Evidence tables used for extracting the data from included studies of the surveillance recommendations of cancer-related fatigue in childhood, adolescent and young adult cancer survivors.

1. What is the **risk and what are risk factors for suffering from Fatigue** in CAYA survivors?				
Ho et al. Psychometric properties of the Chinese version of the fatigue scale-adolescent. 2015				
Study Design **Treatment era** **Years of follow-up** **Fatigue measurement**	**Participants**	**Treatment**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Cross-sectional study **Treatment era:** n.a. **Years of follow-up:** 62% (n=124) have ≥25 months since treatment completed; n=37 (18.5%) 13-24 months; n=39 (19.5%) 6-12 months. **Fatigue measurement:** Fatigue-scale adolescent (FS-A) **Country:** Hong Kong, China	**Sample size:** N=200 adolescent cancer survivors (CCS) N=50 adolescent cancer patients (ACP) **Diagnoses:** • Leukemia n=91 (45.5%) • Lymphoma n=57 (28.5%) • Brain tumor n=33 (16.5%) • Osteosarcoma n=9 (4.5%) • Kidney tumor n=4 (2.0%) • Germ-cell tumor n=6 (3.0%) **Age at diagnosis:** Not available **Age at study:** N=200 CCS: 13-14 years: n=48 (24%) 15-16 years: n=70 (35%) 17-18 years: n=82 (41%) N=50 ACP: 13-14 years: n=13 (26%) 15-16 years: n=18 (36%) 17-18 years: n=19 (38%) **Controls:** N=50 healthy controls (age at study): 13-14 years: n=15 (30%) 15-16 years: n=18 (36%) 17-18 years: n=17 (34%)	ACS: • Surgery n=23 (11.5%) • Chemotherapy n=90 (45%) • Bone Marrow Transplant n=22 (11%) • Mixed: ○ Chemo & radio n=12 (6%) ○ Surgery & chemo n=19 (9.5%) ○ Chemo & bone marrow transplantation n=23 (11.5%) ○ Radio & surgery n=11 (5.5%) ACP: • Surgery n=5 (10%) • Chemotherapy n=22 (44%) • Bone Marrow Transplant n=5 (10%) • Mixed: ○ Chemo & radio n=3 (6%) ○ Surgery & chemo n=5 (10%) ○ Chemo & bone marrow transplantation n=7 (14%) ○ Radio & surgery n=3 (6%)	**Risk:** CCS: mean level of fatigue 28.6 (SD 3.7). ACP: mean level of fatigue 31.3 (SD 5.2) Healthy controls: mean level of fatigue 22.1 (SD 4.8; p<0.001 compared to ACS) **Risk factors:** We do not extract risk factors, as this study did not perform a multivariable analysis.	Selection bias: 0 Convenience sample of 200 survivors. Attrition bias: 1 All answered the fatigue questionnaire. Detection bias: 0 Questionnaire survey, no blinding possible. Confounding: 0 Multivariable analysis were not used. **Total quality: 1/4**

1. What is the **risk and what are risk factors for suffering from Fatigue** in CAYA survivors?				
Macpherson et al. Exercise and Fatigue in Adolescent and Young Adult Survivors of Hodgkin Lymphoma: A Report from the Children's Oncology Group. 2015				
Study Design **Treatment era** **Years of follow-up** **Fatigue measurement**	**Participants**	**Treatment**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Retrospective cohort study with data from a RCT **Treatment era:** Not available **Years of follow-up:** End of therapy, 12 and 36 months post-therapy measurements. **Fatigue measurement:** No standardized measurement **Country:** USA	**Sample size:** N=103 **Diagnoses:** • Hodgkin Lymphoma **Age at diagnosis:** Mean age at dx: 15.46 years (13-21 years) **Age at study:** Not available **Controls:** No controls.	Protocol treatment arm: Rapid early responders: **Rapid early responders:** • ABVE-PC x 4, <CR, IFRT n=47 (45.6%) • ABVE-PC x 4, CR, IFRT n=15 (14.6%) • ABVE-PC x 4, CR, NO IFRT n=26 (25.2%) **Slow early responders:** • ABVE-PC x 4 + IFRT + DECA x 2 n= 10 (9.7%) • ABVE-PC x 4 + IFRT n=5 (4.9%)	**Risk:** "Amount of […] fatigue improved from end of therapy to 36 months post-therapy, although not significantly. Items (Scale 0 "very much so" to 4 "not at all") and means 36 months post-therapy: "felt tired" n=94 mean 2.73 (SD 1.18) "had trouble finishing tasks because tired quickly" n=93 mean 3.46 (SD 0.88) "needed to sleep during the day" n=94 mean 3.25 (SD 0.96) "frustrated by being too tired to do things he/she wanted to do" n=93 mean 3.54 (SD 0.90) "needed to limit social activities because of fatigue" n=94 mean 3.68 (SD 0.79) **Risk factors from generalized estimation equation, and adjusting for sex, age at diagnosis, stage at diagnosis, and protocol treatment arm:** • "[…] amount of exercise was not predictive of fatigue at end of therapy or at 12 or 36 months post-therapy (p>0.05)."	Selection bias: 0 Secondary analysis of data collected as a randomized controlled trial. There's no information on how the randomization was done. One inclusion criterion is "completed a self-report survey at end of treatment, 12 and 36 months" → then it's rather not representative Attrition bias: 1 N=93/103 responded fatigue questions at 36 months → 90.3% Detection bias: 0 Questionnaire survey, no blinding possible. Confounding: 1 Multivariable logistic regression was used to evaluate association with exercise. **Total quality 2/4**

1. What is the **risk and what are risk factors for suffering from Fatigue** in CAYA survivors?				
Daniel et al. Relationship between sleep problems and psychological outcomes in adolescent and young adult cancer survivors and controls. 2016				
Study Design **Treatment era** **Years of follow-up** **Fatigue measurement**	**Participants**	**Treatment**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Cohort study, convenience sample? **Treatment era:** n.a. **Years of follow-up:** on average 12.29 years since dx (range 4-23 years) **Fatigue measurement:** Health Knowledge Inventory, one question about fatigue **Country:** USA	**Sample size:** N=154 survivors **Diagnoses:** • Leukemia n=68 (44.8%) • Lymphoma n=32 (20.8%) • Solid tumor n=53 (34.4%) **Age at diagnosis:** ≤18 years **Age at study:** Mean age 20.08 years (SD 3.17) **Controls:** N=170 healthy AYA controls recruited at preventive or acute primary care appointments. Mean age at study 21.08 years (SD 3.43) p=0.007	**Treatment intensity:** • Least n=5 (4%) • Moderately n=72 (44%) • Very n=57 (36%) • Most intense n=26 (16%)	**Risk:** 40% of survivors reported fatigue problems, compared to 22% of controls. When adjusted for age and income, survivors reported significantly more fatigue compared to controls (OR=2.47, p=0.002). **Risk factors:** We do not extract risk factors, as this study did not perform a multivariable analysis.	Selection bias: 0 Unclear how large original cohort was. Attrition bias: 0 Unclear whether there was missing data or how many participants responded to T1 and T2. Detection bias: 0 Questionnaire survey, no blinding possible. Confounding: 1 Adjusted for age & income. **Total quality: 1/4**

1. What is the **risk and what are risk factors for suffering from Fatigue** in CAYA survivors?				
Barrera et al. Health related quality of life in adolescent and young adult survivors of lower extremity. 2012				
Study Design **Treatment era** **Years of follow-up** **Fatigue measurement**	**Participants**	**Treatment**	**Main outcomes**	**Quality assessment** **Remarks**

Study Design:
Cross-sectional study (Questionnaire survey)
 	
Treatment era:
N/ A
 	
Years of follow-up:
N/ A
 	
Fatigue measurement:
EORTC-QLQ-30
 	
Country:
Canada
	Sample size:
	n = 28
	
	Diagnoses:
	• Lower extremity bone tumors:
	  ○ Osteogenic sarcoma n=23 (82.1%)
	  ○ Ewing's sarcoma n=5 (17.9%)
	
	Age at diagnosis:
	6 – 16 years. Mean age 11.6 years
	
	Age at study:
	18 – 32 years. Mean age at study 25.1 years.
	
