Summary of findings tables, grading of the evidence and detailed conclusions of evidence bone mineral density surveillance

Who needs bone mineral density surveillance?

1a. What is the risk (%) of low and very low BMD in CAYA cancer survivors?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Disease category	Treatment (% treated)	Risk (% low and very low BMD)	Risk of bias
1.a. Risk of low and very low BMD **(n=47 studies)**	Aaron 2019[a]	242	Mean time since treatment is 13.1 years (range 4-29 years)	ALL (100%)	Chemotherapy: Glucocorticoids 100% Methotrexate 100% Radiotherapy: CRT 59% SCT: 0%	BMD Z-score ≤-1: LS 25.2%, TB 25.2% BMD Z-score ≤-2: LS 5.8%, TB 5.8%	SB: unclear AB: low risk DB: low risk
	Benmiloud 2010	89	Mean time since treatment (±SD) 15.0 ± 4.5 years	ALL 83% NHL 17%	Chemotherapy: Prednisolone 100% Dexamethasone 52.8% Methotrexate 100% Radiotherapy: RT at any site: 53.9% CNS RT 36% CRT 32.6% CSRT 3.4% TBI 18.0% SCT: 18.0%	BMD Z-score ≤-1: At any site: 59.1%; At the LS: 50.5% At the FN: 25.8%; At the Hip: 31.5% BMD Z-score ≤-2: At any site: 10.1%; At the LS: 10.1% At the FN: 2.2%; At the Hip: 2.2%	SB: low risk AB: high risk DB: low risk
	Bhandari 2021	446	Median 14.2 years (range 2–65 years) since completing therapy	Leukemia/lymphoma 70.2% Solid tumor 24.9% Nonmalignant hematologic disease 4.9%	Chemotherapy: Glucocorticoids 57.5% Methotrexate 40.4% Radiotherapy: CRT NR TBI ± 24% SCT: 40.8% (30.9% allogeneic)	LS BMD Z-score ≤-1: 33.9%	SB: low risk AB: high risk DB: low risk
	Bloomhardt 2020	542	Mean time since treatment (±SD) 6.0±5.0 years (range 2.0-35.1)	ALL 65.1% Other acute leukemia 6.5% HL 14.6% NHL 13.8%	Chemotherapy: Dexamethasone 59.6% Prednisone 35.4% Any glucocorticoid 95% Cyclophosphamide 85.1% High-dose methotrexate 25.8% Radiotherapy: CRT 20.7% TBI 8.1% SCT: NR	LS BMD Z-score ≤-1: 17.2% LS BMD Z-score ≤-2: 3.5%	SB: high risk AB: low risk DB: low risk
	Choi 2013	78	Mean time from initial diagnosis to measurement of	ALL 49% AML 45% CML 6%	Chemotherapy: Glucocorticoids for chemotherapy 42%	LS BMD Z-score <-2: 25.7% FN BMD Z-score <-2: 24.4%	SB: unclear AB: low risk DB: low risk

		BMD: 4.42±2.47 in males, 5.36±3.2 years in females		Glucocorticoids for GVHD 53% Radiotherapy: 62% SCT: 64%		
	De Matteo 2019	72	Mean (±SD) time since treatment 41.2 ±37.8 months (95% CI: 49.9, 32.5)	ALL (100%)	Chemotherapy: Prednisone 100% Dexamethasone 100% MTX 100% Cyclophosphamide 100% Radiotherapy: 4% SCT: 0%	Proximal phalanx QUS AD-SoS Z-score below −2: 13.8%	SB: unclear AB: low risk DB: unclear
	Den Hoed 2015[b]	346	Median time after cessation of treatment 16.7 years (IQR 12.4–23.0)	ALL 50.0 % AML 4.9 % HL 12.7 % NHL 13.3 % Brain tumour 6.1% Renal tumour 6.1% Sarcoma 5.2% Neuroblastoma 3.7%	Chemotherapy: Prednisone 63.6% Dexamethasone 37.0% Cyclophosphamide 49.7% Methotrexate 64.9% Ifosfamide 10.8% Radiotherapy: Cranial-spinal 16.5% Total body 3.8 % CRT 4.3% Abdominal 2.3% SCT: 4.9%	TB BMD or LS BMD Z-score <−1: 45% of the CCS. 38% TB, 27% LS, 20% at both TB and LS. TB BMD or LS BMD Z-score <−2: 9% (TB), 3% (LS)	SB: high risk AB: low risk DB: low risk
	Esbenshade 2014	171 (91 had DXA)	Median 2.68 years (range 0.03–10.83) off therapy	ALL 70.8% AML 0.6% Lymphoma 21.1% LCH 7.6%	Chemotherapy: Steroids 100% Other agents NR Radiotherapy: NR SCT: NR	BMD Z-score <-1: TB 16.5%, LS 15.7% BMD Z-score <- 2: TB 5.5%, LS 5.6%	SB: low risk AB: high risk DB: low risk
	Gawade 2012[c]	662	Median 26.1 (IQR 21.5, 31.6) years from diagnosis	ALL (100%)	Chemotherapy: Glucocorticoids 100% Methotrexate 100% Cyclophosphamide 66% Radiotherapy: TBI 2% CRT 66% SCT: 2%	QCT LS BMD Z-score <-2: 5.2%	SB: high risk AB: low risk DB: low risk
	Gurney 2014[c]	845	>10 years after diagnosis	ALL (100%)	Chemotherapy: Glucocorticoids 100% Methotrexate 100% Cyclophosphamide % NR Radiotherapy: CRT: 61.3% CRT + spinalRT or TBI 12.5% SCT: 2.5%	QCT LS BMD Z-score <-1: 29.5% QCT LS BMD Z-score <-2: 5.7% cumulative prevalence QCT BMD Z-score of <-1 at age 40 years was 37.9% (95% CI 33.3–42.5%) overall, 46.2% (95%CI 39.9–52.4%) for males and 28.3% (95% CI 21.9–34.9%) for females	SB: unclear AB: low risk DB: low risk
	Henderson 1996	60	At least 12 months post chemotherapy	Wilms 8.3%; PNET 5%	Chemotherapy: Ifofosfamide 3% Glucocorticoids 75%	LS BMD Z-score <-1: 23.3% LS BMD Z-scores <-2: 8.3%	SB: unclear AB: unclear DB: low risk

			Mean time since treatment: 4.3 yrs range 12mths-14.5 yrs	Teratoma 3.3%; Ewing 1.7% Hepatoblastoma 1.7% ALL 50%; ANLL 5% Hodgkin 8.3%; NHL 11.7%	MTX 62% <u>Radiotherapy:</u> CRT 25% <u>SCT</u>: NR		
	Hesseling 1998	97	Median length of FU 112 months	ALL 22.7%; AML 2.1% CNS tumors 16.5% Wilms' tumor 10.3% Lymphoma 16.5% Neuroblastoma 7.2% Other 24.7%	<u>Chemotherapy:</u> NR <u>Radiotherapy:</u> CRT 35% <u>SCT</u>: NR	LS BMD Z-score <-1: 45.4% LS BMD Z-score <-2: 13.4%	SB: high risk AB: low risk DB: low risk
	Hobush 2014	56	Minimum FU 5 years after treatment; Mean FU 15 years (5-48 years)	Ewing sarcoma 89.3% primitive neuro-ectodermal tumor 10.7%	<u>Chemotherapy:</u> Alkylating agents (ifosfamide/cyclophosphamide) 100% <u>Radiotherapy:</u> Local radiation 64% <u>SCT</u>: NR	LS and/or Hip BMD T-score <-1: 55% LS and/or Hip BMD T-score <-2.5 (or Z-score <-2 in adolescents): 13%	SB: high risk AB: low risk DB: low risk
	Holzer 2003	48	Mean 16±2.2 years follow-up	Malignant Osteosarcoma (100%)	<u>Chemotherapy:</u> HD-MTX 100% Cyclophosphamide 100% Ifosfamide 100% <u>Radiotherapy:</u> 2% <u>SCT</u>:NA	LS and/or Hip BMD T-score <-1: 65% LS and/or Hip BMD T-score <-2.5: 21%	SB: high risk AB: low risk DB: low risk
	Hudson 2013[c]	1142	At least 10 years post treatment	Various pediatric tumors (numbers given for n=1713; 1142 had DXA)	<u>Chemotherapy:</u> Methotrexate 82% Glucocorticoids 85% <u>Radiotherapy:</u> HPA radiation 63% *100% of 1142 received either of the treatments above*	Prevalence of osteoporosis (site and BMD cut-point not defined, presumably LS BMD Z-score ≤-2) N = 110/1142 (9.6%), 95% CI 8.0-11.5	SB: high risk AB: low risk DB: low risk
	Isaksson 2020	125	Mean (SD) follow-up 24.3 years (7.1)	Various pediatric tumors	<u>Chemotherapy:</u> GCs 19 (15%) Alkylating agents 16 (13%) Median cyclophosphamide equivalent dose 4854 mg/m^2 MTX 17 (14%) Median methotrexate dose 11 g/m^2	Survivors: LS BMD Z-score ≤-1: 22% TH BMD Z-score ≤-1: 21% Controls: LS BMD Z-score ≤-1: 28% TH BMD Z-score ≤-1: 22%	SB: high risk AB: low risk DB: low risk

				Radiotherapy: CRT 26% SCT: 2%		
	Joyce 2011[c]	493	12.7 to 46.5 years from diagnosis of childhood ALL (median, 27.2y)	ALL (100%)	Glucocorticoids 100% Methotrexate 100% Cyclophosphamide 100% Radiotherapy: CRT 70% SCT: NR	LS BMD Z- scores <–1.0: 28% LS BMD Z-scores <–2.5: 3%	SB: high risk AB: low risk DB: low risk
	Kaste 2006a[c]	320	NR	Leukemia/lymphoma 45.6% Brain tumor 44.4% Solid tumor 10.0%	NR	QCT LS BMD Z-score: <-2: 30% DXA LS BMD Z-score <-2: 27.8%	SB: low risk AB: low risk DB: low risk
	Kaste 2006b[c]	study I n=141, study II n=57	Study I: >4 years after therapy (mean time after dx 11.7 yrs) Study II : 2-5 years after study I (mean time after dx 16.1 yrs)	ALL (100%)	Chemotherapy: MTX 100% Prednisone 100% Radiotherapy: CRT 37% of 57; percentage of 141 NR SCT: 0%	Study I: LS BMD Z-score below the mean (<0) 57.9%; Z-score <-1 10.5%; Z-score <-2 1.5% Study II: LS BMD Z-score below the mean 59.6%; Z-score <-1 19.3%; Z-score <-2 0%	SB: unclear AB: high risk DB: low risk
	Kaste 2009[c]	109	Median 7.5 yrs (5.8-20.7 yrs) from diagnosis to QCT	HL (100%)	Chemotherapy: Cyclophosphamide 67.9% Methotrexate 69% Prednisone 65% Radiotherapy: LS RT 28.4% Pelvic RT 6% SCT: NR	QCT LS BMD Z-score <-1.5: 14.7% QCT LS BMD Z-score <-2.0: 7.3% Restricted to white race: QCT LS BMD Z-score <-1.5: 12.0% QCT LS BMD Z-score <-2.0: 6.0%	SB: low risk AB: low risk DB: high risk
	Kaste 2014[c]	424	Median 8.4 yrs (4.6-19.1) from completion of ALL therapy to entry into study	ALL (100%)	Chemotherapy: Glucocorticoids 100% Methotrexate 100% Cyclophosphamide 100% Radiotherapy: CRT 36.1% SCT: NR	QCT LS BMD Z-score <-1: 48.9% QCT LS BMD Z-score <-2: 6.8%	SB: high risk AB: high risk DB: low risk
	Latoch 2021	326	Median (range) 6.12 (4.0-22.0) years since end of treatment	Various pediatric tumors (excluding brain and bone tumor)	Chemotherapy: Glucocorticoids 71.2% Methotrexate 50.9% Radiotherapy: CRT 25.5% TBI 4% Abdominal RT 16.7% SCT: 7%	LS BMD Z-score <-1: 20% TB BMD Z-score <-1: 24% LS and/or TB BMD Z-score <-2: 8%	SB: high risk AB: low risk DB: low risk
	Lemay 2019[a]	246	Median time since diagnosis 15.2 (range 5.4-28.2) years	ALL (100%)	Chemotherapy: Glucocorticoids 98% Methotrexate 98% Radiotherapy: CRT 40.2% SCT: 0%	LS BMD Z-score <-1: 22%	SB: unclear AB: low risk DB: low risk

	Le Meignen 2011	159	Mean time from diagnosis to DXA 14.66 ± 0.44 yrs	ALL (81.8%) AML (18.2%)	Chemotherapy: Glucocorticoids 86.2% Other chemotherapy NR Radiotherapy: CRT 18.9% TBI 40.4% of HSCT recipients SCT: 34%	BMD Z-score <-2: FN 3.2%; LS 3.8%	SB: low risk AB: high risk DB: high risk
	Leung 2007	155	Median 9 yrs from HSCT (range 3 to 10 years)	54% myeloid malignancy; 26% lymphoid malignancy; 20% non-malignant	Chemotherapy: Alkylator-based conditioning pre-HSCT in 21% Radiotherapy: TBI-based conditioning in 79% SCT: yes (100%)	QCT BMD Z-score <-1: 39% (site NR, presumably LS) The cumulative incidence of BMD Z-score <-1 at 10 years was 47.7% (95%CI 38.4 to 58)	SB: low risk AB: low risk DB: unclear
	Liuhtho 2020	4459	NR	Various pediatric tumors	NR	Billing code osteoporosis (CCS vs. controls): HR 13.1, 95%CI 4.3-39.7	SB: low risk AB: high risk DB: high risk
	Mandel 2004	106	Average time since diagnosis 10.1 years (range 5.5 to 15.4 years)	ALL (100%)	Chemotherapy: Glucocorticoids 100% Methotrexate 100% Radiotherapy: 47% SCT: 0%	LS BMD Z-score <-1: 23% Femoral neck BMD less than 89% of the healthy average: 20%	SB: high risk AB: low risk DB: high risk
	Miyoshi 2008	122	Time since therapy from 2 to 30 years (mean 8.8; median 8.0)	Various pediatric tumors	Chemotherapy: 95% Radiotherapy: 59% SCT: 53%	LS BMD Z-score <-1.7: 42% LS BMD Z-score <-2.6: 11%	SB: low risk AB: low risk DB: low risk
	Molinari 2017	101	At least 5 years	ALL (100%)	Chemotherapy: Glucocorticoids 100% Methotrexate 100% Alkylating agents 56.4% Radiotherapy: 23.8% SCT: NR	<20 years: LS, TB or Hip BMD Z-score <-1.1: 24.1% LS, TB or Hip BMD Z-score <-2: 3.8% >20 years: LS, TB or Hip BMD T-score <-1: 45.5%	SB: high risk AB: low risk DB: low risk
	Muszynska-Roslan 2009	114	Mean time from end of therapy ALL: 2.4 ± 1.9 years HL: 2.8 ± 2.1 years Solid tumor: 3.7 ± 4.6 years	ALL: 37.7% HL: 30.7% Solid Tumor: 31.6%	Chemotherapy: Corticosteroids 68.4% Methotrexate 37.7% Radiotherapy: CRT 24.6% Abdominal XRT 36% SCT: NR	LS or TB BMD Z-score <-2: ALL: 10.5% HL: 6.9% Solid Tumor: 30.5%	SB: high risk AB: low risk DB: low risk
	Pietila 2006	52	Mean 6.4 yrs (range 1.4-14.8 y) after off-therapy	Brain tumors (100%)	Chemotherapy: 24% Steroids 100% Radiotherapy: CRT 21.7% Craniospinal 11.1% Combination of CRT and chemotherapy 19.6% SCT: 0%	TB BMD Z-score <-2: 33%	SB: high risk AB: low risk DB: low risk

	Polgreen 2012	319	Mean time since treatment (±SE) 10.1 ± 0.2 years (range 4.3-17.8)	Leukemia 34.5% Solid tumors 39.8% CNS tumors 25.7%	Chemotherapy: Corticosteroid: 42.0% Radiotherapy: 23.2%) Cranial (CNS) 31 (9.7%), other 43 (13.5%) SCT: 0%	TB BMD Z-score <-1: 11% LS BMD Z-score <-1: 23% TB BMD Z-score <-2: 2.3% LS BMD Z-score <-2: 3.5%	SB: low risk AB: low risk DB: low risk
	Remes 2018	74	Mean time since cessation of tumor therapy (±SD): 18.9 ± 6.1 years	Brain tumors (100%)	Chemotherapy: 63.5% Radiotherapy: Local irradiation: 52.7% Craniospinal with local boost to the tumor bed: 40.5% Cranial with local boost to the tumor bed: 4.1% Stereotactic: 2.7% SCT:NR	LS BMD and/or FN BMD and/or TH Z-score ≤-2: 23.6%	SB: high risk AB: low risk DB: unclear
	Ruza 2006	95 (63 had DXA)	Mean duration of remission was 6.12 years (SD 3.67) in patients with osteosarcomas and 6.11 years (SD 3.73) for Ewing's sarcoma patients	Osteosarcoma 62% Ewing's sarcoma 38%	Chemotherapy: MTX 100% Cyclophosphamide 100% Radiotherapy: NR SCT: NR	LS BMD Z-score <-1: 43.6% FN BMD Z-score <-1: 42.9% LS BMD Z-score <-2: 9.7% FN BMD Z-score <-2: 17.5%	SB: high risk AB: high risk DB: low risk
	Siegel 2017	475	Mean (±SD) time after Rx 5.4 ± 4.3 years	ALL 59.6% AML 7.4% Hodgkins 6.1% NHL 14.3% NBL 4.6% Renal tumour 1.3% Sarcoma 6.1% Other 0.6%	Chemotherapy: Corticosteroid 83.4% Methotrexate 77.1% Radiotherapy: Cranial / craniospinal 13.3% TBI 9.9% SCT: 17.9%	TB or LS BMD Z-scores ≤–1: 29.3% (LS 22.8%, TB 21.9%) TB or LS BMD Z-scores ≤–2: 8.2% (LS 7.4%, TB 4.0%)	SB: low risk AB: low risk DB: low risk
	Siviero-Miachon 2017	56	Mean (±SD) 8.1 (±3.5) yrs post therpay	ALL (100%)	Chemotherapy: MTX 100% Cyclophosphamide 100% Steroids 100% Radiotherapy: CRT 44.6% Spinal XRT 1.8% SCT: 0%	TB BMD Z-score ≤-1: 35.8% LS BMD Z-score ≤-1: 48.2% TB BMD Z-score ≤-2: 5.4% LS BMD Z-score ≤-2: 8.9%	SB: high risk AB: low risk DB: low risk
	Sloof 2019	253	NR	Various pediatric tumors	Chemotherapy: NR Radiotherapy: CRT 36% SCT: 0%	BMD Z-score <-1: 25.4% (site NR)	SB: unclear AB: low risk DB: unclear

	Staba Hogan 2013	213	>3 years after cancer diagnosis	Leukemia 37.6% Non-CNS solid tumor 33.3% Lymphoma 20.2% CNS tumor 8.9%	Chemotherapy: Aklylating agents 63.8% Not otherwise stated Radiotherapy: Any radiation: 48.8% Chest radiation 38% Cranial radiation 27.2% SCT: 14.1%	LS or TB BMD Z-score ≤-1: 20%	SB: unclear AB: unclear DB: low risk
	Tabone 2021	89	Mean (± SD) interval from diagnosis to first scan 7.0 ± 4.7 yrs Mean (± SD) interval from diagnosis to second scan 11.7 ± 5.2 yrs	ALL 76.4% AML 23.6%	Chemotherapy: Glucocorticoids 74% Radiotherapy: CRT 13.6% TBI 42% SCT: 49.4%	LS BMD Z-score ≤-2: 1st 15.7%, 2nd 14.6% FN BMD Z-score ≤-2: 1st 14.5%, 2nd 4.3% TH BMD Z-score ≤-2: 1st 14.5%, 2nd 7.2% TB BMD Z-score ≤-2: 1st 7%, 2nd 9,3%	SB: high risk AB: low risk DB: low risk
	van Atteveld 2019[b/c]	2032 (development) 403 (validation)	Median time since cancer dx: SJLIFE (model development) 21.6 yrs (range 10.4-40.6) Dutch survivors (model validation) 15.1 yrs (range 5.1-39.8)	Various pediatric tumors	Chemotherapy: SJLIFE Alkylating agent 56.6% MTX 53.9% GCs 53.9% Dutch survivors Alkylating agent 50.6% MTX 60.5% GCs 70.0% Radiotherapy: SJLIFE Cranial 33.9% Abdominal 21.7% Dutch survivors Cranial 22.6% Abdominal 6.5% SCT: NR	LS and/or TB BMD Z-score ≤-1: SJLIFE 51.5% (LS 25.1%, TB 48.0%); Dutch survivors 44.7% (LS 27.3%, TB 37.0%) LS and/or TB BMD Z-score ≤-2: SJLIFE 20.2%; Dutch survivors 10.2%	SB: low risk AB: low risk DB: low risk
	van Iersel 2019[c]	3141	Mean time since treatment 24.1 (range 6.8 to 51.1) years	Various pediatric tumors	Chemotherapy: Any 85.2% Alkylating agents 58.8% Radiotherapy: CRT 34.6% SCT: NR	QCT LS BMD Z-scores <-2: 25.6%	SB: high risk AB: high risk DB: low risk
	van Santen 2020	177	Median 16 years (range 1-62)	Craniopharyngioma (100%)	Chemotherapy: 0% Radiotherapy: CRT: 51% ^{90}Yttrium brachytherapy: 13% SCT: None	LS, TB or FN BMD T or Z-score <-1: 50% LS, TB or FN BMD T-score between -1 and -2.5 or Z-score between -1 and -2: 46% LS, TB or FN BMD T-score below -2.5 or Z-score below -2: 24%	SB: high risk AB: high risk DB: low risk

	Watsky 2014[c]	418	Median time from completion of treatment of ALL was 8.5 years (range, 4.5‑19.1 years)	ALL (100%)	Chemotherapy: Corticosteroids 100% MTX 100% Cyclophosphamide 100% Radiotherapy: CRT >24Gy 8.4% SCT: 0%	QCT LS BMD Z-scores <-1: 30.9% QCT LS BMD Z-scores <-2: 6.9%	SB: high risk AB: low risk DB: low risk
	Wei 2018	49	Median (range) time since HSCT-TBI 9.1 (2.3-16.6) years. >2 years after Rx for chemotherapy-only participants	ALL 85% AML 15%	Chemotherapy: NR, apart from steroids 100% Radiotherapy: TBI: 67.3% CRT 33.4% SCT: 67.3%	LS BMD Z-score <-2: 4.1% LS BMAD Z-score <-2: 0%	SB: low risk AB: low risk DB: low risk
	Wilson 2016[c]	862	Median duration between diagnosis and follow-up was 25.1 years (range, 10.5 to 47.7 years)	ALL (100%)	Chemotherapy: HD Methotrexate 60.7% MTX 100% Cyclophosphamide 100% Glucocorticoids 100% Radiotherapy: CRT 48.5% CRT+CS or TBI 12.4% SCT: NR	QCT LS BMD Z-score ≤ -1: 39.4% for men, 20.9% for women QCT LS BMD Z-score ≤ -2.5: 2.8% for men, 0.7% for women	SB: high risk AB: low risk DB: unclear
	Woo Han 2015	108	Mean duration since cancer treatment 9.2 yrs ± 5.4 yrs	Various pediatric tumors	Chemotherapy: 98.2%, type NR Radiotherapy: 55.6% Head and neck radiation: 45% (assuming this is 49 out of the 60 who had radiotherapy but this is not explicit) SCT: 16.7%	BMD Z-score <-1: 52.7% at any site (39.6% LS, 39.2% FN, 38.79% TH) BMD Z-score <-2: 16.7% at any site (13.2% LS, 13.7% FN, 13.9% TH)	SB: high risk AB: low risk DB: low risk
	Zürcher 2020	150	Median 22.2 years since diagnosis (IQR 16.0; 29.1)	Leukemia 35% Lymphoma 21% CNS 11% Other 32%	Chemotherapy: Glucocorticoids: 61% Radiotherapy: CRT 17% SCT: NR	LS, TH and/or FN BMD Z-score <-1 measured by pQCT or DXA: females: 56%, males: 70% LS BMD Z-score <-1 measured by pQCT or DXA: females: 30%, males: 50% pQCT Z-score (tibia 4%) <-1: Total vBMD: females 32.9%, males 55.7% Trabecular vBMD: females 20.5%, males 20.5% Any pQCT site: females 34.3%, males 55.7% DXA Z-scores <-1: FN: females 26.4%, males 23.8% TH: females 16.7%, males 17.9% LS: females 28.6%, males 43.5% Any DXA site: females 41.7%, males 50.0%	SB: unclear AB: low risk DB: low risk

GRADE assessment:

Study design:	+4	Cross-sectional cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 13/47, unclear in 10/47, high in 24/47; Attrition bias low in 35/47, unclear in 2/47, high in 10/47; Detection bias low in 38/47, unclear in 5/47, high in 4/47

Consistency:	0	No important inconsistency: 41/47 studies show an increased risk and 6/47 an equal risk of low and very low BMD compared to healthy controls based on what would be expected from normal distribution.
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients
Publication bias:	0	Unlikely
Effect size:	0	NA
Dose-response:	0	NA
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊖ MODERATE
Conclusion:		CAYA cancer survivors are at risk for low bone mineral density (Z-score ≤-1) (29 studies increased risk, 4 studies equal risk compared to healthy controls) CAYA cancer survivors are at risk for very low bone mineral density (Z-score ≤-2) (36 studies increased risk, 3 studies equal risk compared to healthy controls) Prevalence of low lumbar spine BMD ranges from 10.5% to 50.5% after a follow-up ranging from 2.7 to 27.2 years (28 studies); Prevalence of low total body BMD ranges from 11.0% to 48.0% after a follow-up ranging from 2.7 to 21.6 years (9 studies); Prevalence of low femoral neck BMD ranges from 25.1% to 42.9% after a follow-up ranging from 6.1 to 22.2 years (4 studies); Prevalence of low total hip BMD ranges from 17.3% to 38.8% after a follow-up ranging from 9.2 to 24.3 years (3 studies); Prevalence of low BMD at 1 or more sites ranges from 20% to 59.1% after a follow-up ranging from 5.4 to 22.2 years (12 studies); Prevalence of very low lumbar spine BMD ranges from 1.5% to 25.9% after a follow-up ranging from 2.7 to 26.1 years (23 studies); Prevalence of very low total body BMD ranges from 2.3% to 33% after a follow-up ranging from 2.7 to 21.6 years (7 studies); Prevalence of very low femoral neck BMD ranges from 2.2% to 24.4% after a follow-up ranging from 6.1 to 15.0 years (6 studies); Prevalence of very low total hip BMD ranges from 2.2% to 14.5% after a follow-up ranging from 9.2 to 15.0 years (3 studies); Prevalence of very low BMD at 1 or more sites ranges from 3.8% to 24.0% after a follow-up ranging from 3.0 to 21.6 years (12 studies) in CAYA cancer survivors. (47 studies, 21,262 participants)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

[a/b/c]: (possible) overlap in included patients.

1b. What is the risk (%) of lower BMD in CAYA cancer survivors?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Disease category	Treatment (% treated)	Risk (mean/median BMD Z-score)	Risk of bias
1.b. Risk of lower BMD **(n=30 studies)**	Aaron 2019	242	Mean time since treatment is 13.1 years (range 4-29 years)	ALL (100%)	Chemotherapy: Glucocorticoids 100% Methotrexate 100% Radiotherapy: CRT 59% SCT: 0%	Mean LS BMD Z-score: -0.2 (range -2.9-3.1) Mean TB BMD Z-score: -0.2 (range -3.3-3.5)	SB: unclear AB: low risk DB: low risk
	Alikasifoglu 2005[a]	59	Mean 3.40 (1.77) years after cessation of therapy	ALL (100%)	Chemotherapy: Conventional dose prednisolone 51% Megadose methylprednisolone 49% Cyclophosphamide 100% HD-MTX 100% Radiotherapy: CRT 76% SCT: 0%	Mean (SD) LS BMD Z-score: -1.73 (0.84)	SB: high risk AB: high risk DB: low risk
	Benmiloud 2010	89	Mean time since treatment (±SD) 15.0 ± 4.5 years	ALL 83% NHL 17%	Chemotherapy: Prednisolone 100% Dexamethasone 52.8% Methotrexate 100% Radiotherapy RT at any site: 53.9% CNS RT 36% CRT 32.6% CSRT 3.4% TBI 18.0% SCT 18.0%	Mean LS BMD Z-score: –0.60±1.14 Mean FN BMD Z-score: –0.22±1.04 Mean Hip BMD Z-score: –0.26±0.98	SB: low risk AB: high risk DB: low risk
	Choi 2013	78	Mean time from initial diagnosis to measurement of BMD: 4.42±2.47 in males, 5.36±3.2 years in females	ALL 49% AML 45% CML 6%	Chemotherapy: Glucocorticoids for chemotherapy 42% Glucocorticoids for GVHD 53% Radiotherapy: 62% SCT: 64%	LS BMD Z-score: mean -0.91±1.41 FN BMD Z-score: mean -1.13±1.79	SB: unclear AB: low risk DB: low risk
	De Matteo 2019	72	Mean (±SD) time since treatment 41.2 ±37.8 months (95% CI: 49.9, 32.5)	ALL (100%)	Chemotherapy: Prednisone 100% Dexamethasone 100% MTX 100% Cyclophosphamide 100% Radiotherapy: 4% SCT: 0%	Proximal phalanx (QUS) mean AD-SoS Z-score: −1.22 ± 1.19 (95% CI: −1.5,−0.94)	SB: unclear AB: low risk DB: unclear

	Esbenshade 2014	171 (91 had DXA)	Median 2.68 years (range 0.03–10.83) off therapy	ALL 70.8% AML 0.6% Lymphoma 21.1% LCH 7.6%	Chemotherapy: Steroids 100% Other agents NR Radiotherapy: NR SCT: NR	Median TB BMD Z-score: 0.1 (range -4.2, 3.6) Median LS BMD Z-score: 0.0 (range -4.2, 3.3)	SB: low risk AB: high risk DB: low risk
	Gawade 2012[a]	662	Median 26.1 (IQR 21.5, 31.6) years from diagnosis	ALL (100%)	Chemotherapy: Glucocorticoids 100% Methotrexate 100% Cyclophosphamide 66% Radiotherapy: TBI 2% CRT 66% SCT: 2%	Median QCT LS BMD Z-score: −0.36 (IQR −1.14, 0.36)	SB: high risk AB: low risk DB: low risk
	Henderson 1996	60	At least 12 months post chemotherapy Mean time since treatment: 4.3 yrs range 12mths-14.5 yrs	Wilms 8.3%; PNET 5% Teratoma 3.3%; Ewing 1.7% Hepatoblastoma 1.7% ALL 50%; ANLL 5% Hodgkin 8.3%; NHL 11.7%	Chemotherapy: Ifofosfamide 3% Glucocorticoids 75% MTX 62% Radiotherapy: CRT 25% SCT: NR	Mean LS BMD Z-score for all patients = -0.28 ± 0.14 (SE) Range -3.3 to 1.89	SB: unclear AB: unclear DB: low risk
	Im 2018[a]	856	NR (± 25 yrs)	Various pediatric tumors	Chemotherapy: Methotrexate 100% Glucocorticoid 100% Radiotherapy: CRT 59% SCT: NR	Median QCT LS BMD Z-score (range): −0.4 (−3.5, 5.4)	SB: high risk AB: low risk DB: low risk
	Isaksson 2020	125	Mean (SD) follow-up 24.3 years (7.1)	Various pediatric tumors	Chemotherapy: GCs 19 (15%) Alkylating agents 16 (13%) Median cyclophosphamide equivalent dose 4854 mg/m^2 MTX 17 (14%) Median methotrexate dose 11 g/m^2 Radiotherapy: CRT 26% SCT: 2%	Survivors: Mean LS BMD Z-score: -0.25 (1.11) Mean TH BMD Z-score: -0.17 (1.06) Mean FN BMD Z-score: -0.14 (0.99) Controls: Mean LS BMD Z-score: -0.36 (1.10) Mean TH BMD Z-score: -0.13 (1.09) Mean FN BMD Z-score: -0.16 (1.06)	SB: high risk AB: low risk DB: low risk
	Jones 2008[a]	309	At least 4 years of continuous remission	ALL (100%)	Chemotherapy: MTX 100% Prednisone 100% Radiotherapy: NR SCT: NR	Mean QCT LS BMD Z-score (SD): -0.47 (1.26)	SB: high risk AB: low risk DB: low risk
	Joyce 2011[a]	493	12.7 to 46.5 years from diagnosis of	ALL (100%)	Glucocorticoids 100% Methotrexate 100%	Mean LS BMD Z-scores: –0.3±1.2	SB: high risk AB: low risk

			childhood ALL (median, 27.2y)		Cyclophosphamide 100% Radiotherapy: CRT 70% SCT: NR		DB: low risk
	Kaste 2006a[a]	320	NR	Leukemia/lymphoma 45,6% Brain tumor 44,4% Solid tumor 10,0%	NR	QCT LS BMD Z-score median: -1.43 range: -5.96 to 3.2 DXA LS BMD Z-score median: -1.30 (-5.5 to 2.8)	SB: low risk AB: low risk DB: low risk
	Kaste 2014[a]	424	Median 8.4 yrs (4.6-19.1) from completion of ALL therapy to entry into study	ALL (100%)	Chemotherapy: Glucocorticoids 100% Methotrexate 100% Cyclophosphamide 100% Radiotherapy: CRT 36.1% SCT: NR	QCT LS BMD Z-score, median, range: Females: -0.3 (-3.7 to 3.2) Males -0.6 (-3.9 to 5.1)	SB: high risk AB: high risk DB: low risk
	Latoch 2021	326	Median (range) 6.12 (4.0-22.0) years since end of treatment	Various pediatric tumors (excluding brain and bone tumor)	Chemotherapy: Glucocorticoids 71.2% Methotrexate 50.9% Radiotherapy: CRT 25.5% TBI 4% Abdominal RT 16.7% SCT: 7%	Mean LS BMD Z-score: 1st –0.277, 2nd –0.180 Mean TB BMD Z-score: 1st –0.176, 2nd –0.262	SB: high risk AB: low risk DB: low risk
	Le Meignen 2011	159	Mean time from diagnosis to DXA 14.66 ± 0.44 yrs	ALL (81.8%) AML (18.2%)	Chemotherapy: Glucocorticoids 86.2% Other chemotherapy NR Radiotherapy: CRT 18.9% TBI 40.4% of HSCT recipients SCT: 34%	Mean BMD Z-score ± SE: FN -0.19± 0.08; LS -0.37 ± 0.08	SB: low risk AB: high risk DB: high risk
	Mostoufi-Moab 2012	55	At least a 3 year interval from alloHST (median 6.8 years, range 3.0 to 16.4)	AML 42% ALL 22% CML 11% MDS 9% JML 9% Aplastic anemia 4% Bone marrow failure syndrome 4%	Chemotherapy: Conditioning regimen: Cyclophosphamide + thiotepa (69%) Busulfan + cyclophosphamide (unknown %) Busulfan + Cytoxan ± melphelan or fludarabine (unknown %) Radiotherapy: TBI 69% SCT: 100%	QCT Trabecular vBMD Z-score -1.05 (-1.33 to -0.78) QCT Cortical vBMD Z-score -0.20 (-0.48 to 0.08)	SB: low risk AB: low risk DB: low risk
	Nysom 1998	95	Median 10.7 yrs after diagnosis (3.4-23.4) Median 7.6 yrs after off-therapy (1.2-18.3)	ALL (100%)	Chemotherapy: MTX 100% Corticosteroids 100% Radiotherapy: CRT 41.1% SCT: 0%	Mean TB BMC/area Z-score - 0.17 (- 2.90-2.80) Mean TB BMC Z-score - 0.37 (- 3.33-2.64) Mean TB BMD Z-score - 0.39 (- 3.18-2.44) Mean LS BMD Z-score - 0.55(- 2.99-1.84)	SB: low risk AB: low risk DB: low risk

