Summary of findings tables, grading of the evidence and detailed conclusions of evidence metabolic syndrome surveillance

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	METS in survivors and controls	METS definition used	Effect size *For all analyses: survivors vs normal population*	Risk of bias
Who needs surveillance? 1. What is the risk of the metabolic syndrome in CAYA cancer survivors compared to the general population of the same age? (N = 11 studies)	**Haematological malignancies**						
	Blijdorp, 2013	21 Survivors of AML, MDS or CML treated with chemotherapy and/or HSCT. Controls: 60 matched controls.	Chemo only group: median 21.6 yrs (9.1-30.7 yrs). HSCT group: median 19.0 yrs (11.6-30.0 yrs).	Chemo only survivors (1/12 (8%)) vs controls (3/48 (6%)). HSCT survivors (1/8 (13%)) vs controls (3/48 (6%)). #METS components in 12 chemo only survivors vs 48 controls. #METS components in 8 HSCT survivors vs 48 controls.	NCEP ATP III criteria. Total METS N= 5, 1/12 chemo-only survivors (8%) and 1/8 HSCT survivors (13%), 3/48 (6%) controls.	P = 1.000 P = 0.507 OR 1.31, P = 0.687 OR 24.1, P < 0.001.	SB: High risk AB: Low risk DB: Unclear CF: Low risk
	Friedman, 2017	123 childhood leukemia/lymphoma survivors treated with HSCT and TBI. Controls: random sample of National Health and Nutrition Examination Survey (NHANES) (3 age, sex and ethnicity matched controls per survivor).	Since TBI median 8.0 yrs (1.01-24.6 yrs).	CVRF cluster in survivors vs matched controls. 1991-2000: 5.5% in NHANES vs 5.9% in survivors. 2001-2006: 8.0% in NHANES vs 6.3% in survivors. 2007-2013: 12.1% in NHANES vs 14.4% in survivors.	CVRF cluster (as surrogate for METS, ≥3 IDF criteria). Total METS N=35 (no other descriptives provided).	P = 0.70.	SB: Unclear AB: Low risk DB: Unclear CF: Low risk
	Gurney, 2006	75 childhood ALL survivors treated with radiation and/or chemotherapy. Controls: 730 adults (18-45 yrs) from the the National Health and	Since diagnosis mean 24.6 yrs (± 4.8 yrs)	METS in survivors (N=11 (16.59%, SE 4.74)) vs controls (17.45%, SE 3.02). Total METS in survivors N=11 (14.67%).	NCEP ATP III criteria.	P = 0.87.	SB: High risk AB: Low risk DB: Unclear CF: Low risk

		Nutrition Examination Study (NHANES).					
	Kourti, 2005	52 survivors of childhood ALL treated with chemotherapy only. Controls: prevalence of METS in general US adolescents.	Since completion of therapy median 37 months (range 13–121 months).	METS in survivors (N=3 (5.76%)) vs general US adolescents (4%).	NCEP ATP III criteria.	No significant difference between descriptives (statistics not reported).	SB: Unclear AB: Low risk DB: Unclear CF: High risk
	Ariffin, 2017	87 ALL survivors. Controls: 87 age- and sex matched controls.	Median 18 yrs (IQR 14-22 yrs).	METS in survivors (N=16 (18.4%)) vs controls (N=4 (4.6%)).	At least 3 of the following metabolic risk factors: fasting blood glucose>6.1 mmol/L, hypertension (systolic blood pressure> 130mm Hg or diastolic blood pressure >85mm Hg), hypertriglyceridemia (serum triglycerides>1.7 mmol/L), low high-density lipoprotein (men,<1.03 mmol/L; women,<1.29 mmol/L), a large waistline (men,>102 cm; women,>88 cm).	No statistics performed.	SB: Unclear AB: Low risk DB: Unclear CF: Low risk
	Nottage, 2014	784 ALL survivors. Controls: 777 age-, race- and sex matched US	Median 26.1 yrs (11-45.3 yrs) survival time.	METS in survivors (N=259, 33.6%) vs matched controls (descriptives not provided).	NCEP ATP III criteria. Total METS N=259 (33.6%). No other descriptives provided.	RR 1.43, 95% CI 1.22–1.69.	SB: High risk AB: Low risk DB: Unclear CF: Low risk

	adults from NHANES (2005-2010).					
Oudin, 2018	1025 ALL/AML survivors.	Mean since diagnosis 16.32 ± 0.21 years.	METS in survivors (N=106, 10.3%) vs matched controls (N=145, 4.5%).	NCEP ATP III criteria (2005 version). Total METS survivors N=106 (10.3%). Total METS controls N=145 (4.5%).	OR 2.49, 95% CI 1.91-3.25. P<0.001.	SB: Unclear AB: High risk DB: Unclear CF: High risk
Other malignancies						
Van Waas, 2012	67 nephroblastoma and 36 neuroblastoma survivors. Controls: 61 age- and sex matched controls.	Median 26.2 yrs (6.4-48.9 yrs) survival time for nephroblastima survivors. Median 27.8 yrs (15.0-44.4 yrs) survival time for neuroblastoma survivors.	#METS components in nephroblastoma survivors vs matched controls (descriptives not provided). #METS components in neuroblastoma survivors vs matched controls (descriptives not provided).	NCEP ATP III criteria	OR 4.3. P= 0.093. OR 2.7. P= 0.38.	SB: High risk AB: Low risk DB: Unclear CF: Low risk
Meacham, 2010	8599 survivors of childhood cancer. Controls: 2936 matched siblings.	Since diagnosis >5 yrs (mean/median not reported).	METS in survivors (N=113, 1.3%) vs matched siblings (N=34, 1.2%).	Having at least 3 of the following 4 risk factors – obesity, hypertension, dyslipidemia, and diabetes mellitus or impaired glucose tolerance. Total METS N=113. No other descriptives provided.	OR 1.3, 95% CI 0.9–1.9.	SB: High risk AB: Low risk DB: Unclear CF: Low risk
Talvensaari, 1996	50 survivors of childhood cancer.	Mean follow-up since diagnosis 12.6 (7.9-21.3) years.	METS in survivors (N=8, 16%) vs matched controls (N=1, 2%).	A combination of obesity (relative weight >120%), hyperinsulinemia (fasting plasma insulin >111 pmol/L) and low	P = 0.01.	SB: Low risk AB: Low risk DB: Unclear CF: High risk

					HDL cholesterol (serum HDL <1.07 mmol/L). Total METS in survivors N=8 (16%). Total METS in controls N=1 (2%).		
	Netterlid, 2021	167 female survivors of childhood cancer.	Median follow-up 30 (12–39) years.	METS in survivors (N=24, 14%) vs matched controls (4%)	IDF criteria Total METS in CCS N=24 (14%) Total METS in controls N=? (4%)	P=0.002	SB: High risk AB: Low risk DB: Unclear CF: High risk