	Controls:
	No controls
	Reference scores for the EORTC-QLQ-C30 were obtained from Scott et al. (2008. EORTC QLQ-C30 reference values.) and represent average scores for cancer survivors under the age of 50.
		Limb salvage (LS) n=19:
		• Allograft fusion n=15 (53.6%)
		• Endoprosthesis n=4 (14.3%)
		
		Amputation (AMP) n=9:
		• Van Nes rotationsplasty n=6 (21.4%)
		• Amputation n=3 (10.7%)
			Risk:
			EORTC-QLQ-C30 Fatigue subscale: sample mean 18.65 (SD 20.30). reference score mean 33.9 (SD 26.1). → sign. less fatigue ($p<0.001$) in survivors than reference population.
			LS reported poorer HRQOL than AMP participants for […] fatigue (LS mean 22.81 (SD 18.69), AMP mean 9.88 (SD 21.83); $p=0.033$).
			Female survivors reported significantly more symptoms of Fatigue than male survivors (female: 26.19 (SD 22.05) vs. male: 11.11 (SD 15.71); $p=0.047$)
			Older survivors (≥26 years) reported more symptoms of Fatigue than younger survivors (≥26 years: 23.93 (SD 21.20) vs. ≤25 years: 14.07 (SD 19.00). However, this difference did not reach statistical significance ($p=0.206$).
			
			Risk factors:
			We do not extract risk factors, as this study did not perform a multivariable analysis.
				Selection bias: 0
				sample was identified primarily from the registry (POGONIS) of the Pediatric Oncology Group of Ontario – 70 survivors were eligible, 28 participated → 28/70=40%
				Attrition bias: 1
				28/28 answered the EORTC-QLQ-30 → 100%
				Detection bias: 0
				Questionnaire survey, no blinding possible.
				Confounding: 0
				No multivariate analyses.
				
				Total quality 1/ 4

1. What is the **risk and what are risk factors for suffering from Fatigue** in CAYA survivors?				
De Ruiter et al. Psychosocial profile of pediatric brain tumor survivors with neurocognitive complaints. 2016				
Study Design **Treatment era** **Years of follow-up** **Fatigue measurement**	**Participants**	**Treatment**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: part of the PRISMA study, a randomized placebo-controlled double-blind trial to investigate whether neurofeedback can improve neurocognitive functioning in PBTS **Treatment era:** Unclear. **Years of follow-up:** Mean: 6.98 (SD 3.57) **Fatigue measurement:** CIS (checklist individual strength) **Country:** The Netherlands	**Sample size:** N=82 participants **Diagnoses:** Brain tumors: • High grade: ○ Medulloblastoma n=12 ○ Supratentorial PNET n=8 ○ Ependymoma n=5 ○ Astrocytoma gr III n=5 ○ Germ cell tumor n=4 • Low grade: ○ Low grad glioma n=35 ○ Craniopharyngioma n=7 ○ Plexus papilloma n=6 **Age at diagnosis:** Mean: 6.87 (SD 3.77) **Age at study:** Mean: 13.85 (SD 3.15) **Controls:** N=43 siblings in the age range 8-18 years as control group for the fatigue outcome measure	• Radiotherapy n= 34 (42%) • Chemotherapy n=35 (43%) • Surgery n=72 (88%) (N=37 had surgery only) • Other n=2 (2%) • Biopsy only n=1 • CSF pressure relief only n=1	**Risk**: PBTS reported more concentration problems than the sibling control group ($p<0.01$, medium effect size). A trend toward decreased physical activity in PBTS compared to the sibling control group was found as well as a trend toward a higher total scale compared to the siblings ($p<0.05$, medium effect sizes), indicating more fatigue related problems. The PBTS did not differ from the siblings on subjective fatigue and motivation problems. Survivors had a higher total score of Fatigue (63.23 (SD 21.80) vs. controls: 51.76 (SD 21.88), $p=0.010$) and reported more concentration problems (subscale of the CIS) (19.09 (SD 7.78) vs. controls: 14.45 (SD 7.19), $p=0.003$) **Risk factors**: No risk factor analyses performed.	Selection bias: 0 N=249 eligible, 82 participated → 33% Attrition bias: 1 100% of survivors and 40/43=93% of siblings answered the CIS Detection bias: 0 Questionnaire survey, no blinding possible. Confounding: 0 Only univariate analyses. **Total quality: 1/4** As fatigue was only one of many parameters in a specifiy disease group results expected

1. What is the **risk and what are risk factors for suffering from Fatigue** in CAYA survivors?				
Berg et al. Participation and Self-Management Strategies of Young Adult Childhood Cancer Survivors. 2013				
Study Design **Treatment era** **Years of follow-up** **Fatigue measurement**	**Participants**	**Treatment**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: descriptive study using a survey approach (cross-sectional study) **Treatment era:** N/A **Years of follow-up:** 8.9 ± 4.9 years (range: 3–20) **Fatigue measurement:** Multiple sources for survey, no standardized Fatigue instrument **Country:** USA	**Sample size:** N=42 **Diagnoses:** • Leukemia n=16 (38%) • CNS n=7 (17%) • Lymphoma n=5 (12%) • Hodgkin's lymphoma n= 4 (9.5%) • Wilm's tumor n=4 (9.5%) • Sarcoma n=3 (7%) • Bone n=3 (7%) **Age at diagnosis:** 9.8 ± 5.4 years (range: 1–17) **Age at study:** 20.5 ± 1.8 years **Controls:** No	• Chemotherapy n=12 (28%) • Radiation n=2 (5%) • Chemotherapy/surgery n=6 (14%) • Radiation/surgery n=3 (7%) • Chemotherapy/radiation n=5 (12%) • Chemotherapy/surgery/ radiation n=14 (33%)	**Risk:** Eighty-eight percent (n=37) of the 42 responders struggled with at least one of the six late effects (memory, body image, fatigue, cognition, pain, depression). 22 survivors (52%) reported fatigue, and 8 (36%) reported their fatigue was severe enough to limit work activities. **Risk factors:** Not investigated.	Selection bias: 0 180 eligible, n=42 participants 42/180=23% Attrition bias: 1 42/42 answered late effects question Detection bias: 0 Blinding not possible. Confounding: 0 No multivariate analyses **Total quality 1/4**

1. What is the **risk and what are risk factors for suffering from Fatigue** in CAYA survivors?				
Hamre et al. High Prevalence of Chronic Fatigue in Adult Long-Term Survivors of Acute Lymphoblastic Leukemia and Lymphoma during Childhood and Adolescence. 2013a				
Study Design **Treatment era** **Years of follow-up** **Fatigue measurement**	**Participants**	**Treatment**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Cross-sectional study including mailed questionnaire and 2-day outpatient examination **Treatment era:** Diagnosed between 1970 and 2000 **Years of follow-up:** Survival for >=5 years, median observation time of 21.1 years (range: 6.9 – 39.4 years) **Fatigue measurement:** **11-item Chalder Fatigue Questionnaire (FQ)** **Country:** Norway	**Sample size:** 290 survivors and 1405 controls **Diagnoses:** Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), acute lymphoblastic leukemia (ALL) **Age at diagnosis:** Median age at diagnosis 9.5 years (range: 0.3 – 18.4 years) **Age at study:** Median age at study 29.6 years (18.3 – 54.5 years) **Controls:** Persons representative of the entire Norwegian population, median age at study 34.0 years (range: 19.0 – 50.0 years)	ALL: predominantly based on chemotherapy alone Lymphoma: included in most cases a combination of chemotherapy and radiotherapy, with large-field radiotherapy applied to patients with HL in the 1970s Details of the therapy are described elsewhere: • Moe PJ, Seip M, Finne PH. Intermediate dose methotrexate (IDM) in childhood acute lymphocytic leukemia in Norway. Preliminary results of a national treatment program. Acta Paediatr Scand. 1981;70(1):73–9. • Gustafsson G, Schmiegelow K, Forestier E, et al. Improving outcome through two decades in childhood ALL in the Nordic countries: the impact of high-dose methotrexate in the reduction of CNS irradiation. Nordic Society of Pediatric Haematology and Oncology (NOPHO). Leukemia. 2000; 14(12):2267–75. • Hamre H, Kiserud CE, Ruud E, et al. Gonadal function and parenthood 20 years after treatment for childhood lymphoma: a cross-sectional study. Pediatr Blood Cancer. 2012; 59(2):271–7.	**Risk:** 28% of survivors had CF, 8% of controls had CF (p<0.001) OR for having CF: adjusted OR=4.5 (3.1-6.4), p<0.001 (adjusted for age at study and sex) Risk highest among HL survivors (adjusted OR=5.9 (3.6-9.7), p<0.001), followed by NHL survivors (adjusted OR=4.4 (2.2-9.0), p<0.001) and ALL survivors (adjusted OR=3.6 (2.3-5.7), p<0.001) **Risk factors for chronic fatigue from multivariable logistic regression:** Whole sample of survivors (n=279). (partnership, education, BMI were n.s. in the univariable model and not included in the multivariable model) • NHL (vs. ALL): OR=1.5 (95% CI: 0.6-3.4), p=0.4 • HL (vs ALL): OR=1.7 (0.8-3.5), p=0.2 • Age at survey: OR=1.05 (1.0-1.1), p=0.1 • Treatment 1970-1985 (vs. Treatment after 1985): OR=0.8 (0.3-2.1), p=0.7 • Female (vs. Male): OR=0.8 (0.46-1.5), p=0.6 • Present hypothyroidism (vs. Thyroid status normal): OR=1.4 (0.7-3.0), p=0.4 • **HADS (Hospital Anxiety and Depression Scale) total score: OR=1.15 (1.1-1.2), p<0.001** Sub-analysis ALL survivors (n=148), multivariate (relapse, anthracyclines, radiotherapy, heart function and lung function were were n.s. in the univariable model and not included in the multivariable model): • **Age at survey: OR=1.1 (1.0-1.2), p=0.01** • Treatment 1970-1985 (vs. Treatment after 1985): OR=0.6 (0.2-2.1), p=0.4 • Female (vs. Male): OR=0.9 (0.4-2.1), p=0.8 Sub-analysis HL and NHL survivors (n=131), multivariable (relapse, disease stage, anthracyclines, radiotherapy, heart function and lung function were were n.s. in the univariable model and not included in the multivariable model): • Age at survey: OR=1.0 (0.9-1.1), p=0.5 • Treatment after 1985 (vs. Treatment 1970-1985): OR=0.6 (0.2-2.3), p=0.5 • Female (vs. Male): OR=0.9 (0.4-2.0), p=0.9 • B-symptoms Yes (vs. No): OR=2.5 (1.0-6.2), p=0.05 • B-symptoms Unknown (vs. No): OR=1.0 (0.3-2.7), p=0.9	Selection bias: 0 Survivors: response rate 65% → no Controls: persons representative of the entire Norwegian population → yes Attrition bias: 1 Outcome data for 96.2% of survivors → yes Detection bias: 0 Assessors were not blinded → no Confounding: 1 Adjusted OR and multivariate analyses → yes **Total quality 2/4** Abbreviations: CF: chronic fatigue