	Pietila 2006	52	Mean 6.4 yrs (range 1.4-14.8 y) after off-therapy	Brain tumors (100%)	Chemotherapy: 24% Steroids 100% Radiotherapy: CRT 21.7% Craniospinal 11.1% Combination of CRT and chemotherapy 19.6% SCT: 0%	Mean TB BMD Z-score -1.7 (-5.7 - +0.6)	SB: high risk AB: low risk DB: low risk
	Pluskiewicz 2002	54	Mean (±SD) time since treatment 4.6 years ± 3.4 SD	ALL (100%)	Chemotherapy: MTX 100% Corticosteroids 100% Radiotherapy: CRT 38.9% SCT: NR	Mean QUS Ad-SoS values patients (2018 ±73 m/s) and controls (2003 ±80 m/s), not significantly different.	SB: unclear AB: low risk DB: low risk
	Remes 2018	74	Mean time since cessation of tumor therapy (±SD): 18.9 ± 6.1 years	Brain tumors (100%)	Chemotherapy: 63.5% Radiotherapy: Local irradiation: 52.7% Craniospinal with local boost to the tumor bed: 40.5% Cranial with local boost to the tumor bed: 4.1% Stereotactic: 2.7% SCT:NR	Mean (SD) Z-score: LS BMD -0.83 (1.15); FN BMD right: -0.91 (0.93); left: -0.82 (1.93); Hip BMD right: -0.77 (1.08); left: -0.69 (1.16)	SB: high risk AB: low risk DB: unclear
	Ruza 2006	95 (63 had DXA)	Mean duration of remission was 6.12 years (SD 3.67) in patients with osteosarcomas and 6.11 years (SD 3.73) for Ewing's sarcoma patients	Osteosarcoma 62% Ewing's sarcoma 38%	Chemotherapy: MTX 100% Cyclophosphamide 100% Radiotherapy: NR SCT: NR	Mean BMD Z-score osteosarcoma LS BMD: -0.76 (0.96); FN BMD: -0.88 (1.10) Mean BMD Z-score Ewing´s sarcoma LS BMD: - 0.84 (1.05); FN BMD: -0.76 (1.15)	SB: high risk AB: high risk DB: low risk
	Sawicka-Zukowska 2013	74	Not specifically stated, but the average time at the time of analysis post treatment completion would be 6.6 years	ALL 86.5% Lymphomas 13.5%	Chemotherapy: NR Radiotherapy: CRT 21.6% SCT: NR	Mean TB BMD Z-score -0.01 Mean LS BMD Z-score -0.26 Mean TB BMC Z-score 0.32	SB: unclear AB: unclear DB: low risk
	Siegel 2017	475	Mean (±SD) time after Rx 5.4 ± 4.3 years	ALL 59.6% AML 7.4% Hodgkins 6.1% NHL 14.3% NBL 4.6% Renal tumour 1.3% Sarcoma 6.1% Other 0.6%	Chemotherapy: Corticosteroid 83.4% Methotrexate 77.1% Radiotherapy: Cranial / craniospinal 13.3% TBI 9.9% SCT: 17.9%	Mean BMD Z-score –0.1 ± 1.2 for TB and LS	SB: low risk AB: low risk DB: low risk

	Siviero-Miachon 2017	56	Mean (±SD) time since treatment 8.1 (±3.5) yrs post therapy	ALL (100%)	Chemotherapy: MTX 100% Cyclophosphamide 100% Steroids 100% Radiotherapy: CRT 44.6% Spinal XRT 1.8% SCT: 0%	Mean LS and TB BMD Z-score in irradiated patients –0.78(Mean (±SD) time since treatment 1.04), -0.89 (Mean (±SD) time since treatment 1.0) respectively. In non-irradiated patients -0.79 (Mean (±SD) time since treatment 0.91), -0.37 (Mean (±SD) time since treatment 0.79).	SB: high risk AB: low risk DB: low risk
	Tabone 2021	89	Mean (± SD) interval from diagnosis to first scan 7.0 ± 4.7 yrs Mean (± SD) interval from diagnosis to second scan 11.7 ± 5.2 yrs	ALL 76.4% AML 23.6%	Chemotherapy: Glucocorticoids 74% Radiotherapy: CRT 13.6% TBI 42% SCT: 49.4%	Mean (±SD) LS BMD Z-score: 1st −1.18 ± 1.10, 2nd −1.07 ± 1.05 Mean (±SD) FN BMD Z-score: 1st −0.85 ± 1.02, 2nd −0.64 ± 0.97 Mean (±SD) TH BMD Z-score: 1st −0.78 ± 1.11, 2nd −0.59 ± 1.17 Mean (±SD) TB BMD Z-score: 1st −0.36 ± 1.19, 2nd −0.33 ± 1.16	SB: high risk AB: low risk DB: low risk
	Van Beek 2006	90	Mean (range) 12.7 (2.0-29.7) yrs after dx	ALL (100%)	Chemotherapy: Prednisone 52.2% Dexamethasone 47.8% MTX 71.1% Radiotherapy: CRT 21.1% SCT: 0%	"BM(A)D at the LS and TB was normal in the survivors compared to the controls"	SB: unclear AB: low risk DB: low risk
	van Santen 2020	177	Median 16 years (range 1-62)	Craniopharyngioma (100%)	Chemotherapy: 0% Radiotherapy: CRT: 51% ^{90}Yttrium brachytherapy: 13% SCT: None	Mean TB BMD Z-score: 0.1 ± 1.5 (range, -4.1 to 3.5) Mean FN BMD Z-score: -0.1 ± 1.3 (range, -2.7 to 4.7), Mean LS BMD Z-score: 0.0 ± 2.0 (range, -3.5 to 6.8)	SB: high risk AB: high risk DB: low risk
	Wei 2018	49	Median (range) time since HSCT-TBI 9.1 (2.3-16.6) years. >2 years after Rx for chemotherapy-only participants	ALL 85% AML 15%	Chemotherapy: NR, apart from steroids 100% Radiotherapy: TBI: 67.3% CRT 33.4% SCT: 67.3%	Mean LS BMD Z-score –0.52 (95%CI –0.89, –1.15) Mean LS BMAD Z-score 0.20 (95%CI –0.15, 0.54)	SB: low risk AB: low risk DB: low risk
	Wilson 2016[a]	862	Median duration between diagnosis and follow-up was 25.1 years (range, 10.5 to 47.7 years)	ALL (100%)	Chemotherapy: HD Methotrexate 60.7% MTX 100% Cyclophosphamide 100% Glucocorticoids 100% Radiotherapy: CRT 48.5% CRT+CS or TBI 12.4% SCT: NR	Mean QCT LS BMD Z-score -0.64 (±SD 1.08) for men; -0.04 (±SD 1.18) for women.	SB: high risk AB: low risk DB: unclear

GRADE assessment:
Study design: +4 Cross-sectional cohort studies

Study limitations:	-1	Some limitations: Selection bias low in 8/30, unclear in 7/30, high in 15/30; Attrition bias low in 21/30, unclear in 2/30, high in 7/30; Detection bias low in 26/30, unclear in 3/30, high in 1/30
Consistency:	0	No important inconsistency: 24/30 studies show an increased risk and 6/30 studies show an equal risk of lower BMD compared to healthy controls based on what would be expected from normal distribution.
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients
Publication bias:	0	Unlikely
Effect size:	0	NA
Dose-response:	0	NA
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⨁⨁⨀ MODERATE
Conclusion:		CAYA cancer survivors are at risk for lower bone mineral density. (24 studies increased risk, 6 studies equal risk compared to healthy controls; 6,742 participants)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

[a]: (possible) overlap in included patients.

1c. What is the risk (%) of fractures in CAYA cancer survivors?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Disease category	Treatment (% treated)	Risk (%fractures)	Risk of bias
1.c. Risk of fracture **(n=10 studies)**	Aaron 2019[a]	242	Mean time since treatment is 13.1 years (range 4-29 years)	ALL (100%)	Chemotherapy: Glucocorticoids 100% Methotrexate 100% Radiotherapy: CRT 59% SCT: 0%	At least 1 vertebral fracture (on X-ray): 22.3%	SB: unclear AB: low risk DB: low risk
	Bloomhardt 2020	542	Mean time since treatment (±SD) 6.0±5.0 years (range 2.0-35.1)	ALL 65.1% Other acute leukemia 6.5% HL 14.6% NHL 13.8%	Chemotherapy: Dexamethasone 59.6% Prednisone 35.4% Any glucocorticoid 95% Cyclophosphamide 85.1% High-dose methotrexate 25.8% Radiotherapy: CRT 20.7% TBI 8.1% SCT: NR	Frequency of fractures: Non-digit (1 or more posttreatment) fracture: 21.4% Upper extremity long bone (includes wrist): 12.2% Lower extremity long bone (includes ankle): 5.4% Hand/foot: 4.1% Vertebra: 0.7% Other (clavicle, rib, jaw, pelvis, nose): 3.9% Multiple fractures: 2 fractures: 3.0%; ≥3 fractures: 1.7%	SB: high risk AB: low risk DB: low risk
	Fiscaletti 2021	251	Median 15.1 years (range 5.4 to 28.2 years) since cancer diagnosis	ALL (100%)	Chemotherapy: Glucocorticoids 100% Methotrexate 100% Radiotherapy: CRT 59% SCT: None	Frequency of fractures: Vertebral fractures: 23% Non-vertebral fractures: 31%	SB: low risk AB: low risk DB: low risk
	Hobush 2014	56	Minimum FU 5 years after treatment; Mean FU 15 years (5-48 years)	Ewing sarcoma 89.3% primitive neuro-ectodermal tumor 10.7%	Chemotherapy: Alkylating agents (ifosfamide/cyclophosphamide) 100% Radiotherapy: Local radiation 64% SCT: NR	21 pts (41%) reported 29 fractures (6 (11%) low impact fracture, 15 (27%) high impact fracture)	SB: high risk AB: low risk DB: low risk
	Im 2021	2453 (discovery) 1417 (replication)	At least 5 years Discovery: Approximately 37 years Replication: Approximately 25 years	Various pediatric tumors (excluding bone tumor)	Chemotherapy: Glucocorticoids 47.2% discovery, 48.3% replication IV MTX 18.5% discovery, 29.2% replication IT MTX 38.4% discovery, 38.3% replication Radiotherapy: CRT 45.9% discovery, 38.5% replication SCT: 0% (exclusion criterion)	Fracture frequency (any type post diagnosis) Discovery: 37.9% Replication: 46.0%	SB: high risk AB: low risk DB: high risk
	Lemay 2019[a]	246	Median time since diagnosis 15.2	ALL (100%)	Chemotherapy: Glucocorticoids 98%	Presence of vertebral fracture (on X-ray): 23.2%	SB: unclear AB: low risk

			(range 5.4-28.2) years		Methotrexate 98% Radiotherapy: CRT 40.2% SCT: 0%		DB: low risk
	Liuhto 2020	4459	NR	Various pediatric tumors	NR	Fractures (CCS vs. controls): HR 1.3, 95%CI 1.1-1.6	SB: low risk AB: high risk DB: high risk
	Mueller 2018	3152	Median 9.1 years (range 0.1-27 years) after index date (= 5 years after dx)	Various pediatric tumors	NR	Fractures (CCS vs. controls): HR 1.6, 95%CI 1.1-2.3	SB: low risk AB: high risk DB: high risk
	van Santen 2020	177	Median 16 years (range 1-62)	Craniopharyngioma (100%)	Chemotherapy: 0% Radiotherapy: CRT: 51% ^{90}Yttrium brachytherapy: 13% SCT: None	Fractures: 18% over time (5.8 fractures per 1000 person-years)	SB: high risk AB: high risk DB: high risk
	Wilson 2012	7414	Median length of follow-up was 22.7 years (range, 15.6-34.2 years)	Various pediatric tumors	Chemotherapy: Methotrexate 43.6% Steroids 47% Radiotherapy: CRT 32% Pelvic RT 13% SCT: 0%	Proportion of participants with fractures over their lifetime Survivors: 34.8% Siblings: 38.9%	SB: high risk AB: low risk DB: high risk

GRADE assessment:		
Study design:	+4	Cross-sectional cohort studies
Study limitations:	-2	Some limitations: Selection bias low in 2/3, high in 1/3; Attrition bias low in 1/3, high in 2/3; Detection bias high in 3/3
Consistency:	-1	Important inconsistency, two studies show an increased risk of fractures compared to controls, and one study shows a lower percentage of fractures compared to controls
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients
Publication bias:	0	Unlikely
Effect size:	0	NA
Dose-response:	0	NA
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ VERY LOW
Conclusion:		Increased risk of fractures in CAYA cancer survivors vs. controls. (2 studies significant effect, 1 study no significant effect, 15,025 participants)

GRADE assessment:		
Study design:	+4	Cross-sectional cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 1/8, unclear in 2/8, high in 5/8; Attrition bias low in 7/8, high in 1/8; Detection bias low in 5/8, high in 3/8
Consistency:	0	Percentage of patients with fractures are comparable
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients
Publication bias:	0	Unlikely
Effect size:	0	NA
Dose-response:	0	NA
Plausible confounding:	0	No plausible confounding

Quality of evidence:	⊕⊕⊕⊖ MODERATE
Conclusion:	Incidence of fractures ranges from 18.0% to 46.0% after a follow-up ranging from 6 to 37 years (8 studies) in CAYA cancer survivors. (8 studies, 12,798 participants)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip. [a](possible) overlap in included patients.

1d.What is the risk of low and very low BMD in male versus female CAYA cancer survivors?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.d. Risk low BMD for sex **(n=13 studies)**	Bhandari 2021	446 CCS	Median 14.2 years (range 2–65 years) since completing therapy	Chemotherapy: Glucocorticoids 57.5% Methotrexate 40.4% Radiotherapy: CRT NR TBI ± 24% SCT: 40.8% (30.9% allogeneic)	LS BMD Z-score ≤-1: 33.9%	Multivariable model: LS BMD Z-score <-1: sex NS	SB: low risk AB: high risk DB: low risk CF: low risk
	Bloomhardt 2020	542 CCS	Mean time since treatment (±SD) 6.0±5.0 years (range 2.0-35.1)	Chemotherapy: Dexamethasone 59.6% Prednisone 35.4% Any glucocorticoid 95% Cyclophosphamide 85.1% High-dose methotrexate 25.8% Radiotherapy: CRT 20.7% TBI 8.1% SCT: NR	LS BMD Z-score ≤-1: 17.2% LS BMD Z-score ≤-2: 3.5%	Multivariable model: LS BMD Z-score <-1: male sex OR 1.4, 95%CI 0.9-2.4, p=0.06	SB: high risk AB: low risk DB: low risk CF: high risk
	Den Hoed 2015	346 adult CCS	Median time after cessation of treatment 16.7 years (IQR 12.4–23.0)	Chemotherapy: Prednisone 63.6% Dexamethasone 37.0% Cyclophosphamide 49.7% Methotrexate 64.9% Ifosfamide 10.8% Radiotherapy: Cranial-spinal 16.5% Total body 3.8 % CRT 4.3% Abdominal 2.3% SCT: 4.9%	TB BMD or LS BMD Z-score <−1: 45% of the CCS. 38% TB, 27% LS, 20% at both TB and LS. TB BMD or LS BMD Z-score <−2: 9% (TB), 3% (LS)	Multivariable model: LS BMD Z-score <-1: male gender OR 2.3, 95%CI 1.2-4.2 TB BMD Z-score <-1: male gender OR 1.5, 95%CI 0.9-2.7	SB: high risk AB: low risk DB: low risk CF: low risk
	Gurney 2014[a]	845 adult ALL survivors	>10 years after diagnosis	Chemotherapy: Glucocorticoids 100% Methotrexate 100% Cyclophosphamide % NR Radiotherapy: CRT: 61.3% CRT + spinalRT or TBI 12.5% SCT: 2.5%	QCT LS BMD Z-score ≤-1: 29.5% QCT LS BMD Z-score ≤-2: 5.7%	Multivariable model: QCT LS BMD Z-score ≤-1: male sex OR 2.38, 95%CI 1.74–3.27, p<0.0001	SB: unclear AB: low risk DB: low risk CF: high risk
	Kaste 2006a[a]	320 CCS	NR	NR	QCT LS BMD Z-score: <-2: n=96 (30%)	Multivariable model: LS BMD Z-score <-2: sex NS	SB: low risk AB: low risk DB: low risk CF: unclear

				QCT LS BMD Z-score median: -1.43 range: -5.96 to 3.2 DXA LS BMD Z-score <-2: n=89 (27.8%) DXA LS BMD Z-score median: -1.30 (-5.5 to 2.8)		
Kaste 2006b[a]	study I n=141, study II n=57 ALL survivors	Study I: >4 years after therapy (mean time after dx 11.7 yrs) Study II : 2-5 years after study I (mean time after dx 16.1 yrs)	Chemotherapy: MTX 100% Prednisone 100% Radiotherapy: CRT 37% of 57; percentage of 141 NR SCT: 0%	Study I: LS BMD Z-score <-1 10.5%; LS BMD Z-score <-2 1.5% Study II: LS BMD Z-score <-1 19.3%; LS BMD Z-score <-2 0%	Multivariable model: LS 'low' BMD (Z-score cut-point NR, presumably <-1): study I male sex P=0.051, study II NS	SB: unclear AB: high risk DB: low risk CF: unclear
Kaste 2009[a]	109 HL survivors	Median 7.5 yrs (5.8-20.7 yrs) from diagnosis to QCT	Chemotherapy: Cyclophosphamide 67.9% Methotrexate 69% Prednisone 65% Radiotherapy: LS RT 28.4% Pelvic RT 6% SCT: NR	QCT LS BMD Z-score <-1.5: 14.7% QCT LS BMD Z-score <-2.0: 7.3%	Multivariable model: QCT LS BMD Z-score <-1.5: male sex OR 3.58 (95% CI:1.06–12.10), p=0.040	SB: low risk AB: low risk DB: high risk CF: low risk
Latoch 2021	326 CCS	Median (range) 6.12 (4.0-22.0) years since end of treatment	Chemotherapy: Glucocorticoids 71.2% Methotrexate 50.9% Radiotherapy: CRT 25.5% TBI 4% Abdominal RT 16.7% SCT: 7%	LS BMD Z-score <-1: 20% TB BMD Z-score <-1: 24% LS and/or TB BMD Z-score <-2: 8%	Multivariable model: LS BMD Z-score <-1: male sex OR 1.84, 95%CI 1.00–3.41, p=0.050 TB BMD Z-score <-1: not included in multivariable model	SB: high risk AB: low risk DB: low risk CF: low risk
Leung 2007	155 SCT survivors	Median 9 yrs from HSCT (range 3 to 10 years)	Chemotherapy: Alkylator-based conditioning pre-HSCT in 21% Radiotherapy: TBI-based conditioning in 79% SCT: yes (100%)	QCT BMD Z-score <-1: 39% (site NR, presumably LS)	Multivariable model: QCT BMD Z-score <-1: female sex HR 1.94, 95% CI 1.38 to 2.72, p=0.010	SB: low risk AB: low risk DB: unclear CF: high risk
Polgreen 2012	319 CCS	Mean time since treatment (±SE) 10.1 ± 0.2 years (range 4.3-17.8)	Chemotherapy: Corticosteroid: 42.0% Radiotherapy: 23.2% Cranial (CNS) 9.7%, other 43 13.5% SCT: 0%	TB BMD Z-score <-1: 11% LS BMD Z-score <-1: 23% TB BMD Z-score <-2: 2.3% LS BMD Z-score <-2: 3.5%	Multivariable model: TB BMD Z-score <-1: sex (male vs. female), OR 2.6, 0.8-10.0, p=0.137 LS BMD Z-score <-1: sex (male vs. female), OR 1.6, 95%CI 0.7-3.4, p=0.270	SB: low risk AB: low risk DB: low risk CF: low risk

	Siegel 2017	475 CCS	Mean (±SD) time after Rx 5.4 ± 4.3 years	Chemotherapy: Corticosteroid 83.4% Methotrexate 77.1% Radiotherapy: Cranial / craniospinal 13.3% TBI 9.9% SCT: 17.9%	TB or LS BMD Z-scores ≤–1: 29.3% (LS 22.8%, TB 21.9%) TB or LS BMD Z-scores ≤–2: 8.2% (LS 7.4%, TB 4.0%)	Multivariable model: TB or LS BMD Z-scores ≤–2: male sex, OR 3.4, 95% CI, 1.3–9.0	SB: low risk AB: low risk DB: low risk CF: high risk
	Sloof 2019	253 CCS	NR	Chemotherapy: NR Radiotherapy: CRT 36% SCT: 0%	BMD Z-score <-1: 25.4% (site NR)	Multivariable model: BMD Z-score <-1: female sex OR 1.64, 95%CI 0.80–3.35, p=0.18	SB: unclear AB: low risk DB: unclear CF: unclear
	van Atteveld 2019[a]	2032 adult CCS	Median time since cancer dx: 21.6 yrs (range 10.4-40.6)	Chemotherapy: Alkylating agent 56.6% MTX 53.9% GCs 53.9% Radiotherapy: Cranial 33.9% Abdominal 21.7% SCT: NR	LS and/or TB BMD Z-score ≤-1: 51.5% (LS 25.1%, TB 48.0%) LS and/or TB BMD Z-score ≤-2: 20.2%	Multivariable model: LS and/or TB BMD Z-score ≤-1: male sex β 1.12 (SE 0.14), OR 3.07, 95%CI 2.35-4.02 LS and/or TB BMD Z-score ≤-2: male sex β 1.19 (SE 0.17), OR 3.28, 95%CI 2.37-4.54	SB: low risk AB: low risk DB: low risk CF: low risk

GRADE assessment (outcome low and very low BMD):

Study design:	+4	Cross-sectional cohort studies
Study limitations:	0	No important limitations: Selection bias low in 7/13, unclear in 3/13, high in 3/13; Attrition bias low in 11/13, high in 2/13; Detection bias low in 10/13, unclear in 2/11, high in 1/11; Confounding low in 6/13, unclear in 3/11, high in 4/11
Consistency:	-1	Important inconsistency: five studies show a significant effect for males, one study shows a significant effect for females and seven studies show no significant effect of sex
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients and events
Publication bias:	0	Unlikely
Effect size:	+1	Large magnitude of effect
Dose-response:	0	NA
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⨁⨁⨁ HIGH
Conclusion:		Increased risk of low BMD (Z-score ≤-1 or ≤-2) for male CAYA cancer survivors. (5 studies significant effect, 1 study significant effect in opposite direction, 7 studies no significant effect; 6,309 participants)

GRADE assessment (outcome very low BMD):

Study design:	+4	Cross-sectional cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 3/3; Attrition bias low in 3/3; Detection bias low in 3/3; Confounding low in 1/3, unclear in 1/3, high in 1/3
Consistency:	-1	Important inconsistency: two studies show a significant effect for males, and one study shows no significant effect of sex
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients and events
Publication bias:	0	Unlikely
Effect size:	+1	Large magnitude of effect
Dose-response:	0	NA

Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⨁⨁⊖ MODERATE
Conclusion:		Increased risk of very low BMD (Z-score ≤-2) for male CAYA cancer survivors. (2 studies significant effect, 1 study no significant effect; 2,737 participants)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

[a](possible) overlap in included patients.

1e.What is the risk of lower BMD in male versus female CAYA cancer survivors?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.e. Risk lower BMD for sex **(n=10 studies)**	Benmiloud 2010	89 ALL and NHL survivors	Mean time since treatment (±SD) 15.0 ± 4.5 years	Chemotherapy: Prednisolone 100% Dexamethasone 52.8% Methotrexate 100% Radiotherapy RT at any site: 53.9% CNS RT 36% CRT 32.6% CSRT 3.4% TBI 18.0% SCT 18.0%	BMD Z-score ≤-1.0: At any site: 59.1%; At the LS: 50.5% At the FN: 25.8%; At the Hip: 31.5% BMD Z-score ≤-2: At any site: 10.1%; At the LS: 10.1% At the FN: 2.2%; At the Hip: 2.2%	Multivariable model: LS BMD Z-score (cont.): male gender (p<0.001, β NR) FN and hip BMD Z-score (cont.): NS	SB: low risk AB: high risk DB: low risk CF: low risk
	Den Hoed 2015	346 adult CCS	Median time after cessation of treatment 16.7 years (IQR 12.4–23.0)	Chemotherapy: Prednisone 63.6% Dexamethasone 37.0% Cyclophosphamide 49.7% Methotrexate 64.9% Ifosfamide 10.8% Radiotherapy: Cranial-spinal 16.5% Total body 3.8 % CRT 4.3% Abdominal 2.3% SCT: 4.9%	TB BMD or LS BMD Z-score <−1: 45% of the CCS. 38% TB, 27% LS, 20% at both TB and LS. TB BMD or LS BMD Z-score <−2: 9% (TB), 3% (LS)	Multivariable model: LS BMD Z-score (cont.): male gender β=−0.34; se=0.13, p=0.007 TB BMD Z-score (cont.): male gender NS	SB: high risk AB: low risk DB: low risk CF: low risk
	Hobush 2014	56 Ewing and PNET survivors	Minimum FU 5 years after treatment; Mean FU 15 years (5-48 years)	Chemotherapy: Alkylating agents (ifosfamide/cyclophosphamide) 100% Radiotherapy: Local radiation 64% SCT: NR	LS and/or Hip BMD T-score <-1: 55% LS and/or Hip BMD T-score <-2.5 (or Z-score <-2 in adolescents): 13%	Multivariable model: LS BMD Z-score (cont.): sex NS FN BMD Z-score (cont.): sex NS Hip BMD Z-score (cont.): sex NS	SB: high risk AB: low risk DB: low risk CF: low risk
	Jones 2008[a]	309 ALL survivors	At least 4 years of continuous remission	Chemotherapy: MTX 100% Prednisone 100% Radiotherapy: NR SCT: NR	Mean QCT LS BMD Z-score (SD): -0.47 (1.26)	Multivariable model: QCT LS BMD Z-score (cont.): male sex p=0.005	SB: high risk AB: low risk DB: low risk CF: low risk
	Kaste 2006a[a]	320 CCS	NR	NR	QCT LS BMD Z-score: <-2: n=96 (30%) QCT LS BMD Z-score median: -1.43 range: -5.96 to 3.2	Multivariable model: LS BMD (cont.): sex NS	SB: low risk AB: low risk DB: low risk CF: unclear

					DXA LS BMD Z-score <-2: n=89 (27.8%) DXA LS BMD Z-score median: -1.30 (-5.5 to 2.8)		
	Kaste 2014[a]	424 ALL survivors	Median 8.4 yrs (4.6-19.1) from completion of ALL therapy to entry into study	Chemotherapy: Glucocorticoids 100% Methotrexate 100% Cyclophosphamide 100% Radiotherapy: CRT 36.1% SCT: NR	QCT LS BMD Z-score <-1: 48.9% QCT LS BMD Z-score <-2: 6.8%	Multivariable model: QCT LS BMD Z-score (cont.): male sex β 0.38 (0.15, 0.6) P=0.001	SB: high risk AB: high risk DB: low risk CF: low risk
	Le Meignen 2011	159 ALL and AML survivors	Mean time from diagnosis to DXA 14.66 ± 0.44 yrs	Chemotherapy: Glucocorticoids 86.2% Other chemotherapy NR Radiotherapy: CRT 18.9% TBI 40.4% of HSCT recipients SCT: 34%	BMD Z-score <-2: FN 3.2%; LS 3.8%	Multivariable model: BMD Z-scores (cont.): female sex FN: β 0.18, P=0.03; LS: β -0.01, p=0.91	SB: low risk AB: high risk DB: high risk CF: high risk
	Muszynska-Roslan 2009	114 CCS	Mean time from end of therapy ALL: 2.4 ±1.9 yrs HL: 2.8 ±2.1 yrs Solid tumor: 3.7 ±4.6 yrs	Chemotherapy: Corticosteroids 68.4% Methotrexate 37.7% Radiotherapy: CRT 24.6% Abdominal XRT 36% SCT: NR	LS or TB BMD Z-score <-2: ALL: 10.5% HL: 6.9% Solid Tumor: 30.5%	Multivariable model: TB BMD Z-scores (cont.): female sex p=0.021 LS BMD Z-scores (cont.): female sex p=0.03	SB: high risk AB: low risk DB: low risk CF: unclear
	Nysom 1998	95 ALL survivors	Median 10.7 yrs after diagnosis (3.4-23.4) Median 7.6 yrs after off-therapy (1.2-18.3)	Chemotherapy: MTX 100% Corticosteroids 100% Radiotherapy: CRT 41.1% SCT: 0%	Mean TB BMC/area Z-score - 0.17 (- 2.90-2.80) Mean TB BMC Z-score - 0.37 (- 3.33-2.64) Mean TB BMD Z-score - 0.39 (- 3.18-2.44) Mean LS BMD Z-score - 0.55*(- 2.99-1.84)	TB BMC/Bone area Z-score (cont.): females β 0.41 (95%CI -0.06 to 0.88) LS BMD Z-score (cont.): male sex β 0.37 (95%CI, -0.03 to 0.76).	SB: low risk AB: low risk DB: low risk CF: high risk
	Ruza 2006	95 (63 had DXA) osteosarcoma and Ewing's sarcoma survivors	Mean duration of remission was 6.12 years (SD 3.67) in patients with osteosarcomas and 6.11 years (SD 3.73) for Ewing's sarcoma patients	Chemotherapy: MTX 100% Cyclophosphamide 100% Radiotherapy: NR SCT: NR	LS BMD Z-score <-1: 43.6% FN BMD Z-score <-1: 42.9% LS BMD Z-score <-2: 9.7% FN BMD Z-score <-2: 17.5%	Multivariable model: LS BMD (cont.): male sex p< 0.002 for areal BMD, p=0.12 for BMD Z-scores FN BMD (cont.): male sex NS	SB: high risk AB: high risk DB: low risk CF: low risk

GRADE assessment:

Study design: +4 Cross-sectional cohort studies

Study limitations: -1 Some limitations: Selection bias low in 4/10, high in 6/10; Attrition bias low in 6/10, high in 4/10; Detection bias low in 9/10, high in 1/10; Confounding low in 6/10, unclear in 2/10, high in 2/10

Consistency:	-1	Important inconsistency: five studies show a significant effect for males, two studies show a significant effect for females and three studies show no significant effect of sex
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients and events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	NA
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⨁⨀⨀ LOW
Conclusion:		Increased risk of lower BMD for male CAYA cancer survivors. (5 studies significant effect, 2 studies significant effect in opposite direction, 3 studies no significant effect; 2,007 participants)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

[a](possible) overlap in included patients.