GRADE assessment:		
Study design:	+4	Observational studies.
Study limitations:	-1	Some limitations: selection bias low in 1/11, high in 6/11, unclear in 4/11; attrition bias high in 1/11, low in 10/11; detection bias unclear in 11/11; confounding low in 7/11, high in 4/11.
Consistency:	-1	Some inconsistency: 4 significant results vs 7 non-significant studies.
Directness:	0	Results are direct, population and outcomes broadly generalizable.
Precision:	0	No important imprecision.
Publication bias:	0	Unlikely.
Effect size:	0	Very large magnitude of effect for risk of more METS components (≠METS), only small magnitude of effect for risk of METS.
Dose-response:	0	N/A.
Plausible confounding:	0	No plausible confounding.
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		Increased risk of METS in CAYA cancer survivors vs the normal population. (11 studies, 4 significant; >15.701 participants; >577 events).
Comments:		Different definitions of METS used.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Chemotherapy	METS definition used	Effect size	Risk of bias
Who needs surveillance? 2. Treated after chemotherapy. a. What is the risk after different agents? I Platinum agents. (N = 2 studies)	Meacham, 2010	8599 survivors of childhood cancer.	Since diagnosis >5 yrs (mean/median not reported).	METS in survivors treated with platinum agents (N=367 (4.7%)) vs METS in survivors treated without platinum agents.	Having at least 3 of the following 4 risk factors – obesity, hypertension, dyslipidemia, and diabetes mellitus or impaired glucose tolerance. Total METS N=113. No other descriptives provided.	*Platinum agents vs no platinum agents.* OR 0.9 95% CI 0.2-2.7.	SB: High risk AB: Low risk DB: Unclear CF: Low risk

GRADE assessment:		
Study design:	+4	Observational studies.
Study limitations:	-1	Some limitations: selection bias high in 1/1; attrition bias low in 1/1; detection bias unclear in 1/1; confounding low in 1/1.
Consistency:	0	No important inconsistency: one study.
Directness:	0	Result are direct, population and outcomes broadly generalizable.
Precision:	-1	Some imprecision: only one study performed but narrow CI.
Publication bias:	0	Unlikely.
Effect size:	0	One large magnitude of effect, but for >2 components of METS (≠METS).
Dose-response:	0	Unclear if dose response relationship.
Plausible confounding:	0	No plausible confounding.
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		No significant association between platinum agents and METS in CAYA cancer survivors. (1 study, none significant, 8.599 participants, >367 events).
Comments:		

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Chemotherapy	METS definition used	Effect size	Risk of bias
Who needs surveillance? 2. Treated after chemotherapy. a. What is the risk after different agents? II Anthracyclines. (N = 2 studies)	Meacham, 2010	8599 survivors of childhood cancer.	Since diagnosis >5 yrs (mean/median not reported).	METS in survivors treated with anthracyclines vs no anthracyclines: < 100 mg/m2 N=296 (3.9%). 100-299 mg/m2 n=1223 (16%). >300 mg/m2 n=336 (17.5%).	Having at least 3 of the following 4 risk factors – obesity, hypertension, dyslipidemia, and diabetes mellitus or impaired glucose tolerance. Total METS N=113. No other descriptives provided.	*<100 mg/m2 vs no anthracyclines.* OR 1.6, 95% CI 0.5–4.2. *100-299 mg/m2 vs no anthracyclines.* OR 0.9 95% CI 0.5-1.7. *>300 mg/m2 vs no anthracyclines.* OR 1.0 95% CI 0.6-1.8.	SB: High risk AB: Low risk DB: Unclear CF: Low risk
	Nottage, 2014	784 ALL survivors.	Median 26.1 yrs (11-45.3 yrs) survival time.	METS and cumulative anthracycline dose (100 mg/m2).	NCEP ATP III criteria. METS total N=259 (33.6%). No other descriptives provided.	*100 mg/m2 vs no anthracyclines.* RR 0.89 95% CI 0.78-1.01.	SB: High risk AB: Low risk DB: Unclear CF: Low risk

GRADE assessment:

Study design:	+4	Observational studies.
Study limitations:	-1	Some limitations: selection bias high in 2/2; attrition bias low in 1/1; detection bias unclear in 1/1; confounding low in 1/1.
Consistency:	0	N/A (one study).
Directness:	0	Results are direct, population and outcomes broadly generalizable.
Precision:	0	No important imprecision: high total number of events and narrow CIs.
Publication bias:	0	Unlikely.
Effect size:	0	No large magnitude of effect.
Dose-response:	0	No dose-response relationship.

Plausible confounding:	0	No plausible confounding.
Quality of evidence:		⊕⊕⊕⊖ MODERATE
Conclusion:		No significant association between anthracyclines and METS in CAYA cancer survivors. (2 studies, none significant, 9.383 participants, 372 events).
Comments:		Different definitions of METS used.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Chemotherapy dose	METS definition used	Effect size	Risk of bias
Who needs surveillance? 2. Treated with chemotherapy: b. What is the risk after higher doses (of anthracyclines)? (N = 2 studies)	Meacham, 2010	8599 survivors of childhood cancer.	Since diagnosis >5 yrs (mean/median not reported).	METS in survivors treated with anthracyclines vs METS in survivors treated without anthracyclines: < 100 mg/m2 N=296 (3.9%). 100-299 mg/m2 n=1223 (16%). >300 mg/m2 n=336 (17.5%).	Having at least 3 of the following 4 risk factors – obesity, hypertension, dyslipidemia and diabetes mellitus or impaired glucose tolerance. METS total N=113. No other descriptives provided.	*100 mg/m2 vs none.* OR 1.6, 95% CI 0.5-4.2. *110-299 mg/m2 vs none.* OR 0.9 95% CI 0.5-1.7. *>300 mg/m2 vs none.* OR 1.0 95% CI 0.6-1.8.	SB: High risk AB: Low risk DB: Unclear CF: Low risk
	Nottage, 2014	784 ALL survivors.	Median 26.1 yrs (11-45.3 yrs) survival time.	METS and cumulative anthracycline dose (100 mg/m2).	NCEP ATP III criteria. METS total N=259 (33.6%). No other descriptives provided.	*Per additional dose of 100 mg/m2.* RR 0.89 95% CI 0.78-1.01.	SB: High risk AB: Low risk DB: Unclear CF: Low risk

GRADE assessment:		
Study design:	+4	Observational studies.
Study limitations:	-1	Some limitations: selection bias high in 2/2; attrition bias low in 2/2; detection bias unclear in 2/2; counfounding low in 2/2.
Consistency:	0	No important inconsistency, all studies show non-significant effects.
Directness:	0	Results are direct, population and outcomes broadly generalizable.
Precision:	0	No important imprecision: high total number of events and narrow CIs.
Publication bias:	0	Unlikely.
Effect size:	0	No large magnitude of effect.
Dose-response:	0	Unclear if dose response relationship.
Plausible confounding:	0	No plausible confounding.
Quality of evidence:		⊕⊕⊕⊖ MODERATE
Conclusion:		No significant association between higher anthracycline dose and METS in CAYA cancer survivors. (2 studies, none significant, 9.383 participants, 372 events).
Comments:		Different definitions of METS used.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Chemotherapy	METS definition used	Effect size	Risk of bias

Who needs surveillance? 2. Treated after chemotherapy. a. What is the risk after different agents? III Oral methotrexate. (N = 1 study)	Nottage, 2014	784 ALL survivors.	Median 26.1 yrs (11-45.3 yrs) survival time.	METS in survivors treated with oral methotrexate (N=288 (36.7%)) vs no oral methotrexate (N=496 (63.3%)).	NCEP ATP III criteria. Total METS N=259 (33.6%). No other descriptives provided.	*Oral methotrexate vs no oral methotrexate.* RR 1.24 95% CI 1.02-1.52.	SB: High risk AB: Low risk DB: Unclear CF: Low risk
GRADE assessment:							
Study design:	+4	Observational study.					
Study limitations:	-1	Some limitations: selection bias high in 1/1; attrition bias low in 1/1; detection bias unclear in 1/1; confounding low in 1/1.					
Consistency:	0	N/A (1 study).					
Directness:	0	Results are direct, population and outcomes broadly generalizable.					
Precision:	-1	Some imprecision: only 1 study performed, although narrow CI and high number of events.					
Publication bias:	0	Unlikely.					
Effect size:	0	No large magnitude of effect.					
Dose-response:	0	Unclear if dose response relationship.					
Plausible confounding:	0	No plausible confounding.					
Quality of evidence:		⊕⊕⊖⊖ LOW					
Conclusion:		Increased risk of METS in CAYA cancer survivors treated with oral methotrexate vs no oral methotrexate. (1 study, significant, 784 participants, 259 events).					