1. What is the **risk and what are risk factors for suffering from Fatigue** in CAYA survivors?				
Clanton et al. Fatigue, Vitality, Sleep, and Neurocognitive Functioning in Adult Survivors of Childhood Cancer. A Report from the Childhood Cancer Survivor Study. 2011				
Study Design **Treatment era** **Years of follow-up** **Fatigue measurement**	**Participants**	**Treatment**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Childhood Cancer Survivor Study (CCSS), retrospective cohort study **Treatment era:** Treated between 1970 and 1986 **Years of follow-up:** Survival for >=5 years, mean time since diagnosis 24.0 years (SD=4.7 years, range: 16.2 – 34.3 years) **Fatigue measurement:** Fatigue subscale of the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) **Country:** USA	**Sample size:** 1426 survivors and 384 sibling controls **Diagnoses:** Leukemia 14.0% CNS tumor 15.0% Hodgkin lymphoma (HL) 53.9% Other cancer 17.1% *Survivors of HL were oversampled to represent a majority of the cohort, given the increased rates of fatigue reported in this group* **Age at diagnosis:** Mean age at diagnosis 11.9 years (SD=5.6 years, range: 0 – 21 years) **Age at study:** Mean age at study 35.9 years (SD=7.5 years, range: 19.2 – 53.4 years) **Controls:** Randomly selected sibling controls	**Chemotherapy treatment** Alkylators 50.6% Anthracycline 28.5% Antimetabolite (IV) 18.6% Antimetabolite (IT) 55.8% Corticosteroids 38.0% Epipodophyllotoxin 3.2% **CRT** No CRT 21.7% CRT <20 Gy 54.6% CRT ≥20 Gy 14.1%	**Risk:** Cutoff score of ≥ highest 10% of siblings was used. 197 of 1426 survivors (13.8%) fatigued **Risk factors:** N/A	Selection bias: 0 Survivors of HL were oversampled to represent a majority of the cohort, given the increased rates of fatigue reported in this group; response rates not reported → unclear Attrition bias: 1 Fatigue assessed for the whole study sample → yes Detection bias: 0 Assessors not blinded → no Confounding: 0 Prevalence of fatigue not adjusted → no **Total quality 1/4** Abbreviations: CRT: cranial radiation therapy Gy: grays

1. What is the **risk and what are risk factors for suffering from Fatigue** in CAYA survivors?				
Berg et al. Late Effects of Childhood Cancer, Participation, and Quality of Life of Adolescents. 2009				
Study Design **Treatment era** **Years of follow-up** **Fatigue measurement**	**Participants**	**Treatment**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: 90-minute interview with the adolescents **Treatment era:** N/A **Years of follow-up:** Survivors >=2 years post-cancer intervention; mean time since diagnosis 7.2 years (SD=3.3 years) **Fatigue measurement:** Data gathered from a 90-minute interview with the adolescents; fatigue among late effects reported **Country:** USA	**Sample size:** 25 survivors **Diagnoses:** Acute lymphoblastic leukemia 56% Wilms tumor 16% Non-Hodgkin lymphoma 8% Hodgkin lymphoma 4% Neuroblastoma 4% Ewing sarcoma 4% Renal sarcoma 4% Rhabdomyosarcoma 4% **Age at diagnosis:** Mean age at diagnosis 5.2 years (SD=3.6 years) **Age at study:** Mean age at study 14.0 years (SD=2.2 years) **Controls:** No controls	Chemotherapy 44% Chemotherapy and radiation 20% Chemotherapy, radiation, and surgery 36%	**Risk:** 6 of 25 (24%) survivors reported fatigue (fatigue among late effects reported) **Risk factors:** N/A	Selection bias: 0 Convenience sample of survivors, contacted sample included the first 26 consecutive clinic patients who met the inclusion criteria; 96.2% of contacted survivors participated → no Attrition bias: 1 Outcome from all 25 participating survivors → yes Detection bias: 0 Assessors not blinded → no Confounding: 0 Prevalence of fatigue not adjusted → no **Total quality 1/4**

1. What is the **risk and what are risk factors for suffering from Fatigue** in CAYA survivors?				
Korinthenberg et al. Assessing Quality of Life in Long-Term Survivors after ^{125}I Brachytherapy for Low-Grade Glioma in Childhood. 2011				
Study Design **Treatment era** **Years of follow-up** **Fatigue measurement**	**Participants**	**Treatment**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Cross-sectional study (questionnaire survey) **Treatment era:** 1984-2003 **Years of follow-up:** Median: 134 months from ^{125}I brachytherapy (range 29-293 months) **Fatigue measurement:** EORTC QLQ-30 (only for survivors >18 years) **Country:** Germany	**Sample size:** N=51 (53.7% response rate) **Diagnoses:** Deep-seated low-grade gliomas: • Pilocytic astrocytoma WHO I (n=34) • fibrillary astrocytoma WHO II (n=7) • unspecified astrocytoma (n=3) • oligodendroglioma WHO II (n=3) • oligo-astrocytoma WHO II (n=1) **Age at diagnosis:** Median age of 8.3 years (range 1.5 – 17.7. years) at the time of radiosurgery **Age at study:** N=29 >18 years N= 18 11-17 years N=4 <11 years **Controls:**	Stereotactically-inserted temporary ^{125}I seeds 14 patients underwent repeated ^{125}I radiosurgery due to lack of response or secondary progression 14 patients had undergone treatment other than ^{125}I radiosurgery in the later course (9 surgery only, 2 external beam radiotherapy, 1 chemotherapy, 2 combination of surgery and radiotherapy)	**Risk:** EORTC QLQ-30 mean Fatigue score in n=28 survivors (>18 years): ~28% In the normal population: ~28.8% → Survivors score a bit lower, but not statistically significant. **Risk factors:** We do not extract risk factors, as this study did not perform a multivariable analysis.	Selection bias: 0 Original cohort n=156 CCS. Only 95 (60.9%) were included for the study. Attrition bias: 0 The response rate of the whole study group was 53.7%. Detection bias: 0 Questionnaire survey, no blinding possible. Confounding: 0 Only descriptive statistics and correlations used. **Total quality: 0/4**

