survivors with growth hormone deficiency of frailty (OR 1·85 [0·80–4·28]), but these were not significant. Of the survivors with growth hormone deficiency, 43 (39·4%) of 109 were being treated with growth hormone replacement therapy at the time of the study.

Folic acid deficiency (present in 285 [14·9%] of 1909 survivors) was significantly associated with pre-frailty (OR 1·87 [95% CI 1·31–2·68]) and frailty (OR 2·04 [1·20–3·46]) in multivariable analysis (table 3). Severe vitamin D deficiency (present in 241 [12·6%] of 1908 survivors) had an OR of 1·31 for pre-frailty (95% CI 0·88–1·95) but these increased odds were not significant. Vitamin B12 deficiency (present in 69 [3·6%] of 1909 survivors) was not significantly associated with pre-frailty or frailty in the univariable analysis and was therefore not included in the multivariable model. 89 (17·8%) of 501 survivors with at least one of these biochemical vitamin deficiencies had multiple deficiencies (appendix p 17).

Risk factors for sarcopenia estimated from univariable models (n=1472) are presented in the appendix (pp 11–13). In multivariable analysis for sarcopenia (n=1457), male sex (OR 4·56 [95% CI 2·26–9·17]), lower BMI (continuous, OR 0·52 [0·45–0·60]), cranial irradiation (OR 3·87 [1·80–8·31]), and total body irradiation (OR 4·52 [1·67–12·20]) were significant (table 2). Survivors treated with a cranial irradiation dose of at least 25 Gy had a higher frequency of sarcopenia than did those treated with doses of less than 25 Gy (appendix pp 11–13), but this did not reach significance (p=0·078).

Hypogonadism (OR 3·96 [95% CI 1·40–11·18]), growth hormone deficiency (OR 4·66 [1·44–15·15]), and vitamin B12 deficiency (OR 6·26 [2·17–1·81]) were significantly associated with sarcopenia, whereas bone mineral density Z score ≤–1 and >–2, bone mineral

	Pre-frailty (n=1802)		Frailty (n=1802)		Sarcopenia (n=1457)	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Sex (male)	1·19 (0·92–1·56)	0·19	0·84 (0·55–1·28)	0·42	4·56 (2·26–9·17)	<0·0001
Attained age (per year)	0·98 (0·95–1·02)	0·32	0·97 (0·94–1·01)	0·10	1·00 (0·96–1·05)	0·83
Age at diagnosis, years						
0–10	..	..	1 (ref)	1 (ref)	..	..
10–18	..	..	1·94 (1·19–3·16)	0·0080	..	..
Follow-up time (per year)	0·99 (0·96–1·02)	0·48	..	..	..	..
BMI*	..	..	..	..	0·52 (0·45–0·60)	<0·0001
Underweight	3·38 (1·92–5·95)	<0·0001	3·09 (1·42–6·69)	0·0043	..	..
Normal	1 (ref)	1 (ref)	1 (ref)	1 (ref)	..	..
Overweight	0·71 (0·52–0·99)	0·043	0·66 (0·39–1·15)	0·14	..	..
Obese	1·67 (1·14–2·43)	0·0082	1·31 (0·71–2·42)	0·39	..	..
Cranial irradiation†	2·07 (1·47–2·93)	<0·0001	2·65 (1·59–4·34)	0·0002	3·87 (1·80–8·31)	0·0005
Total body irradiation	3·17 (1·77–5·70)	0·0001	3·28 (1·48–7·28)	0·0034	4·52 (1·67–12·20)	0·0030
Corticosteroid dose, g/m² (PED)						
0	..	..	..	..	1 (ref)	1 (ref)
<10	..	..	..	..	0·38 (0·19–0·76)	0·0061
≥10	..	..	..	..	0·58 (0·16–2·18)	0·42
Cisplatin dose, mg/m²						
0	1 (ref)	1 (ref)	1 (ref)	1 (ref)	..	..
<600	1·02 (0·59–1·77)	0·94	1·31 (0·62–2·78)	0·47	..	..
≥600	3·75 (1·82–7·74)	0·0003	3·93 (1·45–10·67)	0·0073	..	..
Carboplatin dose (per g/m²)	1·08 (0·97–1·20)	0·16	1·15 (1·02–1·31)	0·026	..	..
Alkylating dose, g/m² (CED)						
0	1 (ref)	1 (ref)	1 (ref)	1 (ref)	..	..
<20	0·85 (0·65–1·12)	0·25	1·26 (0·80–1·99)	0·32	..	..
≥20	1·64 (0·82–3·28)	0·16	3·90 (1·65–9·24)	0·0020	..	..