1f.What is the risk of fractures in male versus female CAYA cancer survivors?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.f. Risk fracture for sex **(n=3 studies)**	van Santen 2020	177 craniopharyngioma survivors	Median 16 years (range 1-62)	Chemotherapy: 0% Radiotherapy: CRT: 51% ^{90}Yttrium brachytherapy: 13% SCT: None	Fractures: 18% over time (5.8 fractures per 1000 person-years)	Multivariable model: Fractures: female sex OR 0.3, 95%CI 0.1-0.7, p=0.004	SB: high risk AB: high risk DB: high risk CF: high risk
	Fiscaletti 2021	251 ALL survivors	Median 15.1 years (range 5.4 to 28.2 years) since cancer diagnosis	Chemotherapy: Glucocorticoids 100% Methotrexate 100% Radiotherapy: CRT 59% SCT: None	Frequency of fractures: Vertebral fractures: 23% Non-vertebral fractures: 31%	Multivariable model: Vertebral fractures: male sex RR 1.94, 95%CI 1.16-3.24, p=0.01	SB: low risk AB: low risk DB: low risk CF: low risk
	Kaste 2006a[a]	320 CCS	NR	NR	QCT LS BMD Z-score: <-2: n=96 (30%) QCT LS BMD Z-score median: -1.43 range: -5.96 to 3.2 DXA LS BMD Z-score <-2: n=89 (27.8%) DXA LS BMD Z-score median: -1.30 (-5.5 to 2.8)	Multivariable model: Fractures: male sex OR 2.22, 95%CI 1.001-4.902, p=0.0499	SB: low risk AB: low risk DB: high risk CF: unclear

GRADE assessment:		
Study design:	+4	Cross-sectional cohort study
Study limitations:	-1	Some limitations: Selection bias low in 2/3, high in 1/3; Attrition bias low in 2/3, high in 1/2; Detection bias low in 1/3, high in 2/3; Confounding low in 1/3, unclear in 1/3, high in 1/3
Consistency:	0	No important inconsistency, all studies show a significant association between male sex and fractures
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients and events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	NA
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊖ MODERATE
Conclusion:		Increased risk of fractures for male CAYA cancer survivors. (3 studies significant effect; 748 participants)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-

ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

1g.What is the risk of low and very low BMD in CAYA cancer survivors who were younger versus older at cancer diagnosis?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.g. Risk low BMD for age at cancer diagnosis **(n=7 studies)**	Bloomhardt 2020	542 CCS	Mean time since treatment (±SD) 6.0±5.0 years (range 2.0-35.1)	Chemotherapy: Dexamethasone 59.6% Prednisone 35.4% Any glucocorticoid 95% Cyclophosphamide 85.1% High-dose methotrexate 25.8% Radiotherapy: CRT 20.7% TBI 8.1% SCT: NR	LS BMD Z-score ≤-1: 17.2% LS BMD Z-score ≤-2: 3.5%	Multivariable model: LS BMD Z-score <-1: age at diagnosis (years) 0-4: reference, 5-9: OR 1.6, 95%CI 0.8-3.1, 10-14: OR 2.6, 95%CI 1.4-5.1, 15-19: OR 3.9, 95%CI 1.8-8.3, p<0.01	SB: high risk AB: low risk DB: low risk CF: high risk
	Choi 2013	78 ALL, AML and CML survivors	Mean time from cancer dx: 4.42±2.47 in males, 5.36±3.2 years in females	Chemotherapy: Glucocorticoids for chemotherapy 42% Glucocorticoids for GVHD 53% Radiotherapy: 62% SCT: 64%	LS BMD Z-score <-2: 25.7% FN BMD Z-score <-2: 24.4%	Multivariable model: LS BMD Z-score <-2: age at dx: OR 1.21, 95%CI 0.998 to 1.496, p=0.053	SB: unclear AB: low risk DB: low risk CF: low risk
	Den Hoed 2015	346 adult CCS	Median time after cessation of treatment 16.7 years (IQR 12.4–23.0)	Chemotherapy: Prednisone 63.6% Dexamethasone 37.0% Cyclophosphamide 49.7% Methotrexate 64.9% Ifosfamide 10.8% Radiotherapy: Cranial-spinal 16.5% Total body 3.8 % CRT 4.3% Abdominal 2.3% SCT: 4.9%	TB BMD or LS BMD Z-score <−1: 45% of the CCS. 38% TB, 27% LS, 20% at both TB and LS. TB BMD or LS BMD Z-score <−2: 9% (TB), 3% (LS)	Multivariable model: LS BMD Z-score <-1: age at diagnosis (<12 y vs. >12) OR= 2.3, 95%CI 1.1–4.8 TB BMD Z-score <-1: age at diagnosis (<12 y vs. >12) OR= 0.8, 95%CI 0.4–1.5	SB: high risk AB: low risk DB: low risk CF: low risk
	Latoch 2021	326 CCS	Median (range) 6.12 (4.0-22.0) years since end of treatment	Chemotherapy: Glucocorticoids 71.2% Methotrexate 50.9% Radiotherapy: CRT 25.5% TBI 4% Abdominal RT 16.7% SCT: 7%	LS BMD Z-score <-1: 20% TB BMD Z-score <-1: 24% LS and/or TB BMD Z-score <-2: 8%	Multivariable model: LS BMD Z-score <-1: age at diagnosis (increase per one year) OR 0.94, 95%CI 0.88–1.01, p=0.175 TB BMD Z-score <-1: age at diagnosis (increase per 1 year) OR 0.97, 95%CI 0.91–1.04, p=0.439	SB: high risk AB: low risk DB: low risk CF: low risk
	Siegel 2017	475 CCS	Mean (±SD) time after Rx 5.4 ± 4.3 years	Chemotherapy: Corticosteroid 83.4% Methotrexate 77.1%	TB or LS BMD Z-scores ≤–1: 29.3% (LS 22.8%, TB 21.9%)	Multivariable model:	SB: low risk AB: low risk DB: low risk

				Radiotherapy: Cranial / craniospinal 13.3% TBI 9.9% SCT: 17.9%	TB or LS BMD Z-scores ≤–2: 8.2% (LS 7.4%, TB 4.0%)	TB or LS BMD Z-scores ≤–2: age at diagnosis 10+, OR 2.7, 95% CI, 0.9-8.4	CF: high risk
	Sloof 2019	253 CCS	NR	Chemotherapy: NR Radiotherapy: CRT 36% SCT: 0%	BMD Z-score <-1: 25.4% (site NR)	Multivariable model: BMD Z-score <-1: age at diagnosis <10 years: OR 1.39, 95%CI 0.68–2.82, p=0.37	SB: unclear AB: low risk DB: unclear CF: unclear
	van Atteveld 2019	2032 adult CCS	Median time since cancer dx: 21.6 yrs (range 10.4-40.6)	Chemotherapy: Alkylating agent 56.6% MTX 53.9% GCs 53.9% Radiotherapy: Cranial 33.9% Abdominal 21.7% SCT: NR	LS and/or TB BMD Z-score ≤-1: 51.5% (LS 25.1%, TB 48.0%) LS and/or TB BMD Z-score ≤-2: 20.2%	Multivariable model: LS and/or TB BMD Z-score ≤-1: age at dx NS LS and/or TB BMD Z-score ≤-2: age at dx NS	SB: low risk AB: low risk DB: low risk CF: low risk

GRADE assessment:		
Study design:	+4	Cross-sectional cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 2/7, unclear in 2/7, high in 3/7; Attrition bias low in 7/7; Detection bias low in 6/7, unclear in 1/7; Confounding low in 4/7, unclear in 1/7, high in 2/7
Consistency:	-1	Important inconsistency: one study shows a significant effect for younger age at cancer diagnosis, one study shows a significant effect for older age at diagnosis, and five studies show no significant effect of age at diagnosis
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients and events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	NA
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		No significant effect of age at diagnosis on the risk of low BMD (Z-score ≤-1 or ≤-2) in CAYA cancer survivors. (1 study significant effect, 1 study significant effect in the opposite direction, 5 studies no significant effect; 4,052 participants)
GRADE assessment:		
Study design:	+4	Cross-sectional cohort studies
Study limitations:	0	No limitations: Selection bias low in 2/3, unclear in 1/3; Attrition bias low in 3/3; Detection bias low in 3/3; Confounding low in 2/3, high in 1/3
Consistency:	0	No inconsistency: all studies show no significant effect of age at diagnosis
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients and events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	NA
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊕ HIGH

Conclusion:	No significant effect of age at diagnosis on the risk of very low BMD (Z-score ≤-2) in CAYA cancer survivors. (3 studies no significant effect; 2,585 participants)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

1h.What is the risk of lower BMD in CAYA cancer survivors who were younger versus older at cancer diagnosis?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.h. Risk lower BMD for age at cancer diagnosis **(n=7 studies)**	Alikasifoglu 2005	59 ALL survivors	Mean 3.40 (1.77) years after cessation of therapy	Chemotherapy: Conventional dose prednisolone 51% Megadose methylprednisolone 49% Cyclophosphamide 100% HD-MTX 100% Radiotherapy: CRT 76% SCT: 0%	Mean (SD) LS BMD Z-score Total cohort: -1.73 (0.84)	Multivariable model: LS BMD Z-score (cont.): age at diagnosis: t=0.461, P=0.646	SB: high risk AB: high risk DB: low risk CF: low risk
	Benmiloud 2010	89 ALL and NHL survivors	Mean time since treatment (±SD) 15.0 ± 4.5 years	Chemotherapy: Prednisolone 100% Dexamethasone 52.8% Methotrexate 100% Radiotherapy RT at any site: 53.9% CNS RT 36% CRT 32.6% CSRT 3.4% TBI 18.0% SCT 18.0%	BMD Z-score ≤-1.0: At any site: 59.1%; At the LS: 50.5% At the FN: 25.8%; At the Hip: 31.5% BMD Z-score ≤-2: At any site: 10.1%; At the LS: 10.1% At the FN: 2.2%; At the Hip: 2.2%	Multivariable model: LS, FN and hip BMD Z-score (cont.): NS	SB: low risk AB: high risk DB: low risk CF: low risk
	De Matteo 2019	72 ALL survivors	Mean (±SD) time since treatment 41.2 ±37.8 months (95% CI: 49.9, 32.5)	Chemotherapy: Prednisone 100% Dexamethasone 100% MTX 100% Cyclophosphamide 100% Radiotherapy: 3 (4%) SCT: 0%	Proximal phalanx (QUS) Ad-SoS Z-score below −2 SD: 10/72 (13.8%)	Multivariable model: Ad-SoS Z-score (cont.): Age at ALL diagnosis: R2=0.0351, P=0.01 (negative correlation)	SB: unclear AB: low risk DB: unclear CF: low risk
	Den Hoed 2015	346 adult CCS	Median time after cessation of treatment 16.7 years (IQR 12.4–23.0)	Chemotherapy: Prednisone 63.6% Dexamethasone 37.0% Cyclophosphamide 49.7% Methotrexate 64.9% Ifosfamide 10.8% Radiotherapy: Cranial-spinal 16.5% Total body 3.8 % CRT 4.3% Abdominal 2.3% SCT: 4.9%	TB BMD or LS BMD Z-score <−1: 45% of the CCS. 38% TB, 27% LS, 20% at both TB and LS. TB BMD or LS BMD Z-score <−2: 9% (TB), 3% (LS)	Multivariable model: LS BMD Z-score (cont.): β=−0.16; se=0.14; p=0.26 TB BMD Z-score (cont.): NS	SB: high risk AB: low risk DB: low risk CF: low risk

	Hobush 2014	56 Ewing and PNET survivors	Minimum FU 5 years after treatment; Mean FU 15 years (5-48 years)	Chemotherapy: Alkylating agents (ifosfamide/cyclophosphamide) 100% Radiotherapy: Local radiation 64% SCT: NR	LS and/or Hip BMD T-score <-1: 55% LS and/or Hip BMD T-score <-2.5 (or Z-score <-2 in adolescents): 13%	Multivariable model: LS BMD Z-score (cont.): older age at surgery NS FN BMD Z-score (cont.): older age at surgery p=0.023 Hip BMD Z-score (cont.): older age at surgery NS	SB: high risk AB: low risk DB: low risk CF: low risk
	Le Meignen 2011	159 ALL and AML survivors	Mean time from diagnosis to DXA 14.66 ± 0.44 yrs	Chemotherapy: Glucocorticoids 86.2% Other chemotherapy NR Radiotherapy: CRT 18.9% TBI 40.4% of HSCT recipients SCT: 34%	BMD Z-score <-2: FN 3.2%; LS 3.8%	Multivariable model: BMD Z-scores (cont.): age at dx FN: β -0.005, P=0.96; LS: β 0.06, p=0.57	SB: low risk AB: high risk DB: high risk CF: high risk
	Ruza 2006	95 (63 had DXA) osteosarcoma and Ewing's sarcoma survivors	Mean duration of remission was 6.12 years (SD 3.67) in patients with osteosarcomas and 6.11 years (SD 3.73) for Ewing's sarcoma patients	Chemotherapy: MTX 100% Cyclophosphamide 100% Radiotherapy: NR SCT: NR	LS BMD Z-score <-1: 43.6% FN BMD Z-score <-1: 42.9% LS BMD Z-score <-2: 9.7% FN BMD Z-score <-2: 17.5%	Multivariable model: LS BMD (cont.): younger age at dx p=0.035 for areal BMD, BMD Z-scores NS FN BMD (cont.): younger age at dx NS	SB: high risk AB: high risk DB: low risk CF: low risk

GRADE assessment:		
Study design:	+4	Cross-sectional cohort studies
Study limitations:	-2	Some limitations: Selection bias low in 2/7, unclear in 1/7, high in 4/7; Attrition bias low in 3/7, high in 4/7; Detection bias low in 5/7, unclear in 1/7, high in 1/7; Confounding low in 6/7, high in 1/7
Consistency:	-1	Important inconsistency: two studies show a significant effect for older age at cancer diagnosis, one study shows a significant effect for younger age at diagnosis, and four studies show no significant effect of age at diagnosis
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients and events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	NA
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ VERY LOW
Conclusion:		There is conflicting evidence for the association of age at diagnosis and lower BMD in CAYA cancer survivors. (2 studies significant effect, 1 study significant effect in opposite direction, 4 studies no significant effect; 876 participants)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-

ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

1i.What is the risk of fractures in CAYA cancer survivors who were younger versus older at cancer diagnosis?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.i. Risk fracture for age at diagnosis **(n=2 studies)**	Fiscaletti 2021	251 ALL survivors	Median 15.1 years (range 5.4 to 28.2 years) since cancer diagnosis	Chemotherapy: Glucocorticoids 100% Methotrexate 100% Radiotherapy: CRT 59% SCT: None	Frequency of fractures: Vertebral fractures: 23% Non-vertebral fractures: 31%	Multivariable model: Vertebral fractures: age at diagnosis (yr) RR 1.01, 95%CI 0.96-1.06, p=0.784	SB: low risk AB: low risk DB: low risk CF: low risk
	Wilson 2012	7414 CCS	Median length of follow-up was 22.7 years (range, 15.6-34.2 years)	Chemotherapy: Methotrexate 43.6% Steroids 47% Radiotherapy: CRT 32% Pelvic RT 13% SCT: 0%	Proportion of participants with fractures over their lifetime Survivors: 34.8% Siblings: 38.9%	Multivariable model: Fracture: Males: age at diagnosis 0-4 yrs prevalence ratio (PR), 1.0 (ref); 5-9 yrs PR 0.93, 95%CI 0.83-1.05, p=0.25; 10-14 yrs PR 1.02, 95%CI 0.89-1.16, p=0.82; 15-19 yrs PR 0.98, 95%CI 0.84-1.15, p=0.81. Females: age at diagnosis 0-4 yrs prevalence ratio (PR), 1.0 (ref); 5-9 yrs PR 1.11, 95%CI 0.96-1.29, p=0.16; 10-14 yrs PR 1.10, 95%CI 0.92-1.30, p=0.29; 15-19 yrs PR 0.96, 95%CI 0.79-1.19, p=0.72.	SB: high risk AB: low risk DB: high risk CF: high risk

GRADE assessment:		
Study design:	+4	Retrospective cohort study
Study limitations:	-2	Some limitations: Selection bias low in 1/2, high in 1/2; Attrition bias low in 2/2; Detection bias low in 1/2, high in 1/2; Confounding low in 1/2, high in 1/2
Consistency:	0	No inconsistency: both studies show no significant effect of age at diagnosis
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients and events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	NA
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		No significant effect of age at diagnosis on the risk of fractures in CAYA cancer survivors. (2 studies no significant effect; 7,665 participants)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

1j.What is the risk of low and very low BMD in CAYA cancer survivors with different ethnicities?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.j. Risk low BMD for ethnicity **(n=5 studies)**	Bhandari 2021	446 CCS	Median 14.2 years (range 2–65 years) since completing therapy	Chemotherapy: Glucocorticoids 57.5% Methotrexate 40.4% Radiotherapy: CRT NR TBI ± 24% SCT: 40.8% (30.9% allogeneic)	LS BMD Z-score ≤-1: 33.9%	Multivariable model: LS BMD Z-score <-1: race/ethnicity NS	SB: low risk AB: high risk DB: low risk CF: low risk
	Bloomhardt 2020	542 CCS	Mean time since treatment (±SD) 6.0±5.0 years (range 2.0-35.1)	Chemotherapy: Dexamethasone 59.6% Prednisone 35.4% Any glucocorticoid 95% Cyclophosphamide 85.1% High-dose methotrexate 25.8% Radiotherapy: CRT 20.7% TBI 8.1% SCT: NR	LS BMD Z-score ≤-1: 17.2% LS BMD Z-score ≤-2: 3.5%	Multivariable model: LS BMD Z-score <-1: white race OR 2.5, 95%CI 1.1-5.4, p=0.02	SB: high risk AB: low risk DB: low risk CF: high risk
	Kaste 2006a[a]	320 CCS	NR	NR	QCT LS BMD Z-score: <-2: n=96 (30%) QCT LS BMD Z-score median: -1.43 range: -5.96 to 3.2 DXA LS BMD Z-score <-2: n=89 (27.8%) DXA LS BMD Z-score median: -1.30 (-5.5 to 2.8)	Multivariable model: LS BMD Z-score <-2: by DXA, non-white patients OR 2.60, 95%CI 1.34-5.03, p=0.0046; by QCT, white patients OR 2.97, 95%CI 1.21-7.31, p=0.018	SB: low risk AB: low risk DB: low risk CF: unclear
	Kaste 2006b[a]	study I n=141, study II n=57 ALL survivors	Study I: >4 years after therapy (mean time after dx 11.7 yrs) Study II : 2-5 years after study I (mean time after dx 16.1 yrs)	Chemotherapy: MTX 100% Prednisone 100% Radiotherapy: CRT 37% of 57; percentage of 141 NR SCT: 0%	Study I: LS BMD Z-score <-1 10.5%; LS BMD Z-score <-2 1.5% Study II: LS BMD Z-score <-1 19.3%; LS BMD Z-score <-2 0%	Multivariable model: LS 'low' BMD (Z-score cut-point NR, presumably <-1): study I Caucasian race P=0.003, study II P<0.0001	SB: unclear AB: high risk DB: low risk CF: unclear
	Polgreen 2012	319 CCS	Mean time since treatment (±SE) 10.1 ± 0.2 years (range 4.3-17.8)	Chemotherapy: Corticosteroid: 42.0% Radiotherapy: 23.2% Cranial (CNS) 9.7%, other 13.5% SCT: 0%	TB BMD Z-score <-1: 11% LS BMD Z-score <-1: 23% TB BMD Z-score <-2: 2.3% LS BMD Z-score <-2: 3.5%	Multivariable model: TB BMD Z-score <-1: ethnicity (white non-Hispanic vs. other), OR 1.7, 95%CI 0.5-6.9, p=0.420	SB: low risk AB: low risk DB: low risk CF: low risk

		LS BMD Z-score <-1: ethnicity (white non-Hispanic vs. other), OR 2.6, 95%CI 0.9-9.1, p=0.104
GRADE assessment (outcome low and very low BMD):		
Study design:	+4	Cross-sectional cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 3/5, unclear in 1/5, high in 1/5; Attrition bias low in 3/5, high in 2/5; Detection bias low in 5/5; Confounding low in 2/5, unclear in 2/5, high in 1/5
Consistency:	0	No important inconsistency, all studies show (when BMD was compared to an non-race specific database to generate Z-scores) an association between white ethnic descent and low BMD (3 studies significant)
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients and events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	NA
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⨁⨁⨀ MODERATE
Conclusion:		Increased risk of low BMD (Z-score ≤-1 or ≤-2) for white CAYA cancer survivors. (3 studies significant effect, 2 studies no significant effect; 1,768 participants)
GRADE assessment (outcome very low BMD):		
Study design:	+4	Cross-sectional cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 1/1; Attrition bias low in 1/1; Detection bias low in 1/1; Confounding unclear in 1/1
Consistency:	NA	Only one study available
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Important imprecision, low total number of patients and events and only one study available
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	NA
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⨀⨀⨀ VERY LOW
Conclusion:		Increased risk of very low BMD (Z-score ≤-2) for white CAYA cancer survivors. (1 study significant effect; 320 participants)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

[a](possible) overlap in included patients.

1k.What is the risk of lower BMD in CAYA cancer survivors with different ethnicities?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.k. Risk lower BMD for ethnicity **(n=2 studies)**	Kaste 2006a[a]	320 CCS	NR	NR	QCT LS BMD Z-score: <-2: n=96 (30%) QCT LS BMD Z-score median: -1.43 range: -5.96 to 3.2 DXA LS BMD Z-score <-2: n=89 (27.8%) DXA LS BMD Z-score median: -1.30 (-5.5 to 2.8)	Multivariable model: LS BMD (cont.): non-white race was associated with higher BMD by DXA in L1 (P=0.0221) and in L2 (P=0.0370) and by QCT (P<0.0001).	SB: low risk AB: low risk DB: low risk CF: unclear
	Kaste 2014[a]	424 ALL survivors	Median 8.4 yrs (4.6-19.1) from completion of ALL therapy to entry into study	Chemotherapy: Glucocorticoids 100% Methotrexate 100% Cyclophosphamide 100% Radiotherapy: CRT 36.1% SCT: NR	QCT LS BMD Z-score <-1: 48.9% QCT LS BMD Z-score <-2: 6.8%	Multivariable model: QCT LS BMD Z-score (cont.): non-White vs. White β 0.58 (0.28, 0.89) P=0.0002 *(whites had lower BMD Z-scores)*	SB: high risk AB: high risk DB: low risk CF: low risk

GRADE assessment:		
Study design:	+4	Cross-sectional cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 1/2, high in 1/2; Attrition bias low in 1/2, high in 1/2; Detection bias low in 2/2; Confounding low in 1/2, unclear in 1/2
Consistency:	0	No important inconsistency, both studies show a significant association between white ethnic descent and lower BMD
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients and events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	NA
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊖ MODERATE
Conclusion:		Increased risk of lower BMD for white CAYA cancer survivors. (2 studies significant effect; 744 participants)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

[a](possible) overlap in included patients.

1l.What is the risk of fractures in CAYA cancer survivors with different ethnicities?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.I. Risk fracture for ethnicity **(n=1 study)**	Wilson 2012	7414 CCS	Median length of follow-up was 22.7 years (range, 15.6-34.2 years)	Chemotherapy: Methotrexate 43.6% Steroids 47% Radiotherapy: CRT 32% Pelvic RT 13% SCT: 0%	Proportion of participants with fractures over their lifetime Survivors: 34.8% Siblings: 38.9%	Multivariable model: Fracture: male survivors of non-white ethnic descent prevalence ratio, 0.78; 95% CI, 0.66- 0.92; P= .004	SB: high risk AB: low risk DB: high risk CF: high risk
GRADE assessment:							
Study design:	+4	Retrospective cohort study					
Study limitations:	-3	Some limitations: Selection bias high in 1/1; Attrition bias low in 1/1; Detection bias high in 1/1; Confounding high in 1/1					
Consistency:	NA	Only one study available					
Directness:	0	Results are direct, population and outcomes broadly generalizable					
Precision:	-1	Important imprecision: high total number of patients and events but only one study available					
Publication bias:	0	Unlikely					
Effect size:	0	No large magnitude of effect					
Dose-response:	0	NA					
Plausible confounding:	0	No plausible confounding					
Quality of evidence:		⊕⊖⊖⊖ VERY LOW					
Conclusion:		Decreased risk of fractures for male non-white CAYA cancer survivors. (1 study significant effect; 7,414 participants)					

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

1m.What is the risk of low and very low BMD in CAYA cancer survivors with lower versus higher BMI, body weight, and/or lean mass?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.m. Risk low BMD for lower vs. higher BMI/body weight **(n=10 studies)**	Bloomhardt 2020	542 CCS	Mean time since treatment (±SD) 6.0±5.0 years (range 2.0-35.1)	Chemotherapy: Dexamethasone 59.6% Prednisone 35.4% Any glucocorticoid 95% Cyclophosphamide 85.1% High-dose methotrexate 25.8% Radiotherapy: CRT 20.7% TBI 8.1% SCT: NR	LS BMD Z-score ≤-1: 17.2% LS BMD Z-score ≤-2: 3.5%	Multivariable model: LS BMD Z-score <-1: BMI: underweight OR 3.5, 95%CI 1.1-11.5, normal reference, overweight OR 0.3, 95%CI 0.1-0.6, obese OR 0.3, 95%CI 0.2-0.6, p<0.01	SB: high risk AB: low risk DB: low risk CF: high risk
	Choi 2013	78 ALL, AML and CML survivors	Mean time from cancer dx: 4.42±2.47 in males, 5.36±3.2 years in females	Chemotherapy: Glucocorticoids for chemotherapy 42% Glucocorticoids for GVHD 53% Radiotherapy: 62% SCT: 64%	LS BMD Z-score <-2: 25.7% FN BMD Z-score <-2: 24.4%	Multivariable model: LS BMD Z-score <-2: BMI SDS: OR 0.586, CI 0.362-0.948, p=0.03	SB: unclear AB: low risk DB: low risk CF: low risk
	Den Hoed 2015	346 adult CCS	Median time after cessation of treatment 16.7 years (IQR 12.4–23.0)	Chemotherapy: Prednisone 63.6% Dexamethasone 37.0% Cyclophosphamide 49.7% Methotrexate 64.9% Ifosfamide 10.8% Radiotherapy: Cranial-spinal 16.5% Total body 3.8 % CRT 4.3% Abdominal 2.3% SCT: 4.9%	TB BMD or LS BMD Z-score <−1: 45% of the CCS. 38% TB, 27% LS, 20% at both TB and LS. TB BMD or LS BMD Z-score <−2: 9% (TB), 3% (LS)	Multivariable model: LS BMD Z-score <-1: BMI (cont.) OR 0.9, 95%CI 0.8–0.9; BMI (<18.5 vs. 18.5–25) OR= 3.7, 95%CI 1.3–10.5; BMI (>25 vs. 18.5–25), OR= 0.5, 95%CI 0.3–1.1 TB BMD Z-score <-1: BMI (cont.) OR 0.8, 95%CI 0.8-0.9; BMI (<18.5 vs. 18.5–25), OR= 4.0, 95%CI 1.4–11.1; BMI (>25 vs. 18.5–25), OR= 0.5, 95%CI 0.3–0.9	SB: high risk AB: low risk DB: low risk CF: low risk
	Kaste 2006b[a]	study I n=141, study II n=57 ALL survivors	Study I: >4 years after therapy (mean time after dx 11.7 yrs) Study II : 2-5 years after study I (mean time after dx 16.1 yrs)	Chemotherapy: MTX 100% Prednisone 100% Radiotherapy: CRT 37% of 57; percentage of 141 NR SCT: 0%	Study I: LS BMD Z-score <-1 10.5%; LS BMD Z-score <-2 1.5% Study II: LS BMD Z-score <-1 19.3%; LS BMD Z-score <-2 0%	Multivariable model: LS 'low' BMD (Z-score cut-point NR, presumably <-1): study I not overweight P=0.067, study II NS	SB: unclear AB: high risk DB: low risk CF: unclear
	Kaste 2009[a]	109 HL survivors	Median 7.5 yrs (5.8-20.7 yrs) from diagnosis to QCT	Chemotherapy: Cyclophosphamide 67.9% Methotrexate 69% Prednisone 65%	QCT LS BMD Z-score <-1.5: 14.7% QCT LS BMD Z-score <-2.0: 7.3%	Multivariable model: QCT LS BMD Z-score <-1.5: BMI (kg/m2) normal + underweight vs. overweight + obesity: OR	SB: low risk AB: low risk DB: high risk CF: low risk

				Radiotherapy: LS RT 28.4% Pelvic RT 6% SCT: NR		2.76 (95% CI:0.87–8.76), p=0.086	
	Latoch 2021	326 CCS	Median (range) 6.12 (4.0-22.0) years since end of treatment	Chemotherapy: Glucocorticoids 71.2% Methotrexate 50.9% Radiotherapy: CRT 25.5% TBI 4% Abdominal RT 16.7% SCT: 7%	LS BMD Z-score <-1: 20% TB BMD Z-score <-1: 24% LS and/or TB BMD Z-score <-2: 8%	Multivariable model: LS BMD Z-score <-1: BMI OR 3.57, 95%CI 1.24–10.23, p=0.004 TB BMD Z-score <-1: BMI OR 3.16, 95%CI 1.1–9.07, p=0.032	SB: high risk AB: low risk DB: low risk CF: low risk
	Polgreen 2012	319 CCS	Mean time since treatment (±SE) 10.1 ± 0.2 years (range 4.3-17.8)	Chemotherapy: Corticosteroid: 42.0% Radiotherapy: 23.2% Cranial (CNS) 9.7%, other 13.5% SCT: 0%	TB BMD Z-score <-1: 11% LS BMD Z-score <-1: 23% TB BMD Z-score <-2: 2.3% LS BMD Z-score <-2: 3.5%	Multivariable model: TB BMD Z-score <-1: Percent body fat (1% increase), OR 0.95, 95%CI 0.9-1.0, p=0.070; Lean body mass (1kg increase), OR 0.85, 95%CI 0.8-0.9, p<0.001 LS BMD Z-score <-1: Percent body fat (1% increase), OR 0.97, 95%CI 0.94-1.0, p=0.088 Lean body mass (≤35kg vs. >35kg), OR 4.1, 95%CI 1.8-9.6, p<0.001	SB: low risk AB: low risk DB: low risk CF: low risk
	Siegel 2017	475 CCS	Mean (±SD) time after Rx 5.4 ± 4.3 years	Chemotherapy: Corticosteroid 83.4% Methotrexate 77.1% Radiotherapy: Cranial / craniospinal 13.3% TBI 9.9% SCT: 17.9%	TB or LS BMD Z-scores ≤–1: 29.3% (LS 22.8%, TB 21.9%) TB or LS BMD Z-scores ≤–2: 8.2% (LS 7.4%, TB 4.0%)	Multivariable model: TB or LS BMD Z-scores ≤–2: overweight or obese, OR 0.5, 95% CI, 0.2-1.2	SB: low risk AB: low risk DB: low risk CF: high risk
	Sloof 2019	253 CCS	NR	Chemotherapy: NR Radiotherapy: CRT 36% SCT: 0%	BMD Z-score <-1: 25.4% (site NR)	Multivariable model: BMD Z-score <-1: ideal BMI OR 2.62, 95%CI 1.22–5.62, p=0.01	SB: unclear AB: low risk DB: unclear CF: unclear
	van Atteveld 2019[a]	2032 adult CCS	Median time since cancer dx: 21.6 yrs (range 10.4-40.6)	Chemotherapy: Alkylating agent 56.6% MTX 53.9% GCs 53.9% Radiotherapy: Cranial 33.9% Abdominal 21.7% SCT: NR	LS and/or TB BMD Z-score ≤-1: 51.5% (LS 25.1%, TB 48.0%) LS and/or TB BMD Z-score ≤-2: 20.2%	Multivariable model: LS and/or TB BMD Z-score ≤-1: weight β -0.02 (SE <0.01), OR 0.98, 95%CI 0.97-0.98 LS and/or TB BMD Z-score ≤-2: weight β -0.03 (SE <0.01), OR 0.97, 95%CI 0.96-0.98	SB: low risk AB: low risk DB: low risk CF: low risk
GRADE assessment (outcome low and very low BMD): **Study design:** +4 Cross-sectional cohort studies							

Study limitations:	-1	Some limitations: Selection bias low in 4/10, unclear in 3/10, high in 3/10; Attrition bias low in 9/10, high in 1/10; Detection bias low in 8/10, unclear in 1/10, high in 1/10; Confounding low in 6/10, unclear in 2/10, high in 2/10
Consistency:	0	No important inconsistency, all show an association between lower body weight, BMI or lean mass and low BMD (7 studies significant)
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients and events
Publication bias:	0	Unlikely
Effect size:	+1	Large magnitude of effect
Dose-response:	0	Dose response unclear
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⨁⨁⨁ HIGH
Conclusion:		Increased risk of low BMD (Z-score ≤-1 or ≤-2) for CAYA cancer survivors with low body weight, BMI or lean body mass. (7 studies significant effect, 3 studies no significant effect; 4,621 participants)
GRADE assessment (outcome very low BMD):		
Study design:	+4	Cross-sectional cohort studies
Study limitations:	0	No important limitations: Selection bias low in 2/3, unclear in 1/3; Attrition bias low in 3/3; Detection bias low in 3/3; Confounding low in 2/3, high in 1/3
Consistency:	0	No important inconsistency, all show an association between lower body weight or BMI and low BMD (2 studies significant)
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients and events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Dose response unclear
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⨁⨁⨁ HIGH
Conclusion:		Increased risk of very low BMD (Z-score ≤-2) for CAYA cancer survivors with low body weight or BMI. (2 studies significant effect, 1 study no significant effect; 2,585 participants)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

[a](possible) overlap in included patients.

1n.What is the risk of lower BMD in CAYA cancer survivors with lower versus higher BMI, body weight, and/or lean mass?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.n. Risk lower BMD for lower vs. higher BMI/body weight **(n=10 studies)**	Alikasifoglu 2005[a]	59 ALL survivors	Mean 3.40 (1.77) years after cessation of therapy	Chemotherapy: Conventional dose prednisolone 51% Megadose methylprednisolone 49% Cyclophosphamide 100% HD-MTX 100% Radiotherapy: CRT 76% SCT: 0%	Mean (SD) LS BMD Z-score Total cohort: -1.73 (0.84)	Multivariable model: LS BMD Z-score (cont.): BMI Z-score: t=0.457, P=0.648	SB: high risk AB: high risk DB: low risk CF: low risk
	Den Hoed 2015	346 adult CCS	Median time after cessation of treatment 16.7 years (IQR 12.4–23.0)	Chemotherapy: Prednisone 63.6% Dexamethasone 37.0% Cyclophosphamide 49.7% Methotrexate 64.9% Ifosfamide 10.8% Radiotherapy: Cranial-spinal 16.5% Total body 3.8 % CRT 4.3% Abdominal 2.3% SCT: 4.9%	TB BMD or LS BMD Z-score <−1: 45% of the CCS. 38% TB, 27% LS, 20% at both TB and LS. TB BMD or LS BMD Z-score <−2: 9% (TB), 3% (LS)	Multivariable model: LS BMD Z-score (cont.): BMI (cont.) β=0.06, se=0.01, p<0.001 TB BMD Z-score (cont.): BMI (cont.) β=0.10; se=0.01; p<0.001	SB: high risk AB: low risk DB: low risk CF: low risk
	Henderson 1996	60 CCS	At least 12 months post chemotherapy Mean time since treatment: 4.3 yrs range 12mths-14.5 yrs	Chemotherapy: Ifofosfamide 3% Glucocorticoids 75% MTX 62% Radiotherapy: CRT 25% SCT: NR	LS BMD Z-scores <-2: 5/60 (8.3%) LS BMD Z-score <-1.0: 14/60 (23.3%)	Multivariable model: LS BMD Z-score (cont.): lower weight Z-score R^2= 0.33, p=0.0001	SB: unclear AB: unclear DB: low risk CF: unclear
	Hobush 2014	56 Ewing and PNET survivors	Minimum FU 5 years after treatment; Mean FU 15 years (5-48 years)	Chemotherapy: Alkylating agents (ifosfamide/cyclophosphamide) 100% Radiotherapy: Local radiation 64% SCT: NR	LS and/or Hip BMD T-score <-1: 55% LS and/or Hip BMD T-score <-2.5 (or Z-score <-2 in adolescents): 13%	Multivariable model: LS BMD Z-score (cont.): low BMI NS FN BMD Z-score (cont.): low BMI p=0.002 (p=0.014 after Bonferroni correction) Hip BMD Z-score (cont.): low BMI p<0.001 (p=0.002 after Bonferroni correction)	SB: high risk AB: low risk DB: low risk CF: low risk
	Holzer 2003	48 malignant osteosarcoma survivors	Mean 16±2.2 years follow-up	Chemotherapy: HD-MTX 100% Cyclophosphamide 100%	LS and/or Hip BMD T-score <-1: 65%	Multivariable (?) model: LS and/or Hip BMD T-score (cont.): positive correlation with	SB: high risk AB: low risk DB: low risk

				Ifosfamide 100% Radiotherapy: 2% SCT:NA	LS and/or Hip BMD T-score <-2.5: 21%	body weight (p=0.03, r not reported), BMI NS.	CF: high risk
	Jones 2008[a]	309 ALL survivors	At least 4 years of continuous remission	Chemotherapy: MTX 100% Prednisone 100% Radiotherapy: NR SCT: NR	Mean QCT LS BMD Z-score (SD): -0.47 (1.26)	Multivariable model: QCT LS BMD Z-score (cont.): lower BMI p=0.0003	SB: high risk AB: low risk DB: low risk CF: low risk
	Kaste 2014[a]	424 ALL survivors	Median 8.4 yrs (4.6-19.1) from completion of ALL therapy to entry into study	Chemotherapy: Glucocorticoids 100% Methotrexate 100% Cyclophosphamide 100% Radiotherapy: CRT 36.1% SCT: NR	QCT LS BMD Z-score <-1: 48.9% QCT LS BMD Z-score <-2: 6.8%	Multivariable model: QCT LS BMD Z-score (cont.): BMI (kg/m2) β 0.05 (0.03, 0.07) P<0.0001	SB: high risk AB: high risk DB: low risk CF: low risk
	Muszynska-Roslan 2007	68 CCS	Mean time since end of Rx ranged from 5.5 -21.4 years (8.1 ± 2.9 years for males, 7.5 ± 3.4 years for females)	Chemotherapy: Corticosteroid 85.3% Radiotherapy: CRT 38.2% Abdominal RT 29.4% SCT: NR	NR	Multivariable model: TB BMC values (cont.): lean mass males R2=0.80, p<0.0001; females R2=0.64, p<0.001 LS BMC values (cont.): lean mass males R2=0.75, p<0.0001; females R2=0.40, p<0.001 "Similar associations for fat mass"	SB: high risk AB: low risk DB: low risk CF: low risk
	Remes 2018	74 brain tumor survivors	Mean time since cessation of tumor therapy (±SD): 18.9 ± 6.1 years	Chemotherapy: 63.5% Radiotherapy: Local irradiation: 52.7% Craniospinal with local boost to the tumor bed: 40.5% Cranial with local boost to the tumor bed: 4.1% Stereotactic: 2.7% SCT:NR	LS BMD and/or FN BMD and/or Total Hip Z-score ≤-2: 23.6%	Multivariable model: BMD Z-scores (cont.): BMI, right FN β 0.07 (95% CI 0.04-0.11), p<0.001; left FN β 0.08 (95% CI 0.04-0.12), p<0.001; right total hip: β 0.09 (95% CI 0.05-0.13), p<0.001; left total hip: β 0.10 (95% CI 0.06-0.15), p<0.001; LS β 0.07 (95% CI 0.02-0.11), p=0.006	SB: high risk AB: low risk DB: unclear CF: low risk
	Ruza 2006	95 (63 had DXA) osteosarcoma and Ewing's sarcoma survivors	Mean duration of remission was 6.12 years (SD 3.67) in patients with osteosarcomas and 6.11 years (SD 3.73) for Ewing's sarcoma patients	Chemotherapy: MTX 100% Cyclophosphamide 100% Radiotherapy: NR SCT: NR	LS BMD Z-score <-1: 43.6% FN BMD Z-score <-1: 42.9% LS BMD Z-score <-2: 9.7% FN BMD Z-score <-2: 17.5%	Multivariable model: LS BMD (cont.): lower weight p=0.016 for areal BMD, BMD Z-score NS; BMI areal BMD NS, p=0.038 for BMD Z-score FN BMD (cont.): lower weight p=0.001 for areal BMD, BMD Z-score NS; BMI areal BMD NS, p=0.001 for BMD Z-score	SB: high risk AB: high risk DB: low risk CF: low risk
GRADE assessment: **Study design:**	+4	Cross-sectional cohort studies					

Study limitations:	-1	Some limitations: Selection bias unclear in 1/10, high in 9/10; Attrition bias low in 6/10, unclear in 1/10, high in 3/10; Detection bias low in 9/10, unclear in 1/10; Confounding low in 8/10, unclear in 1/10, high in 1/10
Consistency:	0	No important inconsistency, all studies show an association between lower body weight, BMI or lean mass and low BMD (9 studies significant)
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients and events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Dose response unclear
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⨁⨁⨀ MODERATE
Conclusion:		Increased risk of lower BMD for CAYA cancer survivors with low body weight, BMI or lean body mass. (9 studies significant effect, 1 study no significant effect; 1,539 participants)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

[a](possible) overlap in included patients.