1. What is the **risk and what are risk factors for suffering from Fatigue** in CAYA survivors?				
Geenen et al. Medical Assessment of Adverse Health Outcomes in Long-term survivors of childhood cancer. 2007				
Study Design **Treatment era** **Years of follow-up** **Fatigue measurement**	**Participants**	**Treatment**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Retrospective cohort study **Treatment era:** 1966-1996 **Years of follow-up:** Median follow-up time of 17.0 years (interquartile range 11.6-23.3 years) **Fatigue measurement:** No specific Fatigue measurement, but the "Common Terminology Criteria for Adverse Events version 3.0" **Country:** The Netherlands	**Sample size:** N=1284 (response rate: 94.3%) **Diagnoses:** • Leukemia n=335 (24.6%) • Lymphoma 259 (19.0) • Kidney/Wilms tumor 189 (13.9) • Brain/CNS tumor 107 (7.9) • Bone tumor 116 (8.5) • Soft tissue sarcoma 151 (11.1) • Neuroblastoma 85 (6.2) • Other 120 (8.8) **Age at diagnosis:** 0-4 years: 43.8% (n=596) 5-9 years: 27.8% (n=378) 10-14 years: 22.7% (n=309) 15-18 years: 5.8% (n=79) **Age at study:** Median age at end of follow-up: 24.4 years (n=1194 (88%) younger than 35 years). **Controls:**	• Chemotherapy only (with/without surgery): n=652 (47.9%) • Radiotherapy only (with/without surgery): n=93 (6.8%) • Chemotherapy + radiotherapy first treatment, no recurrence: n=334 (24.5%) • Chemotherapy + radiotherapy first treatment including recurrence treatment: n=180 (13.2%) • Surgery only: n=103 (7.6%)	**Risk:** N=131 (/1284=10.2%) suffer from Fatigue. Of those: n=25: Grade 1 n=98: Grade 2 (indicates moderate fatigue or that causing some difficulty performing some activities of daily living) n= 8: Grade 3/4/5 (Grade 3: severe fatigue interfering with activities of daily living; Grade 4: disabling fatigue) **Risk factors for fatigue in multivariable logistic regression analysis adjusted for follow-up duration and age at diagnosis:** • Female vs. male: RR 2.77 (95% CI 1.94-3.94) • Radiotherapy to head and/or neck vs. none: RR 1.76 (95% CI 1.14-2.71) • Radiotherapy to thorax and/or abdomen vs. none: 1.09 (95% CI 0.64-1.86) • Radiotherapy to head and/or neck and thorax and/or abdomen including craniospinal vs. none: RR 2.43 (95% CI 1.54-3.82) • Radiotherapy to extremities only vs. none: RR 0.99 (95% CI 0.40-2.44) • TBI* vs. none: RR 1.67 (95% CI 0.62-4.47) • Anthracyclines vs. none: RR 1.84 (95% CI 0.99-3.42) • Alkylating agents vs. none: RR 1.40 (95% CI 0.81-2.42) • Anthracyclines and alkylating agents vs. none: RR 1.33 (95% CI 0.75-2.37) • Other chemotherapy only vs. none: RR 1.31 (95% CI 0.74-2.30) • Surgery yes vs. no: RR 1.09 (95% CI 0.76-1.58) • *TBI=total body irradiation	Selection bias: 0 Original cohort consists of n=2596 patients. Only survivors who survived for at least 5 years were included in the study cohort. Attrition bias: 1 Response rate 94.3% Detection bias: 0 Questionnaire survey, no blinding possible. Confounding: 1 Multivariable logistic regression was used to evaluate treatment-related risk factors. **Total quality: 2/4**

1. What is the **risk and what are risk factors for suffering from Fatigue** in CAYA survivors?				
Sterkenburg et al. Survival, hypothalamic obesity, and neuropsychological/psychosocial status after childhood-onset craniopharyngioma: newly reported long-term outcomes. 2015				
Study Design **Treatment era** **Years of follow-up** **Fatigue measurement**	**Participants**	**Treatment**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Cross-sectional study, Questionnaire survey **Treatment era:** Diagnosed in the years: 1966-2000 **Years of follow-up:** Median follow-up time: **16.3 years (range 9.8-36.4)** **Fatigue measurement:** **Multidimensional Fatigue Inventory (MFI-20)** EORTC QLQ-C30 score **Country:** Germany	**Sample size:** N=108 **Diagnoses:** • Childhood-onset craniopharyngioma - n=52 (48%) with hypothalamic involvement (HI) - n=25 (23%) without HI n= 31 (29%) not specified **Age at diagnosis:** Median 8.1 years (range 0.05-18.8) **Age at study:** Median 24.8 years (range 14.8-42.7) **Controls:** Siblings, but not for Fatigue measurements (see remarks)	Degree of resection: • Total n=44 (41%) - n=21 (40%) with hypothalamic involvement (HI) - n=13 (52%) without HI • Subtotal n=54 (50%) - n=29 (56%) with HI - n=10 (40%) without HI Radiotherapy: • All n=36 (33%) - n=20 (38%) with HI - n=7 (28%) without HI Repeated surgery: • All n=23 (21%) - n=17 (33%) with HI - n=3 (12%) without HI	"In the MFI-20 questionnaire, participants with HI showed a higher score in the domains of physical fatigue (mean score of 9.7 vs. 7.2) and reduced motivation (mean score of 7.8 vs. 6.3). The scores of the other MFI-20 domains (general fatigue, reduced activity and mental fatigue) were comparable in CP participants with and without HI." **Risk EORTC QLQ-C30 score:** No HI involvement: median: ca. 21% (0%=no fatigue; 100%=very fatigued) HI involvement: median: ca. 37% (0%=no fatigue; 100%=very fatigued) **Risk MFI-20:** All five domains can have a score from 4-20. General Fatigue: • No HI involvement: Median: ca. 9 • HI involvement: Median: ca. 10 Physical Fatigue: (p=0.024 between HI-no HI) • No HI involvement: Median: 7.2 • HI involvement: Median: 9.7 Reduced activity: • No HI involvement: Median: ca. 6 • HI involvement: Median: ca. 8 Reduced motivation: (p=0.042 between HI-no HI) • No HI involvement: Median: ca. 5 • HI involvement: Median: ca. 7 Mental fatigue: • No HI involvement: Median: ca. 6 • HI involvement: Median: ca. 6.5 **Risk factors:** We do not extract risk factors, as this study did not perform a multivariable analysis.	Selection bias: 0 Patients were recruited from a multinational CP registry, but not clear whether that's population-based. Attrition bias: 0 Originally n=280 patients. N=165 were contacted (58.9%), n=108 participated in the FU survey (38.6%) Detection bias: 0 Questionnaire survey, no blinding possible. Confounding: 0 Only descriptive statistics used. **Total quality: 0/4** They had a sibling control group, but only for the psychosocial status questionnaire, not for the Fatigue outcomes.

1. What is the **risk and what are risk factors for suffering from Fatigue** in CAYA survivors?				
Khan et al. Neurologic morbidity and quality of life in survivors of childhood acute lymphoblastic leukemia: a prospective cross-sectional study. 2014				
Study Design **Treatment era** **Years of follow-up** **Fatigue measurement**	**Participants**	**Treatment**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Prospective, single institution, cross-sectional study **Treatment era:** **Years of follow-up:** Median time from diagnosis 10.2 years (range 5-22.7 years) **Fatigue measurement:** Criteria proposed by Cella et al. (Cella D, Davis K, Breitbart W, Curt G. Fatigue Coalition. Cancer-related fatigue: prevalence of proposed diagnostic criteria in a United States sample of cancer survivors. J Clin Oncol. 2001;19:3385-91. and Common Terminology Criteria for Adverse Events v4.0 (CTCAE) and The Brief Fatigue Inventory **Country:** USA	**Sample size:** N=162 **Diagnoses:** • Childhood acute lymphoblastic leukemia (ALL) **Age at diagnosis:** Median age at cancer diagnosis 3.9 years (range 0.4-18.6 years) **Age at study:** Median age at study enrollment 15.7 years (range 6.9-29.0 years) **Controls:**	Number of intrathecal chemotherapy doses (all participants received triple intrathecal therapy with cytarabine, methotrexate and hydrocortisone): 9-12: n=100 (61.7%) ≥13: n=62 (38.3%) CNS radiation: n=23 (14%) Intravenous methotrexate dose ≥5mg/m^2: n=25 (15%)	**Risk:** Fatigue was determined in 35 (21.6%) participants: 21 (13%) with mild (CTCAE grade-1), 11 (6.8%) with moderate (CTCAE grade-2), and 3 (1.8%) with severe fatigue (CTCAE grade-3). This was confirmed by examining scores on the Brief Fatigue Inventory where three participants scored in the severe range (mean score ≥7) and 12 had moderate fatigue (mean score >4). **Risk factors for fatigue from multivariate logistic regression analyses:** • History of leukemia relapse vs. none OR=8.35, 95% CI: 1.16-59.93, p<0.03 Unclear what other variables were included in the model, only history of leukemia relapse is reported.	Selection bias: 0 "An introductory letter was mailed to all potential participants" - unclear how large the original cohort was. Attrition bias: 0 N=432 met eligibility criteria., n=260 were approached to participate. N=162 participants (response rate 37%) Detection bias: 0 Questionnaire survey, no blinding possible. Confounding: 1 Multivariable analysis were used. **Total quality: 1/4**