The model for pre-frailty was adjusted for amputation (significantly associated with pre-frailty in a univariable model). Empty cells denoted by ".." indicate that this variable was not included in the model. OR=odds ratio. PED=prednisone equivalent dose. CED=cyclophosphamide equivalent dose. *Adjusted for amputation; analysed as a continuous variable for sarcopenia. †Including cranial irradiation for brain tumours and craniospinal irradiation.

Table 2: **Demographic and treatment-related risk factors for pre-frailty, frailty, and sarcopenia using multivariable logistic regression analysis**

density Z score ≤–2, and severe vitamin D deficiency were not (n=1441; table 3). We added the interaction terms sex*growth hormone deficiency and sex*hypogonadism to this model to test for sex differences in the effect of endocrine disorders on sarcopenia, but low numbers hampered this analysis; nine (82%) of 11 of survivors with sarcopenia and growth hormone deficiency, and 11 (92%) of 12 survivors with sarcopenia and hypogonadism were male.

Discussion

In this national Dutch childhood cancer survivor cohort with a mean age of 33 years (median follow-up 25 years), the prevalence of pre-frailty was 20·3%, frailty was 7·4%, and sarcopenia was 4·4%. These frequencies are comparable with previous American studies in survivors with similar follow-up time,[6,8,9] indicating that pre-frailty, frailty, and sarcopenia are inherent to cancer treatment. Additionally, we identified novel associations between demographic, treatment-related, endocrine, as well as lifestyle-related factors and pre-frailty and sarcopenia in survivors.

Although we could not compare the prevalence of pre-frailty, frailty, and sarcopenia that was observed in our study with age-specific normative values from the general population, the occurrence of frailty is conceivably high for this young adult population, illustrated by the fact that it exceeds the prevalence of community-dwelling adults aged 50–65 years from the UK.[23] Our finding that reduced bone mineral density, another condition that is typically observed in older people, was independently associated with pre-frailty and frailty, supports this interpretation. The associations that we found between genotoxic anti-cancer treatments and pre-frailty and frailty as a proxy of aging is consistent with the growing notion that DNA damage is central to multimorbidity and the process of systemic aging in the general population.[24] Biological mechanisms that have been shown to be involved in this process include genome instability, epigenetic alterations, compromised mitochondrial function, proteostatic stress, and telomere dysfunction.[3,9,24]

The observed association between underweight and pre-frailty or frailty is conceivably linked with the presence of low appendicular lean mass in these

	Pre-frailty (n=1512)		Frailty (n=1512)		Sarcopenia (n=1441)	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Hypogonadism	1·48 (0·77–2·83)	0·24	2·27 (0·98–5·27)	0·057	3·96 (1·40–11·18)	0·0093
Growth hormone deficiency	2·25 (1·23–4·09)	0·0082	1·85 (0·80–4·28)	0·15	4·66 (1·44–15·15)	0·010
Hyperthyroidism	3·72 (1·63–8·47)	0·0018	2·87 (1·06–7·76)	0·038	..	..
Bone mineral density*						
Z score >–1	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
–2< Z score ≤–1	1·80 (1·31–2·47)	0·0003	1·42 (0·84–2·39)	0·19	1·48 (0·73–3·02)	0·28
Z score ≤–2	3·37 (2·20–5·15)	<0·0001	2·85 (1·54–5·29)	0·0009	0·98 (0·40–2·42)	0·97
Severe vitamin D deficiency†	1·31 (0·88–1·95)	0·18	..	..	0·94 (0·40–2·24)	0·89
Vitamin B12 deficiency‡	..	..	..	..	6·26 (2·17–1·81)	0·0007
Folic acid deficiency§	1·87 (1·31–2·68)	0·0006	2·04 (1·20–3·46)	0·0081	..	..