1o.What is the risk of low and very low BMD in CAYA cancer survivors with a positive family history and/or genetic polymorphisms?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.o. Risk low BMD for familial factors **(n=1 study)**	Aaron 2019	242 ALL survivors	Mean time since treatment is 13.1 years (range 4-29 years)	Chemotherapy: Glucocorticoids 100% Methotrexate 100% Radiotherapy: CRT 59% SCT: 0%	BMD Z-score ≤-1.0: LS 25.2%, TB 25.2% BMD Z-score ≤-2: LS 5.8%, TB 5.8%	Multivariable model: BMD Z-score ≤-1.0: no SNPs significantly associated BMD Z-score ≤-2: no SNPs significantly associated	SB: unclear AB: low risk DB: low risk CF: low risk
GRADE assessment:							
Study design:	+4	Cross-sectional cohort study					
Study limitations:	-1	Some limitations: Selection bias unclear in 1/1; Attrition bias low in 1/1; Detection bias low in 1/1; Confounding low in 1/1					
Consistency:	NA	Only one study available					
Directness:	0	Results are direct, population and outcomes broadly generalizable					
Precision:	-2	Important imprecision, low total number of patients and events and only one study available					
Publication bias:	0	Unlikely					
Effect size:	0	No large magnitude of effect					
Dose-response:	0	NA					
Plausible confounding:	0	No plausible confounding					
Quality of evidence:		⊕⊖⊖⊖ VERY LOW					
Conclusion:		No significant effect of SNPs on low BMD (Z-score ≤-1 or ≤-2) in CAYA cancer survivors. (1 study no significant effect; 242 participants)					
GRADE assessment:							
Study design:	+4	Cross-sectional cohort study					
Study limitations:	-1	Some limitations: Selection bias unclear in 1/1; Attrition bias low in 1/1; Detection bias low in 1/1; Confounding low in 1/1					
Consistency:	NA	Only one study available					
Directness:	0	Results are direct, population and outcomes broadly generalizable					
Precision:	-2	Important imprecision, low total number of patients and events and only one study available					
Publication bias:	0	Unlikely					
Effect size:	0	No large magnitude of effect					
Dose-response:	0	NA					
Plausible confounding:	0	No plausible confounding					
Quality of evidence:		⊕⊖⊖⊖ VERY LOW					
Conclusion:		No significant effect of SNPs on very low BMD (Z-score ≤-2) in CAYA cancer survivors. (1 study no significant effect; 242 participants)					

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

1p.What is the risk of lower BMD in CAYA cancer survivors with a positive family history and/or genetic polymorphisms?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.p. Risk lower BMD for familial factors **(n=4 studies)**	Den Hoed 2016	334 adult CCS	Median follow up time 18 yrs (range 5-40 yrs)	Chemotherapy: Cyclophosphamide 46% Ifosfamide 3% Methotrexate 95% Radiotherapy: Cranial-spinal 17% Total body 4% Brain Tumor 4% Abdominal 3% SCT: 4.2%	Mean BMDLS Z-score -0.27 (SD: 1.03) Mean BMDTB Z-score -0.47 (SD: 1.10)	Multivariable model: LS BMD Z-score (cont.): rs2504063 ESR1 (G/G vs. A/A-A/G) -0.83 (0.29) vs. -0.58 (0.27), p=0.07; rs599083 LRP5 (G/G vs. T/T-T/G) -0.95 (0.31) vs. -0.46 (0.27), p=0.01 TB BMD Z-score (cont.): rs2504063 ESR1 (G/G vs. A/A-A/G) -1.16 (0.27) vs. -0.82 (0.25), p=0.01; rs599083 LRP5 (G/G vs. T/T-T/G) -1.20 (0.29) vs. -0.78 (0.25), p=0.02 Other candidate SNPs NS	SB: high risk AB: low risk DB: low risk CF: low risk
	Im 2018[a]	856 ALL survivors	NA (± 25 yrs)	Chemotherapy: Methotrexate 100% Glucocorticoid 100% Radiotherapy: CRT 59% SCT: NR	Median QCT LS BMD Z-score (range): −0.4 (−3.5, 5.4)	Of the six regulatory 3-SNP interactions identified as candidate interactions (P < 3.5 x 10−11) among cancer survivors exposed to treatments, five SNPs (1. rs901466: C>G + rs7569568: G>A + rs921319: T>C; 2. rs1020745: G>A + rs2110167: A>G + rs10444471: G>T; 3. rs1894331: G>T + rs10773093: T>C + rs4768783: C>T; 4. rs7321815: C>A + rs9315069: T>C + rs913071: C>T; 5. rs887890: T>G + rs7142110: G>A + rs1884632: C>G) were replicated in an independent cohort of survivors (N = 1428) as modifiers of treatment effects on QCT LS BMD Z-score (P < 0.05).	SB: high risk AB: low risk DB: low risk CF: high risk
	Jones 2008[a]	309 ALL survivors	At least 4 years of continuous remission	Chemotherapy: MTX 100% Prednisone 100% Radiotherapy: NR SCT: NR	Mean QCT LS BMD Z-score (SD): -0.47 (1.26)	Multivariable model: QCT LS BMD Z-score (cont.): The G allele at the rs1876828 SNP was associated with lower z scores (P=.02) in males but tended to have the opposite association in females (P=.09)	SB: high risk AB: low risk DB: low risk CF: low risk
	Sawicka-Zukowska 2013	74 ALL and lymphoma survivors	Not specifically stated, but the average time at the time of	Chemotherapy: NR Radiotherapy: CRT 21.6% SCT: NR	Mean TB BMD Z-score -0.0132 Mean LS BMD Z-score -0.2610	Q223R polymorphism of leptin receptor not associated with BMD: TB BMD Z-score (cont.): p=0.423 LS BMD Z-score (cont.): p=0.457	SB: unclear AB: unclear DB: low risk CF: low risk

		analysis post treatment completion would be 6.6 years	Mean TB BMC Z-score 0.3244	
GRADE assessment:				
Study design:	+4	Cross-sectional cohort studies		
Study limitations:	-1	Some limitations: Selection bias unclear in 1/4, high in 3/4; Attrition bias low in 3/4, unclear in 1/4; Detection bias low in 4/4; Confounding low in 3/4, high in 1/4		
Consistency:	NA	All studies assessed different candidate SNPs		
Directness:	0	Results are direct, population and outcomes broadly generalizable		
Precision:	-1	Important imprecision, high total number of patients and events but all studies assessed different candidate SNPs		
Publication bias:	0	Unlikely		
Effect size:	0	No large magnitude of effect		
Dose-response:	0	NA		
Plausible confounding:	0	No plausible confounding		
Quality of evidence:		⨁⨁⨀⨀ LOW		
Conclusion:		Increased risk of lower BMD in CAYA cancer survivors with SNPs on rs2504063, rs599083, and rs1876828 (in males), or certain combination of SNPs (1. rs901466: C>G + rs7569568: G>A + rs921319: T>C; 2. rs1020745: G>A + rs2110167: A>G + rs10444471: G>T; 3. rs1894331: G>T + rs10773093: T>C + rs4768783: C>T; 4. rs7321815: C>A + rs9315069: T>C + rs913071: C>T; 5. rs887890: T>G + rs7142110: G>A + rs1884632: C>G). (3 studies significant effect, 1 study no significant effect; 44,439 participants)		

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

[a](possible) overlap in included patients.

1q. What is the risk of fractures in CAYA cancer survivors with a positive family history and/or genetic polymorphisms?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias

1.q. Risk fracture for familial factors **(n=1 study)**	Im 2021	2453 (discovery) 1417 (replication) CCS	At least 5 years Discovery: Approximately 37 years Replication: Approximately 25 years	Chemotherapy: Glucocorticoids 47.2% discovery, 48.3% replication IV MTX 18.5% discovery, 29.2% replication IT MTX 38.4% discovery, 38.3% replication Radiotherapy: CRT 45.9% discovery, 38.5% replication SCT: 0% (exclusion criterion)	Fracture frequency (any type post diagnosis) Discovery: 37.9% Replication: 46.0%	Multivariable model: Fracture: SNP replicated (only in females) is rs1406815 (HAGHL gene), HR 1.43, p=8.2 × 10−9 Treatment-stratified analysis of this SNP in females: No head/neck RT: HR 1.22, 95%CI 0.95–1.57, p=0.11 Any RT: HR=1.88, 95%CI 1.54-2.28, p=2.4 × 10−10 >36 Gray only: HR 3.79, 95%CI 1.95–7.34, p=8.2 × 10−5	SB: high risk AB: low risk DB: high risk CF: unclear
GRADE assessment:							
Study design:	+4	Retrospective cohort study					
Study limitations:	-2	Some limitations: Selection bias high in 1/1; Attrition bias low in 1/1; Detection bias high in 1/1; Confounding unclear in 1/1					
Consistency:	NA	Only one study available					
Directness:	0	Results are direct, population and outcomes broadly generalizable					
Precision:	-1	Important imprecision: high total number of patients and events but only one study available					
Publication bias:	0	Unlikely					
Effect size:	0	No large magnitude of effect					
Dose-response:	0	NA					
Plausible confounding:	0	No plausible confounding					
Quality of evidence:		⊕⊖⊖⊖ VERY LOW					
Conclusion:		Increased risk of fractures in female CAYA cancer survivors with a SNP on rs1406815, especially in those treated with (cranial) radiotherapy. (1 study significant effect; 3,870 participants)					

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

1r.What is the risk of low and very low BMD in CAYA cancer survivors treated with corticosteroids as anti-cancer treatment?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.r. Risk low BMD for corticosteroids **(n=5 studies)**	Bloomhardt 2020	542 CCS	Mean time since treatment (±SD) 6.0±5.0 years (range 2.0-35.1)	Chemotherapy: Dexamethasone 59.6% Prednisone 35.4% Any glucocorticoid 95% Cyclophosphamide 85.1%	LS BMD Z-score ≤-1: 17.2% LS BMD Z-score ≤-2: 3.5%	Multivariable model: LS BMD Z-score <-1: dexamethasone (y/n) OR 1.4, 95%CI 0.8-2.5, p=0.22	SB: high risk AB: low risk DB: low risk CF: high risk

				High-dose methotrexate 25.8% Radiotherapy: CRT 20.7% TBI 8.1% SCT: NR			
	Den Hoed 2015	346 adult CCS	Median time after cessation of treatment 16.7 years (IQR 12.4–23.0)	Chemotherapy: Prednisone 63.6% Dexamethasone 37.0% Cyclophosphamide 49.7% Methotrexate 64.9% Ifosfamide 10.8% Radiotherapy: Cranial-spinal 16.5% Total body 3.8 % CRT 4.3% Abdominal 2.3% SCT: 4.9%	TB BMD or LS BMD Z-score <−1: 45% of the CCS. 38% TB, 27% LS, 20% at both TB and LS. TB BMD or LS BMD Z-score <−2: 9% (TB), 3% (LS)	Multivariable model: LS BMD Z-score <-1: prednisone (yes vs. no) OR 1.5, 95%CI 0.8–2.6; dexamethasone (yes vs. no) OR 1.5, 95%CI 0.8–2.9 TB BMD Z-score <-1: prednisone (yes vs. no) OR=1.8, 95%CI 1.0–3.1, p<0.05; dexamethasone (yes vs. no) OR=1.1, 95%CI 0.6–1.9	SB: high risk AB: low risk DB: low risk CF: low risk
	Polgreen 2012	319 CCS	Mean time since treatment (±SE) 10.1 ± 0.2 years (range 4.3-17.8)	Chemotherapy: Corticosteroid: 42.0% Radiotherapy: 23.2% Cranial (CNS) 9.7%, other 13.5% SCT: 0%	TB BMD Z-score <-1: 11% LS BMD Z-score <-1: 23% TB BMD Z-score <-2: 2.3% LS BMD Z-score <-2: 3.5%	Multivariable model: TB BMD Z-score <-1: steroid exposure (yes vs. no) NS LS BMD Z-score <-1: steroid exposure (yes vs. no), OR 1.9, 95%CI 1.0-3.5, p=0.042	SB: low risk AB: low risk DB: low risk CF: low risk
	Siegel 2017	475 CCS	Mean (±SD) time after Rx 5.4 ± 4.3 years	Chemotherapy: Corticosteroid 83.4% Methotrexate 77.1% Radiotherapy: Cranial / craniospinal 13.3% TBI 9.9% SCT: 17.9%	TB or LS BMD Z-scores ≤–1: 29.3% (LS 22.8%, TB 21.9%) TB or LS BMD Z-scores ≤–2: 8.2% (LS 7.4%, TB 4.0%)	Multivariable model: TB or LS BMD Z-scores ≤–2: steroid exposure, OR 2.7, 95% CI, 0.8-8.6	SB: low risk AB: low risk DB: low risk CF: high risk
	van Atteveld 2019	2032 adult CCS	Median time since cancer dx: 21.6 yrs (range 10.4-40.6)	Chemotherapy: Alkylating agent 56.6% MTX 53.9% GCs 53.9% Radiotherapy: Cranial 33.9% Abdominal 21.7% SCT: NR	LS and/or TB BMD Z-score ≤-1: 51.5% (LS 25.1%, TB 48.0%) LS and/or TB BMD Z-score ≤-2: 20.2%	Multivariable model: LS and/or TB BMD Z-score ≤-1: GCs (yes vs. no) NS LS and/or TB BMD Z-score ≤-2: GCs (yes vs. no) NS	SB: low risk AB: low risk DB: low risk CF: low risk

GRADE assessment (outcome low and very low BMD):

Study design:	+4	Cross-sectional cohort studies
Study limitations:	0	No important limitations: Selection bias low in 3/5, high in 2/5; Attrition bias low in 5/5; Detection bias low in 5/5; Confounding low in 3/5, high in 2/5
Consistency:	-1	Some inconsistency, only two studies showed a significant effect of corticosteroids and the other 3 showed no significant effect
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients and events
Publication bias:	0	Unlikely

Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear if there is a dose response in both studies that showed a significant effect
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⨁⨁⊖ MODERATE
Conclusion:		Increased risk of low BMD (Z-score ≤-1 or ≤-2) after corticosteroids in CAYA cancer survivors. (2 studies significant effect, 3 studies no significant effect; 3,714 participants)
GRADE assessment (outcome very low BMD):		
Study design:	+4	Cross-sectional cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 2/2; Attrition bias low in 2/2; Detection bias low in 2/2; Confounding low in 1/2, high in 1/2
Consistency:	0	No important inconsistency, both studies showed no significant effect of corticosteroids
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients and events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear if there is a dose response in both studies that showed a significant effect
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⨁⨁⊖ MODERATE
Conclusion:		No significant effect of corticosteroids on very low BMD (Z-score ≤-2) in CAYA cancer survivors. (2 studies no significant effect; 2,507 participants)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

1s.What is the risk of lower BMD in CAYA cancer survivors treated with corticosteroids as anti-cancer treatment?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.s. Risk lower BMD for corticosteroids **(n=3 studies)**	Den Hoed 2015	346 adult CCS	Median time after cessation of treatment 16.7 years (IQR 12.4–23.0)	Chemotherapy: Prednisone 63.6% Dexamethasone 37.0% Cyclophosphamide 49.7% Methotrexate 64.9% Ifosfamide 10.8% Radiotherapy: Cranial-spinal 16.5% Total body 3.8 % CRT 4.3% Abdominal 2.3% SCT: 4.9%	TB BMD or LS BMD Z-score <−1: 45% of the CCS. 38% TB, 27% LS, 20% at both TB and LS. TB BMD or LS BMD Z-score <−2: 9% (TB), 3% (LS)	Multivariable model: LS BMD Z-score (cont.): prednisone (yes vs. no) NS; dexamethasone (yes vs. no) NS TB BMD Z-score (cont.): prednisone (yes vs. no) β=−0.25; se=0.12; p=0.03; dexamethasone (yes vs. no) NS	SB: high risk AB: low risk DB: low risk CF: low risk
	Isaksson 2020	125 CCS	Mean (SD) follow-up 24.3 years (7.1)	Chemotherapy: GCs 19 (15%) Alkylating agents 16 (13%) Median cyclophosphamide equivalent dose 4854 mg/m^2 MTX 17 (14%) Median methotrexate dose 11 g/m^2 Radiotherapy: CRT 26% SCT: 2%	Survivors: LS BMD Z-score ≤-1: 22% TH BMD Z-score ≤-1: 21% Controls: LS BMD Z-score ≤-1: 28% TH BMD Z-score ≤-1: 22%	Multivariable model: LS BMD (cont.): difference GCs (yes vs. controls) 0.036 95%CI -0.034 to 0.105, p=0.31 TH BMD (cont.): difference GCs (yes vs. controls) 0.050, 95%CI -0.025 to 0.125, p=0.19	SB: high risk AB: low risk DB: low risk CF: high risk
	Le Meignen 2011	159 ALL and AML survivors	Mean time from diagnosis to DXA 14.66 ± 0.44 yrs	Chemotherapy: Glucocorticoids 86.2% Other chemotherapy NR Radiotherapy: CRT 18.9% TBI 40.4% of HSCT recipients SCT: 34%	BMD Z-score <-2: FN 3.2%; LS 3.8%	Multivariable model: BMD Z-scores (cont.): GCs treatment (yes vs. no) FN: β 0.14, P=0.35; LS: β 0.19, p=0.23	SB: low risk AB: high risk DB: high risk CF: high risk

GRADE assessment:		
Study design:	+4	Cross-sectional cohort studies
Study limitations:	-2	Important limitations: Selection bias low in 1/3, high in 2/3; Attrition bias low in 2/3, high in 1/3; Detection bias low in 2/3, high in 1/3; Confounding low in 1/3, high in 2/3
Consistency:	-1	Important inconsistency, one study shows a significant effect of corticosteroid treatment and two studies show no significant effect
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients and events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear if there is a dose response in the study that showed a significant effect

Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⊖⊖⊖ VERY LOW
Conclusion:		Increased risk of lower BMD after corticosteroids in CAYA cancer survivors. (1 study significant effect, 2 studies no significant effect; 630 participants)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

1t.What is the risk of fractures in CAYA cancer survivors treated with corticosteroids as anti-cancer treatment?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.t. Risk fracture for corticosteroids **(n=2 studies)**	Im 2021[a]	2453 (discovery) 1417 (replication) CCS	At least 5 years Discovery: Approximately 37 years Replication: Approximately 25 years	Chemotherapy: Glucocorticoids 47.2% discovery, 48.3% replication IV MTX 18.5% discovery, 29.2% replication IT MTX 38.4% discovery, 38.3% replication Radiotherapy: CRT 45.9% discovery, 38.5% replication SCT: 0% (exclusion criterion)	Fracture frequency (any type post diagnosis) Discovery: 37.9% Replication: 46.0%	Multivariable model (discovery cohort): Fracture: corticosteroids (any vs. none) HR 1.13, 95%CI 0.96-1.32, p=0.14	SB: high risk AB: low risk DB: high risk CF: unclear
	Wilson 2012[a]	7414 CCS	Median length of follow-up was 22.7 years (range, 15.6-34.2 years)	Chemotherapy: Methotrexate 43.6% Steroids 47% Radiotherapy: CRT 32% Pelvic RT 13% SCT: 0%	Proportion of participants with fractures over their lifetime Survivors: 34.8% Siblings: 38.9%	Multivariable model: Fracture: Males: glucocorticoid (yes vs. no) prevalence ratio (PR), 1.07, 95%CI 0.96-1.19, p=0.19. Females: NR (p>0.2 in univariable analysis)	SB: high risk AB: low risk DB: high risk CF: high risk

GRADE assessment:		
Study design:	+4	Retrospective cohort study
Study limitations:	-3	Some limitations: Selection bias high in 2/2; Attrition bias low in 2/2; Detection bias high in 2/2; Confounding unclear in 1/2, high in 1/1
Consistency:	0	No important inconsistency, both studies showed no significant effect of corticosteroids
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients and events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	NA
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ VERY LOW
Conclusion:		No significant effect of corticosteroids on the risk of fractures in CAYA cancer survivors. (2 studies no significant effect; 9,867 participants)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

[a](possible) overlap in included patients.

1u.What is the risk of low and very low BMD in CAYA cancer survivors treated with higher vs. lower doses corticosteroids?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.u. Risk low BMD for corticosteroid dose **(n=3 studies)**	Choi 2013	78 ALL, AML and CML survivors	Mean time from cancer dx: 4.42±2.47 in males, 5.36±3.2 years in females	Chemotherapy: Glucocorticoids for chemotherapy 42% Glucocorticoids for GVHD 53% Radiotherapy: 62% SCT: 64%	LS BMD Z-score <-2: 25.7% FN BMD Z-score <-2: 24.4%	Multivariable model: LS BMD Z-score <-2: Longer duration of glucocorticoids for GvHD: OR 1.124, 95%CI 1.052 to 1.2, p=0.001	SB: unclear AB: low risk DB: low risk CF: low risk
	Gurney 2014	845 adult ALL survivors	>10 years after diagnosis	Chemotherapy: Glucocorticoids 100% Methotrexate 100% Cyclophosphamide % NR Radiotherapy: CRT: 61.3% CRT + spinalRT or TBI 12.5% SCT: 2.5%	QCT LS BMD Z-score ≤-2: 5.7% QCT LS BMD Z-score ≤-1: 29.5%	Multivariable model: QCT LS BMD Z-score ≤-1: cumulative prednisone equivalents OR 1.00, 95%CI 0.96–1.04, p=0.95	SB: unclear AB: low risk DB: low risk CF: high risk
	Mandel 2004	106 ALL survivors	Average time since diagnosis 10.1 years (range 5.5 to 15.4 years)	Chemotherapy: Glucocorticoids 100% Methotrexate 100% Radiotherapy: 47% SCT: 0%	LS BMD Z-score <-1: 23% FN BMD less than 89% of the healthy average: 20%	Multivariable model: FN BMD < 89% of the healthy average: GCs dose OR 2.81, p = 0.049	SB: high risk AB: low risk DB: high risk CF: high risk

GRADE assessment (outcome low and very low BMD):

Study design:	+4	Cross-sectional cohort studies
Study limitations:	-2	Some limitations: Selection bias unclear in 2/3, high in 1/3; Attrition bias low in 3/3; Detection bias low in 2/3, high in 1/3; Confounding low in 1/3, high in 2/3
Consistency:	0	No important inconsistency, 2 studies show a significant effect of higher vs. lower doses corticosteroids and 1 study shows no significant effect
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients and events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	+1	Dose response relationship as higher doses are associated with an increased risk as compared to lower doses
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊖ MODERATE
Conclusion:		Increased risk of low BMD (Z-score ≤-1 or ≤-2) after higher versus lower doses corticosteroids in CAYA cancer survivors. (2 studies significant effect, 1 study no significant effect; 1,029 participants)

GRADE assessment (outcome very low BMD):

Study design:	+4	Cross-sectional cohort study
Study limitations:	-1	Some limitations: Selection bias unclear in 1/1; Attrition bias low in 1/1; Detection bias low in 1/1; Confounding low in 1/1
Consistency:	NA	Only one study available
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Important imprecision, low total number of patients and events and only one study available
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect

Dose-response:	0	Dose response relationship as higher doses are associated with an increased risk as compared to lower doses, but only assessed in one study
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⊖⊖⊖ VERY LOW
Conclusion:		Increased risk of very low BMD (Z-score ≤-2) after higher versus lower doses corticosteroids in CAYA cancer survivors. (1 study significant effect; 78 participants)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

1v.What is the risk of lower BMD in CAYA cancer survivors treated with higher vs. lower doses corticosteroids?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.v. Risk lower BMD for corticosteroid dose **(n=5 studies)**	Alikasifoglu 2005[a]	59 ALL survivors	Mean 3.40 (1.77) years after cessation of therapy	Chemotherapy: Conventional dose prednisolone 51% Megadose methylprednisolone 49% Cyclophosphamide 100% HD-MTX 100% Radiotherapy: CRT 76% SCT: 0%	Mean (SD) LS BMD Z-score Total cohort: -1.73 (0.84)	LS BMD Z-score: Group 1 (conventional dose prednisolone) vs. Group 2 (megadose methylprednisolone): -1.75 (0.83) vs. -1.66 (1.21), P = 0.736.	SB: high risk AB: high risk DB: low risk CF: low risk
	Benmiloud 2010	89 ALL and NHL survivors	Mean time since treatment (±SD) 15.0 ± 4.5 years	Chemotherapy: Prednisolone 100% Dexamethasone 52.8% Methotrexate 100% Radiotherapy RT at any site: 53.9% CNS RT 36% CRT 32.6% CSRT 3.4% TBI 18.0% SCT 18.0%	BMD Z-score ≤-1.0: At any site: 59.1%; At the LS: 50.5% At the FN: 25.8%; At the Hip: 31.5% BMD Z-score ≤-2: At any site: 10.1%; At the LS: 10.1% At the FN: 2.2%; At the Hip: 2.2%	Multivariable model: LS BMD Z-score (cont.): NS FN and Hip BMD Z-score (cont.): additional cumulative DEXA dose p=0.014, β not reported (negative effect)	SB: low risk AB: high risk DB: low risk CF: low risk
	De Matteo 2019	72 ALL survivors	Mean (±SD) time since treatment 41.2 ±37.8 months (95% CI: 49.9, 32.5)	Chemotherapy: Prednisone 100% Dexamethasone 100% MTX 100% Cyclophosphamide 100% Radiotherapy: 4% SCT: 0%	Proximal phalanx (QUS) Ad-SoS Z-score below −2 SD: 13.8%	Multivariable model: Ad-SoS Z-score (cont.): cumulative dose of steroids NS	SB: unclear AB: low risk DB: unclear CF: low risk
	Jones 2008[a]	309 ALL survivors	At least 4 years of continuous remission	Chemotherapy: MTX 100% Prednisone 100% Radiotherapy: NR SCT: NR	Mean QCT LS BMD Z-score (SD): -0.47 (1.26)	Multivariable model: QCT LS BMD Z-score (cont.): Protocol group (high antimetabolite + high GCs [mean Z-score -0.95] vs. low antimetabolite + high GCs [mean Z-score -0.49] vs. high antimetabolite + low GCs [mean Z-score -0.06]), p<0.001	SB: high risk AB: low risk DB: low risk CF: low risk
	Kaste 2014[a]	424 ALL survivors	Median 8.4 yrs (4.6-19.1) from completion of	Chemotherapy: Glucocorticoids 100% Methotrexate 100% Cyclophosphamide 100%	QCT LS BMD Z-score <-1: 48.9% QCT LS BMD Z-score <-2: 6.8%	Multivariable model: QCT LS BMD Z-score (cont.): GCs dose (mg/m2): <5,000 vs. ≥5,000 β 0.72 (0.29, 1.14) P=0.001	SB: high risk AB: high risk DB: low risk CF: low risk

		ALL therapy to entry into study: Radiotherapy: CRT 36.1% SCT: NR
GRADE assessment:		
Study design:	+4	Cross-sectional cohort studies
Study limitations:	-2	Some limitations: Selection bias low in 1/5, unclear in 1/5, high in 3/5; Attrition bias low in 2/5, high in 3/5; Detection bias low in 4/5, unclear in 1/5; Confounding low in 5/5
Consistency:	0	No important inconsistency, three studies show a significant effect of higher vs. lower doses corticosteroids and two studies show no significant effect
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients and events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	+1	Dose response relationship as higher doses are associated with an increased risk as compared to lower doses
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⨁⨁⊖ MODERATE
Conclusion:		Increased risk of lower BMD after higher versus lower doses corticosteroids in CAYA cancer survivors. (3 studies significant effect, 2 studies no significant effect; 953 participants)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

[a](possible) overlap in included patients.

1w.What is the risk of fractures in CAYA cancer survivors treated with higher vs. lower doses corticosteroids?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.w. Risk fracture for corticosteroid dose **(n=1 study)**	Fiscaletti 2021	251 ALL survivors	Median 15.1 years (range 5.4 to 28.2 years) since cancer diagnosis	Chemotherapy: Glucocorticoids 100% Methotrexate 100% Radiotherapy: CRT 59% SCT: None	Frequency of fractures: Vertebral fractures: 23% Non-vertebral fractures: 31%	Multivariable model: Vertebral fractures: prednisone equivalent dose (per 1000 mg/m2): RR 1.05, 95%CI 1.00-1.10, p=0.03	SB: low risk AB: low risk DB: low risk CF: low risk
GRADE assessment:							
Study design:	+4	Retrospective cohort study					
Study limitations:	0	No important limitations: Selection bias low in 1/1; Attrition bias low in 1/1; Detection bias low in 1/1; Confounding low in 1/1					
Consistency:	NA	Only one study available					
Directness:	0	Results are direct, population and outcomes broadly generalizable					
Precision:	-2	Important imprecision: low total number of patients and events and only one study available					
Publication bias:	0	Unlikely					
Effect size:	0	No large magnitude of effect					
Dose-response:	0	NA					
Plausible confounding:	0	No plausible confounding					
Quality of evidence:		⊕⊕⊖⊖ LOW					
Conclusion:		Increased risk of vertebral fractures after higher versus lower doses corticosteroids in CAYA cancer survivors. (1 study significant effect; 251 participants)					

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

[a](possible) overlap in included patients.

1x.What is the risk of lower BMD in CAYA cancer survivors treated with dexamethasone vs. prednisone?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.x. Risk lower BMD for dexa vs. pred **(n=1 study)**	Van Beek 2006	90 ALL survivors	Mean 12.7 yrs after dx (2.0-29.7)	Chemotherapy: Prednisone 52.2% Dexamethasone 47.8% MTX 71.1% Radiotherapy: CRT 21.1% SCT: 0%	NR	Multivariable model: LS, TB BM(A)D Z-score (cont.): dexa vs. pred NS	SB: unclear AB: low risk DB: low risk CF: low risk

GRADE assessment:		
Study design:	+4	Cross-sectional cohort study
Study limitations:	-1	Some limitations: Selection bias unclear in 1/1; Attrition bias low in 1/1; Detection bias low in 1/1; Confounding low in 1/1
Consistency:	NA	Only one study available
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Important imprecision, low total number of patients, number of events NR and only one study available
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	NA
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ VERY LOW
Conclusion:		No significant effect of treatment with dexamethasone versus prednisone on lower BMD in CAYA cancer survivors. (1 study no significant effect; 90 participants)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

1y.What is the risk of low and very low BMD in CAYA cancer survivors treated with methotrexate?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.y. Risk low BMD for methotrexate **(n=4 studies)**	Bloomhardt 2020	542 CCS	Mean time since treatment (±SD) 6.0±5.0 years (range 2.0-35.1)	Chemotherapy: Dexamethasone 59.6% Prednisone 35.4% Any glucocorticoid 95% Cyclophosphamide 85.1% High-dose methotrexate 25.8% Radiotherapy: CRT 20.7% TBI 8.1% SCT: NR	LS BMD Z-score ≤-1: 17.2% LS BMD Z-score ≤-2: 3.5%	Multivariable model: LS BMD Z-score <-1: high-dose methotrexate (y/n) OR 0.9, 95%CI 0.5-1.6, p=0.79	SB: high risk AB: low risk DB: low risk CF: high risk
	Den Hoed 2015	346 adult CCS	Median time after cessation of treatment 16.7 years (IQR 12.4–23.0)	Chemotherapy: Prednisone 63.6% Dexamethasone 37.0% Cyclophosphamide 49.7% Methotrexate 64.9% Ifosfamide 10.8% Radiotherapy: Cranial-spinal 16.5% Total body 3.8 % CRT 4.3% Abdominal 2.3% SCT: 4.9%	TB BMD or LS BMD Z-score <–1: 45% of the CCS. 38% TB, 27% LS, 20% at both TB and LS. TB BMD or LS BMD Z-score <–2: 9% (TB), 3% (LS)	Multivariable model: LS BMD Z-score <-1: methotrexate (yes vs. no) OR 1.3, 95%CI 0.7–2.4 TB BMD Z-score <-1 methotrexate (yes vs. no) OR 1.4, 95%CI 0.8–2.5	SB: high risk AB: low risk DB: low risk CF: low risk
	Siegel 2017	475 CCS	Mean (±SD) time after Rx 5.4 ± 4.3 years	Chemotherapy: Corticosteroid 83.4% Methotrexate 77.1% Radiotherapy: Cranial / craniospinal 13.3% TBI 9.9% SCT: 17.9%	TB or LS BMD Z-scores ≤–1: 29.3% (LS 22.8%, TB 21.9%) TB or LS BMD Z-scores ≤–2: 8.2% (LS 7.4%, TB 4.0%)	Multivariable model: TB or LS BMD Z-scores ≤–2: MTX (yes vs. no) NS	SB: low risk AB: low risk DB: low risk CF: high risk
	van Atteveld 2019	2032 adult CCS	Median time since cancer dx: 21.6 yrs (range 10.4-40.6)	Chemotherapy: Alkylating agent 56.6% MTX 53.9% GCs 53.9% Radiotherapy: Cranial 33.9% Abdominal 21.7% SCT: NR	LS and/or TB BMD Z-score ≤-1: 51.5% (LS 25.1%, TB 48.0%) LS and/or TB BMD Z-score ≤-2: 20.2%	Multivariable model: LS and/or TB BMD Z-score ≤-1: MTX (yes vs. no) NS LS and/or TB BMD Z-score ≤-2: MTX (yes vs. no) NS	SB: low risk AB: low risk DB: low risk CF: low risk
GRADE assessment: **Study design:** +4 Cross-sectional cohort studies **Study limitations:** -1 Some limitations: Selection bias low in 2/4, high in 2/4; Attrition bias low in 4/4; Detection bias low in 4/4; Confounding low in 2/4, high in 2/4							

Consistency:	0	No important inconsistency, all studies show no significant effect of MTX treatment
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients and events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No dose response relationship of higher doses MTX and low BMD
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⨁⨁⊖ MODERATE
Conclusion:		No significant effect of methotrexate on low BMD (Z-score ≤-1 or ≤-2) in CAYA cancer survivors. (4 studies no significant effect; 3,395 participants)
GRADE assessment:		
Study design:	+4	Cross-sectional cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 2/2; Attrition bias low in 2/2; Detection bias low in 2/2; Confounding low in 1/2, high in 1/2
Consistency:	0	No important inconsistency, all studies show no significant effect of MTX treatment
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients and events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No dose response relationship of higher doses MTX and low BMD
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⨁⨁⊖ MODERATE
Conclusion:		No significant effect of methotrexate on very low BMD (Z-score ≤-2) in CAYA cancer survivors. (2 studies no significant effect; 2,507 participants)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

1z.What is the risk of lower BMD in CAYA cancer survivors treated with methotrexate?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.z. Risk lower BMD for methotrexate **(n=2 studies)**	Den Hoed 2015	346 adult CCS	Median time after cessation of treatment 16.7 years (IQR 12.4–23.0)	Chemotherapy: Prednisone 63.6% Dexamethasone 37.0% Cyclophosphamide 49.7% Methotrexate 64.9% Ifosfamide 10.8% Radiotherapy: Cranial-spinal 16.5% Total body 3.8 % CRT 4.3% Abdominal 2.3% SCT: 4.9%	TB BMD or LS BMD Z-score <−1: 45% of the CCS. 38% TB, 27% LS, 20% at both TB and LS. TB BMD or LS BMD Z-score <−2: 9% (TB), 3% (LS)	Multivariable model: LS BMD Z-score (cont.): methotrexate (yes vs. no) NS TB BMD Z-score (cont.): methotrexate (yes vs. no) NS	SB: high risk AB: low risk DB: low risk CF: low risk
	Isaksson 2020	125 CCS	Mean (SD) follow-up 24.3 years (7.1)	Chemotherapy: GCs 19 (15%) Alkylating agents 16 (13%) Median cyclophosphamide equivalent dose 4854 mg/m^2 MTX 17 (14%) Median methotrexate dose 11 g/m^2 Radiotherapy: CRT 26% SCT: 2%	Survivors: LS BMD Z-score ≤-1: 22% TH BMD Z-score ≤-1: 21% Controls: LS BMD Z-score ≤-1: 28% TH BMD Z-score ≤-1: 22%	Multivariable model: LS BMD (cont.): difference MTX (yes vs. controls) 0.047, 95%CI -0.025 to 0.119, p=0.20 TH BMD (cont.): difference MTX (yes vs. controls) 0.033, 95%CI -0.044 to 0.110, p=0.40	SB: high risk AB: low risk DB: low risk CF: high risk