1. What is the **risk and what are risk factors for suffering from Fatigue** in CAYA survivors?				
Calaminus et al. Quality of life in long-term survivors following treatment for Hodgkin's disease during childhood and adolescence in the German multicenter studies between 1978 and 2002. 2014				
Study Design **Treatment era** **Years of follow-up** **Fatigue measurement**	**Participants**	**Treatment**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Cross-sectional study; Questionnaire survey **Treatment era:** 1978-2002 **Years of follow-up:** Time (in years) since diagnosis: mean 15.26 (range 4.24-28.73) **Fatigue measurement:** EORTC QLQ-C30 **Country:** Germany	**Sample size:** N=725 **Diagnoses:** • Hodgkin's disease (HD) **Age at diagnosis:** Mean 13.63 years (standard deviation (SD) 3.09 years) **Age at study:** Mean 28.44 years (SD 5.21 years) **Controls:** The sample of HD survivors was compared to an age-adjusted sub-sample of the German norm population (all participants included were between 21 and 41 years, n=659) randomly drawn from a major population-based, representative norm group. Mean age at study: 32.69 years (SD 5.68 years)	Maximum dose radiotherapy: • None 30 (4.1%) • ≤20 Gy 167 (23.1%) • >20≤30 Gy 299 (41.2%) • >30 Gy 229 (31.6%) Chemotherapy cycles: • 0: 28 (3.9%) • 2: 334 (46.1%) • 3: 1 (0.1%) • 4: 155 (21.4%) • 6: 207 (28.7%)	**Risk:** Stratified by sex: Males: mean score survivors: 19.02 (SD 21.7) vs. controls 7.85 (SD14.6) Females: mean score survivors: 26.57 (SD 24.8) vs. controls 14.02 (SD 20.09) **Risk factors for fatigue from three-way factorial ANOVA test:** Not reported in detail.	Selection bias: 0 Original cohort: 2169 patients eligible. N=725 participated in the survey → <75%. Attrition bias: 0 Only n=725/2169 answered the fatigue question. Detection bias: 0 Questionnaire survey, no blinding possible. Confounding: 1 Three-way factorial ANOVA test **Total quality: 1/4**

1. What is the **risk and what are risk factors for suffering from Fatigue** in CAYA survivors?				
Yi et al. Perceived long-term and physical health problems after cancer: Adolescent and young adult survivors of childhood cancer in Korea. 2014				
Study Design **Treatment era** **Years of follow-up** **Fatigue measurement**	**Participants**	**Treatment**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Cross-sectional study, questionnaire survey **Treatment era:** **Years of follow-up:** Mean time since diagnosis 12.03 years (standard deviation (SD) 5.94 years; range 2-29 years) **Fatigue measurement:** Survivors could indicate whether they suffer from fatigue (yes/no) as one item of ten. SF-8 (Medical Outcomes Study Short Form-8) **Country:** Korea	**Sample size:** N=225 **Diagnoses:** • Hematological cancers n=159 (71.9%) • Solid or soft tissue tumors n=32 (14.5%) • CNS or brain tumors n=30 (13.6%) **Age at diagnosis:** Mean: 9.89 years (range 0-18 years) **Age at study:** Mean: 21.9 years (range 15-38 years) **Controls:**	Not reported.	**Risk:** Chronic fatigue: Yes 58/225 = 25.78% **Risk factors:** We do not extract risk factors, as this study did not perform a multivariable analysis.	Selection bias: 0 Patients were recruited through websites and support groups. Attrition bias: 1 All n=225 participants were included in the analysis. Detection bias: 0 Questionnaire survey, no blinding possible. Confounding: 1 Multivariate regression analyses were used, but not with Fatigue as the dependent variable. **Total quality: 2/4**

1. What is the **risk and what are risk factors for suffering from Fatigue** in CAYA survivors?				
Zeller et al. Chronic Fatigue in Long-term Survivors of Childhood Lymphomas and Leukemia: Persistence and Associated Clinical Factors. 2014				
Study Design **Treatment era** **Years of follow-up** **Fatigue measurement**	**Participants**	**Treatment**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Case-control study **Treatment era:** 1970-2002 **Years of follow-up:** Median 25.3 years (range 11.3-39.9) **Fatigue measurement:** **Fatigue Questionnaire (FQ)** **Country:** Norway	**Sample size:** Total n=62/102 **Diagnoses:** • Lymphoma n=33 • Acute lymphoblastic leukemia (ALL) n=29 **Age at diagnosis:** Not mentioned. **Age at study:** Mean 34.05 years **Years of follow-up:** Mean 23.5 years Controls did not differ from “cases” (with chronic fatigue (CF)) in sex, age at study, diagnosis, therapy, follow-up time	Radiation therapy: • CF: 43% • Controls: 57% Cum. Anthracycline dose (mg): • CF: mean 166.2 (SD 139.9) • Controls: 170.0 (SD 127.6)	**Risk:** No prevalence measure given, case-control study! FQ total score: CF: median 20.0 (range 13-32) Controls: median 10.5 (range 4-24) CF cases had significantly higher levels in FQ than controls (p<0.001) **Risk factors for persistent chronic fatigue (PCF) caseness from multiple logistic regression analysis:** • Insomnia: not significant • PHQ9 score: not significant • Pain severity score: not significant • Number of steps per day: not significant • Level of depressive symptoms (PHQ8 score) remained the only significant predictor of PCF (OR 1.3, 95%CI:1.1-1.7, p=0.014)	Selection bias: 0 Original cohort was 430 survivors, only 102 were included for this study. Attrition bias: 0 62/102 were analyzed. Detection bias: 0 Questionnaire survey, no blinding possible. Confounding: 1 Multivariate statistics were used. **Total quality: 1/4**

1. What is the **risk and what are risk factors for suffering from Fatigue** in CAYA survivors?				
McClellan et al. Understanding the functional late effects and informational needs of adult survivors of childhood cancer. 2013				
Study Design **Treatment era** **Years of follow-up** **Fatigue measurement**	**Participants**	**Treatment**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Descriptive, mixed methods survey - Questionnaires - Qualitative content analysis of additional information provided in the questionnaire. **Treatment era:** Not stated **Years of follow-up:** n.a. **Fatigue measurement:** No standardized fatigue measurement. **Country:** USA	**Sample size:** N=271 **Diagnoses:** • Grouped into: • Leukemia/lymphomas (48%) • Solid tumors (33%) • Brain tumors (19%) **Age at diagnosis:** Mean age 10 yrs (5.22 SD) **Age at study:** mean age of 24 years (18 to 38) **Controls:** none	Describe treatment intensity as defined by: ITR-2 (Werba et al.,2007) 92% received at a minimum moderately intense treatment 50% received higher intesity treatmetn, including relapse protocols or transplant	**Risk:** Main outcome: Number of late effects from a list compiled by the authors + late effects added in an open question option by the survivors. The overall incidence of fatigue in survivors in this sample was 30% but brain tumor survivors reported 47% **Risk factors:** Data was not extracted for the risk factors, because no multivariable analyses were done.	Selection bias: 1 response rate of 47.5%, convenience sample. Recruited from tumor registries at two US hospitals. Excluding those not receiving treatment from an oncologist. Attrition bias: 1 N=710 invited N = 139 unknown address N = 271% responded (47.5%) Higher response rate among non-Hispanic whites than blacks. Detection bias: 0 Not possible Confounding: 0 Only simple statistics and qualitative analyses done **Total quality: 2/4**