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Radiotherapy	METS definition used	Effect size	Risk of bias
Who needs surveillance? 3. Treated with radiotherapy: a. Cranial (N = 8 studies)	Chow, 2010	26 ALL survivors treated with HSCT and TBI. 48 ALL survivors without HSCT (chemotherapy, 10.4% also cranial RT).	Since HSCT median 6 yrs (1-13 yrs). Since diagnosis HSCT group median 10.5 yrs (1-15 yrs). Since treatment for non-HSCT	METS in survivors treated with CRT and/or TBI (N=41) vs METS in survivors with no RT to brain (N=33). TBI only: N=16 TBI+CRT: N=10 CRT only: N=5	≥ 3 cardiometabolic traits, IDF criteria. Total METS (≥3 IDF criteria) N=8 (27.3%).	*CRT and/or TBI vs no RT to brain.* ORs ranged from 5-6 (data not shown. Text indicates this result is significant).	SB: High risk AB: Low risk DB: Unclear CF: Low risk

			survivors median 10 yrs (3-18 yrs).			
	Friedman, 2017	123 childhood leukemia/lymphoma survivors treated with HSCT and TBI. 38 (30.9%) received CRT before HSCT.	Since TBI mediam 8.0 yrs (1.01-24.6 yrs).	METS in survivors treated with CRT (30.9%) vs METS in survivors treated without CRT (69.1%).	CVRF cluster (as surrogate for METS, ≥3 IDF criteria). Total METS in survivors N=35 (no other descriptives provided).	*CRT vs no CRT.* HR 4.0, 95% CI 1.7-9.6 P = 0.002.	SB: Unclear AB: Low risk DB: Unclear CF: Low risk
	Meacham, 2010	8599 survivors of childhood cancer. Controls: 2936 matched siblings.	Since diagnosis >5 yrs (mean/median not reported).	METS in survivors treated with cranial radiation (and no spinal radiation, N=2075 (24.0%)) vs METS in survivors treated without radiation (N=2740 (31.9%). METS in survivors treated with cranial radiation (with spinal radiation, N=427 (5.0%)) vs METS in survivors treated without radiation. TBI: 1.2%	Having at least 3 of the following 4 risk factors – obesity, hypertension, dyslipidemia, and diabetes mellitus or impaired glucose tolerance. Total METS N=113. No other descriptives provided.	*CRT and no spinal RT vs no RT.* OR 1.2 95% CI 0.6-2.3. *CRT and spinal RT vs no RT.* OR 1.5 95% CI 0.5-3.8.	SB: High risk AB: Low risk DB: Unclear CF: Low risk
	Nottage, 2014	784 ALL survivors.	Median 26.1 yrs (11-45.3 yrs) survival time.	METS in survivors treated with CRT without CSI (N=96 (12.2%)) vs METS in survivors treated without CRT (N=277 (35.3%)).	NCEP ATP III criteria. Total METS N=259 (33.6%). No other descriptives provided.	*CRT without CSI vs no CRT.* RR 1.88 95% CI 1.32-2.67.	SB: High risk AB: Low risk DB: Unclear CF: Low risk

				METS in survivors treated with CRT and CSI (N=411 (52.4%)) vs METS in survivors treated without CRT.		*CRT + CSI vs no CRT.* RR 1.67 95% CI 1.26-2.23.	
	Oudin, 2011	184 ALL/AML survivors.	Mean 15.4 yrs (3.4-30.2 yrs).	METS in survivors treated with CNS irradiation (N=27 (14.7%)) vs METS in controls (chemotherapy only, N=97 (52.7%)).	NCEP ATP III criteria. METS CNS irradiation N=3 (11.1%). METS chemotherapy only N=5 (5.2%).	*CNS RT vs chemo only.* OR 1.7 95% CI 0.3-9.0. P = 0.51.	SB: Unclear AB: Low risk DB: Unclear CF: Low risk
	Saultier, 2016	650 childhood ALL survivors treated without HSCT.	Since diagnosis mean follow-up 16.00 (±6.79) yrs.	METS in survivors treated with 18Gy CNS radiation vs survivors treated without CNS radiation. METS in survivors treated with 18Gy CNS radiation vs survivors treated without CNS radiation.	NCEP ATP III criteria. METS total N=45 (6.9%). No other descriptives provided.	*18 Gy CNS radiation vs no CNS radiation.* OR 0.92 95% CI 0.37-2.29, P=0.866. *24 Gy CNS radiation vs no CNS radiation.* OR 1.87 95% CI 0.56-6.27, P=0.309.	SB: Low risk AB: Low risk DB: Unclear CF: Low risk
	Oudin, 2018	1025 ALL/AML survivors.	Mean since diagnosis 16.32 ± 0.21 years.	METS in survivors with CNS irradiation and chemotherapy (N=143 (13.9%)) vs matched controls (N=3203)	NCEP ATP III criteria (2005 version). Total METS survivors N=106 (10.3%). Total METS controls N=145 (4.5%). METS CNS irradiation and chemotherapy N=18 (12.6%).	*CNS+chemo vs matched controls.* OR= 2.32 (95%CI: 1.36-3.97). P=0.002.	SB: Unclear AB: High risk DB: Unclear CF: High risk

	Smith, 2014	1639 survivors of childhood cancer.	Since diagnosis mean 25.6 (± 7.6) years.	METS in survivors with CRT (N=621 (37.9%)) vs no CRT (rest of cohort, no descriptives provided).	NCEP ATP III (2001). Total METS females N=258 (31.0%) and males N=262 (31.5%).	*CRT vs no CRT males.* RR not significant (data not shown). *CRT vs no CRT females.* RR 1.4, 95% CI 1.2-1.8.	SB: High risk AB: Low risk DB: Unclear CF: Low risk

GRADE assessment:		
Study design:	+4	Observational studies.
Study limitations:	-1	Some limitations: selection bias high in 4/8, low in 1/8, unclear in 3/8; attrition bias high in 1/8, low in 7/8; detection bias unclear in 8/8; counfounding low in 7/8, high in 1/8.
Consistency:	0	No important inconsistency: all significant effects show increased risk of METS in CAYA cancer survivors after CRT.
Directness:	0	Results are direct, population and outcomes broadly generalizable.
Precision:	0	No important imprecision: most significant results have very narrow CIs, and high number of participants and events.
Publication bias:	0	Unlikely.
Effect size:	0	No large magnitude of effect.
Dose-response:	0	Unclear if dose response relationship.
Plausible confounding:	0	No plausible confounding.
Quality of evidence:		⊕⊕⊕⊖ MODERATE
Conclusion:		Increased risk of METS in CAYA cancer survivors treated with C(S)RT vs no C(S)RT. (8 studies, 5 significant, 13.079 participants, 561 events).
Comments:		Different definitions of METS used.