GRADE assessment:		
Study design:	+4	Cross-sectional cohort studies
Study limitations:	-2	Some limitations: Selection bias high in 2/2; Attrition bias low in 2/2; Detection bias low in 2/2; Confounding low in 1/2, high in 1/2
Consistency:	0	No important inconsistency, both studies show no significant effect of MTX treatment
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients and events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No dose response relationship of higher doses MTX and low BMD
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		No significant effect of methotrexate on lower BMD in CAYA cancer survivors. (2 studies no significant effect; 471 participants)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray

absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

1aa.What is the risk of fractures in CAYA cancer survivors treated with methotrexate?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.aa. Risk fracture for methotrexate **(n=2 studies)**	Fiscaletti 2021	251 ALL survivors	Median 15.1 years (range 5.4 to 28.2 years) since cancer diagnosis	Chemotherapy: Glucocorticoids 100% Methotrexate 100% Radiotherapy: CRT 59% SCT: None	Frequency of fractures: Vertebral fractures: 23% Non-vertebral fractures: 31%	Multivariable model: Vertebral fractures: MTX NS	SB: low risk AB: low risk DB: low risk CF: low risk
	Wilson 2012	7414 CCS	Median length of follow-up was 22.7 years (range, 15.6-34.2 years)	Chemotherapy: Methotrexate 43.6% Steroids 47% Radiotherapy: CRT 32% Pelvic RT 13% SCT: 0%	Proportion of participants with fractures over their lifetime Survivors: 34.8% Siblings: 38.9%	Multivariable model: Fracture: female survivors treated with MTX vs. no MTX, prevalence ratio, 1.15; 95% CI, 1.03-1.27; P=0.001 Male survivors treated with MTX vs. no MTX, prevalence ratio, 1.07; 95% CI, 0.96-1.18; P=0.22	SB: high risk AB: low risk DB: high risk CF: high risk

GRADE assessment:		
Study design:	+4	Cross-sectional cohort study
Study limitations:	-2	Some limitations: Selection bias low in 1/2, high in 1/2; Attrition bias low in 2/2; Detection bias low in 1/2, high in 1/2; Confounding low in 1/2, high in 1/2
Consistency:	-1	Important inconsistency: one study shows a significant effect of MTX treatment (in female CAYA cancer survivors) and one no significant effect
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients and events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Dose response relationship of higher MTX doses and fracture not assessed
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ VERY LOW
Conclusion:		Increased risk of fracture after methotrexate in female CAYA cancer survivors. (1 study significant effect, 1 study no significant effect; 7,665 participants)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

1bb.What is the risk of low and very low BMD in CAYA cancer survivors treated with higher vs. lower doses methotrexate?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.bb. Risk low BMD for methotrexate dose **(n=1 study)**	Gurney 2014	845 adult ALL survivors	>10 years after diagnosis	Chemotherapy: Glucocorticoids 100% Methotrexate 100% Cyclophosphamide % NR Radiotherapy: CRT: 61.3% CRT + spinal RT or TBI 12.5% SCT: 2.5%	QCT LS BMD Z-score ≤-1: 29.5% QCT LS BMD Z-score ≤-2: 5.7%	Multivariable model: QCT LS BMD Z-score ≤-1: cumulative MTX dose per 1,000 mg/m^2 units OR 1.00, 95%CI 0.97–1.02, p=0.97	SB: unclear AB: low risk DB: low risk CF: high risk

GRADE assessment:		
Study design:	+4	Cross-sectional cohort study
Study limitations:	-1	Some limitations: Selection bias unclear in 1/1; Attrition bias low in 1/1; Detection bias low in 1/1; Confounding high in 1/2
Consistency:	NA	Only one study available
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Important imprecision, high total number of patients and events but only one study available
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No dose response relationship of higher doses MTX and low BMD
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		No significant effect of higher versus lower doses methotrexate on low BMD (Z-score ≤-1 or ≤-2) in CAYA cancer survivors. (1 study no significant effect; 845 participants)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

1cc.What is the risk of lower BMD in CAYA cancer survivors treated with higher vs. lower doses methotrexate?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.cc. Risk lower BMD for methotrexate dose **(n=1 study)**	De Matteo 2019	72 ALL survivors	Mean (±SD) time since treatment 41.2 ±37.8 months (95% CI: 49.9, 32.5)	Chemotherapy: Prednisone 100% Dexamethasone 100% MTX 100% Cyclophosphamide 100% Radiotherapy: 3 (4%) SCT: 0%	Proximal phalanx (QUS) Ad-SoS Z-score below −2 SD: 10/72 (13.8%)	Multivariable model: Ad-SoS Z-score (cont.): cumulative dose of MTX NS	SB: unclear AB: low risk DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Cross-sectional cohort studies
Study limitations:	-1	Some limitations: Selection bias unclear in 1/1; Attrition bias low in 1/1; Detection bias unclear in 1/1; Confounding low in 1/1
Consistency:	NA	Only one study available
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Important imprecision, low total number of patients and events and only one study available
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No dose response relationship of higher doses MTX and lower BMD
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ VERY LOW
Conclusion:		No significant effect of higher versus lower doses methotrexate on lower BMD in CAYA cancer survivors. (1 study no significant effect; 72 participants)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

1dd.What is the risk of fractures in CAYA cancer survivors treated with higher vs. lower doses methotrexate?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.dd. Risk fracture for methotrexate dose **(n=1 study)**	Im 2021	2453 (discovery) 1417 (replication) CCS	At least 5 years Discovery: Approximately 37 years Replication: Approximately 25 years	Chemotherapy: Glucocorticoids 47.2% discovery, 48.3% replication IV MTX 18.5% discovery, 29.2% replication IT MTX 38.4% discovery, 38.3% replication Radiotherapy: CRT 45.9% discovery, 38.5% replication SCT: 0% (exclusion criterion)	Fracture frequency (any type post diagnosis) Discovery: 37.9% Replication: 46.0%	Multivariable (sex-combined) model (discovery cohort): Fracture: IV methotrexate dose (100 g/m2): HR 1.20, 95%CI 1.00-1.45, p=0.05 IT methotrexate dose (100 mg/m2): HR=1.07, 95%CI 0.99-1.15, p=0.08 Females: IV methotrexate dose (100 g/m2): HR=1.02, 95%CI 0.76-1.37, p=0.90 IT methotrexate dose (100 mg/m2): HR=0.99, 95%CI 0.88-1.12, p=0.89 Males: IV methotrexate dose (100 g/m2): HR=1.46, 95%CI 1.15-1.85, p=1.8x10-3 IT methotrexate dose (100 mg/m2): HR=1.11, 95%CI 1.02-1.22, p=0.02	SB: high risk AB: low risk DB: high risk CF: unclear

GRADE assessment:		
Study design:	+4	Retrospective cohort study
Study limitations:	-2	Some limitations: Selection bias high in 1/1; Attrition bias low in 1/1; Detection bias high in 1/1; Confounding unclear in 1/1
Consistency:	NA	Only one study available
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Important imprecision: high total number of patients and events but only one study available
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	NA
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ VERY LOW
Conclusion:		Increased risk of fracture after higher versus lower doses methotrexate in male CAYA cancer survivors. (1 study significant effect; 2,453 participants)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray

absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

1ee.What is the risk of low and very low BMD in CAYA cancer survivors treated with ifosfamide?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.ee. Risk low BMD for ifosfamide **(n=2 studies)**	Den Hoed 2015	346 adult CCS	Median time after cessation of treatment 16.7 years (IQR 12.4–23.0)	Chemotherapy: Prednisone 63.6% Dexamethasone 37.0% Cyclophosphamide 49.7% Methotrexate 64.9% Ifosfamide 10.8% Radiotherapy: Cranial-spinal 16.5% Total body 3.8 % CRT 4.3% Abdominal 2.3% SCT: 4.9%	TB BMD or LS BMD Z-score <−1: 45% of the CCS. 38% TB, 27% LS, 20% at both TB and LS. TB BMD or LS BMD Z-score <−2: 9% (TB), 3% (LS)	Multivariable model: LS BMD Z-score <-1: ifosfamide (yes vs. no) OR 1.1, 95%CI 0.5–2.4 TB BMD Z-score <-1 ifosfamide (yes vs. no) OR 0.8, 95%CI 0.3–1.9	SB: high risk AB: low risk DB: low risk CF: low risk
	van Atteveld 2019	2032 adult CCS	Median time since cancer dx: 21.6 yrs (range 10.4-40.6)	Chemotherapy: Alkylating agent 56.6% MTX 53.9% GCs 53.9% Radiotherapy: Cranial 33.9% Abdominal 21.7% SCT: NR	LS and/or TB BMD Z-score ≤-1: 51.5% (LS 25.1%, TB 48.0%) LS and/or TB BMD Z-score ≤-2: 20.2%	Multivariable model: LS and/or TB BMD Z-score ≤-1: alkylating agent (ifosfamide/cyclophosphamide, yes vs. no) NS LS and/or TB BMD Z-score ≤-2: alkylating agent (ifosfamide/cyclophosphamide, yes vs. no) NS	SB: low risk AB: low risk DB: low risk CF: low risk

GRADE assessment:		
Study design:	+4	Cross-sectional cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 1/2, high in 1/2; Attrition bias low in 2/2; Detection bias low in 2/2; Confounding low in 2/2
Consistency:	0	No important inconsistency, both studies show no significant effect of ifosfamide treatment
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients and events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Dose response relationship of higher ifosfamide doses and low BMD not assessed
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊖ MODERATE
Conclusion:		No significant effect of ifosfamide on low BMD (Z-score ≤-1 or ≤-2) in CAYA cancer survivors. (2 studies no significant effect; 2,378 participants)

GRADE assessment:		
Study design:	+4	Cross-sectional cohort studies
Study limitations:	0	No limitations: Selection bias low in 1/1; Attrition bias low in 1/1; Detection bias low in 1/1; Confounding low in 1/1
Consistency:	NA	Only one study available

Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Important imprecision, high total number of patients and events, but only one study available
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Dose response relationship of higher ifosfamide doses and low BMD not assessed
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊖ MODERATE
Conclusion:		No significant effect of ifosfamide on very low BMD (Z-score ≤-2) in CAYA cancer survivors. (1 study no significant effect; 2,032 participants)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

1ff.What is the risk of lower BMD in CAYA cancer survivors treated with ifosfamide?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.ff. Risk lower BMD for ifosfamide **(n=1 study)**	Den Hoed 2015	346 adult CCS	Median time after cessation of treatment 16.7 years (IQR 12.4–23.0)	Chemotherapy: Prednisone 63.6% Dexamethasone 37.0% Cyclophosphamide 49.7% Methotrexate 64.9% Ifosfamide 10.8% Radiotherapy: Cranial-spinal 16.5% Total body 3.8 % CRT 4.3% Abdominal 2.3% SCT: 4.9%	TB BMD or LS BMD Z-score <−1: 45% of the CCS. 38% TB, 27% LS, 20% at both TB and LS. TB BMD or LS BMD Z-score <−2: 9% (TB), 3% (LS)	Multivariable model: LS BMD Z-score (cont.): ifosfamide (yes vs. no) NS TB BMD Z-score (cont.): ifosfamide (yes vs. no) NS	SB: high risk AB: low risk DB: low risk CF: low risk

GRADE assessment:		
Study design:	+4	Cross-sectional cohort study
Study limitations:	-1	Some limitations: Selection bias high in 1/1; Attrition bias low in 1/1; Detection bias low in 1/1; Confounding low in 1/1
Consistency:	NA	Only one study available
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Important imprecision, high total number of patients and events but only one study available
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Dose response relationship of higher ifosfamide doses and low BMD not assessed
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⨁⨀⨀ LOW
Conclusion:		No significant effect of ifosfamide on lower BMD in CAYA cancer survivors. (1 study no significant effect; 346 participants)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

1gg.What is the risk of low and very low BMD in CAYA cancer survivors treated with cyclophosphamide?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.gg. Risk low BMD for cyclophosphamide **(n=3 studies)**	Bloomhardt 2020	542 CCS	Mean time since treatment (±SD) 6.0±5.0 years (range 2.0-35.1)	Chemotherapy: Dexamethasone 59.6% Prednisone 35.4% Any glucocorticoid 95% Cyclophosphamide 85.1% High-dose methotrexate 25.8% Radiotherapy: CRT 20.7% TBI 8.1% SCT: NR	LS BMD Z-score ≤-1: 17.2% LS BMD Z-score ≤-2: 3.5%	Multivariable model: LS BMD Z-score <-1: cyclophosphamide equivalent dose, 0: Reference 1-8000: OR 0.8, 95%CI 0.4-1.6, >8000: OR 1.1, 95%CI 0.4-2.9, p=0.67	SB: high risk AB: low risk DB: low risk CF: high risk
	Den Hoed 2015	346 adult CCS	Median time after cessation of treatment 16.7 years (IQR 12.4–23.0)	Chemotherapy: Prednisone 63.6% Dexamethasone 37.0% Cyclophosphamide 49.7% Methotrexate 64.9% Ifosfamide 10.8% Radiotherapy: Cranial-spinal 16.5% Total body 3.8 % CRT 4.3% Abdominal 2.3% SCT: 4.9%	TB BMD or LS BMD Z-score <−1: 45% of the CCS. 38% TB, 27% LS, 20% at both TB and LS. TB BMD or LS BMD Z-score <−2: 9% (TB), 3% (LS)	Multivariable model: LS BMD Z-score <-1: cyclophosphamide (yes vs. no) OR 1.7 95%CI 0.9–2.9 TB BMD Z-score <-1 cyclophosphamide (yes vs. no) OR 1.5, 95%CI 0.9–2.6	SB: high risk AB: low risk DB: low risk CF: low risk
	van Atteveld 2019	2032 adult CCS	Median time since cancer dx: 21.6 yrs (range 10.4-40.6)	Chemotherapy: Alkylating agent 56.6% MTX 53.9% GCs 53.9% Radiotherapy: Cranial 33.9% Abdominal 21.7% SCT: NR	LS and/or TB BMD Z-score ≤-1: 51.5% (LS 25.1%, TB 48.0%) LS and/or TB BMD Z-score ≤-2: 20.2%	Multivariable model: LS and/or TB BMD Z-score ≤-1: alkylating agent (ifosfamide/cyclophosphamide, yes vs. no) NS LS and/or TB BMD Z-score ≤-2: alkylating agent (ifosfamide/cyclophosphamide, yes vs. no) NS	SB: low risk AB: low risk DB: low risk CF: low risk

GRADE assessment:		
Study design:	+4	Cross-sectional cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 1/3, high in 2/3; Attrition bias low in 3/3; Detection bias low in 3/3; Confounding low in 2/3, high in 1/3
Consistency:	0	No important inconsistency, all studies show no significant effect of cyclophosphamide treatment
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients and events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No dose response relationship of higher cyclophosphamide doses and low BMD

Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⨁⨁⨀ MODERATE
Conclusion:		No significant effect of cyclophosphamide on low BMD (Z-score ≤-1 or ≤-2) in CAYA cancer survivors. (3 studies no significant effect; 2,920 participants)
GRADE assessment:		
Study design:	+4	Cross-sectional cohort studies
Study limitations:	0	No limitations: Selection bias low in 1/1; Attrition bias low in 1/1; Detection bias low in 1/1; Confounding low in 1/1
Consistency:	NA	Only one study available
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Important imprecision, high total number of patients and events, but only one study available
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No dose response relationship of higher cyclophosphamide doses and low BMD
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⨁⨁⨀ MODERATE
Conclusion:		No significant effect of cyclophosphamide on very low BMD (Z-score ≤-2) in CAYA cancer survivors. (1 study no significant effect; 2,032 participants)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

1hh.What is the risk of lower BMD in CAYA cancer survivors treated with cyclophosphamide?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.hh. Risk lower BMD for cyclophosphamide **(n=1 study)**	Den Hoed 2015	346 adult CCS	Median time after cessation of treatment 16.7 years (IQR 12.4–23.0)	Chemotherapy: Prednisone 63.6% Dexamethasone 37.0% Cyclophosphamide 49.7% Methotrexate 64.9% Ifosfamide 10.8% Radiotherapy: Cranial-spinal 16.5% Total body 3.8 % CRT 4.3% Abdominal 2.3% SCT: 4.9%	TB BMD or LS BMD Z-score <−1: 45% of the CCS. 38% TB, 27% LS, 20% at both TB and LS. TB BMD or LS BMD Z-score <−2: 9% (TB), 3% (LS)	Multivariable model: LS BMD Z-score (cont.): cyclophosphamide (yes vs. no) NS TB BMD Z-score (cont.): cyclophosphamide (yes vs. no) NS	SB: high risk AB: low risk DB: low risk CF: low risk

GRADE assessment:		
Study design:	+4	Cross-sectional cohort study
Study limitations:	-1	Some limitations: Selection bias high in 1/1; Attrition bias low in 1/1; Detection bias low in 1/1; Confounding low in 1/1
Consistency:	NA	Only one study available
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Important imprecision, high total number of patients and events but only one study available
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No dose response relationship of higher cyclophosphamide doses and low BMD
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		No significant effect of cyclophosphamide on lower BMD in CAYA cancer survivors. (1 study no significant effect; 346 participants)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

1ii.What is the risk of fractures in CAYA cancer survivors treated with alkylating agents?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.ii. Risk fracture for alkylating agents **(n=1 study)**	Wilson 2012	7414 CCS	Median length of follow-up was 22.7 years (range, 15.6-34.2 years)	Chemotherapy: Methotrexate 43.6% Steroids 47% Radiotherapy: CRT 32% Pelvic RT 13% SCT: 0%	Proportion of participants with fractures over their lifetime Survivors: 34.8% Siblings: 38.9%	Multivariable model: Fracture: Males: alkylating agent (yes vs. no) prevalence ratio (PR), 1.08, 95%CI 0.99-1.17, p=0.10. Females: NR (p>0.2 in univariable analysis)	SB: high risk AB: low risk DB: high risk CF: high risk

GRADE assessment:		
Study design:	+4	Retrospective cohort study
Study limitations:	-3	Important limitations: Selection bias high in 1/1; Attrition bias low in 1/1; Detection bias high in 1/1; Confounding high in 1/1
Consistency:	NA	Only one study available
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Important imprecision: high total number of patients and events but only one study available
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	NA
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ VERY LOW
Conclusion:		No significant effect of alkylating agents on the risk of fractures in CAYA cancer survivors. (1 study no significant effect; 7,414 participants)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

1jj.What is the risk of lower BMD in CAYA cancer survivors treated with higher vs. lower doses cyclophosphamide?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.jj. Risk lower BMD for cyclophosphamide dose **(n=2 studies)**	Bloomhardt 2020	542 CCS	Mean time since treatment (±SD) 6.0±5.0 years (range 2.0-35.1)	Chemotherapy: Dexamethasone 59.6% Prednisone 35.4% Any glucocorticoid 95% Cyclophosphamide 85.1% High-dose methotrexate 25.8% Radiotherapy: CRT 20.7% TBI 8.1% SCT: NR	LS BMD Z-score ≤-1: 17.2% LS BMD Z-score ≤-2: 3.5%	Multivariable model: LS BMD Z-score <-1: cyclophosphamide equivalent dose, 0: Reference 1-8000: OR 0.8, 95%CI 0.4-1.6, >8000: OR 1.1, 95%CI 0.4-2.9, p=0.67	SB: high risk AB: low risk DB: low risk CF: high risk
	De Matteo 2019	72 ALL survivors	Mean (±SD) time since treatment 41.2 ±37.8 months (95% CI: 49.9, 32.5)	Chemotherapy: Prednisone 100% Dexamethasone 100% MTX 100% Cyclophosphamide 100% Radiotherapy: 3 (4%) SCT: 0%	Proximal phalanx (QUS) Ad-SoS Z-score below −2 SD: 10/72 (13.8%)	Multivariable model: Ad-SoS Z-score (cont.): cumulative dose of cyclophosphamide NS	SB: unclear AB: low risk DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-2	Some limitations: Selection bias unclear in 1/2, high in 1/2; Attrition bias low in 2/2; Detection bias low in 1/2, unclear in 1/2; Confounding low in 1/2, high in 1/2
Consistency:	0	No important inconsistency, both studies show no significant effect of cyclophosphamide dose
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No dose response relationship of higher cyclophosphamide doses and lower BMD
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		No significant effect of higher versus lower doses cyclophosphamide on lower BMD in CAYA cancer survivors. (2 studies no significant effect; 614 participants)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

1kk. What is the risk of lower BMD in CAYA cancer survivors treated with higher vs. lower doses 6-mercaptopurine?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.kk. Risk lower BMD for 6-MP dose **(n=1 study)**	De Matteo 2019	72 ALL survivors	Mean (±SD) time since treatment 41.2 ±37.8 months (95% CI: 49.9, 32.5)	Chemotherapy: Prednisone 100% Dexamethasone 100% MTX 100% Cyclophosphamide 100% Radiotherapy: 3 (4%) SCT: 0%	Proximal phalanx (QUS) Ad-SoS Z-score below −2 SD: 10/72 (13.8%)	Multivariable model: Ad-SoS Z-score (cont.): cumulative dose of 6-MP NS	SB: unclear AB: low risk DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Cross-sectional cohort study
Study limitations:	-1	Some limitations: Selection bias unclear in 1/1; Attrition bias low in 1/1; Detection bias unclear in 1/1; Confounding low in 1/1
Consistency:	NA	Only one study available
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Important imprecision, low total number of patients and only one study available
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No dose response relationship of higher 6-MP doses and lower BMD
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ VERY LOW
Conclusion:		No significant effect of higher versus lower doses 6-mercaptopurine on lower BMD in CAYA cancer survivors. (1 study no significant effect; 72 participants)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

1ll. What is the risk of low and very low BMD in CAYA cancer survivors treated with cranial or craniospinal irradiation?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.ll. Risk low BMD for CRT/CSRT **(n=8 studies)**	Bloomhardt 2020	542 CCS	Mean time since treatment (±SD) 6.0±5.0 years (range 2.0-35.1)	Chemotherapy: Dexamethasone 59.6% Prednisone 35.4% Any glucocorticoid 95% Cyclophosphamide 85.1% High-dose methotrexate 25.8% Radiotherapy: CRT 20.7% TBI 8.1% SCT: NR	LS BMD Z-score ≤-1: 17.2% LS BMD Z-score ≤-2: 3.5%	Multivariable model: LS BMD Z-score <-1: cranial radiation (y/n) OR 1.1, 95%CI 0.6-1.9, p=0.86	SB: high risk AB: low risk DB: low risk CF: high risk
	Den Hoed 2015	346 adult CCS	Median time after cessation of treatment 16.7 years (IQR 12.4–23.0)	Chemotherapy: Prednisone 63.6% Dexamethasone 37.0% Cyclophosphamide 49.7% Methotrexate 64.9% Ifosfamide 10.8% Radiotherapy: Cranial-spinal 16.5% Total body 3.8 % CRT 4.3% Abdominal 2.3% SCT: 4.9%	TB BMD or LS BMD Z-score <−1: 45% of the CCS. 38% TB, 27% LS, 20% at both TB and LS. TB BMD or LS BMD Z-score <−2: 9% (TB), 3% (LS)	Multivariable model: LS BMD Z-score <-1: Cranial/cranial-spinal (yes vs. no) NA TB BMD Z-score <-1: Cranial/cranial-spinal (yes vs. no) OR 2.5, 95%CI 1.2–5.2	SB: high risk AB: low risk DB: low risk CF: low risk
	Gurney 2014[a]	845 adult ALL survivors	>10 years after diagnosis	Chemotherapy: Glucocorticoids 100% Methotrexate 100% Cyclophosphamide % NR Radiotherapy: CRT: 61.3% CRT + spinalRT or TBI 12.5% SCT: 2.5%	QCT LS BMD Z-score ≤-2: 5.7% QCT LS BMD Z-score ≤-1: 29.5%	Multivariable model: QCT LS BMD Z-score ≤-1: CRT dose <24Gy vs. 0 Gy OR 1.11, 95%CI 0.67-1.82, p=0.69; CRT dose ≥24Gy vs. 0 Gy OR 2.05, 95%CI 1.21-3.46, p=0.007; Craniospinal irradiation OR 1.88, 95% CI 1.05–3.37, p=0.033	SB: unclear AB: low risk DB: low risk CF: high risk
	Isaksson 2020	125 CCS	Mean (SD) follow-up 24.3 years (7.1)	Chemotherapy: GCs 19 (15%) Alkylating agents 16 (13%) Median cyclophosphamide equivalent dose 4854 mg/m^2 MTX 17 (14%) Median methotrexate dose 11 g/m^2 Radiotherapy: CRT 26% SCT: 2%	Survivors: LS BMD Z-score ≤-1: 22% TH BMD Z-score ≤-1: 21% Controls: LS BMD Z-score ≤-1: 28% TH BMD Z-score ≤-1: 22%	Multivariable model: LS BMD Z-score ≤-1: CRT (yes vs. control group) OR 1.5, 95%CI 0.69-3.5, p=0.29 TH BMD Z-score ≤-1: CRT (yes vs. control group) OR 1.5, 95%CI 0.65-3.7, p=0.33	SB: high risk AB: low risk DB: low risk CF: low risk

	Latoch 2021	326 CCS	Median (range) 6.12 (4.0-22.0) years since end of treatment	Chemotherapy: Glucocorticoids 71.2% Methotrexate 50.9% Radiotherapy: CRT 25.5% TBI 4% Abdominal RT 16.7% SCT: 7%	LS BMD Z-score <-1: 20% TB BMD Z-score <-1: 24% LS and/or TB BMD Z-score <-2: 8%	Multivariable model: LS BMD Z-score <-1: Radiotherapy to the head and neck OR 2.54, 95%CI 1.32–4.90, p=0.016 TB BMD Z-score <-1: Radiotherapy to the head and neck OR 1.74, 95%CI 0.92–3.32, p=0.089	SB: high risk AB: low risk DB: low risk CF: low risk
	Polgreen 2012	319 CCS	Mean time since treatment (±SE) 10.1 ± 0.2 years (range 4.3-17.8)	Chemotherapy: Corticosteroid: 42.0% Radiotherapy: 23.2%) Cranial (CNS) 9.7%, other 13.5% SCT: 0%	TB BMD Z-score <-1: 11% LS BMD Z-score <-1: 23% TB BMD Z-score <-2: 2.3% LS BMD Z-score <-2: 3.5%	Multivariable model: TB BMD Z-score <-1: radiation exposure (CNS vs. none), OR 7.9; 95%CI 3.0-20.8, p<0.001 LS BMD Z-score <-1: radiation exposure (CNS vs. none), OR 2.5; 95%CI 1.0-5.7, p=0.040	SB: low risk AB: low risk DB: low risk CF: low risk
	Siegel 2017	475 CCS	Mean (±SD) time after Rx 5.4 ± 4.3 years	Chemotherapy: Corticosteroid 83.4% Methotrexate 77.1% Radiotherapy: Cranial / craniospinal 13.3% TBI 9.9% SCT: 17.9%	TB or LS BMD Z-scores ≤–1: 29.3% (LS 22.8%, TB 21.9%) TB or LS BMD Z-scores ≤–2: 8.2% (LS 7.4%, TB 4.0%)	Multivariable model: TB or LS BMD Z-scores ≤–2: TBI, cranial, or craniospinal radiation OR 5.2, 95% CI, 1.8–14.9	SB: low risk AB: low risk DB: low risk CF: high risk
	van Atteveld 2019[a]	2032 adult CCS	Median time since cancer dx: 21.6 yrs (range 10.4-40.6)	Chemotherapy: Alkylating agent 56.6% MTX 53.9% GCs 53.9% Radiotherapy: Cranial 33.9% Abdominal 21.7% SCT: NR	LS and/or TB BMD Z-score ≤-1: 51.5% (LS 25.1%, TB 48.0%) LS and/or TB BMD Z-score ≤-2: 20.2%	Multivariable model: LS and/or TB BMD Z-score ≤-1: cranial irradiation β 0.75 (SE 0.11), OR 2.11, 95%CI 1.69-2.63 LS and/or TB BMD Z-score ≤-2: cranial irradiation β 0.73 (SE 0.13), OR 2.07, 95%CI 1.59-2.68	SB: low risk AB: low risk DB: low risk CF: low risk

GRADE assessment (outcome low and very low BMD):

Study design:	+4	Cross-sectional cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 3/8, unclear in 1/8, high in 4/8; Attrition bias low in 8/8; Detection bias low in 8/8; Confounding bias low in 5/8, high in 3/8
Consistency:	0	No important inconsistency, all studies show an effect of C(S)RT (6 significant)
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients and events
Publication bias:	0	Unlikely
Effect size:	+1	Large magnitude of effect
Dose-response:	0	Dose response relationship as higher doses are associated with an increased risk as compared to lower doses, but only assessed in one study
Plausible confounding:	0	No plausible confounding

Quality of evidence:		⨁⨁⨁⨁ HIGH
Conclusion:		Increased risk of low BMD (Z-score ≤-1 or ≤-2) after cranial irradiation in CAYA cancer survivors. (6 studies significant effect, 2 studies no significant effect; 5,010 participants)
GRADE assessment (outcome very low BMD):		
Study design:	+4	Cross-sectional cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 2/2; Attrition bias low in 2/2; Detection bias low in 2/2; Confounding bias low in 1/2, high in 1/2
Consistency:	0	No important inconsistency, both studies show a significant effect of C(S)RT
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients and events
Publication bias:	0	Unlikely
Effect size:	+1	Large magnitude of effect
Dose-response:	0	Dose response relationship as higher doses are associated with an increased risk as compared to lower doses, but only assessed in one study
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⨁⨁⨁ HIGH
Conclusion:		Increased risk of very low BMD (Z-score ≤-2) after cranial irradiation in CAYA cancer survivors. (2 studies significant effect; 2,507 participants)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.
*(possible) overlap in included patients.

1mm. What is the risk of lower BMD in CAYA cancer survivors treated with cranial or craniospinal irradiation?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.mm. Risk lower BMD for CRT/CSRT **(n=8 studies)**	Alikasifoglu 2005	59 ALL survivors	Mean 3.40 (1.77) years after cessation of therapy	Chemotherapy: Conventional dose prednisolone 51% Megadose methylprednisolone 49% Cyclophosphamide 100% HD-MTX 100% Radiotherapy: CRT 76% Group 1: 63.3% SCT: 0%	Mean (SD) LS BMD Z-score Total cohort: -1.73 (0.84)	LS BMD Z-score: Group 1: CRT vs. no CRT, -1.85 (0.86) vs. -1.58 (0.79), p=0.404 Multivariable model: CRT: t=0.613, P=0.542	SB: high risk AB: high risk DB: low risk CF: low risk
	Benmiloud 2010	89 ALL and NHL survivors	Mean time since treatment (±SD) 15.0 ± 4.5 years	Chemotherapy: Prednisolone 100% Dexamethasone 52.8% Methotrexate 100% Radiotherapy RT at any site: 53.9% CNS RT 36% CRT 32.6% CSRT 3.4% TBI 18.0% SCT 18.0%	BMD Z-score ≤-1.0: At any site: 59.1%; At the LS: 50.5% At the FN: 25.8%; At the Hip: 31.5% BMD Z-score ≤-2: At any site: 10.1%; At the LS: 10.1% At the FN: 2.2%; At the Hip: 2.2%	Multivariable model: LS BMD Z-score (cont.): NS FN and Hip BMD Z-score (cont.): therapeutic regimen (chemo [mean Z-score -0.28] vs. chemo+CRT [mean Z-score -0.96] vs. chemo+BMT/TBI [mean Z-score -0.69]**)** p=0.01, β not reported	SB: low risk AB: high risk DB: low risk CF: low risk
	Den Hoed 2015	346 adult CCS	Median time after cessation of treatment 16.7 years (IQR 12.4–23.0)	Chemotherapy: Prednisone 63.6% Dexamethasone 37.0% Cyclophosphamide 49.7% Methotrexate 64.9% Ifosfamide 10.8% Radiotherapy: Cranial-spinal 16.5% Total body 3.8 % CRT 4.3% Abdominal 2.3% SCT: 4.9%	TB BMD or LS BMD Z-score <−1: 45% of the CCS. 38% TB, 27% LS, 20% at both TB and LS. TB BMD or LS BMD Z-score <−2: 9% (TB), 3% (LS)	Multivariable model: LS BMD Z-score (cont.): Cranial/cranial-spinal (yes vs. no) NA TB BMD Z-score (cont.): Cranial/cranial-spinal (yes vs. no) β=−0.53; se=0.19; p<0.001	SB: high risk AB: low risk DB: low risk CF: low risk
	Henderson 1996	60 CCS	> 12 months post Rx Mean time since treatment: 4.3 yrs range 12mths-14.5 yrs	Chemotherapy: Ifofosfamide 3% Glucocorticoids 75% MTX 62% Radiotherapy: CRT 25% SCT: NR	LS BMD Z-scores <-2: 8.3% LS BMD Z-score <-1.0: 23.3%	Multivariable model: LS BMD Z-score (cont.): lower weight SDS R2=0.33; low Ca intake cumulative R2=0.42; lower height SDS cumulative R2=0.49; CRT cumulative R2=0.51, p=0.15	SB: unclear AB: unclear DB: low risk CF: unclear

	Isaksson 2020	125 CCS	Mean (SD) follow-up 24.3 years (7.1)	Chemotherapy: GCs 19 (15%) Alkylating agents 16 (13%) Median cyclophosphamide equivalent dose 4854 mg/m^2 MTX 17 (14%) Median methotrexate dose 11 g/m^2 Radiotherapy: CRT 26% SCT: 2%	Survivors: LS BMD Z-score ≤-1: 22% TH BMD Z-score ≤-1: 21% Controls: LS BMD Z-score ≤-1: 28% TH BMD Z-score ≤-1: 22%	Multivariable model: LS BMD (cont.): difference CRT (yes vs. control group) −0.071, 95%CI −0.124 to −0.018, p=0.009 TH BMD (cont.): difference CRT (yes vs. control group) −0.076, 95%CI −0.133 to −0.019, p=0.009	SB: high risk AB: low risk DB: low risk CF: high risk
	Pietila 2006	52 brain tumor survivors	Mean 6.4 yrs (range 1.4-14.8 y) after off-therapy	Chemotherapy: 24% Steroids 100% Radiotherapy: CRT 21.7% Craniospinal 11.1% Combination of CRT and chemotherapy 19.6% SCT: 0%	TB BMD Z-score <-2: 33%	Multivariable model: TB BMD Z-score (cont.): CRT, R^2 NR, p=0.100; CSRT, R^2 NR, p=0.034	SB: high risk AB: low risk DB: low risk CF: low risk
	Remes 2018	74 brain tumor survivors	Mean time since cessation of tumor therapy (±SD): 18.9 ± 6.1 years	Chemotherapy: 63.5% Radiotherapy: Local irradiation: 52.7% Craniospinal with local boost to the tumor bed: 40.5% Cranial with local boost to the tumor bed: 4.1% Stereotactic: 2.7% SCT:NR	LS BMD and/or FN BMD and/or Total Hip Z-score ≤-2: 23.6%	Multivariable model: BMD Z-scores (cont.): CRT NS for all sites; CSRT NS for all sites	SB: high risk AB: low risk DB: unclear CF: low risk
	Van Beek 2006	90 ALL survivors	Mean 12.7 yrs after dx (2.0-29.7)	Chemotherapy: Prednisone 52.2% Dexamethasone 47.8% MTX 71.1% Radiotherapy: CRT 21.1% SCT: 0%	NR	Multivariable model: LS, TB BM(A)D Z-score (cont.): CRT NS	SB: unclear AB: low risk DB: low risk CF: low risk