1. What is the **risk and what are risk factors for suffering from Fatigue** in CAYA survivors?				
Kanellopoulos et al. Factors Associated With Poor Quality of Life in Survivors of childhood Acute Lymphoblastic Leukemia and Lymphoma. 2013				
Study Design **Treatment era** **Years of follow-up** **Fatigue measurement**	**Participants**	**Treatment**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: - Questionnaire study - Recruited from hospital records **Treatment era:** NHL and HL: 1970-2000 ALL: 1970-2002 **Years of follow-up:** 21 years (range: 7–39 years) **Fatigue measurement:** **The fatigue questionnaire (FQ). (Chalders fatigue questionnaire)** **Country:** Norway	**Sample size:** N=285 **Diagnoses:** • N= 91 Hodgkin lymphoma (HL) • N=45 Non-Hodgkin (NHL) • N = 149 Acute lymphoblastic leukemia (ALL) **Age at diagnosis:** 10 years (range: 0–18 years) ALL patients being younger at diagnosis (median: 5, range: 0–16 years) than lymphoma patients (median: 14, range: 2–18 years) **Age at study:** 30 years (range: 18–54 years), **Controls:** Age matched controls from the general population (Statistics Norway)	HL: The majority of the patients had received a combination of irradiation of the involved fields and a chemotherapy regimen comprising alkylating agents, podophyllotoxins, vinka alkaloids, low-dose anthracyclines, and glucocorticoids. NHL: From the late 1980s onward, defined protocols (Berlin–Frankfurt–Münster-regimens, CHOP [cyclophosphamide, doxorubicin, vincristine, and prednisolone]) have been used. Infrequently, the protocols included limited-field radiotherapy. ALL: was predominantly based on chemotherapy only. The treatment protocols used [Norwegian protocol until 1980, NOPHO (Nordic Society of Paediatric Haematology and Oncology) protocols from 1981] have previously been described in detail [13–15]. Prophylactic craniospinal irradiation (18–24 Gy) has not been used routinely in Norway after 1975. Its use was restricted to a small number of patients with high risk disease, overt CNS leukemia or relapse.	**Risk:** Total fatigue: mean=13.9 (SD 5.3) Cases of chronic fatigue: 27% SF-36 Vitality: Survivors 51.1 (SD 21.6) Controls 60.1 (SD 19.3) p_{adj}<0.001 (adjusted for education, paired relationship, and work) Fatigue as a predictor of QoI (SF-36 dichotomised into poor and good) Fatigue OR 1.17 (95% CI: 1.08-1.27) predicting QoL, adjusted for a range of demographic and health variables. Population scores for fatigue not provided. **Risk factors:** Fatigue used as a predictor variable only	Selection bias: 1 - Random sample selected from national cohort or from hospital records of Norway's largest hospital (more than 50% of childhood cancer patients) - Response rate overall: 69% Attrition bias: 1 HL/NHL: N=220 invited N = 141 responded (67%) ALL: N=210 invited N = 160 agreed to participate in clinical study N = 155 completed questionnaires (74%) Excluded N = 10 were excluded due to incomplete data Compared to respondents, non-responders were significantly more likely to be male, and lymphoma patients. There were no significant differences concerning age at diagnosis, age at survey, or followup time Detection bias: 0 Not possible, questionnaire study Confounding: 0 fatigue as a predictor – not as an outcome **Total quality: 2/4**

1. What is the **risk and what are risk factors for suffering from Fatigue** in CAYA survivors?				
Hamre et al. Serum cytokines and chronic fatigue in adults surviving after childhood leukemia and lymphoma 2013b				
Study Design **Treatment era** **Years of follow-up** **Fatigue measurement**	**Participants**	**Treatment**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Questionnaire and Clinical study **Treatment era:** NHL and HL: 1970-2000 ALL: 1970-2002 **Years of follow-up:** 21 years (range: 7–39 years) **Fatigue measurement: The fatigue questionnaire (FQ). (Chalders fatigue questionnaire)** → Scored chronic fatigue (CF) or not **Country:** Norway	**Sample Size:** n=232 **Diagnoses:** • n=68 Hodgkin lymphoma (HL) • n=47 Non-Hodgkin (NHL) • n=117 Acute lymphoblastic leukemia (ALL) **Age at diagnosis:** Median 9.6 (Range 0.3–18.0) years, **Age at study:** Median 29.7 (Range 18.6–54.5) years **Controls:** Survivors without chronic fatigue	**Chemotherapy only:** 90% of ALL survivors 57% of NHL survivors 37% HL **Radiation only:** 0% ALL 2% NHL 18% HL **Chemo and radiation therapy:** 10% ALL 41% NHL 63% HL A total of 15 survivors had received radiotherapy to the central nervous system (CNS), 12 being ALL survivors. Among the 62 survivors who had undergone treatment with mediastinal irradiation 90% were HL survivors	**Risk:** In total: 28% had CF Highest for HL survivors (36%); NHL, 26% and ALL 24% **Risk factors:** First, the impact of possible confounders were explored in univariate analyses, variables which displayed odds ratio's (OR) with p-values ≤0.1, were included in the final analysis (diagnosis, age, gender, BMI and reduced heart function). Results of logistic regression analysis (unclear whether uni- or multivariable): • Older age at survey; Age OR=1.04 (95% CI: 1.00–1.1) *p*=0.03 • Female gender OR=1.09 (95%CI: 0.6-1.9), p=0.8 • Diagnosis: NHL (Ref. ALL): OR=1.3 (95% CI: 0.6–2.8), *p*=0.6 • Diagnosis: HL (Ref. ALL) OR=1.8 (95% CI: 0.9–3.3), *p* =0.08 • Smoking OR=1.34 (95%CI=0.7-2.5), p=0.3 • BMI OR=1.1 (95%CI:1.0-1.1), p=0.1 • Regular use of analgesics OR=1.6 (95%CI:0.7-3.7), p=0.2 • Reduced heart function OR=1.8 (95%CI:1.0-3.3), p=0.06 • T-cell origin: Yes (Ref. No): OR=10.3 (95% CI: 2.7–39.3), *p*=0.01 • T-cell origin: Unknown (Ref. No): OR=1.7 (95%CI:0.7-3.9), p=0.2 • CNS-irradiation OR=0.9 (95%CI:0.3-2.9), p=0.9 • B-symptoms at diagnosis: Yes (Ref. No): OR =2.5 (95% CI: 1.0–6.2), *p*=0.05; • B-symptoms at diagnosis: Unknown (Ref. No): OR=1.1 (95% CI:0.4–3.1), p=0.9 • A multivariable logistic regression model with CF as outcome and various cytokine level measures as predictor variables, no associations were significant.	Selection bias: 1 - Unselected sample. - Sample recruited from national cohort or from hospital records of Norway's largest hospital (more than 50% of childhood cancer patients) - Response rate overall: 69% Attrition bias: 1 -Eligible: n = 434 -Non-responses: n = 134 -Excluded for various reasons (questionnaire data only, pregnant, secondary cancer etc)N = 68 -Included N = 232 Detection bias: 0 Not possible, questionnaire study Confounding: 1 Multivariable analysis were used. **Total quality: 3/4**

1. What is the **risk and what are risk factors for suffering from Fatigue** in CAYA survivors?				
Gordijn et al. Sleep, fatigue, depression, and quality of life in survivors of childhood acute lymphoblastic leukemia 2013				
Study Design **Treatment era** **Years of follow-up** **Fatigue measurement**	**Participants**	**Treatment**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Questionnaire study Child and parental proxy reports **Treatment era:** 1997-2008 **Years of follow-up:** 36 (interquartile range 22–62) months after finishing treatment **Fatigue measurement:** PedsQL™ multidimensional fatigue scale (child and parent reports) **Country:** The Netherlands	**Sample Size:** n = 62 children **Diagnoses:** ALL **Age at diagnosis:** Not provided **Age at study:** Mean age: 9.7 (SD 3.2), range 5 – 17 yrs **Controls:** Dutch norm references	All participants had been successfully treated according to the Dutch Childhood Oncology Group (DCOG) ALL-9 or ALL-10 protocol between May 1997 and February 2008 in the VU University Medical Center Amsterdam, the University Medical Center Utrecht or the Radboud University Nijmegen Medical Center in the Netherlands. Based on clinical and biological factors and on the response to treatment, patients treated according to the ALL-9 protocol were classified in a nonhigh risk (NHR) or a high risk (HR) group and patients treated according to the ALL-10 protocol were classified in a standard risk (SR), a medium risk (MR) or a high risk (HR) group. Both ALL treatment protocols did not include cranial irradiation.	**Risk** Effect sizes varied from moderate to large, with parents rating the ALL survivors as having more general fatigue and total fatigue than the norm. Fatigue reported by survivors themselves did not differ from the Dutch norm: Child report: Total fatigue mean 78.73* (SD 12.49) vs. Dutch norm mean 76.84* (SD 12.67) (p=0.399) Parent report: Total fatigue mean 74.25* (SD 17.94) vs. Dutch norm 81.21* (SD 12.62) (p=0.004) (*higher score = less symptoms of fatigue) **Risk factors:** Data was not extracted for the risk factors, because no multivariable analyses were done.	Selection bias: 1 - Response rate overall: 42% - Recruited from treating hospital Attrition bias: 1 -invited: n = 146 -responses from n= 62 No significant differences emerged among participants and non-participants with respect to age, gender, treatment protocol, risk group stratification, and time since end of treatment. Detection bias: 0 Not possible, questionnaire study Confounding: 0 fatigue as a predictor – not as an outcome **Total quality: 2/4**