PICO 3b. No studies identified that evaluated the effect of radiotherapy to the hypothalamic-pituitary axis on METS in CAYA cancer survivors.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Radiotherapy	METS definition used	Effect size	Risk of bias
Who needs surveillance? 3. Treated with radiotherapy: c. Abdominal (N = 1 study)	Meacham, 2010	8599 survivors of childhood cancer.	Since diagnosis >5 yrs (mean/median not reported).	METS in survivors treated with abdominal radiation (and no chest radiation, N=566 (6.6%)) vs METS in survivors treated without radiation (N=2740 (31.9%). METS is survivors treated with abdominal radiation (with chest radiation, N=734 (8.5%)) vs METS in survivors treated without radiation.	Having at least 3 of the following 4 risk factors – obesity, hypertension, dyslipidemia and diabetes mellitus or impaired glucose tolerance. METS total N=113. No other descriptives provided.	*Abdominal radiation (without chest radiation) vs no radiation.* OR 1.9 95% CI 0.7-4.2. *Abdominal radiation (and chest radiation) vs no radiation.* OR 2.3 95% CI 1.2-2.4.	SB: High risk AB: Low risk DB: Unclear CF: Low risk

GRADE assessment:		
Study design:	+4	Observational studies.
Study limitations:	-1	Some limitations: selection bias high in 1/1; attrition bias low in 1/1; detection bias unclear in 1/1; counfounding low in 1/1.
Consistency:	0	Not applicable (1 study).
Directness:	0	Results are direct, population and outcomes broadly generalizable.
Precision:	-1	Some imprecision: only one study performed but no (very) wide CIs.
Publication bias:	0	Unlikely.
Effect size:	0	No large magnitude of effect.
Dose-response:	0	Unclear if dose response relationship.
Plausible confounding:	0	No plausible confounding.
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		No significant association between abdominal radiation and METS in CAYA cancer survivors; Increased risk of METS in CAYA cancer survivors treated with a combination of abdominal radiation and chest radiation vs no radiotherapy. (1 study, 1 significant, 8599 participants; 113 events).

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Radiotherapy	METS definition used	Effect size	Risk of bias
Who needs surveillance? 3. Treated with radiotherapy: d. Other fields (N = 1 study)	Meacham, 2010	8599 survivors of childhood cancer.	Since diagnosis >5 yrs (mean/median not reported).	METS in survivors treated with chest radiation (and no abdominal radiation, N=610 (7.1%)) vs METS in survivors treated without radiation (N=2740 (31.9%)). METS in survivors treated in other fields (N=585 (6.8%)) vs METS in survivors treated without radiation (N=2750 (31.9%)).	Having at least 3 of the following 4 risk factors – obesity, hypertension, dyslipidemia, and diabetes mellitus or impaired glucose tolerance. METS total N=113. No other descriptives provided.	*Chest radiation vs no radiation.* OR 1.2 95% CI 0.5-2.7. *Radiation to other fields vs no radiation.* OR 1.2 95% CI 0.4-2.6.	SB: High risk AB: Low risk DB: Unclear CF: Low risk

GRADE assessment:		
Study design:	+4	Observational study.
Study limitations:	-1	Some limitations: selection bias high in 1/1; attritition bias low in 1/1; detection bias unclear in 1/1; counfounding low in 1/1.
Consistency:	0	Not applicable (1 study).
Directness:	0	Results are direct, population and outcomes broadly generalizable.
Precision:	-1	Some imprecision: only one study performed but narrow CIs.
Publication bias:	0	Unlikely.
Effect size:	0	No large magnitude of effect.
Dose-response:	0	Unclear if dose response relationship.
Plausible confounding:	0	No plausible confounding.
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		No significant association between radiotherapy to other fields and METS in CAYA cancer survivors. (1 study, not significant, 8599 participants, 113 events).

PICO 3e. No studies identified that evaluated the effect of radiotherapy dose on METS in CAYA cancer survivors.

PICO 4. No studies identified that evaluated the effect of hormonal therapy on METS in CAYA cancer survivors.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	HSCT	METS definition used	Effect size	Risk of bias
Who needs surveillance? 5. Treated with stem cell transplantation. a. SCT and TBI. (N = 5 studies)	Chow, 2010	26 ALL survivors treated with HSCT and TBI. 48 ALL survivors treated without HSCT (chemotherapy, 10.4% also cranial RT).	Since HSCT median 6 yrs (1-13 yrs). Since diagnosis HSCT group median 10.5 yrs since dx (1-15 yrs). Since treatment for non-HSCT survivors median 10 yrs (3-18 yrs).	METS in survivors treated with HSCT and TBI (N=26 (35.1%)) vs METS in survivors treated without HSCT (N=48 (64.9%)).	≥2 cardiometabolic traits, IDF criteria. ≥3 cardiometabolic traits, IDF criteria. ≥2 cardiometabolic traits, NCEP ATP III criteria. ≥3 cardiometabolic traits, NCEP ATP III criteria. Total METS (≥3 IDF criteria) N=8 (27.3%). METS HSCT (≥3 IDF criteria) N=6 (23.1%). METS no HSCT (≥3 IDF criteria) N=2 (4.2%).	*HSCT+TBI vs no HSCT.* OR 5.13, 95% CI 1.54-17.15. *HSCT+TBI vs no HSCT.* OR 16.72, 95% CI 1.66-168.80. P < 0.01. *HSCT+TBI vs no HSCT.* OR 4.16, 95% CI 1.07-16.10. *HSCT+TBI vs no HSCT.* OR 22.99, 95% CI 1.41-373.65.	SB: High risk AB: Low risk DB: Unclear CF: Low risk
	Meacham, 2010	8599 survivors of childhood cancer.	Since diagnosis >5 yrs (mean/median not reported).	METS in survivors treated with TBI, N=99 (1.2%)) vs METS in survivors treated without radiation (N=2740 (31.9%)).	Having at least 3 of the following 4 risk factors – obesity, hypertension, dyslipidemia, and diabetes mellitus or impaired glucose tolerance. METS total N=113. No other descriptives provided.	*HSCT + TBI vs no radiation.* OR 5.5 95% CI 1.5-15.8.	SB: High risk AB: Low risk DB: Unclear CF: Low risk

	Oudin, 2011	184 ALL/AML survivors.	Mean 15.4 yrs (3.4-30.2 yrs).	METS in survivors treated with SCT and TBI (N=43 (23.4%)) vs METS in survivors treated with chemotherapy only (N=97 (52.7%)).	NCEP ATP III criteria. Total METS N=17 (9.2%). METS SCT and TBI N=8 (18.6%). METS chemotherapy only N=5 (5.2%).	*HSCT+TBI vs chemotherapy only.* OR 3.9 95% CI 1.1-13.3. P = 0.03.	SB: Unclear AB: Low risk DB: Unclear CF: Low risk
	Oudin, 2015	170 childhood ALL survivors treated with HSCT.	Since HSCT mean follow-up 14.5 years (±6.1).	METS in survivors TBI (N=124 (72.9%)) vs METS in survivors treated without TBI (N=46 (27.1%)).	NCEP ATP III criteria. METS total N=29 (17.1%). No other descriptives provided.	*HSCT + TBI vs no TBI.* OR 1.47 95% CI 0.50–4.27. P = 0.48.	SB: Unclear AB: Low risk DB: Unclear CF: Low risk
	Oudin, 2018	1025 ALL/AML survivors.	Mean since diagnosis 16.32 ± 0.21 years.	METS in survivors with SCT and TBI (N=168 (16.4%) vs matched controls (N=3203)	NCEP ATP III criteria (2005 version). Total METS survivors N=106 (10.3%). Total METS controls N=145 (4.5%). METS SCT and TBI N=39 (23.3)%	*HSCT+TBI vs matched controls.* OR=6.26, 95%CI: 4.17-9.36. P<0.001.	SB: Unclear AB: High risk DB: Unclear CF: High risk