GRADE assessment:		
Study design:	+4	Cross-sectional cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 1/8, unclear in 2/8, high in 5/8; Attrition bias low in 5/8, unclear in 1/8, high in 2/8; Detection bias low in 7/8, unclear in 1/8; Confounding bias low in 6/8, unclear in 1/8, high in 1/8
Consistency:	-1	Important inconsistency, four studies show a significant effect of C(S)RT and four studies show no significant effect of C(S)RT
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients and events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear if there is a dose response in the studies that showed a significant effect
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW

Conclusion:	Increased risk of lower BMD after cranial irradiation in CAYA cancer survivors. (4 studies significant effect, 4 studies no significant effect; 895 participants)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

1nn. What is the risk of fractures in CAYA cancer survivors treated with cranial or craniospinal irradiation?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.w. Risk fracture for CRT/CSRT **(n=1 study)**	Fiscaletti 2021	251 ALL survivors	Median 15.1 years (range 5.4 to 28.2 years) since cancer diagnosis	Chemotherapy: Glucocorticoids 100% Methotrexate 100% Radiotherapy: CRT 59% SCT: None	Frequency of fractures: Vertebral fractures: 23% Non-vertebral fractures: 31%	Multivariable model: Vertebral fractures: CRT NS	SB: low risk AB: low risk DB: low risk CF: low risk

GRADE assessment:		
Study design:	+4	Retrospective cohort study
Study limitations:	0	No important limitations: Selection bias low in 1/1; Attrition bias low in 1/1; Detection bias low in 1/1; Confounding low in 1/1
Consistency:	NA	Only one study available
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Important imprecision: low total number of patients and events and only one study available
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	NA
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		No significant effect of cranial irradiation on the risk of vertebral fractures in CAYA cancer survivors. (1 study significant effect; 251 participants)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

1oo. What is the risk of low and very low BMD in CAYA cancer survivors treated with higher vs. lower doses cranial or craniospinal irradiation?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.oo. Risk low BMD for cranial irradiation dose **(n=1 study)**	Gurney 2014	845 adult ALL survivors	>10 years after diagnosis	Chemotherapy: Glucocorticoids 100% Methotrexate 100% Cyclophosphamide % NR Radiotherapy: CRT: 61.3% CRT + spinalRT or TBI 12.5% SCT: 2.5%	QCT LS BMD Z-score ≤-2: 5.7% QCT LS BMD Z-score ≤-1: 29.5%	Multivariable model: QCT LS BMD Z-score ≤-1: CRT dose <24Gy vs. 0 Gy OR 1.11, 95%CI 0.67-1.82, p=0.69; CRT dose ≥24Gy vs. 0 Gy OR 2.05, 95%CI 1.21-3.46, p=0.007	SB: unclear AB: low risk DB: low risk CF: high risk

GRADE assessment:		
Study design:	+4	Cross-sectional cohort study
Study limitations:	-1	Some limitations: Selection bias unclear in 1/1; Attrition bias low in 1/1; Detection bias low in 1/1; Confounding bias high in 1/1
Consistency:	NA	Only one study available
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Important imprecision, high total number of patients and events but only one study available
Publication bias:	0	Unlikely
Effect size:	0	Large magnitude of effect, but only one study
Dose-response:	0	Dose response relationship as higher doses are associated with an increased risk as compared to lower doses, but only one study
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⨁⨀⨀ LOW
Conclusion:		Increased risk of low BMD (Z-score ≤-1 or ≤-2) after higher versus lower doses cranial irradiation in CAYA cancer survivors. (1 study significant effect; 845 participants)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

1pp. What is the risk of fractures in CAYA cancer survivors treated with higher vs. lower doses cranial or craniospinal irradiation?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.pp. Risk fracture for cranial irradiation dose **(n=1 study)**	Im 2021	2453 (discovery) 1417 (replication) CCS	At least 5 years Discovery: Approximately 37 years Replication: Approximately 25 years	Chemotherapy: Glucocorticoids 47.2% discovery, 48.3% replication IV MTX 18.5% discovery, 29.2% replication IT MTX 38.4% discovery, 38.3% replication Radiotherapy: CRT 45.9% discovery, 38.5% replication SCT: 0% (exclusion criterion)	Fracture frequency (any type post diagnosis) Discovery: 37.9% Replication: 46.0%	Multivariable (sex-combined) model (discovery cohort): Fracture: radiation dosimetry dose (10 Gy) HR 0.99, 95%CI 0.95-1.03, p=0.58	SB: high risk AB: low risk DB: high risk CF: unclear

GRADE assessment:		
Study design:	+4	Retrospective cohort study
Study limitations:	-2	Some limitations: Selection bias high in 1/1; Attrition bias low in 1/1; Detection bias high in 1/1; Confounding unclear in 1/1
Consistency:	NA	Only one study available
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Important imprecision: high total number of patients and events but only one study available
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	NA
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ VERY LOW
Conclusion:		No significant effect of higher versus lower doses cranial irradiation on the risk of fractures in CAYA cancer survivors. (1 study no significant effect; 2,453 participants)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

1qq. What is the risk of low and very low BMD in CAYA cancer survivors treated with hematopoietic stem cell transplantation?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.qq. Risk low BMD for HSCT **(n=2 studies)**	Den Hoed 2015	346 adult CCS	Median time after cessation of treatment 16.7 years (IQR 12.4–23.0)	Chemotherapy: Prednisone 63.6% Dexamethasone 37.0% Cyclophosphamide 49.7% Methotrexate 64.9% Ifosfamide 10.8% Radiotherapy: Cranial-spinal 16.5% Total body 3.8 % CRT 4.3% Abdominal 2.3% SCT: 4.9%	TB BMD or LS BMD Z-score <−1: 45% of the CCS. 38% TB, 27% LS, 20% at both TB and LS. TB BMD or LS BMD Z-score <−2: 9% (TB), 3% (LS)	Multivariable model: LS BMD Z-score <-1: HSCT (yes vs. no) OR 1.3, 95%CI 0.4-4.1 TB BMD Z-score <-1: HSCT (yes vs. no) OR 1.3, 95%CI 0.4-3.8	SB: high risk AB: low risk DB: low risk CF: low risk
	Siegel 2017	475 CCS	Mean (±SD) time after Rx 5.4 ± 4.3 years	Chemotherapy: Corticosteroid 83.4% Methotrexate 77.1% Radiotherapy: Cranial / craniospinal 13.3% TBI 9.9% SCT: 17.9%	TB or LS BMD Z-scores ≤–1: 29.3% (LS 22.8%, TB 21.9%) TB or LS BMD Z-scores ≤–2: 8.2% (LS 7.4%, TB 4.0%)	Multivariable model: TB or LS BMD Z-scores ≤–2: HSCT OR 0.2, 95% CI, 0.1-0.9	SB: low risk AB: low risk DB: low risk CF: high risk

GRADE assessment:		
Study design:	+4	Cross-sectional cohort studies
Study limitations:	-2	Important limitations: Selection bias low in 1/2, high in 1/2; Attrition bias low in 2/2; Detection bias low in 2/2; Confounding low in 1/2, high in 1/2
Consistency:	0	No important inconsistency, 1 study shows no significant effect of HSCT, and 1 study shows a decreased risk after HSCT
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients and events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	NA
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		No significant effect of HSCT on the risk of low BMD (Z-score ≤-1 and ≤-2) in CAYA cancer survivors. (1 study no significant effect, 1 study significant effect in opposite direction; 821 participants)

GRADE assessment:		
Study design:	+4	Cross-sectional cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 1/1; Attrition bias low in 1/1; Detection bias low in 1/1; Confounding high in 1/1
Consistency:	NA	Only one study available
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Important imprecision, high total number of patients and events, but only one study available
Publication bias:	0	Unlikely

Effect size:	0	No large magnitude of effect
Dose-response:	0	NA
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		No increased risk of very low BMD (Z-score ≤-2) after HSCT in CAYA cancer survivors. (1 study significant effect in opposite direction; 475 participants)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

1rr. What is the risk of lower BMD in CAYA cancer survivors treated with hematopoietic stem cell transplantation without total body irradiation?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.rr. Risk lower BMD for HSCT **(n=2 studies)**	Den Hoed 2015	346 adult CCS	Median time after cessation of treatment 16.7 years (IQR 12.4–23.0)	Chemotherapy: Prednisone 63.6% Dexamethasone 37.0% Cyclophosphamide 49.7% Methotrexate 64.9% Ifosfamide 10.8% Radiotherapy: Cranial-spinal 16.5% Total body 3.8 % CRT 4.3% Abdominal 2.3% SCT: 4.9%	TB BMD or LS BMD Z-score <−1: 45% of the CCS. 38% TB, 27% LS, 20% at both TB and LS. TB BMD or LS BMD Z-score <−2: 9% (TB), 3% (LS)	Multivariable model: LS BMD Z-score (cont.): HSCT NS TB BMD Z-score (cont.): HSCT NS	SB: high risk AB: low risk DB: low risk CF: low risk
	Le Meignen 2011	159 ALL and AML survivors	Mean time from diagnosis to DXA 14.66 ± 0.44 yrs	Chemotherapy: Glucocorticoids 86.2% Other chemotherapy NR Radiotherapy: CRT 18.9% TBI 40.4% of HSCT recipients SCT: 34%	BMD Z-score <-2: FN 3.2%; LS 3.8%	Multivariable model: BMD Z-scores (cont.): SCT FN: β -0.24, P=0.006; LS: β 0.05, p=0.56	SB: low risk AB: high risk DB: high risk CF: high risk

GRADE assessment:		
Study design:	+4	Cross-sectional cohort studies
Study limitations:	-3	Important limitations: Selection bias low in 1/2, high in 1/2; Attrition bias low in 1/2, high in 1/2; Detection bias low in 1/2, high in 1/2; Confounding low in 1/2, high in 1/2
Consistency:	-1	Important inconsistency, 1 study shows a significant effect of HSCT and 1 study shows no significant effect
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients and events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	NA
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ VERY LOW
Conclusion:		Increased risk of lower BMD after HSCT in CAYA cancer survivors. (1 study significant effect, 1 study no significant effect; 505 participants)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant;

OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

1ss. What is the risk of low and very low BMD in CAYA cancer survivors treated with hematopoietic stem cell transplantation and total body irradiation?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.ss. Risk low BMD for TBI **(n=5 studies)**	Bhandari 2021	446 CCS	Median 14.2 years (range 2–65 years) since completing therapy	Chemotherapy: Glucocorticoids 57.5% Methotrexate 40.4% Radiotherapy: CRT NR TBI ± 24% SCT: 40.8% (30.9% allogeneic)	LS BMD Z-score ≤-1: 33.9%	Multivariable model: LS BMD Z-score <-1: HCT (allogeneic [majority had TBI] vs. no or autologous): OR 2.63, 95%CI 1.17-5.91, p=0.02	SB: low risk AB: high risk DB: low risk CF: low risk
	Den Hoed 2015	346 adult CCS	Median time after cessation of treatment 16.7 years (IQR 12.4–23.0)	Chemotherapy: Prednisone 63.6% Dexamethasone 37.0% Cyclophosphamide 49.7% Methotrexate 64.9% Ifosfamide 10.8% Radiotherapy: Cranial-spinal 16.5% Total body 3.8 % CRT 4.3% Abdominal 2.3% SCT: 4.9%	TB BMD or LS BMD Z-score <−1: 45% of the CCS. 38% TB, 27% LS, 20% at both TB and LS. TB BMD or LS BMD Z-score <−2: 9% (TB), 3% (LS)	Multivariable model: LS BMD Z-score <-1: TBI (yes vs. no) NA TB BMD Z-score <-1: TBI (yes vs. no) OR 0.9, 95%CI 0.3-3.4	SB: high risk AB: low risk DB: low risk CF: low risk
	Latoch 2021	326 CCS	Median (range) 6.12 (4.0-22.0) years since end of treatment	Chemotherapy: Glucocorticoids 71.2% Methotrexate 50.9% Radiotherapy: CRT 25.5% TBI 4% Abdominal RT 16.7% SCT: 7%	LS BMD Z-score <-1: 20% TB BMD Z-score <-1: 24% LS and/or TB BMD Z-score <-2: 8%	Multivariable model: LS BMD Z-score <-1: not included in the multivariable model TB BMD Z-score <-1: stem cell transplantation (majority had TBI): OR 3.13, 95%CI 1.02–9.63, p=0.046	SB: high risk AB: low risk DB: low risk CF: low risk
	Leung 2007	155 SCT survivors	Median 9 yrs from HSCT (range 3 to 10 years)	Chemotherapy: Alkylator-based conditioning pre-HSCT in 21% Radiotherapy: TBI-based conditioning in 79% SCT: yes (100%)	QCT BMD Z-score <-1: 39% (site NR, presumably LS)	Multivariable model: QCT BMD Z-score <-1: TBI HR 1.96; 95% CI 1.1-3.07, p=0.022	SB: low risk AB: low risk DB: unclear CF: high risk
	Siegel 2017	475 CCS	Mean (±SD) time after Rx 5.4 ± 4.3 years	Chemotherapy: Corticosteroid 83.4% Methotrexate 77.1% Radiotherapy:	TB or LS BMD Z-scores ≤–1: 29.3% (LS 22.8%, TB 21.9%) TB or LS BMD Z-scores ≤–2: 8.2% (LS 7.4%, TB 4.0%)	Univariable model: TB or LS BMD Z-scores ≤–1: TBI 42.6% vs. no TBI 27.8%, p=0.03 TB or LS BMD Z-scores ≤–2: TBI 12.8% vs. no TBI 7.7%, p=0.13	SB: low risk AB: low risk DB: low risk CF: high risk

			Cranial / craniospinal 13.3% TBI 9.9% SCT: 17.9%	Multivariable model: TB or LS BMD Z-scores ≤–2: TBI, cranial, or craniospinal radiation OR 5.2, 95% CI, 1.8–14.9
GRADE assessment:				
Study design:	+4	Cross-sectional cohort studies		
Study limitations:	0	No important limitations: Selection bias low in 3/5, high in 2/5; Attrition bias low in 4/5, high in 1/5; Detection bias low in 4/5, unclear in 1/5; Confounding low in 3/5, high in 2/5		
Consistency:	0	No important inconsistency: 4 studies show a significant effect of HSCT + TBI and 1 study shows no significant effect		
Directness:	0	Results are direct, population and outcomes broadly generalizable		
Precision:	0	No important imprecision, high total number of patients and events		
Publication bias:	0	Unlikely		
Effect size:	+1	Large magnitude of effect		
Dose-response:	0	Dose response relationship of higher TBI doses and low BMD not assessed		
Plausible confounding:	0	No plausible confounding		
Quality of evidence:		⨁⨁⨁⨁ HIGH		
Conclusion:		Increased risk of low BMD (Z-score ≤-1 or ≤-2) after TBI in CAYA cancer survivors. (4 studies significant effect, 1 study no significant effect; 1748 participants)		

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

1tt. What is the risk of lower BMD in CAYA cancer survivors treated with total body irradiation?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.tt. Risk lower BMD for TBI **(n=4 studies)**	Benmiloud 2010	89 ALL and NHL survivors	Mean time since treatment (±SD) 15.0 ± 4.5 years	Chemotherapy: Prednisolone 100% Dexamethasone 52.8% Methotrexate 100% Radiotherapy RT at any site: 53.9% CNS RT 36% CRT 32.6% CSRT 3.4% TBI 18.0% SCT 18.0%	BMD Z-score ≤-1.0: At any site: 59.1%; At the LS: 50.5% At the FN: 25.8%; At the Hip: 31.5% BMD Z-score ≤-2: At any site: 10.1%; At the LS: 10.1% At the FN: 2.2%; At the Hip: 2.2%	Multivariable model: LS BMD Z-score (cont.): NS FN and Hip BMD Z-score (cont.): therapeutic regimen (chemo [mean Z-score -0.28] vs. chemo+CRT [mean Z-score -0.96] vs. chemo+BMT/TBI [mean Z-score -0.69]**)** p=0.01, β not reported	SB: low risk AB: high risk DB: low risk CF: low risk
	Den Hoed 2015	346 adult CCS	Median time after cessation of treatment 16.7 years (IQR 12.4–23.0)	Chemotherapy: Prednisone 63.6% Dexamethasone 37.0% Cyclophosphamide 49.7% Methotrexate 64.9% Ifosfamide 10.8% Radiotherapy: Cranial-spinal 16.5% Total body 3.8 % CRT 4.3% Abdominal 2.3% SCT: 4.9%	TB BMD or LS BMD Z-score <−1: 45% of the CCS. 38% TB, 27% LS, 20% at both TB and LS. TB BMD or LS BMD Z-score <−2: 9% (TB), 3% (LS)	Multivariable model: LS BMD Z-score (cont.): TBI NS TB BMD Z-score (cont.): TBI NS	SB: high risk AB: low risk DB: low risk CF: low risk
	Le Meignen 2011	159 ALL and AML survivors	Mean time from diagnosis to DXA 14.66 ± 0.44 yrs	Chemotherapy: Glucocorticoids 86.2% Other chemotherapy NR Radiotherapy: CRT 18.9% TBI 40.4% of HSCT recipients SCT: 34%	BMD Z-score <-2: FN 3.2%; LS 3.8%	Multivariable model: BMD Z-scores (cont.): TBI FN: β -0.14, P=0.31; LS: β 0.23, p=0.12	SB: low risk AB: high risk DB: high risk CF: high risk
	Mostoufi-Moab 2012	55 SCT survivors	At least a 3 year interval from alloHST (median 6.8 years, range 3.0 to 16.4)	Chemotherapy: Conditioning regimen: Cyclophosphamide + thiotepa (69%) Busulfan + cyclophosphamide (unknown %) Busulfan + Cytoxan ± melphelan or fludarabine (unknown %)	Trabecular vBMD Z-score -1.05 (-1.33 to -0.78) Cortical vBMD Z-score -0.20 (-0.48 to 0.08)	Multivariable model: Lower trabecular vBMD Z-scores: TBI -1.30 ± 1.40 versus no TBI -0.49 ± 0.88; p=0.01 Lower cortical vBMD Z-scores: NS	SB: low risk AB: low risk DB: low risk CF: low risk

		Radiotherapy: TBI 69% SCT: 100%
GRADE assessment:		
Study design:	+4	Cross-sectional cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 3/4, high in 1/4; Attrition bias low in 2/4, high in 2/4; Detection bias low in 3/4, high in 1/4; Confounding low in 3/4, high in 1/4
Consistency:	-1	Important inconsistency, 2 studies show a significant effect of TBI and 2 studies show no significant effect
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients and events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Dose response relationship of higher TBI doses and low BMD not assessed
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		Increased risk of lower BMD after TBI in CAYA cancer survivors. (2 studies significant effect, 2 studies no significant effect; 649 participants)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

1uu. What is the risk of low and very low BMD in CAYA cancer survivors treated with abdominal/pelvic irradiation?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.uu. Risk low BMD for abdominal/pelvic RT **(n=2 studies)**	Den Hoed 2015	346 adult CCS	Median time after cessation of treatment 16.7 years (IQR 12.4–23.0)	Chemotherapy: Prednisone 63.6% Dexamethasone 37.0% Cyclophosphamide 49.7% Methotrexate 64.9% Ifosfamide 10.8% Radiotherapy: Cranial-spinal 16.5% Total body 3.8 % CRT 4.3% Abdominal 2.3% SCT: 4.9%	TB BMD or LS BMD Z-score <−1: 45% of the CCS. 38% TB, 27% LS, 20% at both TB and LS. TB BMD or LS BMD Z-score <−2: 9% (TB), 3% (LS)	Multivariable model: LS BMD Z-score <-1: abdominal irradiation (yes vs. no) NR TB BMD Z-score <-1 abdominal irradiation (yes vs. no) OR=3.0, 95%CI 0.6–14.5 TB BMD Z-score (cont.): NS	SB: high risk AB: low risk DB: low risk CF: low risk
	van Atteveld 2019	2032 adult CCS	Median time since cancer dx: 21.6 yrs (range 10.4-40.6)	Chemotherapy: Alkylating agent 56.6% MTX 53.9% GCs 53.9% Radiotherapy: Cranial 33.9% Abdominal 21.7% SCT: NR	LS and/or TB BMD Z-score ≤-1: 51.5% (LS 25.1%, TB 48.0%) LS and/or TB BMD Z-score ≤-2: 20.2%	Multivariable model: LS and/or TB BMD Z-score ≤-1: abdominal irradiation NS LS and/or TB BMD Z-score ≤-2: abdominal irradiation β 0.48 (SE 0.14), OR 1.61, 95%CI 1.23-2.11	SB: low risk AB: low risk DB: low risk CF: low risk

GRADE assessment:		
Study design:	+4	Cross-sectional cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 1/2, high in 1/2; Attrition bias low in 2/2; Detection bias low in 2/2; Confounding low in 2/2
Consistency:	0	No important inconsistency, all show effect of abdominal/pelvic irradiation (1 significant)
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	No important imprecision, high total number of patients and events, although only one study showed a significant effect
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Dose response relationship of higher abdominal/pelvic irradiation doses and low BMD not assessed
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		Increased risk of low BMD (Z-score ≤-1 or ≤-2) after abdominal/pelvic irradiation in CAYA cancer survivors. (1 study significant effect, 1 study no significant effect; 2,378 participants)

GRADE assessment:		
Study design:	+4	Cross-sectional cohort studies
Study limitations:	0	No limitations: Selection bias low in 1/1; Attrition bias low in 1/1; Detection bias low in 1/1; Confounding low in 1/1
Consistency:	NA	Only one study available
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Important imprecision, high total number of patients and events, but only one study available

Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Dose response relationship of higher abdominal/pelvic irradiation doses and low BMD not assessed
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊖ MODERATE
Conclusion:		Increased risk of very low BMD (Z-score ≤-2) after abdominal/pelvic irradiation in CAYA cancer survivors. (1 study significant effect; 2,032 participants)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

1vv. What is the risk of lower BMD in CAYA cancer survivors treated with abdominal/pelvic irradiation?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.vv. Risk lower BMD for abdominal/pelvic RT **(n=1 study)**	Den Hoed 2015	346 adult CCS	Median time after cessation of treatment 16.7 years (IQR 12.4–23.0)	Chemotherapy: Prednisone 63.6% Dexamethasone 37.0% Cyclophosphamide 49.7% Methotrexate 64.9% Ifosfamide 10.8% Radiotherapy: Cranial-spinal 16.5% Total body 3.8 % CRT 4.3% Abdominal 2.3% SCT: 4.9%	TB BMD or LS BMD Z-score <–1: 45% of the CCS. 38% TB, 27% LS, 20% at both TB and LS. TB BMD or LS BMD Z-score <–2: 9% (TB), 3% (LS)	Multivariable model: LS BMD Z-score (cont.): abdominal irradiation (yes vs. no) NR TB BMD Z-score (cont.): abdominal irradiation (yes vs. no) NS	SB: high risk AB: low risk DB: low risk CF: low risk

GRADE assessment:		
Study design:	+4	Cross-sectional cohort study
Study limitations:	-1	Important limitations: Selection bias high in 1/1; Attrition bias low in 1/1; Detection bias low in 1/1; Confounding low in 1/1
Consistency:	NA	Only one study available
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Important imprecision, high total number of patients and events but only one study available
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Dose response relationship of higher abdominal/pelvic irradiation doses and low BMD not assessed
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		No significant effect of abdominal/pelvic irradiation on lower BMD in CAYA cancer survivors. (1 study no significant effect; 346 participants)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

1ww.What is the risk of fractures in CAYA cancer survivors treated with abdominal/pelvic irradiation?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.ww. Risk fracture for abdominal/pelvic irradiation **(n=1 study)**	Wilson 2012	7414 CCS	Median length of follow-up was 22.7 years (range, 15.6-34.2 years)	Chemotherapy: Methotrexate 43.6% Steroids 47% Radiotherapy: CRT 32% Pelvic RT 13% SCT: 0%	Proportion of participants with fractures over their lifetime Survivors: 34.8% Siblings: 38.9%	Multivariable model: Fracture: Males: pelvic irradiation (yes vs. no) prevalence ratio (PR), 1.07, 95%CI 1.00-1.19, p=0.25. Females: NR (p>0.2 in univariable analysis)	SB: high risk AB: low risk DB: high risk CF: high risk

GRADE assessment:		
Study design:	+4	Retrospective cohort study
Study limitations:	-3	Important limitations: Selection bias high in 1/1; Attrition bias low in 1/1; Detection bias high in 1/1; Confounding high in 1/1
Consistency:	NA	Only one study available
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Important imprecision: high total number of patients and events but only one study available
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	NA
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ VERY LOW
Conclusion:		No significant effect of abdominal/pelvic irradiation on the risk of fractures in CAYA cancer survivors. (1 study no significant effect; 7,414 participants)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

1xx. What is the risk of low and very low BMD in CAYA cancer survivors with growth hormone deficiency?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Treated with GH (%)	Effect size	Risk of bias
1.xx. Risk low BMD for GHD **(n=6 studies)**	Bloomhardt 2020	542 CCS	Mean time since treatment (±SD) 6.0±5.0 years (range 2.0-35.1)	Chemotherapy: Dexamethasone 59.6% Prednisone 35.4% Any glucocorticoid 95% Cyclophosphamide 85.1% High-dose methotrexate 25.8% Radiotherapy: CRT 20.7% TBI 8.1% SCT: NR	LS BMD Z-score ≤-1: 17.2% LS BMD Z-score ≤-2: 3.5%	NR	Multivariable model: LS BMD Z-score <-1: GHD (y/n) OR 2.1, 95%CI 0.8-5.1, p=0.12	SB: high risk AB: low risk DB: low risk CF: high risk
	Chemaitilly 2015[a]	748 adult CCS exposed to CRT	Mean age since primary cancer diagnosis 27.3 years (range 10.8 to 47.7)	Chemotherapy: NR Radiotherapy: CRT 58% SCT: NR	Untreated GHD vs. no GHD Low QCT LS BMD (Z-score ≤-2): 10.3% vs. 5.8%	0%	Multivariable low QCT LS BMD model: Untreated GHD: OR 1.78, 95% CI 0.99 to 3.18, p=0.05	SB: high risk AB: low risk DB: low risk CF: high risk
	Siegel 2017	475 CCS	Mean (±SD) time after Rx 5.4 ± 4.3 years	Chemotherapy: Corticosteroid 83.4% Methotrexate 77.1% Radiotherapy: Cranial / craniospinal 13.3% TBI 9.9% SCT: 17.9%	TB or LS BMD Z-scores ≤–1: 29.3% (LS 22.8%, TB 21.9%) TB or LS BMD Z-scores ≤–2: 8.2% (LS 7.4%, TB 4.0%)	70%	Multivariable model: TB or LS BMD Z-scores ≤–2: GHD, OR 0.6, 95% CI, 0.1-5.1	SB: low risk AB: low risk DB: low risk CF: high risk
	van Iersel 2019[a]	3141 CCS	Mean time since treatment 24.1 (range 6.8 to 51.1) years	Chemotherapy: Any 85.2% Alkylating agents 58.8% Radiotherapy: CRT 34.6% SCT: NR	QCT LS BMD Z-scores <-2: 25.6%	NR	Multivariable model: LS BMD Z-scores ≤–2: GHD OR 2.16, 95%CI 1.68 to 2.78, p=0.0001	SB: high risk AB: high risk DB: low risk CF: unclear
	van Iersel 2020[a]	355 ependymoma and low-grade glioma survivors	Median duration since RT 10.1 (range, 0.1-19.6) years	Chemotherapy: Yes 35% Alkylating agents 16% Radiotherapy: C(S)RT 100% SCT: 0%	NR	63.3%	Multivariable model: LS BMD Z-scores ≤–2: GHD OR 3.47, 95%CI 1.16-10.40, p=0.03	SB: low risk AB: unclear DB: low risk CF: high risk
	Wilson 2016[a]	862 adult ALL survivors	Median duration between diagnosis and follow-up was	Chemotherapy: HD Methotrexate 60.7% MTX 100% Cyclophosphamide 100% Glucocorticoids 100%	QCT LS BMD Z-score ≤ -1: 39.4% for men, 20.9% for women	1%	Multivariable model: QCT LS BMD Z-score ≤ -1: men with GHD OR, 1.59; 95% CI, 1.02 to 2.49;	SB: high risk AB: low risk DB: unclear CF: unclear

		25.1 years (range, 10.5 to 47.7 years)	Radiotherapy: CRT 48.5% CRT+CS or TBI 12.4% SCT: NR	QCT LS BMD Z-score ≤ -2.5: 2.8% for men, 0.7% for women	women with GHD OR, 2.18; 95% CI, 1.26 to 3.78
GRADE assessment:					
Study design:	+4	Cross-sectional cohort studies			
Study limitations:	-2	Important limitations: Selection bias low in 2/6, high in 4/6; Attrition bias low in 4/6, unclear in 1/6, high in 1/6; Detection bias low in 5/6, unclear in 1/6; Confounding unclear in 2/6, high in 4/6			
Consistency:	0	No important inconsistency, three studies report a significant effect of GHD,and three studies reportnon-significant effects			
Directness:	0	Results are direct, population and outcomes broadly generalizable			
Precision:	0	No important imprecision, high total number of patients and events			
Publication bias:	0	Unlikely			
Effect size:	+1	Large magnitude of effect			
Dose-response:	0	NA			
Plausible confounding:	0	No plausible confounding			
Quality of evidence:		⊕⊕⊕⊖ MODERATE			
Conclusion:		Increased risk of low BMD (Z-score ≤-1 or ≤-2) for CAYA cancer survivors with growth hormone deficiency. (3 studies significant effect, 3 studies no significant effect; 6,123 participants; In 3 studies, 1%, 63%, and 70% of survivors with GHD had been treated with GH replacement therapy [in 2 studies this proportion was not reported])			
GRADE assessment:					
Study design:	+4	Cross-sectional cohort studies			
Study limitations:	-2	Important limitations: Selection bias low in 2/4, high in 2/4; Attrition bias low in 2/4, unclear in 1/4, high in 1/4; Detection bias low in 4/4; Confounding unclear in 1/4, high in 3/4			
Consistency:	0	No important inconsistency, two studies report a significant effect of GHD, and two studies report non-significant effects			
Directness:	0	Results are direct, population and outcomes broadly generalizable			
Precision:	0	No important imprecision, high total number of patients and events			
Publication bias:	0	Unlikely			
Effect size:	0	No large magnitude of effect			
Dose-response:	0	NA			
Plausible confounding:	0	No plausible confounding			
Quality of evidence:		⊕⊕⊖⊖ LOW			
Conclusion:		Increased risk of very low BMD (Z-score ≤-2) for CAYA cancer survivors with growth hormone deficiency. (2 studies significant effect, 2 studies no significant effect; 4,719 participants; In 2 studies, 63% and 70% of survivors with GHD had been treated with GH replacement therapy [in the other study this proportion was not reported])			

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

[a](possible) overlap in included patients.