1. What is the **risk and what are risk factors for suffering from Fatigue** in CAYA survivors?				
Manley et al. Sleep dysfunction in long term survivors of craniopharyngioma 2012				
Study Design **Treatment era** **Years of follow-up** **Fatigue measurement**	**Participants**	**Treatment**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Questionnaire and Clinical study **Treatment era:** 2003-2007 **Years of follow-up:** median follow up time was 130.5 months (range, 24–312 months) **Fatigue measurement:** Unsure – clinic specific symptom list assessed using questionnaires and interview No standardized tool **Country:** USA	**Sample Size:** n = 28 **Diagnoses:** • craniopharyngioma **Age at diagnosis:** median age at the time of diagnosis was 8 years (range 2–16 years). **Age at study:** 29.7 (18.6–54.5) years **Controls:** Survivors without chronic fatigue	Surgery for all (gross or subtotal resection) Some radiotherapy (N = 22?) No chemotherapy	**Risk** 14 of 28 reported fatigue (50%) **Risk factors:** Data was not extracted for the risk factors, because no multivariable analyses were done.	Selection bias: 1 - Recruited from survivorship care clinic at hospital - - participation rate: 39,5% Attrition bias: 1 -Eligible: n = 71 Of which: - n = 27 no clinical data available - n = 15 lost to follow up - n = 1 diseased - n = 28 included in study Detection bias: 0 Not possible, questionnaire study Confounding: 0 fatigue as a predictor – not as an outcome **Total quality: 2/4**

1. What is the **risk and what are risk factors for suffering from Fatigue** in CAYA survivors?				
Nagai et al. Fatigue in survivors of childhood acute lymphoblastic and myeloid leukemia in Japan. 2012				
Study Design **Treatment era** **Years of follow-up** **Fatigue measurement**	**Participants**	**Treatment**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Questionnaire **Treatment era:** Not provided **Years of follow-up:** Mean 5.8 years (SD 3.8) **Fatigue measurement:** Self-made (12 items) Chalder fatigue scale **Country:** Japan	**Sample Size:** n = 81 **Diagnoses:** ALL 77.8% and AML 22.2% **Age at diagnosis:** Mean 6.7 years (SD 3.5) **Age at study:** Mean 14.1 years (SD 5.7) **Controls:** n = 243 healthy controls	Chemotherapy only n=45 (55.6%) Chemotherapy + radiation n=8 (9.9%) Chemotherapy + SCT n=10 (12.3%) Chemotherapy + radiation + SCT n=18 (22.2%)	**Risk** Fatigue prevalence not reported Fatigue scores: Physical fatigue: mean 3.5 vs. 4.2 (in controls), p<0.05 Decreased function: mean 3.7 vs. 4.2 (in controls), p=0.084 Altered mood: mean 2.6 vs. 2.9 (in controls), p=0.31 Total: mean 9.8 vs. 11.4 (in controls), p<0.05 Mean total fatigue scores were significantly lower in leukemia survivors (indicating less fatigue) than in controls. NB their Fatigue measure confounded with questions consistent with symptoms of depression and anxiety **Risk factors from multiple regression analysis:** Total fatigue was associated with: - Present age (years): β=0.24, p<0.05 - Gender: β=0.35, p>0.05 - Diagnosis: β=-0.02, p>0.05 - Cranial irradiation: β=-0.04, p>0.05 - Total body irradiation: β=2.72, p>0.05 - Duration after completion of treatment (years): β=-0.45, p<0.05	Selection bias: 1 - Recruited from treating hospital and attended follow-up clinic - participation rate: 90% Attrition bias: 1 -total available survivors: n = 90 - n = 81 included in study Detection bias: 0 Not possible, questionnaire study Confounding: 0 **Total quality: 2/4**

1. What is the **risk and what are risk factors for suffering from Fatigue** in CAYA survivors?				
Mört et al. Fatigue in Young Survivors of Extracranial Childhood Cancer: A Finnish Nationwide Survey. 2011				
Study Design **Treatment era** **Years of follow-up** **Fatigue measurement**	**Participants**	**Treatment**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Cross-sectional quantitative study (Questionnaires) **Treatment era:** Not stated, but calculated from that the oldest survivor were 18 at study mean they were diagnosed apr. from 1988-2001 **Years of follow-up:** N/A **Fatigue measurement:** **PedsQL Multidimensional Fatigue Scale** **Country:** Finland	**Sample size:** N=199 **Diagnoses:** • Leukemia n=110 (55%) • Non-Hodgkin Lymphoma n=13 (13%) • Hodgkin Lymphoma n=5 (3%) • Neuroblastoma n=15 (8%) • Wilms tumor n=16 (8%) • Gondal tumor n=7 (4%) • Osteosarcoma n=6 (3%) • Retinoblastoma n=6 (3%) • Soft tissue sarcoma n=13 (7%) • Other n=8 (4%) **Age at diagnosis:** Mean 3.6 years old. Range 0-12 **Age at study:** Mean 14.4 years old. Range 11-18 **Controls:** Matched controls N=252	Surgery only n=7 (4%) Chemotherapy (alone or with surgery) n=115 (58%) Radiation (alone or with chemotherapy or surgery) n=32 (16%) Stem cell transplantation n=19 (10%) Not known or stated N=19 (10%)	**Risk:** PedsQL Multidimensional Fatigue Scale captures total fatigue (TF), general fatigue (GF), sleep or rest fatigue (SF), and cognitive fatigue (CF) • The controls reported significantly more fatigue than the survivors (Total fatigue: Survivors Median 83.33; Controls Median 80.56, p<0.01). • Survivors scored more Total fatigue when compared with their parent proxy scores, but not statistically significant (Total fatigue: Survivors Median 83.33; Parents of Survivors Median 84.03, p>0.05) **Risk factors for Total Fatigue from multivariate regression analysis:** Lower scores indicate more fatigue. • Age at study: β=-1.87, p<0.001 • Gender: female (Ref. male) β =2.99, p>0.05 • Diagnosis: NHL (Ref. leukemia) β =-2.49, p>0.05 • Diagnosis: Sarcoma (Ref. leukemia) β =-13.28, p<0.01 • Diagnosis: NBL (Ref. leukemia) β =-2.3, p>0.05 • Diagnosis: Other (Ref. Leukemia) β =-0.85, p>0.05 • Treatment: Chemotherapy (Ref. surgery alone) β =-4.2, p>0.05 • Treatment: Radiation (Ref. surgery alone) β =-8.73, p>0.05 • Treatment: SCT (Ref. surgery alone) β =-3.17, p>0.05 • Treatment: Other treatment (Ref. surgery alone) β =-5.09, p>0.05 • Length of survival: More than 10 years (Ref. 10 years or less) β =-3.6, p>0.05 • Additional diagnosis: No (Ref. Yes) β =2.2, p>0.05 • Remedial education: No (Ref. Yes) β =-1.43, p>0.05 • Overall average grade: β =2.47, p>0.05 • Self-rated happiness: No (Ref. Yes) β =-1.13, p>0.05 • HRQoL score: β =0.87, p<0.001	Selection bias: 0 Population-based study n= 384 received questionnaire. N=199 (53%) replied No information about non-responders Attrition bias: 1 Detection bias: 0 Questionnaire survey, no blinding possible. Confounding bias: 1 Multivariable analysis were used. **Total quality: 2/4**

1. What is the **risk and what are risk factors for suffering from Fatigue** in CAYA survivors?				
Johannsdottir et al. Increased Prevalence of Chronic Fatigue Among Survivors of Childhood Cancers: A Population-Based Study. 2012				
Study Design **Treatment era** **Years of follow-up** **Fatigue measurement**	**Participants**	**Treatment**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Cross sectional study. **Treatment era:** 1985-2001 **Years of follow-up:** **4-20 years** **Fatigue measurement:** **Fatigue Questionnaire (FQ)** **Country:** Norway	**Sample size:** N= 398 151 young group (YG) (13-18 years) 247 older group (OG) (19 and above) **Diagnoses:** • Acute myeloid leukemia (AML), n=90 • Infratentorial astrocytoma (IA) n=125 • Wilms tumor (WT) n=183 **Age at diagnosis:** 1-18 mean 5 years old **Age at study:** 13-34 **Controls:** N=763	**AML:** Stem cell transplantation n=56 (60%) Chemotherapy only n=34 (40%) **IA:** 75% surgery only 16% radiotheraphy in addition The rest 9% treatment unknown **WT:** 57% surgery and chemotherapy 40% supplementary radiotherapy	**Risk:** 11% of the survivors had chronic fatigue (significantly more prevalent in the OG (13.6%) than in the YG (6.8%), P<0.05) • Risk of chronic fatigue (CF): Survivors (OG) vs. controls: OR 3.29 (95% CI 1.90-5.70; from multivariable logistic regression, adjusted for age, sex, education, marital status, employment, social benefits) **Risk factors for chronic fatigue in univariate analysis:** • Older aged females had sig. higher levels of fatigue (Mental fatigue (MF); Physical fatigue (PF) and Total fatigue (TF) compared with general population. • Older aged survivors had higher levels of fatigue compared to younger aged survivors (TF 12.4 vs. 10.9; P<0.01, PF 8.0 vs. 7.0; P<0.01, and MF 4.4 vs. 4.0; P<0.05). **Risk factors for chronic fatigue from multivariable logistic regression analysis (n=33 OG; n=44 GP):** • **Age at assessment: OR 1.08 (95% CI 1.01-1.16)** • Females vs. males: OR 1.54 (95% CI 0.94-2.54) • Academic education yes vs. no: OR 0.63 (95% CI 0.36-1.12) • Married/cohabiting yes vs. no: OR 1.09 (95% CI 0.64-1.85) • Gainfully employed yes vs. no: OR 1.18 (95% CI 0.67-2.07) • Receiving social benefits yes vs. no: OR 1.79 (95% CI 0.61-5.26)	Selection bias: 1 Population-based Survey study from the Nordic countries (Norway, Denmark, Sweden, Finland, and Iceland). Attrition bias: 0 65% response rate among the young group and 74% among the older group n= 567 received questionnaire. N=398 replied Detection bias: 0 Questionnaire survey, no blinding possible. Confounding bias: 1 Multivariable analysis were used. **Total quality: 2/4**