Models adjusted for sex, attained age, BMI, and each other variable in the model. The model for pre-frailty was also adjusted for amputation (significantly associated with pre-frailty in a univariable model). Empty cells denoted by ".." indicate that this variable was not included in the model. OR=odds ratio. *At one or more skeletal sites (lumbar spine, total body, or total hip). †25-hydroxyvitamin D concentrations <30 nmol/L. ‡Vitamin B12 concentrations <150 pmol/L or ≥150 and <220 pmol/L and homocysteine concentrations >19 µmol/L. §Folic acid concentrations <6·8 nmol/L.

Table 3: **Endocrine and lifestyle-related risk factors for pre-frailty, frailty, and sarcopenia using multivariable logistic regression analysis**

individuals, as lower fat mass Z score was not associated with pre-frailty or frailty in the univariable analysis. The relationship between obesity and pre-frailty (mainly observed in female survivors) is thought to be twofold. First, obese individuals have a greater risk of disability and impaired physical function.[25] Second, obesity is linked with a pro-inflammatory state, which might be part of the physiological basis of frailty.[25] Alternatively, as in the general population, altered body composition (ie, reduced lean mass and increased fat mass) might be the result of systemic ageing as reflected by pre-frailty, although this often happens without concomitant changes in BMI.[26] The bimodal pattern in the relationship between BMI and pre-frailty has also been observed in older people.[27]

We postulate that many of the identified treatment-related risk factors for pre-frailty, frailty, and sarcopenia affect these adverse outcomes not only through direct DNA damage but also through endocrine disorders. Our findings are in line with previously reported univariable associations between growth hormone deficiency and primary hypogonadism and frailty in survivors.[11,12] Moreover, in our study, growth hormone deficiency and hypogonadism were independently associated with one or more ageing phenotypes, highlighting the importance of both disorders. Additionally, we found that hyperthyroidism was significantly associated with pre-frailty, which is in accordance with a large prospective study in older people which showed that higher free thyroxine concentrations were associated with incident frailty.[28] Cranial irradiation (especially doses ≥25 Gy) and total body irradiation were consistently associated with pre-frailty, frailty, and sarcopenia, which might be through growth hormone deficiency, primary or secondary hypogonadism, or hyperthyroidism.[11,29,30] Results in this study are in line with previous literature showing an association between cisplatin doses of at least 600 mg/m² and frailty.[8] Furthermore, we found that higher doses of carboplatin and high doses of alkylating agents (≥20 g/m²) were significantly associated with frailty. This might in part be through primary hypogonadism,[12,31] but alkylating agents and platinum-based drugs could also affect the development of frailty by causing DNA damage.[32]

It is important to identify survivors at risk for pre-frailty, frailty, and sarcopenia early, as these phenotypes are characterised by an increased susceptibility to multiple morbidities and excess mortality. Our study identified several novel risk factors for pre-frailty, frailty, and sarcopenia in survivors, which could aid in the identification of at-risk individuals and targeted intervention. Primary prevention through dose reduction or changes in administration of associated treatment modalities without hampering anti-tumour efficacy would be optimal, but this is not always possible. However, for some agents such as platinum, achieving lower cumulative doses or alternative compounds are being investigated for some disease types.[33] In the meantime, interventions such as nutritional support and physical activity (especially resistance exercise) have been shown to attenuate hallmarks of ageing in the general population.[34,35] Additionally, our data suggest that treating hyperthyroidism as well as adequate supplementation in case of hypogonadism, growth hormone deficiency, or folic acid and vitamin B12 deficiencies might have the potential to prevent or remediate frailty or sarcopenia in survivors. However, causality cannot be proven in a cross-sectional study. Although counterintuitive, there is evidence that attenuation of the growth hormone/IGF-1 somatotropic axis, which also occurs with natural ageing and after DNA damage, is actually part of a beneficial response that shifts priorities from growth to maintenance and resilience mechanisms which aim to slow down accelerated ageing.[36] This emphasises not

only the importance of surveillance of endocrine deficiencies, but also of adequate endocrine counselling and close monitoring of survivors receiving hormone replacement therapy.