1yy. What is the risk of lower BMD in CAYA cancer survivors with growth hormone deficiency?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Treated with GH (%)	Effect size	Risk of bias
1.yy. Risk lower BMD for GHD **(n=2 studies)**	Benmiloud 2010	89 ALL and NHL survivors	Mean time since treatment (±SD) 15.0 ± 4.5 years	Chemotherapy: Prednisolone 100% Dexamethasone 52.8% Methotrexate 100% Radiotherapy RT at any site: 53.9% CNS RT 36% CRT 32.6% CSRT 3.4% TBI 18.0% SCT 18.0%	BMD Z-score ≤-1.0: At any site: 59.1%; At the LS: 50.5% At the FN: 25.8%; At the Hip: 31.5% BMD Z-score ≤-2: At any site: 10.1%; At the LS: 10.1% At the FN: 2.2%; At the Hip: 2.2%	10%	Multivariable model: LS, FN and Hip BMD Z-score (cont.): GHD NS	SB: low risk AB: high risk DB: low risk CF: low risk
	Mostoufi-Moab 2012	55 SCT survivors	At least a 3 year interval from alloHST (median 6.8 years, range 3.0 to 16.4)	Chemotherapy: Conditioning regimen: Cyclophosphamide + thiotepa (69%) Busulfan + cyclophosphamide (unknown %) Busulfan + Cytoxan ± melphelan or fludarabine (unknown %) Radiotherapy: TBI 69% SCT: 100%	Trabecular vBMD Z-score -1.05 (-1.33 to -0.78) Cortical vBMD Z-score -0.20 (-0.48 to 0.08)	50%	Multivariable model: Lower trabecular vBMD Z-scores (cont.): GHD -1.56 ± 1.62 versus -0.84 ± 1.12; p=0.07 Lower cortical vBMD Z-scores (cont.): NS	SB: low risk AB: low risk DB: low risk CF: low risk

GRADE assessment:		
Study design:	+4	Cross-sectional cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 2/2; Attrition bias low in 1/2, high in 1/2; Detection bias low in 2/2; Confounding low in 2/2
Consistency:	0	No important inconsistency, both studies show no significant effect of GHD
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Important imprecision, low total number of patients and events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	NA
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		No significant effect of GHD on lower BMD in CAYA cancer survivors. (2 studies no significant effect; 144 participants; In the 2 studies, 10% and 50% of survivors with GHD had been treated with GH replacement therapy)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray

absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

1zz. What is the risk of low and very low BMD in CAYA cancer survivors with hypogonadism?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Treated with sex steroids (%)	Effect size	Risk of bias
1.zz. Risk low BMD for hypogonadism **(n=8 studies)**	Bloomhardt 2020	542 CCS	Mean time since treatment (±SD) 6.0±5.0 years (range 2.0-35.1)	Chemotherapy: Dexamethasone 59.6% Prednisone 35.4% Any glucocorticoid 95% Cyclophosphamide 85.1% High-dose methotrexate 25.8% Radiotherapy: CRT 20.7% TBI 8.1% SCT: NR	LS BMD Z-score ≤-1: 17.2% LS BMD Z-score ≤-2: 3.5%	NR	Multivariable model: LS BMD Z-score <-1: hypogonadism (y/n) OR 0.9, 95%CI 0.3-2.4, p=0.83	SB: high risk AB: low risk DB: low risk CF: high risk
	Chemaitilly 2015[a]	748 adult CCS exposed to CRT	Mean age since primary cancer diagnosis 27.3 years (range 10.8 to 47.7)	Chemotherapy: NR Radiotherapy: CRT 58% SCT: NR	Untreated LH/FSHD vs. no LH/FSHD Low QCT LS BMD (Z-score ≤-2): 16.4% vs. 7.1%	0%	Multivariable low QCT LS BMD model: Untreated LH/FSHD: OR 2.42, 95% CI 1.10 to 5.30, p=0.03	SB: high risk AB: low risk DB: low risk CF: high risk
	Chemaitilly 2017[a]	921 adult CCS	Median 24 years after cancer diagnosis (range 10.2 to 48.1)	Chemotherapy: Alkylating agents 58.8% Radiotherapy: Pelvic RT 13.3% Ovarian RT 21.7% Hypothalamic/pituitary radiation 31.6% SCT: NR	POI vs. no POI Low QCT LS BMD (Z-score ≤-2): 14.1% vs. 2.4%	0%	Multivariable low QCT LS BMD model: Primary ovarian insufficiency: OR 5.07, 95% CI 1.97 to 13.05	SB: high risk AB: low risk DB: low risk CF: low risk
	Isaksson 2020	125 CCS	Mean (SD) follow-up 24.3 years (7.1)	Chemotherapy: GCs 19 (15%) Alkylating agents 16 (13%) Median cyclophosphamide equivalent dose 4854 mg/m^2 MTX 17 (14%) Median methotrexate dose 11 g/m^2 Radiotherapy: CRT 26% SCT: 2%	Survivors: LS BMD Z-score ≤-1: 22% TH BMD Z-score ≤-1: 21% Controls: LS BMD Z-score ≤-1: 28% TH BMD Z-score ≤-1: 22%	0%	Multivariable model: LS BMD Z-score <-1: untreated hypogonadism vs. eugonadal OR 1.5, 95%CI 0.46-5.1, p= 0.48 TH BMD Z-score <-1: untreated hypogonadism vs. eugonadal OR 4.1, 96%CI 1.3-14, p=0.02	SB: high risk AB: low risk DB: low risk CF: low risk
	Polgreen 2012	319 CCS	Mean time since treatment (±SE) 10.1 ± 0.2 years (range 4.3-17.8)	Chemotherapy: Corticosteroid: 42.0% Radiotherapy: 23.2%)	TB BMD Z-score <-1: 11% LS BMD Z-score <-1: 23%	NR	Multivariable model: TB BMD Z-score <-1: hypogonadism OR 11.2, 95%CI 3.7-35.8, p<0.001	SB: low risk AB: low risk DB: low risk CF: low risk

				Cranial (CNS) 9.7%, other 13.5% SCT: 0%	TB BMD Z-score <-2: 2.3% LS BMD Z-score <-2: 3.5%		LS BMD Z-score <-1: hypogonadism OR 4.3, 95%CI 1.6-11.8, p=0.003	
	Siegel 2017	475 CCS	Mean (±SD) time after Rx 5.4 ± 4.3 years	Chemotherapy: Corticosteroid 83.4% Methotrexate 77.1% Radiotherapy: Cranial / craniospinal 13.3% TBI 9.9% SCT: 17.9%	TB or LS BMD Z-scores ≤–1: 29.3% (LS 22.8%, TB 21.9%) TB or LS BMD Z-scores ≤–2: 8.2% (LS 7.4%, TB 4.0%)	NR	Multivariable model: TB or LS BMD Z-scores ≤–2: gonadal dysfunction OR 4.3, 95%CI, 1.4–13.0	SB: low risk AB: low risk DB: low risk CF: high risk
	van Iersel 2019[a]	3141 CCS	Mean time since treatment 24.1 (range 6.8 to 51.1) years	Chemotherapy: Any 85.2% Alkylating agents 58.8% Radiotherapy: CRT 34.6% SCT: NR	QCT LS BMD Z-scores <-2: 25.6%	0%	Multivariable model: LS BMD Z-scores ≤–2: untreated LH/FSHD OR 2.4 95%CI 1.35 to 4.26, p=0.003	SB: high risk AB: high risk DB: low risk CF: unclear
	Wilson 2016[a]	862 adult ALL survivors	Median duration between diagnosis and follow-up was 25.1 years (range, 10.5 to 47.7 years)	Chemotherapy: HD Methotrexate 60.7% MTX 100% Cyclophosphamide 100% Glucocorticoids 100% Radiotherapy: CRT 48.5% CRT+CS or TBI 12.4% SCT: NR	QCT LS BMD Z-score ≤ -1: 39.4% for men, 20.9% for women QCT LS BMD Z-score ≤ -2.5: 2.8% for men, 0.7% for women	Women 21%; men 34%	Multivariable model: QCT LS BMD Z-score ≤ -1: men with insufficient/deficient testosterone status OR 0.67, 95% CI 0.39 to 1.13; women with POI OR 1.61; 95% CI, 0.76 to 3.39	SB: high risk AB: low risk DB: unclear CF: unclear

GRADE assessment:		
Study design:	+4	Cross-sectional cohort studies
Study limitations:	-2	Important limitations: Selection bias low in 2/8, high in 6/8; Attrition bias low in 7/8, high in 1/8; Detection bias low in 7/8, unclear in 1/8; Confounding low in 3/8, unclear in 2/8, high in 3/8
Consistency:	-1	Some inconsistency, seven studies show an effect of hypogonadism (6 significant), but one study shows an effect in the opposite direction (not significant)
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients and events
Publication bias:	0	Unlikely
Effect size:	+1	Large magnitude of effect
Dose-response:	0	NA
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		Increased risk of low BMD (Z-score ≤-1 or ≤-2) in CAYA cancer survivors with hypogonadism. (6 studies significant effect, 2 studies no significant effect; 7,133 participants; In 1 study, 21% of female and 34% of male survivors with hypogonadism had been treated with sex steroid replacement therapy [in 3 studies this proportion was not reported])
GRADE assessment:		
Study design:	+4	Cross-sectional cohort studies

Study limitations:	-2	Important limitations: Selection bias low in 1/2, high in 1/2; Attrition bias low in 1/2, high in 1/2; Detection bias low in 2/2; Confounding unclear in 1/2, high in 1/2
Consistency:	0	No important inconsistency, both studies show a significant effect of hypogonadism
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients and events
Publication bias:	0	Unlikely
Effect size:	+1	Large magnitude of effect
Dose-response:	0	NA
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⨁⨁⨀ MODERATE
Conclusion:		Increased risk of very low BMD (Z-score ≤-2) in CAYA cancer survivors with hypogonadism. (2 studies significant effect; 3,616 participants; The proportion of survivors with hypogonadism that had been treated with sex steroid replacement therapy was 0% in one study and not reported in the other study)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

[a](possible) overlap in included patients.

1aaa. What is the risk of lower BMD in CAYA cancer survivors with hypogonadism?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Treated with sex steroids (%)	Effect size	Risk of bias
1.aaa. Risk lower BMD for hypogonadism **(n=2 studies)**	Benmiloud 2010	89 ALL and NHL survivors	Mean time since treatment (±SD) 15.0 ± 4.5 years	Chemotherapy: Prednisolone 100% Dexamethasone 52.8% Methotrexate 100% Radiotherapy RT at any site: 53.9% CNS RT 36% CRT 32.6% CSRT 3.4% TBI 18.0% SCT 18.0%	BMD Z-score ≤-1.0: At any site: 59.1%; At the LS: 50.5% At the FN: 25.8%; At the Hip: 31.5% BMD Z-score ≤-2: At any site: 10.1%; At the LS: 10.1% At the FN: 2.2%; At the Hip: 2.2%	Women 13% (64% OCP); men 18%	Multivariable model: LS, FN and Hip BMD Z-score (cont.): hypogonadism NS	SB: low risk AB: high risk DB: low risk CF: low risk
	Isaksson 2020	125 CCS	Mean (SD) follow-up 24.3 years (7.1)	Chemotherapy: GCs 19 (15%) Alkylating agents 16 (13%) Median cyclophosphamide equivalent dose 4854 mg/m^2 MTX 17 (14%) Median methotrexate dose 11 g/m^2 Radiotherapy: CRT 26% SCT: 2%	Survivors: LS BMD Z-score ≤-1: 22% TH BMD Z-score ≤-1: 21% Controls: LS BMD Z-score ≤-1: 28% TH BMD Z-score ≤-1: 22%	0%	Multivariable model: LS BMD (cont.): difference untreated hypogonadism vs. eugonadal −0.102, 95%CI −0.174 to -0.030, p=0.006 TH BMD (cont.): difference untreated hypogonadism vs. eugonadal −0.139, 95%CI −0.210 to −0.067, p<0.001	SB: high risk AB: low risk DB: low risk CF: high risk

GRADE assessment:		
Study design:	+4	Cross-sectional cohort study
Study limitations:	-2	Some limitations: Selection bias low in 1/2, high in 1/2; Attrition bias low in 1/2, high in 1/2; Detection bias low in 2/2; Confounding low in 1/2, high in 1/2
Consistency:	-1	Some inconsistency, one study shows a significant effect of hypogonadism but one study shows no significant effect
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Important imprecision, low total number of patients and events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	NA
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ VERY LOW
Conclusion:		Increased risk of lower BMD in CAYA cancer survivors with hypogonadism. (1 study significant effect, 1 study no significant effect; 214 participants; In 1 study, 13% of female and 18% of male survivors with hypogonadism had been treated with sex steroid replacement therapy; 64% of female survivors with hypogonadism were using oral contraceptives)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OCP=oral contraceptive pill; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

1bbb. What is the risk of low and very low BMD in CAYA cancer survivors with endocrine dysfunction?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.bbb. Risk low BMD for endocrine dysfunction **(n=1 study)**	Woo Han 2015	108	Mean duration since cancer treatment 9.2 yrs ± 5.4 yrs	Chemotherapy: 98.2%, type NR Radiotherapy: 55.6% Head and neck radiation: 45% (assuming this is 49 out of the 60 who had radiotherapy but this is not explicit) SCT: 16.7%	BMD Z-score <-1: 52.7% at any site (39.6% LS, 39.2% FN, 38.7% TH) BMD Z-score <-2: 16.7% at any site (13.2% LS, 13.7% FN, 13.9% TH)	Multivariable model: BMD Z-score <-1: endocrine dysfunction* LS OR 3.6, 95% IC 1.51–9.60, p 0.004; FN OR 2.72, 95% IC 1.15–6.47, p=0.023; TH OR 4.2, 95% IC(1.69–10.52, p=0.002 *Endocrine dysfunction was defined as either GHD, hypogonadism or thyroid dysfunction CTCAE grade 2 or higher	SB: high risk AB: low risk DB: low risk CF: high risk

GRADE assessment:		
Study design:	+4	Cross-sectional cohort study
Study limitations:	-2	Some limitations: Selection bias high in 1/1; Attrition bias low in 1/1; Detection bias low in 1/1; Confounding high in 1/1
Consistency:	NA	Only one study available
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Important imprecision, low total number of participants AND only one study available
Publication bias:	0	Unlikely
Effect size:	0	Large magnitude of effect, but only one study
Dose-response:	0	NA
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ VERY LOW
Conclusion:		Increased risk of low BMD (Z-score ≤-1 or ≤-2) in CAYA cancer survivors with endocrine dysfunction. (1 study significant effect; 108 participants)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

1ccc. What is the risk of low and very low BMD in CAYA cancer survivors with an inadequate intake of vitamin D (and/or calcium) or biochemical deficiencies?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.ccc. Risk low BMD for inadequate Ca/Vit D intake or biochemical deficiencies **(n=2 studies)**	Bhandari 2021	446 CCS	Median 14.2 years (range 2–65 years) since completing therapy	Chemotherapy: Glucocorticoids 57.5% Methotrexate 40.4% Radiotherapy: CRT NR TBI ± 24% SCT: 40.8% (30.9% allogeneic)	LS BMD Z-score ≤-1: 33.9%	Multivariable model: LS BMD Z-score <-1: VDD (25OHD <20 ng/ml) OR 3.58, 95%CI 1.33-9.59, p=0.01	SB: low risk AB: high risk DB: low risk CF: low risk
	Polgreen 2012	319 CCS	Mean time since treatment (±SE) 10.1 ± 0.2 years (range 4.3-17.8)	Chemotherapy: Corticosteroid: 42.0% Radiotherapy: 23.2% Cranial (CNS) 9.7%, other 13.5% SCT: 0%	TB BMD Z-score <-1: 11% LS BMD Z-score <-1: 23% TB BMD Z-score <-2: 2.3% LS BMD Z-score <-2: 3.5%	Multivariable model: TB BMD Z-score <-1: dietary vitamin D and calcium, NS LS BMD Z-score <-1: dietary vitamin D and calcium, NS	SB: low risk AB: low risk DB: low risk CF: low risk

GRADE assessment:		
Study design:	+4	Cross-sectional cohort study
Study limitations:	0	No important limitations: Selection bias low in 1/1; Attrition bias low in 1/1; Detection bias low in 1/1; Confounding low in 1/1
Consistency:	NA	Only one study available
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Important imprecision, high total number of patients and events but only one study available
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	NA
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊖ MODERATE
Conclusion:		No significant effect of inadequate dietary vitamin D and calcium intake on low BMD (Z-score ≤-1 or ≤-2) in CAYA cancer survivors. (1 study no significant effect; 319 participants)

GRADE assessment:		
Study design:	+4	Cross-sectional cohort study
Study limitations:	-1	Some limitations: Selection bias low in 1/1; Attrition bias high in 1/1; Detection bias low in 1/1; Confounding low in 1/1
Consistency:	NA	Only one study available
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Important imprecision, high total number of patients and events but only one study available
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	NA
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		Increased risk of low BMD (Z-score ≤-1 or ≤-2) in CAYA cancer survivors with vitamin D deficiency (25OHD levels <20 ng/ml).

	(1 study significant effect; 446 participants)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

1ddd. What is the risk of lower BMD in CAYA cancer survivors with an inadequate intake of calcium or biochemical deficiencies?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.ddd. Risk lower BMD for inadequate Ca/Vit D intake **(n=1 study)**	Henderson 1996	60 CCS	At least 12 months post chemotherapy Mean time since treatment: 4.3 yrs range 12mths-14.5 yrs	Chemotherapy: Ifofosfamide 3% Glucocorticoids 75% MTX 62% Radiotherapy: CRT 25% SCT: NR	LS BMD Z-scores <-2: 8.3% LS BMD Z-score <-1.0: 23.3%	Multivariable model: LS BMD Z-score (cont.): lower weight R2=0.33; low Ca intake cumulative R2=0.42, p=0.004	SB: unclear AB: unclear DB: low risk CF: unclear

GRADE assessment:		
Study design:	+4	Cross-sectional cohort study
Study limitations:	-2	Important limitations: Selection bias unclear in 1/1; Attrition bias unclear in 1/1; Detection bias low in 1/1; Confounding unclear in 1/1
Consistency:	NA	Only one study available
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Important imprecision, low total number of patients and events and only one study available
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	NA
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ VERY LOW
Conclusion:		Increased risk of lower BMD in CAYA cancer survivors with inadequate dietary intake of calcium. (1 study significant effect; 60 participants)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

1eee. What is the risk of low and very low BMD in CAYA cancer survivors with a lack of physical activity?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.eee. Risk low BMD for lack of physical activity **(n=4 studies)**	Kaste 2006b	study I n=141, study II n=57 ALL survivors	Study I: >4 years after therapy (mean time after dx 11.7 yrs) Study II : 2-5 years after study I (mean time after dx 16.1 yrs)	Chemotherapy: MTX 100% Prednisone 100% Radiotherapy: CRT 37% of 57; percentage of 141 NR SCT: 0%	Study I: LS BMD Z-score <-1 10.5%; LS BMD Z-score <-2 1.5% Study II: LS BMD Z-score <-1 19.3%; LS BMD Z-score <-2 0%	Multivariable model: LS 'low' BMD (Z-score cut-point NR, presumably <-1): study I exercise/week P=0.051, study II NS	SB: unclear AB: high risk DB: low risk CF: unclear
	Lemay 2019	246 ALL survivors	Median time since diagnosis 15.2 (range 5.4-28.2) years	Chemotherapy: Glucocorticoids 98% Methotrexate 98% Radiotherapy: CRT 40.2% SCT: 0%	LS BMD Z-score <-1: 22%	Multivariable model: LS BMD Z-score <-1: physical activity (≥150 min moderate-to-vigorous leisure physical activities per week) adjusted preventive fraction 0.60, 95%CI 0.20-0.80, p<0.01	SB: unclear AB: low risk DB: low risk CF: low risk
	Polgreen 2012	319 CCS	Mean time since treatment (±SE) 10.1 ± 0.2 years (range 4.3-17.8)	Chemotherapy: Corticosteroid: 42.0% Radiotherapy: 23.2% Cranial (CNS) 9.7%, other 13.5% SCT: 0%	TB BMD Z-score <-1: 11% LS BMD Z-score <-1: 23% TB BMD Z-score <-2: 2.3% LS BMD Z-score <-2: 3.5%	Multivariable model: TB BMD Z-score <-1: screen time (≥2h/day vs. 0-1h/day), OR 4.1, 95%CI 1.3-18.6, p=0.033 Physical activity score, NS LS BMD Z-score <-1: screen time, NS; physical activity score (1U increase), OR 0.99, 95%CI 0.99-1.0, p=0.042	SB: low risk AB: low risk DB: low risk CF: low risk
	Sloof 2019	253 CCS	NR	Chemotherapy: NR Radiotherapy: CRT 36% SCT: 0%	BMD Z-score <-1: 25.4% (site NR)	Multivariable model: BMD Z-score <-1: Any physical activity OR 0.38, 95%CI 0.16–0.88, p=0.03	SB: unclear AB: low risk DB: unclear CF: unclear

GRADE assessment:		
Study design:	+4	Cross-sectional cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 1/4, unclear in 3/4; Attrition bias low in 3/4, high in 1/4; Detection bias low in 3/4, unclear in 1/4; Confounding low in 2/4, unclear in 2/4
Consistency:	0	No important inconsistency, all studies show effect of a lack of physical activity (3 significant)
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients and events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	NA
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊖ MODERATE

Conclusion:	Increased risk of low BMD (Z-score ≤-1 or ≤-2) in CAYA cancer survivors with a lack of physical activity. (3 studies significant effect, 1 study no significant effect; 959 participants)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

1fff. What is the risk of lower BMD in CAYA cancer survivors with a lack of physical activity?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.fff. Risk lower BMD for lack of physical activity **(n=2 studies)**	Joyce 2011	493 ALL survivors	12.7 to 46.5 years from diagnosis of childhood ALL (median, 27.2y)	Chemotherapy: Glucocorticoids 100% Methotrexate 100% Cyclophosphamide 100% Radiotherapy: CRT 70% SCT: NR	Mean LS BMD Z-scores: –0.3±1.2 LS BMD Z-scores < –2.5: 3% LS BMD Z- scores between –1.0 and –2.5: 26%	Associations between BMD and muscle strength in lower extremities (R2 range, 0.33– 0.40, P-value range <0.001 to 0.11) and strong, significant associations in upper extremities (left-side R2=0.558; right-side R2=0.560, P<0.001)	SB: high risk AB: low risk DB: low risk CF: low risk
	Zürcher 2020	150 CCS	Median 22.2 years since diagnosis (IQR 16.0; 29.1)	Chemotherapy: Glucocorticoids: 61% Radiotherapy: CRT 17% SCT: NR	LS, TH and/or FN BMD Z-score <-1 measured by pQCT or DXA: females: 56%, males: 70% Any pQCT site: females 34.3%, males 55.7% Any DXA site: females 41.7%, males 50.0%	Multivariable model: Total vBMD: IPD mid vs. low, beta 6.6 (95%CI -8,64 to 21,84), p=0.40; high vs. low beta 11.62 (95%CI -4,16 to 27,40), p=0.15 Trabecular vBMD: IPD mid vs. low, beta 6,16 (95%CI -7,59 to 19,91), p=0.38; high vs. low beta 14.43 (95%CI -0,19 to 28,67), **p=0.049** Cortical vBMD: IPD mid vs. low, beta -11,51 (95%CI -19,94 to -3,07), p=0.008; high vs. low beta -8.77 (95%CI -17,48 to -0,07), p=0.050 FN BMD Z-score: IPD mid vs. low, beta 0.2 (95%CI -0,2 to 0,5), p=0.36; high vs. low beta 0.4 (95%CI 0 to 0.8), **p=0.044** TH BMD Z-score: IPD mid vs. low, beta 0.1 (95%CI -0,2 to 0,4), p=0.47; high vs. low beta 0.4 (95%CI 0.06 to 0.7), **p=0.022** LS BMD Z-score: IPD mid vs. low, beta 0.08 (95%CI -0,4 to 0,5), p=0.73; high vs. low beta 0.14 (95%CI -0.3 to 0.6), p=0.54	SB: unclear AB: low risk DB: low risk CF: low risk

GRADE assessment:		
Study design:	+4	Cross-sectional cohort studies
Study limitations:	-1	Some limitations: Selection bias unclear in 1/2, high in 1/2; Attrition bias low in 2/2; Detection bias low in 2/2; Confounding low in 2/2
Consistency:	0	No important inconsistency, both studies show a significant effect of a lack of physical activity
Directness:	-1	Results are indirect, i.e. low muscle strength might be a consequence of a lack of physical activity

Precision:	0	No important imprecision, high total number of patients and events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	NA
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		Increased risk of lower BMD in CAYA cancer survivors with a lack of physical activity. (2 studies significant effect; 643 participants)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IPD=impact peak duration; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

1ggg.What is the risk of fractures in CAYA cancer survivors with a lack of physical activity?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.ggg. Risk fracture for lack of physical activity **(n=2 studies)**	Lemay 2019	246 ALL survivors	Median time since diagnosis 15.2 (range 5.4-28.2) years	Chemotherapy: Glucocorticoids 98% Methotrexate 98% Radiotherapy: CRT 40.2% SCT: 0%	Presence of vertebral fracture (VF, on X-ray): 23.2%	Multivariable model: VF: physical activity (≥150 min moderate-to-vigorous leisure physical activities per week) adjusted preventive fraction −0.05, 95%CI −1.01 to 0.45, NS	SB: unclear AB: low risk DB: low risk CF: low risk
	Wilson 2012	7414 CCS	Median length of follow-up was 22.7 years (range, 15.6-34.2 years)	Chemotherapy: Methotrexate 43.6% Steroids 47% Radiotherapy: CRT 32% Pelvic RT 13% SCT: 0%	Proportion of participants with fractures over their lifetime Survivors: 34.8% Siblings: 38.9%	Multivariable model: Fracture: Males: meets guidelines for physical activity (yes vs. no) prevalence ratio (PR), 1.08, 95%CI 1.00-1.17, p=0.07. Females: limitation to activity (yes vs. no) prevalence ratio (PR), 1.08, 95%CI 0.96-1.22, p=0.20.	SB: high risk AB: low risk DB: high risk CF: high risk

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-2	Some limitations: Selection bias unclear in 1/2, high in 1/2; Attrition bias low in 2/2; Detection bias low in 1/2, high in 1/2; Confounding low in 1/2, high in 1/2
Consistency:	0	No important inconsistency, both studies show no significant effect of a lack of physical activity
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients and events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	NA
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⨁⨀⨀ LOW
Conclusion:		No significant effect of lack of physical activity on the risk of fractures in CAYA cancer survivors. (2 studies no significant effect; 7,660 participants)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

1hhh. What is the risk of low and very low BMD in CAYA cancer survivors who smoke?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.hhh. Risk low BMD for smoking **(n=4 studies)**	Den Hoed 2015	346 adult CCS	Median time after cessation of treatment 16.7 years (IQR 12.4–23.0)	Chemotherapy: Prednisone 63.6% Dexamethasone 37.0% Cyclophosphamide 49.7% Methotrexate 64.9% Ifosfamide 10.8% Radiotherapy: Cranial-spinal 16.5% Total body 3.8 % CRT 4.3% Abdominal 2.3% SCT: 4.9%	TB BMD or LS BMD Z-score <−1: 45% of the CCS. 38% TB, 27% LS, 20% at both TB and LS. TB BMD or LS BMD Z-score <−2: 9% (TB), 3% (LS)	Multivariable model: LS BMD Z-score <-1: current smoking (yes vs. no) OR 1.5 95%CI 0.8–2.8 TB BMD Z-score <-1 current smoking (yes vs. no) OR 1.1 95%CI 0.6–2.1	SB: high risk AB: low risk DB: low risk CF: low risk
	Sloof 2019	253 CCS	NR	Chemotherapy: NR Radiotherapy: CRT 36% SCT: 0%	BMD Z-score <-1: 25.4% (site NR)	Multivariable model: BMD Z-score <-1: no smoking OR 0.60, 95%CI 0.21–1.69, p=0.34	SB: unclear AB: low risk DB: unclear CF: unclear
	van Atteveld 2019[a]	2032 adult CCS	Median time since cancer dx: 21.6 yrs (range 10.4-40.6)	Chemotherapy: Alkylating agent 56.6% MTX 53.9% GCs 53.9% Radiotherapy: Cranial 33.9% Abdominal 21.7% SCT: NR	LS and/or TB BMD Z-score ≤-1: 51.5% (LS 25.1%, TB 48.0%) LS and/or TB BMD Z-score ≤-2: 20.2%	Multivariable model: LS and/or TB BMD Z-score ≤-1: current smoking β 0.39 (SE 0.11), OR 1.48, 95%CI 1.19-1.85 LS and/or TB BMD Z-score ≤-2: current smoking NS	SB: low risk AB: low risk DB: low risk CF: low risk
	Wilson 2016[a]	862 adult ALL survivors	Median duration between diagnosis and follow-up was 25.1 years (range, 10.5 to 47.7 years)	Chemotherapy: HD Methotrexate 60.7% MTX 100% Cyclophosphamide 100% Glucocorticoids 100% Radiotherapy: CRT 48.5% CRT+CS or TBI 12.4% SCT: NR	QCT LS BMD Z-score ≤ -1: 39.4% for men, 20.9% for women QCT LS BMD Z-score ≤ -2.5: 2.8% for men, 0.7% for women	Multivariable model: QCT LS BMD Z-score ≤ -1: current smoking men OR 1.71, 95% CI 1.02 to 2.85; Current smoking women OR 1.14, 95% CI 0.59 to 2.20;	SB: high risk AB: low risk DB: unclear CF: unclear

GRADE assessment (outcome low and very low BMD):

Study design:	+4	Cross-sectional cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 1/4, unclear in 1/4, high in 2/4; Attrition bias low in 4/4; Detection bias low in 2/4, unclear in 2/4; Confounding low in 2/4, unclear in 2/4
Consistency:	0	No important inconsistency, all studies show an effect of smoking (2 significant)
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients and events

Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	NA
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊖ MODERATE
Conclusion:		Increased risk of low BMD (Z-score ≤-1 or ≤-2) in CAYA cancer survivors who are currently smoking. (2 studies significant effect, 2 studies no significant effect; 3,493 participants)
GRADE assessment (outcome very low BMD):		
Study design:	+4	Cross-sectional cohort study
Study limitations:	0	No limitations: Selection bias low in 1/1; Attrition bias low in 1/1; Detection bias low in 1/1; Confounding low in 1/1
Consistency:	NA	Only one study available
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Important imprecision, high total number of patients and events but only one study available
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	NA
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊖ MODERATE
Conclusion:		No significant effect of current smoking on very low BMD (Z-score ≤-2) in CAYA cancer survivors. (1 study no significant effect; 2,032 participants)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

[a](possible) overlap in included patients.

1iii. What is the risk of lower BMD in CAYA cancer survivors who smoke?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.iii. Risk lower BMD for smoking **(n=1 study)**	Den Hoed 2015	346 adult CCS	Median time after cessation of treatment 16.7 years (IQR 12.4–23.0)	Chemotherapy: Prednisone 63.6% Dexamethasone 37.0% Cyclophosphamide 49.7% Methotrexate 64.9% Ifosfamide 10.8% Radiotherapy: Cranial-spinal 16.5% Total body 3.8 % CRT 4.3% Abdominal 2.3% SCT: 4.9%	TB BMD or LS BMD Z-score <−1: 45% of the CCS. 38% TB, 27% LS, 20% at both TB and LS. TB BMD or LS BMD Z-score <−2: 9% (TB), 3% (LS)	Multivariable model: LS BMD Z-score (cont.): current smoking (yes vs. no) NS TB BMD Z-score (cont.): current smoking (yes vs. no) NS	SB: high risk AB: low risk DB: low risk CF: low risk

GRADE assessment:		
Study design:	+4	Cross-sectional cohort studies
Study limitations:	-1	Some limitations: Selection bias high in 1/1; Attrition bias low in 1/1; Detection bias low in 1/1; Confounding low in 1/1
Consistency:	NA	Only one study available
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Important imprecision, high total number of patients and events but only one study available
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	NA
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		No significant effect of current smoking on lower BMD in CAYA cancer survivors. (1 study no significant effect; 346 participants)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

1jjj. What is the risk of fractures in CAYA cancer survivors who smoke?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.jjj. Risk low BMD for smoking **(n=1 study)**	Wilson 2012	7414 CCS	Median length of follow-up was 22.7 years (range, 15.6-34.2 years)	Chemotherapy: Methotrexate 43.6% Steroids 47% Radiotherapy: CRT 32% Pelvic RT 13% SCT: 0%	Proportion of participants with fractures over their lifetime Survivors: 34.8% Siblings: 38.9%	Multivariable model: Fracture: male survivors with prior smoking history, prevalence ratio, 1.24; 95% CI, 1.14-1.34; P < .001; female survivors with prior smoking history, prevalence ratio, 1.09; 95% CI, 0.98-1.21; P=0.12	SB: high risk AB: low risk DB: high risk CF: high risk
GRADE assessment:							
Study design:	+4	Cross-sectional cohort study					
Study limitations:	-3	Some limitations: Selection bias high in 1/1; Attrition bias low in 1/1; Detection bias high in 1/1; Confounding high in 1/1					
Consistency:	NA	Only one study available					
Directness:	0	Results are direct, population and outcomes broadly generalizable					
Precision:	-1	Important imprecision, high total number of patients and events but only one study available					
Publication bias:	0	Unlikely					
Effect size:	0	No large magnitude of effect					
Dose-response:	0	NA					
Plausible confounding:	0	No plausible confounding					
Quality of evidence:		⊕⊖⊖⊖ VERY LOW					
Conclusion:		Increased risk of fractures for male CAYA cancer survivors with prior smoking history. (1 study significant effect; 7,414 participants)					

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

1kkk. What is the risk of low and very low BMD in CAYA cancer survivors who drink alcohol?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
1.kkk. Risk low BMD for alcohol **(n=1 study)**	Wilson 2016	862 adult ALL survivors	Median duration between diagnosis and follow-up was 25.1 years (range, 10.5 to 47.7 years)	Chemotherapy: HD Methotrexate 60.7% MTX 100% Cyclophosphamide 100% Glucocorticoids 100% Radiotherapy: CRT 48.5% CRT+CS or TBI 12.4% SCT: NR	LS BMD Z-score ≤ -1: 39.4% for men, 20.9% for women LS BMD Z-score ≤ -2.5: 2.8% for men, 0.7% for women	Multivariable model: LS BMD Z-score ≤ -1: Women: moderate alcohol consumption vs. never OR 2.09, 95% CI 1.14 to 3.83; risky alcohol consumption vs. never OR 2.03, 95% CI 0.97 to 4.24. Men: moderate alcohol consumption vs. never OR 0.98, 95% CI 0.60 to 1.60; risky alcohol consumption vs. never OR 0.65, 95% CI 0.37 to 1.13.	SB: high risk AB: low risk DB: unclear CF: unclear

GRADE assessment:		
Study design:	+4	Retrospective cohort study
Study limitations:	-2	Some limitations: Selection bias high in 1/1; Attrition bias low in 1/1; Detection bias unclear in 1/1; Confounding unclear in 1/1
Consistency:	NA	Only one study available
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Important imprecision, high total number of patients and events, but one study available
Publication bias:	0	Unlikely
Effect size:	0	Large magnitude of effect, but only one study
Dose-response:	0	NA
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⊖⊖⊖ VERY LOW
Conclusion:		There is conflicting evidence for the association of alcohol consumption and low BMD (Z-score ≤-1 or ≤-2) in CAYA cancer survivors. (1 study conflicting results; 862 participants)

Abbreviations: AB=attrition bias; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CAYA=childhood, adolescent and young adult; CF=confounding; CI=confidence interval; CML=chronic myeloid leukemia; cont.=continuous; β=regression coefficient; BMC= bone mineral content; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; DB=detection bias; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HL=Hodgkin's lymphoma; HR=hazard ratio; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; PNET=primitive neuro-ectodermal tumor; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SB=selection bias; SCT=stem cell transplantation; SE=standard error; SD=standard deviation; TB=total body; TBI=total body irradiation; TH=total hip.

What surveillance modality should be used?

2a. What is the diagnostic value of QCT compared to DXA in CAYA cancer survivors?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Diagnostic tests	Outcome definition	Diagnostic values Agreement between the tests	Risk of bias
2.a. Diagnostic value of QCT vs. DXA for detecting low BMD **(n=2 studies)**	Kaste 2006	320 survivors of childhood cancer	Time since stop therapy not specified.	-QCT at LS - DXA at lumbar spine in anterior projections of L1–L4 and lateral projections of L2–L4	NA	No diagnostic values of QCT compared to DXA presented. Significant linear relationship between average BMD of the L1–L2 as measured by DXA and QCT (Pearson correlation coefficient 0.52, P < 0.0001). Correlation between DXA-derived BMAD and QCT BMD (Pearson correlation coefficient 0.60, P<0.0001). Significant linear relationship between DXA and QCT Z-scores (Pearson correlation coefficient 0.64, P < 0.0001. Agreement of QCT and DXA with diagnosis of Z score <-2 was fair K=0.32.	SB: unclear IB: unclear RB: unclear VB: low risk AB: low risk
	Brennan 1999	31 survivors of childhood ALL	Participants were at least 2 years from completion of cancer therapy 6.8 till 28.6 years after cranial radiation (median 17.8 years)	- QCT: T12 to L3 - DXA: Integral (mixed cortical and trabecular) bone of L2 to L4 and right femoral neck	NA	No diagnostic values of QCT compared to DXA presented. No significant correlation between QCT and DXA spine: 0.33; p=0.08 Significant correlation between QCT and DXA femoral neck: 0.53; p=0.004	SB: unclear IB: low risk RB: low risk VB: unclear AB: unclear

GRADE assessment:		
Study design:	+4	Cohort studies
Study limitations:	-1	Some limitations: Selection bias unclear in 2/2; Index test bias low in 1/2, unclear in 1/2; Reference test bias low in 1/2, unclear in 1/2; Verification bias low in 1/2, unclear in 1/2; Attrition bias low in 1/2, unclear in 1/2
Consistency:	-1	Inconsistency of the correlation between DXA and QCT of the lumbar spine across the studies
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	NA
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⨁⨀⨀ LOW
Conclusion:		No studies evaluated the diagnostic value of QCT compared to DXA. QCT and DXA derived BMD and BMD Z-scores are significantly correlated in CAYA cancer survivors. (2 studies significant effect; 351 participants)

Abbreviations: AB=attrition bias; ALL=acute lymphoblastic leukemia; BMD=bone mineral density; CAYA=childhood, adolescent and young adult; DXA=Dual-Energy X-Ray Absorptiometry; IB=index test bias; QCT=quantitative computed tomography; RB=reference test bias; SB=selection bias; VB=verification bias.

2b. What is the diagnostic value of QUS compared to DXA in CAYA cancer survivors?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Diagnostic tests	Outcome definition	Diagnostic values Agreement between the tests	Risk of bias
2.b. Diagnostic value of QUS vs. DXA for detecting low BMD **(n=1 study)**	Azcona 2003	36 survivors of malignant bone tumor	Mean disease-free survival 4.97 years (range 3.6-6.3)	-QUS of the distal metaphysis of the proximal phalanxes of the last four fingers of the nondominant hand -DXA of the lumbar spine (L1-L4)	Osteopenia: Z-score ≤-1	QUS vs. DXA Sensitivity: 36.4% (range 12.8%-66.4%) Specificity: 80.0% (range 61.1-92.3%) PPV: 44.4% (range 20.9%-70.8%) NPV: 74.1% (range 63.7%-82.3%) Diagnostic accuracy: 66.7% (range 50.2%-80.5%) Correlation QUS (Ad-SOS; m/s) and DXA (g/cm^2): r =0.44, p= 0.008	SB: unclear IB: unclear RB: unclear VB: unclear AB: low risk

GRADE assessment:		
Study design:	+4	Cohort study
Study limitations:	-1	Some limitations: Selection bias unclear in 1/1; Index test bias unclear in 1/1; Reference test bias unclear in 1/1; Verification bias unclear in 1/1; Attrition bias low in 1/1
Consistency:	NA	Only one study available
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Low total number of participants AND only one study available
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	NA	NA
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ VERY LOW
Conclusion:		The diagnostic value of QUS to detect low BMD is moderate as compared to DXA (sensitivity 36.4%, specificity 80.0%, PPV 44.4%, NPV 74.1%, diagnostic accuracy 66.7%). (1 study; 36 participants)

Abbreviations: AB=attrition bias; Ad-SoS=amplitude-dependent speed of sound; BMD=bone mineral density; CAYA=childhood, adolescent and young adult; DXA=Dual-Energy X-Ray Absorptiometry; IB=index test bias; QUS=quantitative ultrasound; RB=reference test bias; SB=selection bias; VB=verification bias.