GRADE assessment:

Study design:	+4	Observational studies.
Study limitations:	-1	Some limitations: selection bias unclear in 3/5, high in 2/5; attritition bias high in 1/5, low in 4/5; detection bias unclear in 5/5; confounding low in 4/5, high in 1/5.
Consistency:	0	No important inconsistency: all significant results show increased risk of METS in CAYA cancer survivors after HSCT + TBI.
Directness:	0	Results are direct, population and outcomes broadly generalizable.
Precision:	-1	Some imprecision; CI intervals of significant results are wide, although high number of participants and events.
Publication bias:	0	Unlikely.
Effect size:	+1	Large magnitude of effect for all significant results.
Dose-response:	0	Unclear if dose response relationship.

Plausible confounding:	0	No plausible confounding.
Quality of evidence:		⊕⊕⊕⊖ MODERATE
Conclusion:		Increased risk of METS in CAYA cancer survivors treated with a combination of HSCT and TBI vs. no HSCT, chemotherapy only or matched controls. (5 studies, 4 significant, 10.052 participants, 273 events (in survivors)).
Comments:		Different definitions of METS used.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	HSCT	METS definition used	Effect size	Risk of bias
Who needs surveillance? 5. Treated with stem cell transplantation. b. SCT without TBI. (N = 2 studies)	Oudin, 2011	184 ALL/AML survivors.	Mean 15.4 yrs (3.4-30.2 yrs).	METS in survivors treated with SCT and without TBI (N=17 (9.2%)) vs survivors treated with chemotherapy only (N=97 (52.7%)).	NCEP ATP III criteria. Total METS N=17 (9.2%). METS SCT without TBI N=1 (5.9%). METS chemotherapy only N=5 (5.2%).	*SCT (without TBI) vs chemo only.* OR 1.1 95% CI 0.1-14.1. P = 0.96.	SB: Unclear AB: Low risk DB: Unclear CF: Low risk
	Oudin, 2018	1025 ALL/AML survivors. 3203 age- and sex-matched controls.	Mean since diagnosis 16.32 ± 0.21 years.	METS in survivors with SCT and without TBI (N=77 (7.5%)) vs matched controls (N=3203).	NCEP ATP III criteria (2005 version). Total METS survivors N=106 (10.3%). Total METS controls N=145 (4.5%). No other descriptives provided. METS SCT and no TBI N=7 (9.1%).	*SCT (without TBI) vs matched controls.* OR=2.18, 95%CI: 0.97-4.86. P=0.057.	SB: Unclear AB: High risk DB: Unclear CF: High risk

GRADE assessment:		
Study design:	+4	Observational studies.
Study limitations:	-1	Some limitations: selection bias unclear in 2/2; attritition bias high in 1/2, low in 1/2; detection bias unclear in 2/2; counfounding low in 1/2, high in 1/2.
Consistency:	0	No important inconsistency (both studies non-significant results).
Directness:	0	Results are direct, population and outcomes broadly generalizable.
Precision:	-1	Some imprecision: wide CIs.
Publication bias:	0	Unlikely.

Effect size:	0	No significant effect.
Dose-response:	0	N/A.
Plausible confounding:	0	No plausible confounding.
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		No significant association between HSCT without TBI and METS in CAYA cancer survivors. (2 studies, not significant, 1209 participants, 123 events (in survivors)).

PICO 6. No studies identified that evaluated the effect of surgery on METS in CAYA cancer survivors.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Steroids	METS definition used	Effect size	Risk of bias
Who needs surveillance? 7. Treated with steroids: a. Is type of steroids, dose or potency relevant? (N = 3 studies)	Oudin, 2015	170 childhood ALL survivors treated with HSCT.	Since HSCT mean follow-up 14.5 years (±6.1).	METS and each additional 500 mg/m2 steroid dose post HSCT.	NCEP ATP III criteria. METS total N=29 (17.1%). No other descriptives provided.	*Each additional 500 mg/m2 steroid dose.* OR 0.99 95% CI 0.97–1.01. P = 0.44. Type of steroids not specified.	SB: Unclear AB: Low risk DB: Unclear CF: Low risk
	Nottage, 2014	784 ALL survivors.	Median 26.1 yrs (11-45.3 yrs) survival time.	METS and cumulative prescribed prednisone-equivalent dose (100 mg/m2).	NCEP ATP III criteria Total METS N=259 (33.6%). No other descriptives provided.	*Each additional 100 mg/m2 prednisone-equivalent dose.* RR 0.99 95% CI 0.97-1.01.	SB: High risk AB: Low risk DB: Unclear CF: Low risk
GRADE assessment:							
Study design:	+4	Observational studies.					
Study limitations:	-1	Some limitations: selection bias high in 1/2, unclear in 1/2; attritition bias low in 2/2; detection bias unclear in 2/2; counfounding low in 2/2.					
Consistency:	0	No important inconsistency: no significant result showing increased risk of METS in CAYA cancer survivors after steroids.					
Directness:	0	Results are direct, population and outcomes broadly generalizable.					
Precision:	0	No important imprecision: no significant effects.					
Publication bias:	0	Unlikely.					
Effect size:	0	No large magnitude of effect.					
Dose-response:	0	Unclear if dose response relationship.					
Plausible confounding:	0	No plausible confounding.					

Quality of evidence:	⊕⊕⊕⊖ MODERATE
Conclusion:	No significant association between steroids and METS in CAYA cancer survivors. (2 studies, none significant, 954 participants, 288 events).
Comments:	…

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Gender	METS definition used	Effect size	Risk of bias
Who needs surveillance? 8. Does the risk of METS in CAYA cancer survivors differ between sexes? (N = 4 studies)	Meacham, 2010	8599 survivors of childhood cancer.	Since diagnosis >5 yrs (mean/median not reported).	METS in female survivors vs male survivors (descriptives not provided).	Having at least 3 of the following 4 risk factors – obesity, hypertension, dyslipidemia, and diabetes mellitus or impaired glucose tolerance. Total METS N=113. No other descriptives provided.	*Females vs males.* OR 0.8 95% CI 0.5-1.2.	SB: High risk AB: Low risk DB: Unclear CF: Low risk
	Oudin, 2015	170 childhood ALL survivors treated with HSCT.	Since HSCT mean follow-up 14.5 years (±6.1).	METS in female survivors (N=78 (45.9%)) vs METS in male survivors (N=92 (54.1%)).	NCEP ATP III criteria. METS total N=29 (17.1%). No other descriptives provided.	*Females vs males.* OR 1.95, 95% CI 0.8-4.89. P = 0.15.	SB: Unclear AB: Low risk DB: Unclear CF: Low risk
	Oudin, 2011	184 ALL/AML survivors. Males (51.6%). Females (48.4%).	Mean 15.4 yrs (3.4-30.2 yrs).	METS in male survivors (N=8 (8.4%)) vs female survivors (N=9 (10.1%)).	NCEP ATP III criteria. Total METS N=17 (9.2%). Female METS N=9 (10.1%). Male METS N=8 (8.4%).	*Males vs females.* OR 0.7 95% CI 0.2-2.0. P=0.48.	SB: Unclear AB: Low risk DB: Unclear CF: Low risk
	Saultier, 2016	650 childhood ALL survivors treated without HSCT.	Since diagnosis mean follow-up 16.00 (±6.79) yrs.	METS in male survivors vs female survivors.	NCEP ATP III criteria. METS total N=45 (6.9%). No other descriptives provided.	*Males vs females.* OR 2.64; 95% CI 1.32-5.29. P=0.006.	SB: Low risk AB: Low risk DB: Unclear CF: Low risk
GRADE assessment: Study design:	+4	Observational studies.					