Our results need to be interpreted in the context of some limitations. First, there was no control group of healthy young adults available to compare our pre-frailty, frailty, and sarcopenia prevalence with, which limited our ability to assess the magnitude to which these conditions are increased in survivors. Second, because the frailty and sarcopenia phenotypes have been established in older adults, these phenotypes (as defined in this study) might not fully capture reduced physiological reserve and reduced muscle function in young adults and underestimate their true impact. Third, only about 50% of eligible survivors participated in this study. As several characteristics of the participants differed significantly from the non-participants, selection bias could be present and might have led to an overestimation or underestimation of the reported prevalence of pre-frailty or frailty. However, from all non-participants, detailed treatment data were only available from non-responders and not from refusers, and the characteristics of survivors with complete frailty measurements were similar compared with those of non-participants plus participants with incomplete frailty measurements. Fourth, we used low physical functioning as a proxy of slowness, which could underestimate the occurrence of this component, although physical functioning correlated significantly with distance covered during the 6-min walking test in a subgroup. Fifth, we defined hypogonadism as survivors that had ever been diagnosed with this disorder, which induced a conceivable underestimation of its true prevalence. Finally, the final inclusion of 2003 survivors somewhat limited the number of variables that we could include in our models. However, all variables that were significant in univariable analysis were included.

In conclusion, in this national Dutch cohort of childhood cancer survivors, we validated previously described prevalence of pre-frailty, frailty, and sarcopenia in American childhood cancer survivors, indicating that these phenomena are inherent to cancer treatment and identified novel risk factors. These findings help to target individuals at high-risk of these debilitating ageing phenotypes and provide insights into new opportunities to potentially prevent them in upfront treatment but also during adult survivorship, which could increase survival and quality of life. Our findings suggest that early identification and adequate counselling for endocrine disorders, as well as supplementation of dietary deficiencies, might be crucial in minimising the risk of pre-frailty, frailty, and sarcopenia for childhood cancer survivors. Future interventional studies are needed to assess the effect of these strategies.

Contributors

JEvA, SMFP, MMvdH-E, and SJCMMN contributed to the study funding, concept, and design. JEvA, DTCdW, VGP, RAJN, MGGH, LCMK, MAG, HM-S, WJET, ACHdV, JJL, EvD-dB, HJHvdP, SMFP, MvdH-vdL, ABV, ML, DB, IH, SAAvdB, SJCMMN, and MMvdH-E contributed to data acquisition. JEvA, MF, SMFP, SJCMMN, and MMvdH-E contributed to data analysis and interpretation. JEvA, MMvdH-E, and SJCMMN drafted the manuscript. JEvA, DTCdW, VGP, MF, RAJN, MGGH, LCMK, MAG, HM-S, WJET, ACHdV, JJL, EvD-dB, HJvdP, SMFP, MvdH-vdL, ABV, ML, DB, HMvS, IH, SAAvdB, JdH, JHJH, SJCMMN, and MMvdH-E contributed to manuscript revision and approval. JEvA, MF, MvdH-vdL, SJCMMN, and MMvdH-E had full access to all data in the study and take responsibility for data integrity, verification, and analysis. All authors had access to all the data reported in the study and accept responsibility for the decision to submit for publication.

Declaration of interests

IH has institutional contracts with Abbott, Siemens Healthineers, and Beckman Coulter. All other authors declare no competing interests.

Data sharing

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

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