Recommendations in existing clinical practice guidelines in other populations (2 childhood cancer guidelines, 1 general pediatric guideline)

What surveillance modality should be used?	
Kuhlen et al. Guidance to Bone Morbidity in Children and Adolescents Undergoing Allogeneic Hematopoietic Stem Cell Transplantation. Biol Blood Marrow Transplant. 2020 Feb;26(2):e27-e37.	
Recommendation[1]	**Level of evidence[2]**
Yearly screening by DXA scan of the lumbar spine (L1 to L4) and whole body should be performed before and 12 months after HSCT.	Level 2
Yearly screening for vertebral fractures using either DXA VFA or lateral spine X-rays should be performed and assessed by a pediatric radiologist using the Genant score.	Level 2

Abbreviations: DXA=dual energy X-ray absorptiometry; HSCT=hematopoietic stem cell transplantation; VFA=vertebral fracture assessment.

[1] **Grades of recommendation**
Not provided in the manuscript

[2] **Level of evidence**
1: evidence from at least 1 randomized trial
2: evidence from cohort studies, case-control studies, and time series
3: opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees, and provide our practice whenever no evidence is available

What surveillance modality should be used?	
Marcucci et al. Bone Health in Childhood Cancer: Review of the Literature and Recommendations for the Management of Bone Health in Childhood Cancer Survivors. Ann Oncol. 2019 Jun 1;30(6):908-920.	
Recommendation[1]	**Level of evidence[2]**
We recommend the use of DEXA at the spine and femur, based on age, to diagnose and monitor BMD changes in these patients.	Moderate
The use of QCT should be avoided because of the higher radiation dose applied.	Very low
In the future, imaging methods based on magnetic resonance imaging or bone densitometer using ultrasound, such as the recent radiofrequency echography multi-spectrometry technique, may be considered, especially in the pediatric population, to closely monitor quantity and quality of the trabecular and cortical bone tissue. However, such techniques must still be validated and standardized in the pediatric population.	Very low

Abbreviations: BMD=bone mineral density; DEXA=dual energy X-ray absorptiometry; QCT=quantitative computed tomography.

[1] Grades of recommendation
Not provided in the manuscript

[2] Level of evidence according to GRADE
High: further research is unlikely to change the confidence in the estimate of effect.
Moderate: further research is likely to have an important impact on the confidence in the estimate of effect and may change the estimate.
Low: further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate.
Very low: any estimate of effect is very uncertain.

What surveillance modality should be used?	
Gordon et al. 2013 Pediatric Position Development Conference: Executive Summary and Reflections. J Clin Densitom. 2014 Apr-Jun;17(2):219-24.	
Recommendation[1]	**Level of evidence[2]**
Modality	
A: DXA is the preferred method for assessing BMC and areal BMD (aBMD).	Good
C: There is no preferred method for QCT for clinical application in children and adolescents.	Fair
B: QCT, peripheral QCT, and high-resolution peripheral QCT are primarily the research techniques used to characterize bone deficits in children. They can be used clinically in children where appropriate reference data and expertise are available.	Fair
Site	
B: The posteroanterior spine and total body less head (TBLH) are the preferred skeletal sites for performed BMC and aBMD measurements in most pediatric subjects. Other sites may be useful depending on the clinic need.	Fair
B: The hip is not a preferred measurement site in growing children because of variability in skeletal development. *Update 2019: Proximal femur DXA measurements can be used, if reference data are available, for assessing children with reduced weight bearing and mechanical loading of the lower extremities or in children at-risk for bone fragility who would benefit from continuity of DXA measurements through the transition into adulthood.*	Fair *Not reported*
B: Soft tissue measures in conjunction with whole-body scans may be helpful in evaluating patients with chronic conditions associated malnutrition or with muscle and skeletal deficits.	Fair
Normative values	
A: An appropriate data set must include a sample of healthy representatives of the general population sufficiently large to capture variability in bone measures that takes into consideration gender, age, and race/ethnicity.	Good
B: In children with short stature or growth delay, spine and TBLH BMC and aBMD results should be adjusted. For the spine, adjust either BMD or the height Z-score. For TBLH, adjust using the height Z-score.	Fair
A: T-scores should not appear in pediatric DXA reports.	Good
Nomenclature	
C: ‘‘Low bone mass or bone mineral density’’ is the preferred term for pediatric DXA reports when BMC or aBMD Z-scores are less than or equal to -2.0 standard deviation.	Poor
B: The term ‘‘osteoporosis’’ should not appear in pediatric DXA reports without a clinically significant fracture history.	Good
C: The term ‘‘osteopenia’’ should not appear in pediatric DXA reports.	Fair/Poor
Osteoporosis diagnosis	
C: The diagnosis of osteoporosis in children and adolescents should not be made on the basis of densitometric criteria alone.	Poor
C: In the absence of vertebral compression (crush) fractures, the diagnosis of osteoporosis is indicated by the presence of both a clinically significant fracture history and BMD Z-score of -2.0 or lower. A clinically significant fracture history is one or more of the following: (1) 2 or more long-bone fractures by the age of 10 yr; (2) 3 or more long-bone fractures at any	Poor

age up to age 19 yr. A bone mineral content (BMC)/BMD Z-score higher than -2.0 does not preclude the possibility of skeletal fragility and increased fracture risk.	
Update 2019: DXA VFA may be used as a substitute for spine radiography in the identification of symptomatic and asymptomatic VF.	*Not reported*
Update 2019: The Genant semiquantitative method should be used for VFA in children.	*Not reported*

Abbreviations: BMC=bone mineral content; BMD=bone mineral density; DXA=dual energy X-ray absorptiometry; QCT=quantitative computed tomography; TBLH=total body less head; VFA=vertebral fracture assessment.

[1] **Grades of recommendation**
A: strong recommendation supported by the evidence
B: supported by some evidence
C: supported primarily by expert opinion

[2] **Level of evidence**
Good: evidence included consistent results from well-designed, well-conducted studies in representative populations
Fair: evidence is sufficient to determine effects on outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies
Poor: evidence is insufficient to assess the effects on outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information

Summary:

Recommendations in existing clinical practice guidelines in other populations (2 childhood cancer guidelines, 1 general pediatric guideline)	
DXA is the preferred method for BMD surveillance	Evidence-based guidelines
The lumbar spine (L1-L4) and total body less head (children) or total hip (adolescents and adults) are the preferred skeletal sites to measure BMD	Evidence-based guidelines
The use of QCT should be avoided	Evidence-based guidelines

When should surveillance be initiated and at what frequency should it be performed?

2.c What is the likelihood of change (improvement or deterioration) of BMD over time in CAYA cancer survivors? What is the timing of such change?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	1st evaluation	2nd evaluation	Change over time	Risk of bias
2.c. Risk over time of low BMD **(n=9 studies)**	Demirkaya 2011	66 children treated for lymphoma or solid tumors	First evaluation: mean 2.62 ± 1.44 years after completion of treatment Second evaluation: mean 6.55 ± 1.71 years	-Normal: 23 (34.8%) -Osteopenia: 26 (39.4%) -Osteoporosis: 17 (25.8%) Mean LS BMD Z-score -1.26 ± 1.12 (range -4.3 to 2.0)	-Normal: 46 (69.6%) -Osteopenia: 13 (19.7%) -Osteoporosis: 7 (10.6%) Mean LS BMD Z-score -0.48 ± 1.25 (range -3.30 to 3.40)	Significant recovery was observed in LS BMD Z-scores at second evaluation (p=0.001) No significant correlation was detected between follow-up duration and LS BMD Z-score.	SB: unclear AB: low risk DB: low risk
	Kaste 2006b	57 survivors of childhood ALL (study I 141, study II 57)	First evaluation: (study I): >4 years after therapy (mean time after dx 11.7 yrs) Second evaluation: (study II): 2-5 years after study I (mean time after dx 16.1 yrs)	QCT LS BMD Z-score below the mean (<0) 57.9%, QCT LS BMD Z-score <-1: 10.5%	QCT LS BMD Z-score below the mean 59.6%, QCT LS BMD Z-score <-1: 19.3%	Increase in trabecular BMD of 9.3 mg/cc (p=0.003) and an increase of mean BMD Z-score of 0.21 (P=0.04). Cortical BMD (38 survivors) increased significantly between the two studies (P<0.001). Cortical BMD had a significantly greater gain than trabecular BMD (P=0.045).	SB: unclear AB: high risk DB: low risk
	Latoch 2021	326 CCS (123 had 2 DXA scans)	Mean time between the second (DXA2) and first (DXA1) densitometry was 5.54 years (mean age, 17.11 ± 3.67 vs. 11.57 ± 4.03 years	Mean LS BMD Z-score: −0.277 LS BMD Z-score <-2: n=9 LS BMD Z-score <−1 and ≥ −2: n=28 Mean TB BMD Z-score: −0.176 TB BMD Z-score <-2: n=18 TB BMD Z-score <−1 and ≥ −2: n=23	Mean LS BMD Z-score: −0.180 LS BMD Z-score <-2: n=6 LS BMD Z-score <−1 and ≥ −2: n=14 Mean TB BMD Z-score: −0.262 TB BMD Z-score <-2: n=6 TB BMD Z-score <−1 and ≥ −2: n=19	Mean LS BMD Z-scores between DXA1 and DXA2 increased, mean TB BMD Z-scores decreased, both not significant (p=0.842 and p=0.293) The number of patients with LS and TB BMD Z-scores <-2 and <-1 decreased over time (significance unclear)	SB: high risk AB: high risk DB: low risk
	Marinovic 2005	37 survivors of childhood ALL 74 controls matched by age, sex and pubertal stage from a large, healthy	First evaluation: median 2.2 years (range: 0.1–3.1 years) after completion of treatment	Median TB BMD: slightly non-significantly reduced in ALL survivors vs. controls (p=0.06)	No difference from control subjects was found in TB BMD (p=0.23)	Both groups showed an annual increment in BMD measurements TB BMD (but not LS BMD) demonstrated a significantly higher increase in ALL patients vs. controls (p=0.01)	SB: low risk AB: low risk DB: low risk

		group of 266 white children who were longitudinally investigated for BMD	Second evaluation: 1 year after first evaluation	Median LS BMD: significantly lower in ALL survivors vs. controls (p=0.04)	LS BMD slightly, but not significantly reduced (p=0.06)	TB BMD: Patients change: 0.034 (0023; 0044); Control change: 0.025 (0014; 0031) LS BMD: Patients change: 0.039 (0022; 0074); Control change: 0.034 (0006; 0053) LS BMAD: Patients change: 0.004 (0002; 0008); Control change: 0.002 (0004; 0008)	
	Gurney 2014	400 survivors of childhood ALL	First evaluation: Median 8.5 years before second evaluation Second evaluation: not specified; at least 10 years post-diagnosis	QCT LS BMD Z-score ≤-2: 61 (15.2%)	QCT LS BMD Z-score ≤-2: 28 (7.0%)	367 (91.8%) either improved their LS BMD Z-score category or remained stable over the follow-up period – 67% of those who previously had a LS BMD Z-score of ≤-2 improved by 1 or more categories at second evaluation	SB: unclear AB: low risk DB: low risk
	Pluijm 2015	188 adult childhood cancer survivors	Median period between DXA scans was 3.2 years (range 0.9-10.9 years)	NR	TB BMD at 2nd evaluation: mean Z-score 0.08 increase (p>0.01) LS BMD at 2nd evaluation: mean Z-score 0.06 increase (p=0.03)	Significant increase in TB and LS BMD Z-scores between 1st and 2nd evaluation (p<0.01 and p=0.03) TB BMD increased significantly over time in AML, NHL and renal tumor survivors, and LS BMD in AML, but not in ALL survivors. Analyzed by gender, TB BMD and LS BMD improved significantly only in males. Peak bone mass for LS BMD seemed to be reached at about age 23; TB BMD tended to increase until age 26/27	SB: high risk AB: high risk DB: low risk
	Pluskiewicz 2004	38 survivors of childhood ALL 1402 controls who were healthy pupils randomly selected from schools in the same urban region of Poland.	First evaluation: 2 years before second evaluation Second evaluation: mean 5.7 ± 2.9 years after completion of treatment	Mean Ad-SoS values in the whole group of survivors and in boys not significantly different from controls; girls significantly higher Mean Ad-SoS value	Ad-SoS in patients was significantly higher than in controls; Same trends were observed in both genders, but without significance Mean Ad-SoS value	Mean Ad-SoS in survivors increased (p <0.001 boys; p<0.001 girls) compared with baseline Survivors: Ad-SoS increased in 37 (97.4%) Ad-SoS increased more than the least significant change in 31 (81.6%)	SB: high risk AB: high risk DB: unclear

		The control group consisted of different subjects at baseline and follow-up.		1990±76 m/s in survivors vs. 1973±64 m/s in controls	2045±86 m/s in survivors vs. 2016±86 m/s in controls	Controls: NR	
	Muszynska-Roslan 2009	114 survivors of childhood cancer	First evaluation: Mean years from completion of treatment ALL: 2.4±1.9 years HL: 2.8±2.1 years Solid tumor: 3.7±4.6 years Second evaluation: Mean years from completion of treatment ALL: 5.8±3.4 years HL: 6.3±2.9 years Solid tumor: 6.9±4.6 years	LS or TB BMD Z-score ≤-2: ALL: 10.5% HL: 6.9% Solid Tumor: 30.5% Median TB BMD Z-score: ALL: 0.26±1.7 HL: 0.11±0.9 Solid Tumor: -1.14±1.2 Median LS BMD Z-score: ALL: 0.23±1.3 HL: 0.23±1.1 Solid Tumor: -1.13±1.1	LS or TB BMD Z-score ≤-2: ALL: 8.7% HL: 6.9% Solid Tumor: 16.6% Median TB BMD Z-score: ALL:0.12±1.5 HL: -0.09±1.2 Solid Tumor: -0.40±0.6 Median LS BMD Z-score: ALL: 0.15±1.6 HL: -0.09±0.8 Solid Tumor: -0.40 ±0.8	No conclusions reported regarding the change of BMD Z-scores between the first and second evaluation. Increasing age was independently associated with higher *Z*-scores of TB BMD (p=0.021) and LS BMD (p=0.03)	SB: high risk AB: low risk DB: low risk
	Tabone 2021	89 leukemia survivors	First evaluation: Mean (± SD) interval from diagnosis 7.0 ± 4.7 yrs Second evaluation: Mean (± SD) interval from diagnosis 11.7 ± 5.2 yrs	Proportion of survivors with a BMD Z-score ≤-2 LS: 15.7% FN: 14.5% TH: 14.5% TB: 7%	Proportion of survivors with a BMD Z-score ≤-2 LS: 14.6% FN: 4.3% TH: 7.2% TB: 9.3% Mean difference in BMD Z-score between the first and second scan: LS: +0.11, 95%CI −0.05 to 0.28, p=0.170 FN: +0.21, 95%CI 0.02–0.40, p=0.033 TH: +0.19, 95%CI 0.01-0.38, p=0.036 TB: +0.03, 95%CI −0.19 to 0.25, p=0.815	Significant increase in mean FN and TH BMD Z-scores between 1st and 2nd evaluation (p=0.033 and p=0.036) Significant decrease in the proportion of survivors with a FN BMD Z-score ≤-2 (p=0.04) Changes in mean BMD Z-score and Z-score ≤-2 at other skeletal sites were not significant	SB: high risk AB: low risk DB: low risk
GRADE assessment: **Study design:**	+4	Longitudinal cohort studies					

Study limitations:	-1	Some limitations: Selection bias low in 1/9, unclear in 3/9, high in 5/9; Attrition bias low in 5/9, high in 4/9; Detection bias low in 8/9, unclear in 1/9
Consistency:	0	No important inconsistency, all studies show an increase of BMD at follow-up
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	NA
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⨁⨁⊖ MODERATE
Conclusion:		BMD Z-scores increase over time from 2 years until at least 10 years since end of cancer treatment in CAYA cancer survivors. (7 studies significant effect, 1 study significance unclear, 1 study non-significant increase; 1112 participants)

Abbreviations: AB=attrition bias; Ad-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; BMD=bone mineral density; CAYA=childhood, adolescent and young adult; CF=confounding; DB=detection bias; dx=diagnosis; DXA=Dual-energy X-Ray Absorptiometry; HL=Hodgkin's lymphoma; IB=index test bias; LS=lumbar spine; NA=not applicable; NHL=non-Hodgkin lymphoma; NR=not reported; SB=selection bias; TB=total body.

2.d What is the association between low and very low BMD and fractures in CAYA cancer survivors?
(Does surveillance of impaired BMD lead to less fractures in CAYA cancer survivors?)

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Treatment (% treated)	Events	Effect size	Risk of bias
2.d. Risk fractures for low BMD **(n=3 studies)**	Bloomhardt 2020	542 CCS	Mean time since treatment (±SD) 6.0±5.0 years (range 2.0-35.1)	Chemotherapy: Dexamethasone 59.6% Prednisone 35.4% Any glucocorticoid 95% Cyclophosphamide 85.1% High-dose methotrexate 25.8% Radiotherapy: CRT 20.7% TBI 8.1% SCT: NR	Non-digit (1 or more post-treatment) fracture: 21.4% Upper extremity long bone (includes wrist): 12.2% Lower extremity long bone (includes ankle): 5.4%	Univariable model: Any nondigit post-therapy fracture: Z-score <-1 (y/n) OR 2.2, 95% CI 1.3-3.7, Long bone fracture: Z-score <-1 (y/n) OR 2.7, 95% CI 1.5-4.7	SB: high risk AB: low risk DB: low risk CF: high risk
	Fiscaletti 2021	251 ALL survivors	Median 15.1 years (range 5.4 to 28.2 years) since cancer diagnosis	Chemotherapy: Glucocorticoids 100% Methotrexate 100% Radiotherapy: CRT 59% SCT: None	Vertebral fractures: 23% Non-vertebral fractures: 31%	Multivariable model: Vertebral fractures: LS BMD Z-score: RR 0.91, 95%CI 0.75-1.11, p=0.350	SB: low risk AB: low risk DB: low risk CF: low risk
	van Santen 2020	177 craniopharyngioma survivors	Median 16 years (range 1-62)	Chemotherapy: 0% Radiotherapy: CRT: 51% ^{90}Yttrium brachytherapy: 13% SCT: None	Fractures: 18% over time (5.8 fractures per 1000 person-years)	Univariable model: Fractures: osteopenia (y/n) OR 2.6, 95%CI 0.9-7.7, p=0.09; osteoporosis (y/n) OR 2.1, 95%CI 0.7-6.4, p=0.21	SB: high risk AB: high risk DB: high risk CF: high risk

GRADE assessment:		
Study design:	+4	Cross-sectional cohort studies
Study limitations:	-3	Some limitations: Selection bias high in 2/2; Attrition bias low in 1/2, high in 1/2; Detection bias low in 1/2, high in 1/2; Confounding high in 2/2
Consistency:	0	No important inconsistency, both studies show an association between low BMD and fractures (1 significant)
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients and events
Publication bias:	0	Unlikely
Effect size:	+1	Large magnitude of effect
Dose-response:	0	NA
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		Significant association between (very) low BMD (Z-score ≤-1 or ≤-2) and fractures in CAYA cancer survivors. (1 study significant effect, 1 study no significant effect; 719 participants)

GRADE assessment:		
Study design:	+4	Cross-sectional cohort studies
Study limitations:	0	No important limitations: Selection bias low in 1/1; Attrition bias low in 1/1; Detection bias low in 1/1; Confounding low in 1/1
Consistency:	NA	Only one study available
Directness:	0	Results are direct, population and outcomes broadly generalizable

Precision:	-2	Important imprecision: low total number of patients and events and only one study available
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	NA
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		No significant association between lower BMD Z-scores (continuous) and fractures in CAYA cancer survivors. (1 study no significant effect; 251 participants)

Abbreviations: AB=attrition bias; BMD=bone mineral density; CCS=childhood cancer survivors; CF=confounding bias; CRT=cranial radiotherapy; DB=detection bias; NA=not applicable; NR=not reported; OR=odds ratio; SB=selection bias; SCT=stem cell transplantation; SD=standard deviation; TBI=total body irradiation.

What should be done when abnormalities are identified?

3a. Does assurance of a minimum daily intake of vitamin D or vitamin D supplements improve BMD and/or prevent fractures in CAYA cancer survivors?
Does assurance of a minimum daily intake of calcium or calcium supplements improve BMD and/or prevent fractures in CAYA cancer survivors?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Intervention	Controls	Effect intervention	Risk of bias
3.a. Effect of vitamin D / calcium supplementation on BMD **(n=1 study)**	Kaste 2014	424 survivors of childhood ALL Intervention group: 275 with BMD Z-score <0 Control group: 134 with a LS BMD Z-score > 0	Median time since treatment 8.4 yrs (range 4.6-19.1) 24 months of follow-up from start intervention	Nutritional counseling to encourage recommended daily intake of calcium and cholecalciferol Once daily calcium carbonate (1,000 mg) and cholecalciferol (800 IU) during 24 months	Nutritional counseling to encourage recommended daily intake of calcium and cholecalciferol Placebo	LS BMD Z-score change supplement vs. placebo β 0.03, 95%CI -0.13-0.19, p=0.70	SB: high risk AB: high risk DB: low risk PB: low risk

GRADE assessment:		
Study design:	+4	Randomized controlled trial
Study limitations:	-2	Limitations: Selection bias high in 1/1; Attrition bias high in 1/1; Detection bias low in 1/1; Performance bias low in 1/1
Consistency:	NA	Only one study available
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	High total number of participants, but only one study available AND confidence interval includes possible benefit from vitamin D supplementation
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Dose-response relationship between vitamin D doses and BMD change not assessed
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⊖⊖⊖ VERY LOW
Conclusion:		No significant effect of calcium and vitamin D supplementation on BMD in CAYA cancer survivors. (1 study no significant effect; 424 participants)

Abbreviations: AB=attrition bias; ALL=acute lymphoblastic leukemia; CAYA=childhood, adolescent and young adult; CI=confidence interval; β=regression coefficient; BMD=bone mineral density; DB=detection bias; LS=lumbar spine; NA=not applicable; PB=performance bias; SB=selection bias.

3b. Does physical exercise improve BMD and/or prevent fractures in CAYA cancer survivors?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Intervention	Controls	Effect intervention	Risk of bias
3.b. Effect of physical exercise on BMD **(n=1 study)**	Dubnov-Raz 2015	33 survivors of childhood cancer Intervention group: 21 Control group: 12	Median time since treatment 3.0 yrs (range 0.9-5.5) 6 months of follow-up from start intervention	"Go active" gym provided a three time supervised group-based exercise session per week during six months that included 15 minutes of aerobic warm-up, 30 minutes of strengthening/cardiac conditioning activities using bands, balls, games, free weights, and 10-15 minutes of active cool down with walking and stretching.	Maintain current lifestyle	Intervention vs. control group: Lumber BMD Z-score: p=0.90 Lumber BMD g/cm2: p=0.13 Total body BMC (g) p=0.70 Total body BMD (g/cm^2) p=0.39 Femoral head BMD (g/cm^2) p=0.18 (No effect measures reported)	SB: high risk AB: unclear DB: high risk PB: high risk

GRADE assessment:		
Study design:	+2	Non-randomized controlled trial
Study limitations:	-3	Limitations: Selection bias high in 1/1; Attrition bias unclear in 1/1; Detection bias high in 1/1; Performance bias high in 1/1
Consistency:	NA	Only one study available
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Low total number of participants AND only one study available
Publication bias:	0	Unlikely
Effect size:	0	Magnitude of effect not described
Dose-response:	0	Relationship between higher exposure to exercise and BMD change not assessed
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ VERY LOW
Conclusion:		No significant effect of physical exercise on BMD in CAYA cancer survivors. (1 study no significant effect; 21 participants)

Abbreviations: AB=attrition bias; CAYA=childhood, adolescent and young adult; BMD=bone mineral density; DB=detection bias; NA=not applicable; PB=performance bias; SB=selection bias.

3c. Does treatment with a vibrating plate improve BMD and/or prevent fractures in CAYA cancer survivors?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Intervention	Controls	Effect intervention	Risk of bias
3.c. Effect of vibrating plate on BMD **(n=1 study)**	Mogil 2016	65 survivors of childhood cancer Intervention group: 32 Control group: 33	> 5 years from cancer diagnosis 1 year of follow-up from start intervention	Low-magnitude (<1.0g), high frequency mechanical stimulation (LMS) device used at home, 10 minutes twice daily for 1 year. Calcium (800-1200mg/d) and vitamin D supplements (cholecalciferol, 400 IU/d)	The placebo group stood on a device identical in appearance to the active platform. The placebo device emitted a 500-Hz audible hum but did not deliver the signal. Calcium (800-1200mg/d) and vitamin D supplements (cholecalciferol, 400 IU/d)	Difference total-body BMD mean (SD) Z-scores (intention to treat analysis) Intervention group (n=22): 0.25 (0.78) (95% CI -0.09 to 0.59); Control group (n=26): –0.19 (0.79) (95% CI -0.51 to 0.12); Intervention vs. control p=0.05 Difference L1, L2 BMD Z-score (intention to treat analysis): Intervention group (n=22): 0.08 (0.51) (95% CI -0.13 to 0.30); Control group (n=26): 0.14 (0.51) (95% CI -0.06 to 0.35); Intervention vs. control p=0.68 Tibial trabecular bone among participants completing 70% or more of the prescribed sessions increased by a mean of 11.2% (95%CI, 5.2 to 17.2%); Tibial trabecular bone among participants completing less than 70% who decreased by a mean of −1.3%(95%CI, −7.3 to 4.7%); P = 0.02	SB: low risk AB: high risk DB: low risk PB: low risk

GRADE assessment:		
Study design:	+4	Randomized controlled trial
Study limitations:	-1	Limitations: Selection bias low in 1/1; Attrition bias high in 1/1; Detection bias low in 1/1; Performance bias low in 1/1
Consistency:	NA	Only one study available
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Reasonable total number of participants, but confidence interval includes possible decrease in BMD in the intervention group AND only one study available
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Significant relationship between higher exposure to the vibrating plate (>70% completed sessions vs. <70%) and BMD change
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⊖⊖⊖ VERY LOW

Conclusion:	No significant effect of twice daily treatment with a vibrating plate on total body BMD Z-score in CAYA cancer survivors in an intention-to-treat analysis (p=0.05), although there was a significant improvement of tibial trabecular bone content among participants completing 70% or more of the prescribed sessions. (1 study no significant effect in the intention-to-treat analysis, significant effect in the per-protocol analysis; 65 participants)

Abbreviations: AB=attrition bias; CAYA=childhood, adolescent and young adult; BMD=bone mineral density; DB=detection bias; IU=international units; NA=not applicable; PB=performance bias; SB=selection bias; SD=standard deviation.

3d. Does growth hormone replacement therapy improve BMD and/or prevent fractures in CAYA cancer survivors?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Intervention	Controls	Effect intervention	Risk of bias
3.d. Effect of growth hormone replacement therapy on BMD **(n=3 studies)**	Van den Heijkant 2011	20 survivors of childhood ALL with low BMD (<-1 SD) at the LS or femoral sites and/or low IGF-1 (<-1 SD) No controls	Mean time since treatment completion 20.7±3.2 years 2 years of follow-up from start intervention	Human Growth hormone (Eli Lilly penfill system) given subcutaneously for 2 years. The initial dose was 0.1 mg/m^2 of body surface. The dose was increased every 2 weeks by 0.1 mg/m^2 until IGF-1 rose above the mean of a reference group in all 20 participants (both with and without GHD).	-	After 24 months of GH treatment: -Significant increase in crude total body BMD measurements (g/cm2) (p=0.005); -No significant effect on other skeletal sites or total body BMC (Kg); Significant increase in FN BMD Z-score (p=0.02). -Increase in total body BMD significantly higher in GHD survivors vs. non-GHD survivors (p=0.004). *Effect size NR for all findings.*	SB: high risk AB: high risk DB: high risk PB: high risk
	Follin 2011	31 survivors of ALL with GHD: GH treatment (n=18), and no GH treatment (n=13) Control group: 28 matched population controls (similar in sex, age, residence and smoking habits)	Years since treatment completion GH group: 21 (8-27) No GH group: 19 (9-27) 5 years of follow-up from start intervention	GH treatment: 0.5 mg/day for women and men (Humantrope Eli Lilly) for 5 years.	Survivor controls: untreated GHD who had regular contact with a doctor or nurse for 5 years. Population controls: no information.	No significant difference in BMD and BMAD after 5 years at any site in GH treated survivors vs. non-GH treated survivors and controls Median net difference femoral Z-scores GH-treated vs. non-GH-treated survivors: -0.20 vs. -0.25 Median net difference Z-scores at L2–L4 levels GH-treated vs. non-GH-treated survivors: -0.10 vs. -0.25	SB: high risk AB: low risk DB: unclear PB: high risk
	Cohen 2012	36 survivors of childhood brain tumor 29 with GHD; 20 treated for GHD, 9 untreated GHD 7 without GHD	8.5 ± 3.6 years 1 year of follow-up from start intervention	rhGH	No growth hormone replacement	Among patients with GHD (n=29), those treated (n=20) with rhGH for >1 year had significantly higher BMD and BMD Z-scores of the hip (BMD 0.970±0.032 vs. 0.803±0.045, p=0.006; BMD Z-scores -0.365±0.259 vs. -1.533±0.460, p=0.03), spine (BMD 0.978±0.027 vs. 0.779±0.036, p<0.0001; BMD Z-scores -0.115±0.255 vs. -2.067±0.429, p<0.0001) and femoral neck (BMD 0.878±0.033 vs. 0.725±0.034, p=0.01; BMD Z-scores -0.385±0.273 vs. -	SB: high risk AB: high risk DB: high risk PB: high risk

			1.378±0.342, p=0.043) compared to those untreated (n=9) Significantly higher BMAD and BMAD Z-scores of the spine (BMAD 0.150±0.004 vs. 0.131±0.007, p=0.02; BMAD Z-scores 0.248±0.264 vs. -1.368±0.418, p=0.002) but not of the femoral neck (BMAD 0.168±0.006 vs. 0.157±0.009, p=0.33; BMAD Z-scores -0.130±0.255 vs. -0.706±0.393, p=0.22) among GH treated survivors vs. non-GH treated survivors
GRADE assessment:			
Study design:	+2	One uncontrolled single arm trial, two retrospective observational studies	
Study limitations:	-3	Limitations: Selection bias high in 3/3; Attrition bias low in 1/3, high in 2/3; Detection bias unclear in 1/3, high in 2/3; Performance bias high in 3/3	
Consistency:	-1	Inconsistency of the effect of the intervention across the studies	
Directness:	0	Results are direct, population and outcomes broadly generalizable	
Precision:	-1	Small total number of participants	
Publication bias:	0	Unlikely	
Effect size:	0	Magnitude of effect not described	
Dose-response:	0	Dose-response relationship between GH doses and BMD change not assessed	
Plausible confounding:	0	No plausible confounding	
Quality of evidence:		⨁⊖⊖⊖ VERY LOW	
Conclusion:		Significant effect of growth hormone replacement therapy in GH deficient survivors to increase BMD in CAYA cancer survivors. (2 significant effect, 1 no significant effect; 80 participants)	

Abbreviations: AB=attrition bias; ALL=acute lymphoblastic leukemia; CAYA=childhood, adolescent and young adult; BMAD=bone mineral apparent density; BMC=bone mineral content; BMD=bone mineral density; DB=detection bias; GH=growth hormone; GHD=growth hormone deficiency; LS=lumbar spine; NR=not reported; PB=performance bias; rhGH=recombinant human growth hormone; SB=selection bias; SD=standard deviation.

Recommendations in existing clinical practice guidelines in other populations (2 childhood cancer guidelines)

What should be done when abnormalities are identified?	
Kuhlen et al. Guidance to Bone Morbidity in Children and Adolescents Undergoing Allogeneic Hematopoietic Stem Cell Transplantation. Biol Blood Marrow Transplant. 2020 Feb;26(2):e27-e37.	
Recommendation[1]	**Level of evidence[2]**
Adequate calcium and vitamin D intake are important for preventing osteomalacia and rickets but will not prevent or treat OP. The minimum intakes known to prevent rickets are ≥500 mg/d of calcium and 10 µg (400 IU)/d of vitamin D; higher vitamin D intakes (12.5 to 25 µg or 500 to 1000 IU) have been recommended for children and adolescents at risk of vitamin D deficiency due to factors and conditions that reduce synthesis or intake (e.g., restricted exposure to sun, high latitude during winter/spring season, and low dietary calcium intake). Target 25(OH)D levels should be above 50 nmol/L. There is no benefit in higher 25(OH)D levels from vitamin D supplementation.	Level 1
Pubertal delay due to hypogonadism and other endocrinopathies need to be assessed on a regular basis and if necessary pediatric endocrinologists consulted	Level 2
Muscle force enhances bone accrual. Thus, promoting physical activity and exercise during and after HSCT is of particular importance, within the limits of illness.	Level 2
Basically, diagnosis and treatment of OP in children and adolescents should follow the ISCD guidance of pediatric OP. Therein, BP treatment is reserved for older patients with overt bone fragility and low potential for BMD restitution and vertebral body reshaping.	Level 2
In case of significant functional impairment limiting QoL, age becomes less important and treatment may be initiated.	Level 2
However, the ISCD guidance only provides recommendations for children with standard ALL. As in children and adolescents with ALL undergoing HSCT, more complications and poor outcome are probably more likely. BP therapy may be used in younger patients with serious complications, bone pain, and therefore less potential for recovery, as long as ISCD criteria of OP are fulfilled.	Level 3

Abbreviations: ALL=acute lymphoblastic leukemia; BMD=bone mineral density; BP=bisphosphonate; OP=osteoporosis; HSCT=hematopoietic stem cell transplantation; ISCD=international society of clinical densitometry; QoL=quality of life.

[1] **Grades of recommendation**
Not provided in the manuscript

[2] **Level of evidence**
1: evidence from at least 1 randomized trial
2: evidence from cohort studies, case-control studies, and time series
3: opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees, and provide our practice whenever no evidence is available

What should be done when abnormalities are identified?	
Marcucci et al. Bone Health in Childhood Cancer: Review of the Literature and Recommendations for the Management of Bone Health in Childhood Cancer Survivors. Ann Oncol. 2019 Jun 1;30(6):908-920.	
Recommendation[1]	**Level of evidence[2]**
When low BMD (juvenile osteoporosis) is reported, Z-score ≤2 or T-score ≤2.5 (based on age, pubertal development, and growth process), and/or fragility fractures, and/or chronic use of glucocorticoids, antiresorptive treatments (bisphosphonate) should be taken into consideration.	Childhood/adolescent/young adult age: low Adulthood: moderate
Recommendations regarding adequate calcium (or diet intake) and vitamin D supplementations, in case of deficit, in addition to adequate physical activity, to avoid negative lifestyles, should always be given, irrespective of BMD, as recommended in the general population.	Low
It is important to counsel survivors to avoid smoking, alcohol, cannabis, and excessive use of caffeine.	Not reported
If necessary, correction of endocrine alterations or other modifiable risk factors of impaired bone quantity/quality should be evaluated	Low

Abbreviations: BMD=bone mineral density.

[1] Grades of recommendation
Not provided in the manuscript

[2] Level of evidence according to GRADE
High: further research is unlikely to change the confidence in the estimate of effect.
Moderate: further research is likely to have an important impact on the confidence in the estimate of effect and may change the estimate.
Low: further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate.
Very low: any estimate of effect is very uncertain.

Summary:

Recommendations in existing clinical practice guidelines in other populations (2 childhood cancer guidelines)	
In patients with severe bone fragility and low potential for BMD restitution, bisphosphonate treatment should be considered	Evidence-based guidelines
Adequate calcium and vitamin D intake is important. Only in case of deficit, supplementation is warranted	Evidence-based guidelines
Negative lifestyles such as smoking and alcohol use should be avoided	Evidence-based guideline
Adequate physical activity is important and should be promoted.	Evidence-based guidelines
The presence of endocrinopathies such as hypogonadism should be evaluated and corrected if necessary	Evidence-based guidelines