Study limitations:	-1	Some limitations: selection bias low in 1/4, high in 1/4, unclear in 2/4; attritition bias low in 4/4; detection bias unclear in 4/4; counfounding low in 4/4.
Consistency:	-1	Some inconsistency: 1 significant effect vs 3 unsignificant effects.
Directness:	0	Results are direct, population and outcomes broadly generalizable.
Precision:	-1	Some imprecision: only 1 significant effect.
Publication bias:	0	Unlikely.
Effect size:	0	No large magnitude of effect.
Dose-response:	0	N/A.
Plausible confounding:	0	No plausible confounding.
Quality of evidence:		⊕⊖⊖⊖ VERY LOW
Conclusion:		Increased risk of METS in male versus female CAYA cancer survivors. (4 studies, 1 significant, 6.903 participants, 204 events).
Comments:		Different definitions of METS used.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Age at treatment	METS definition used	Effect size	Risk of bias
Who needs surveillance? 9. Does the risk of METS in CAYA cancer survivors depend on the age at diagnosis / treatment? (N = 2 studies)	Oudin, 2015	170 childhood ALL survivors treated with HSCT.	Since HSCT mean follow-up 14.5 years (±6.1).	METS and age at HSCT.	NCEP ATP III criteria. METS total N=29 (17.1%). No other descriptives provided.	No significant association (data not shown).	SB: Unclear AB: Low risk DB: Unclear CF: Low risk
	Meacham, 2010	8599 survivors of childhood cancer. Controls: 2936 matched siblings.	Since diagnosis >5 yrs (mean/median not reported).	Age at diagnosis: <5yrs (N=3573 (41.6%)) vs 15-20 yrs (N=1396 (16.2%)). 5-9 yrs (1940 (22.6%)) vs 15-20 yrs. 10-14 yrs (N=1690 (19.7%)) vs 15-20 yrs.	Having at least 3 of the following 4 risk factors – obesity, hypertension, dyslipidemia, and diabetes mellitus or impaired glucose tolerance. Total METS N=113. No other descriptives provided.	*<5yrs vs 15-20 yrs.* OR 1.3 95% CI 0.6-3.0. *5-9 yrs vs 15-20 yrs.* OR 1.3 95% CI 0.6-2.6. *10-14 yrs vs 15-20 yrs.* OR 1.2 95% CI 0.7-2.2.	SB: High risk AB: Low risk DB: Unclear CF: Low risk

GRADE assessment:		
Study design:	+4	Observational studies.
Study limitations:	-1	Some limitations: selection bias high in 1/2, unclear in 1/2; attritition bias low in 2/2; detection bias unclear in 2/2; counfounding low in 2/2.
Consistency:	0	No important inconsistency: both studies unsignificant.
Directness:	0	Results are direct, population and outcomes broadly generalizable.
Precision:	0	No important imprecision; large study group and number of events.
Publication bias:	0	Unlikely.
Effect size:	0	No large effect size.
Dose-response:	0	Unclear if 'dose' response relationship.
Plausible confounding:	0	No plausible confounding.
Quality of evidence:		⨁⨁⨁⨀ MODERATE
Conclusion:		No significant association between age at diagnosis or HSCT and METS in CAYA cancer survivors. (2 studies, not significant, 8.769 participants, 142 events).

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Gonadal hormone status	METS definition used	Effect size	Risk of bias
Who needs surveillance? 10. What is the evidence that endocrine abnormalities affect the risk of metabolic syndrome in CAYA cancer survivors? a. Gonadal hormone status (N = 2 studies)	Bandak, 2017	158 testicular cancer survivors.	Mean 9.7 yrs (4.1-17.1 yrs)	Total testosterone METS 9.8 (7.6-11.7) vs no METS 12.9 (10.4-15.7). Free testosterone METS 211 (177-278) vs no METS 258 (195-305).	IDF criteria Total METS N=35 (22%). No other descriptives provided.	*(Higher) TT levels and METS.* Age adjusted OR 0.81, 95% CI 0.72-0.91, P=0.001 *(Higher) free T levels and METS.* Age adjusted OR 0.995, 95% CI 0.990-1.000, P=0.08	SB: Unclear AB: Low risk DB: Unclear CF: Low risk
	Lopez, 2021	255 childhood leukemia survivors.	Not reported	METS in CCS with testosterone deficiency vs CCS with normal Leydig cell function METS in CCS with partial testosterone deficiency vs CCS with normal Leydig cell function	NCEP ATP III criteria. METS = 25% in CCS with testosterone deficiency (N~33) METS = 12.1% in CCS with partial	*METS in CCS with testosterone deficiency vs normal Leydig cell function* OR = 2.909, P=0.05 (not significant) *METS in CCS with partial testosterone deficiency vs normal Leydig cell function* not significant (data not shown)	SB: Unclear AB: Low risk DB: Unclear CF: Low risk

			testosterone deficiency (N~5) METS = 8.8% in CCS with normal Leydig cell function (N~7)
GRADE assessment:			
Study design:	+4	Observational studies.	
Study limitations:	-1	Limitations unclear: selection bias unclear in 2/2; attritition bias low in 2/2; detection bias unclear in 2/2; counfounding low in 2/2.	
Consistency:	0	No important inconsistency.	
Directness:	0	Results are direct, population and outomes broadly generalizable.	
Precision:	-1	Some imprecision: only 1 significant effect.	
Publication bias:	0	Unlikely.	
Effect size:	0	No large magnitude of effect.	
Dose-response:	0	Unclear if dose response relationship.	
Plausible confounding:	0	No plausible confounding.	
Quality of evidence:		⊕⊕⊖⊖⊖ LOW	
Conclusion:		Increased risk of METS in TC survivors with lower but not necessarily abnormal total testosterone levels. (2 studies, 1 significant, 413 participants, 80 events).	

PICO 10b. No studies identified that evaluated the effect of thyroid hormone deficiency or excess on METS in CAYA cancer survivors.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Growth hormone / pituitary hormone deficiency or excess	METS definition used	Effect size	Risk of bias
Who needs surveillance? 10. What is the evidence that endocrine abnormalities affect the risk of metabolic syndrome in CAYA cancer survivors?	Friedman, 2017	123 childhood leukemia/lymphoma survivors treated with HSCT and TBI.	Since TBI mediam 8.0 yrs (1.01-24.6 yrs).	METS in survivors with GH deficiency (N=27 (22.0%)) vs METS in survivors without GH deficiency (N=96 (78.0%)). 18/27 survivors elected to receive treatment for GH deficiency.	CVRF cluster (as surrogate for METS, ≥3 IDF criteria). Total METS in survivors N=35 (no other descriptives provided).	*GH deficiency vs no GH deficiency.* HR 8.6, 95% CI 2.1-34.4. P = 0.002.	SB: Unclear AB: Low risk DB: Unclear CF: Low risk

c. Growth hormone or other pituitary hormone deficiencies or excess (N = 1 study)		
GRADE assessment:		
Study design:	+4	Observational study.
Study limitations:	-1	Some limitations: selection bias unclear in 1/1; attritition bias low in 1/1; detection bias unclear in 1/1; counfounding low in 1/1.
Consistency:	0	N/A (1 study performed).
Directness:	0	Results are direct, population and outcomes broadly generalizable.
Precision:	-2	Important imprecision: only one study performed and very wide CI.
Publication bias:	0	Unlikely.
Effect size:	+1	Large magnitude of effect.
Dose-response:	0	Unclear if 'dose' response relationship.
Plausible confounding:	0	No plausible confounding.
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		Increased risk of METS in CAYA cancer survivors with GH deficiency vs without GH deficiency. (1 study, 1 significant, 123 participants, 27 events).

PICO 10d. No studies identified that evaluated the effect of treatment of endocrine abnormalities on METS in CAYA cancer survivors.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Lifestyle factor	METS definition used	Effect size	Risk of bias
Who needs surveillance? 11. Is the risk of METS in CAYA cancer survivors associated with lifestyle factors? a. Smoking, physical activity, diet? I. Smoking.	Meacham, 2010	8599 survivors of childhood cancer. Controls: 2936 matched siblings.	Since diagnosis >5 yrs (mean/median not reported).	METS in former smoker (N=1156 (13.7%)) vs never smoker (N=5859 (69.6%)). METS in current smoker (N=1402 (16.7%)) vs never smoker.	Having at least 3 of the following 4 risk factors – obesity, hypertension, dyslipidemia, and diabetes mellitus or impaired glucose tolerance. Total METS N=113. No other descriptives provided.	*Former smoker vs never smoker.* OR 0.9 95% CI 0.5-1.6. *Current smoker vs never smoker.* OR 1.1 95% CI 0.6-1.9.	SB: High risk AB: Low risk DB: Unclear CF: Low risk

(N = 1 study)		
GRADE assessment:		
Study design:	+4	Observational study.
Study limitations:	-1	Some limitations: selection bias high in 1/1; attritition bias low in 1/1; detection bias unclear in 1/1; confounding low in 1/1.
Consistency:	0	N/A (1 study performed).
Directness:	0	Results are direct, population and outcomes broadly generalizable.
Precision:	-1	Only 1 study performed yet narrow CIs and high number of events.
Publication bias:	0	Unlikely.
Effect size:	0	No large magnitude of effect.
Dose-response:	0	Unclear if dose response relationship.
Plausible confounding:	0	No plausible confounding.
Quality of evidence:		⨁⨁⨀⨀ LOW
Conclusion:		No significant association between smoking and METS in CAYA cancer survivors. (1 study, not significant, 8599 participants, 113 events).

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Lifestyle factor	METS definition used	Effect size	Risk of bias
Who needs surveillance? 11. Is the risk of METS in CAYA cancer survivors associated with lifestyle factors? a. Smoking, physical activity, diet? II. Physical activity. (N = 1 study)	Meacham, 2010	8599 survivors of childhood cancer. Controls: 2936 matched siblings.	Since diagnosis >5 yrs (mean/median not reported).	METS and sedentary lifestyle N=1950 (22.7%) vs no sedentary lifestyle N=7=6616 (77.0%) (unknown N=33 (0.3%)).	Having at least 3 of the following 4 risk factors – obesity, hypertension, dyslipidemia, and diabetes mellitus or impaired glucose tolerance. Total METS N=113. No other descriptives provided.	*Sedentary lifestyle vs no sedentary lifestyle.* OR 1.7 95% CI 1.1-1.6.	SB: High risk AB: Low risk DB: Unclear CF: Low risk
	Tonorezos, 2013	118 ALL survivors.	Since treatment mean 17.5 years.	Physical energy expenditure and METS.	NCEP ATP III (2001). Total METS N=21 (17.8%).	Inclusion of PAEE in the logistic regression models did not alter the findings (i.e., no significant effect on development of METS).	SB: Unclear AB: Low risk DB: Unclear CF: High risk
GRADE assessment:							

Study design:	+4	Observational study.
Study limitations:	-1	Some limitations: selection bias high in 1/2, unclear in 1/2; attritition bias low in 2/2; detection bias unclear in 2/2; confounding high in 1/2, low in 1/2.
Consistency:	0	N/A (1 study performed).
Directness:	0	Results are direct, population and outcomes broadly generalizable.
Precision:	-1	Some imprecision: only 1 significant effect yet narrow CIs and high number of events.
Publication bias:	0	Unlikely.
Effect size:	0	No large magnitude of effect.
Dose-response:	0	Unclear if dose response relationship.
Plausible confounding:	0	No plausible confounding.
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		Increased risk of METS in CAYA cancer survivors who have a sedentary lifestyle vs no sedentary lifestyle. (2 studies, 1 significant, 8.717 participants, 134 events).
Comments:		Different definitions of METS used.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Lifestyle factor	METS definition used	Effect size	Risk of bias
Who needs surveillance? 11. Is the risk of METS in CAYA cancer survivors associated with lifestyle factors? a. Smoking, physical activity, diet? III. Diet. (N = 1 study)	Tonorezos, 2013	118 ALL survivors.	Since treatment mean 17.5 years.	METS in survivors with Mediterranean diet score 4-5 vs 0-3. METS in survivors with Mediterranean diet score 6-8 vs 0-3.	NCEP ATP III (2001). Total METS N=21 (17.8%).	*4-5 vs 0-3.* OR 0.9, 95% CI 0.3-2.7. *6-8 vs 0-3.* OR 0.1, 95% CI 0.01-0.9.	SB: Unclear AB: Low risk DB: Unclear CF: High risk

GRADE assessment:		
Study design:	+4	Observational study.
Study limitations:	-1	Some limitations: selection bias unclear in 1/1; attritition bias low in 1/1; detection bias unclear in 1/1; confounding high in 1/1.
Consistency:	0	N/A (1 study performed).
Directness:	0	Results are direct, population and outcomes broadly generalizable.
Precision:	-1	Some imprecision: only 1 study performed yet narrow CIs and moderate number of events.
Publication bias:	0	Unlikely.
Effect size:	0	No large magnitude of effect.
Dose-response:	0	Unclear if dose response relationship.

Plausible confounding:	0	No plausible confounding.
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		Decreased risk of METS in CAYA cancer survivors who have a diet that highly resembles a Mediterranean diet vs a diet that does not resemble a Mediterranean diet. (1 study, 1 significant, 118 participants, 21 events).

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Lifestyle factor	METS definition used	Effect size	Risk of bias
Who needs surveillance? 11. Is the risk of METS in CAYA cancer survivors associated with lifestyle factors? a. Smoking, physical activity, diet? IV. Adherence to lifestyle guidelines. (N = 1 study)	Smith, 2014	1639 survivors of childhood cancer.	Since diagnosis mean 25.6 (± 7.6) years.	METS in survivors that do not adhere to WCRF/AICR guidelines vs survivors that do adhere.	NCEP ATP III (2001). Total METS females N=258 (31.0%) and males N=262 (31.5%).	*No adherence vs adherence to guidelines, males.* RR 2.2, 95% CI 1.6-3.0. *No adherence vs adherence to guidelines, females.* RR 2.4, 95% CI 1.7-3.3.	SB: High risk AB: Low risk DB: Unclear CF: Low risk

GRADE assessment:		
Study design:	+4	Observational study.
Study limitations:	-1	Some limitations: selection bias high in 1/1; attritition bias low in 1/1; detection bias unclear in 1/1; confounding low in 1/1.
Consistency:	0	N/A (1 study performed).
Directness:	0	Results are direct, population and outcomes broadly generalizable.
Precision:	-1	Some imprecision: only 1 study performed yet narrow CIs and high number of events.
Publication bias:	0	Unlikely.
Effect size:	0	No large magnitude of effect.
Dose-response:	0	Unclear if dose response relationship.
Plausible confounding:	0	No plausible confounding.
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		Increased risk of METS in CAYA cancer survivors that do not adhere to lifestyle guidelines vs survivors that adhere to lifestyle guidelines. (1 study, significant, 1639 participants, 258 events).

PICO 11b. No studies identified that evaluated the effect of lifestyle interventions on METS in CAYA cancer survivors.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Pre-treatment factor	METS definition used	Effect size	Risk of bias
Who needs surveillance? 12. Is there a role of pre-treatment factors (e.g. birth weight, body weight status at diagnosis)? (N = 3 studies)	Oudin, 2015	170 childhood ALL survivors treated with HSCT.	Since HSCT mean follow-up 14.5 years (±6.1).	METS and one standard deviation higher BMI-z score at HSCT.	NCEP ATP III criteria. METS total N=29 (17.1%). No other descriptives provided.	*Higher BMI-z score.* OR 1.57 95% CI 1.18–2.08. P = 0.002.	SB: Unclear AB: Low risk DB: Unclear CF: Low risk
	Saultier, 2016	650 childhood ALL survivors treated without HSCT.	Since diagnosis mean follow-up 16.00 (±6.79) yrs.	METS and each additional BMI-z score unit at diagnosis.	NCEP ATP III criteria. METS total N=45 (6.9%). Obese without METS N=22 (3.7%), Obese with METS N=19 (45.2%).	*Higher BMI-z score.* OR 1.15 95% CI 1.01-1.32. P=0.037.	SB: Low risk AB: Low risk DB: Unclear CF: Low risk
	Nirmal, 2021	277 childhood ALL survivors.	Since treatment 5.4 years (2.1 to 18.5 years).	METS and one standard deviation higher BMI-z score at diagnosis	NCEP ATP III criteria. METS total N=14 (8.7%).	*Higher BMI-z score.* Not significant, data not reported.	SB: Unclear AB: Low risk DB: Unclear CF: High risk

GRADE assessment:		
Study design:	+4	Observational study.
Study limitations:	0	No important limitations: selection bias low in 1/3, unclear in 2/3; attrition bias low in 3/3; detection bias unclear in 3/3; confounding low in 2/3, high in 1/3.
Consistency:	0	No important inconsistency (2 significant effects, both in the same direction).
Directness:	0	Results are direct, population and outcomes broadly generalizable.
Precision:	0	No important imprecision, narrow CIs and moderate number of events.
Publication bias:	0	Unlikely.
Effect size:	0	No large magnitude of effect.
Dose-response:	0	Unclear if dose response relationship.
Plausible confounding:	0	No plausible confounding.
Quality of evidence:		⊕⊕⊕⊕ HIGH
Conclusion:		Increased risk of METS in CAYA cancer survivors with a higher versus lower BMI at primary cancer diagnosis. (3 studies, 2 significant, 1 unsignificant, 1.097 particpants, 88 events).

PICO 13. No studies identified that evaluated mortality related to METS in CAYA cancer survivors.

PICO 14. Clinical question (what is the effect of age at diagnosis on METS risk) combined with PICO 9.

PICO 1. No studies identified that evaluated the latency time to develop METS in CAYA cancer survivors.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Improvement/deterioration METS parameters	METS definition used	Effect size	Risk of bias
At what age or time from exposure should surveillance be initiated and at what frequency should surveillance be performed? 2. What is the likelihood of change (improvement or deterioration) of METS parameters in CAYA cancer survivors after cancer treatment? a. What is the timing of such change? (N = 3 studies)	Friedman, 2017[1]	123 childhood leukemia/lymphoma survivors treated with HSCT and TBI.	Since TBI median 8.0 yrs (1.01-24.6 yrs)	Cumulative incidence CVRF cluster 5 and 10 yrs post HSCT (with time point 0 = 1 yrs post TBI).	CVRF cluster (as surrogate for METS, ≥3 IDF criteria). Total METS in survivors N=35 (no other descriptives provided).	5 yr cum incidence 10.6%, 95% CI 5.6-17.5. 10 yr cum incidence 28.4%, 95% CI 18.8-38.7.	SB: Unclear AB: Low risk DB: Unclear
	Saultier, 2016	650 childhood ALL survivors treated without HSCT.	Since diagnosis mean follow-up 16.00 (±6.79) yrs.	Cumulative prevalence of METS at 20, 25, 30 and 35 yrs of age.	NCEP ATP III criteria. METS total N=45 (6.9%). No other descriptives provided.	*Cumulative prevalence* 20 yrs, 1.3% (95% CI 0.6-2.7). 25 yrs, 6.1% (95% CI 4.0-9.1). 30 yrs, 10.8% (95% CI 7.2-15.9). 35 yrs, 22.4% (95% CI 15.1-32.6).	SB: Low risk AB: Low risk DB: Unclear
	Oudin, 2018	1025 ALL/AML survivors.	Mean since diagnosis 16.32 ± 0.21 years.	Cumulative incidence of METS at 25 years and 30 years of age.	NCEP ATP III criteria (2005 version). Total METS survivors N=106 (10.3%).	*Cumulative incidence* 25 yrs: 7.86% (95%CI: 5.99-10.29). 30 yrs: 14.42% (95%CI: 11.22-18.43).	SB: Unclear AB: High risk DB: Unclear
GRADE assessment:							
Study design:	+4	Observational studies.					
Study limitations:	0	No important limitations: selection bias low in 1/3, unclear in 2/3; attrition bias high in 1/3, low in 2/3; detection bias unclear in 3/3.					
Consistency:	0	No important inconsistency: all results show increasing prevalence/risk of METS over time.					

[1] Cumulative incidence over time presented in graph by Friedman, 2017, Oudin, 2015 and Oudin, 2018.

Directness:	0	Results are direct, population and outcomes broadly generalizable.
Precision:	0	No important imprecision.
Publication bias:	0	Unlikely.
Effect size:	0	No large magnitude of effect.
Dose-response:	0	Unclear if 'dose' response relationship.
Plausible confounding:	0	No plausible confounding.
Quality of evidence:		⨁⨁⨁⨁ HIGH
Conclusion:		The cumulative incidence of METS increases over time. (3 studies, 1.798 participants, 186 events).
Comments:		Different definitions of METS used.