1. What is the **risk and what are risk factors for suffering from Fatigue** in CAYA survivors?				
Kenney et al. Health Status of the Oldest Adult Survivors of Cancer During Childhood. 2010				
Study Design **Treatment era** **Years of follow-up** **Fatigue measurement**	**Participants**	**Treatment**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Cross sectional Survey study **Treatment era:** 1947-1968 **Years of follow-up:** 36-65 **Fatigue measurement:** Functional Assessment of Chronic Illness Therapy-Fatigue. **Country:** USA	**Sample size:** N=55 (63% response rate) **Diagnoses:** • Sarcoma n=18 (33%) • NHL N=10 (18) • Wilms tumor n=10 (18%) • Hodgkin lymphoma n=6 (11%) • Neuroblastoma n=5 (9%) • Other N=6 (11%) **Age at diagnosis:** 0-18 mean 8 years old **Age at study:** 51-71 mean 56 years old **Controls:** N=32	Surgery only n=4 (7%) Radiation only n=15 (27%) Chemotherapy only n=14 (26%) Radiation and chemotherapy n=22 (40%)	**Risk:** Scores on the fatigue scale range from 0 to 52, with higher scores indicating better functioning and less fatigue; scores <30 can be interpreted as indicating significant fatigue Survivors' mean fatigue score of 40.56 (standard deviation [SD] 10.40) was significantly lower that the siblings' mean of 45.19 (SD 6.88, *t*=.2.43, *p*=0.02), indicating more significant problems with fatigue. A larger proportion of survivors had fatigue scores in the clinically significant range (8 of 50 [16%]) compared with siblings (1 of 32 [3.1%]) (OR=5.90), but the difference only approached statistical significance (Fisher exact test, *P*=0.067). **Risk factors:** Data was not extracted for the risk factors, because no multivariable analyses were done.	Selection bias: 0 single institution cohort Of 1100 survivors in the cohort, 222 were eligible by birth date, 115 for this analysis (68 deceased, rest different reasons) resulting in 107 potential cases. Of them 16 were deceased. So 88 were enrolled in the study. Attrition bias: 0 63% response rate n= 88 received questionnaire. N=55 replied Analysis of nonparticipants available similar to respondents on demographic variables. Detection bias: 0 Questionnaire survey, no blinding possible. Confounding bias:1 Multivariable analysis were used. **Total quality: 1/4**

1. What is the **risk and what are risk factors for suffering from Fatigue** in CAYA survivors?				
Blaauwbroek et al. The effect of exercise counselling with feedback from a pedometer on fatigue in adult survivors of childhood cancer: a pilot study. 2009				
Study Design **Treatment era** **Years of follow-up** **Fatigue measurement**	**Participants**	**Treatment**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Intervention study **Treatment era:** n.a. **Years of follow-up:** Mean since diagnosis 21.8. range 14.7-28.9 **Fatigue measurement:** Visual Analogue Scale for chronic fatigue (VAS fatigue) Checklist individual strength (CIS) **Country:** The Netherlands	**Sample size:** N=46 **Diagnoses:** • Leukemia n=22 (46.8%) • Malignant lymphoma n=6 (12.8) • Bone tumor n=4 (8.5) • Soft tissue sarcoma n=3 (6.4%) • Wilms tumor n=1(2.1%) • Langerhans cell histiocytosis n=2 (4.3%) • CNS tumor n=6 (12.8%) • Other n=3 (6.4%) **Age at diagnosis:** Mean age 8 years. Range 1.5-14.8 **Age at study:** Median age 29 years. Range 18-61 **Controls:** N=33 (recruited by the survivors among healthy siblings or peers)	Chemotherapy only 22 (47.8%) Surgery only 2 (4.4%) Radiotherapy only 0 Chemo and radiotherapy 22 (47.8) Cranial radiation 12 (26.1)	**Risk:** Fatigue was the primary outcome and it was measured with a visual analogue scale for fatigue and the CIS. The CIS is a validated 20-item questionnaire, that is designed to measure four aspects of fatigue that may have been experienced during the previous 2 weeks 67/254 (26.4%) survivors had a VAS score of ≥70mm. Mean CIS score before the intervention was 81.42 (SD 20.14) for survivors and 47.39 (SD 19.06) for controls, p<0.0005. **Risk factors:** Data was not extracted for the risk factors, because no multivariable analyses were done.	Selection bias: 0 Attrition bias: 0 n= 486 eligible n=453 were sent questionnaire respons rate 56%. 46 were enrolled into the study but eight dropped out Detection bias: 0 Confounding bias:0 Descriptive statistics and Linear regression used. **Total quality: 0/4**

1. What is the **risk and what are risk factors for suffering from Fatigue** in CAYA survivors?				
Mulrooney et al. Fatigue and Sleep Disturbance in Adult Survivors of Childhood Cancer. A report from the Childhood Cancer Survivor Study (CCSS). 2008				
Study Design **Treatment era** **Years of follow-up** **Fatigue measurement**	**Participants**	**Treatment**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Epidemiologic study; Sleep questionnaire from the Childhood Cancer Survivor Study (CCSS), sent with the second follow-up questionnaire **Treatment era:** Diagnosed between 1970 and 1986 **Years of follow-up:** Survival for >=5 years following diagnosis; 15-19 years 26.1% 20-24 years 34.1% 25-29 years 26.0% 30+ years 13.9% **Fatigue measurement:** Fatigue subscale of the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) **Country:** USA	**Sample size:** 1897 survivors and 369 siblings as controls **Diagnoses:** Leukemia 15.7% CNS malignancy 15.8% Hodgkin disease 52.5% Soft tissue sarcoma 7.9% Bone cancer 8.2%; *Oversampling of Hodgkin disease survivors due to reports of excessive fatigue in this population* **Age at diagnosis:** Diagnosed before the age of 21 years; 0-4 years 18.6% 5-9 years 20.6% 10-14 years 27.6% 15+ years 33.3% **Age at study:** 18-29 years 23.8% 30-39 years 46.3% 40-49 years 28.0% 50+ years 1.8% **Controls:** Nearest-age siblings from the study participants (n=369)	**Chemotherapy** Yes 59.1% No 40.9% **Radiation** Yes 70.2% No 29.8%	**Risk:** Comparison of mean fatigue scores: Survivors had significantly lower mean fatigue score (40.8) than their siblings (42.0), p=0.02 (comparison adjusted for age at study and sex; lower score indicates more fatigue) Prevalence of fatigue: 364/1897 (19.2%) **Risk factors from multivariate logistic regression analysis (cancer- or treatment-related variables):** *OR for being fatigued* • Diagnosis: CNS malignancy (Ref. ALL): OR=1.3, 95%CI:0.8-2.1 • Diagnosis: Hodgkin disease (Ref. ALL): OR=1.2, 95%CI:0.7-1.8 • Diagnosis: Soft tissue sarcoma (Ref. ALL): OR=1.0, 95%CI:0.6-1.7 • Diagnosis: Bone cancer (Ref. ALL): OR=1.3, 95%CI: 0.7-2.3 • Age at diagnosis: 0-4 years (Ref. 15+ years): OR= 0.7, 95%CI:0.4-1.2 • Age at diagnosis: 5-9 years (Ref. 15+ years): OR=0.9, 95%CI:0.6-1.4 • Age at diagnosis: 10-14 years (Ref. 15+ years): OR=0.8, 95%CI:0.6-1.1 • Radiation: Yes (Ref. No): OR=1.7, 95%CI:1.3-2.3 • Chemotherapy: Yes (Ref. No): OR=1.0, 95%CI:0.8-1.4 **Risk factors from multivariate logistic regression analysis (medical conditions and sociodemographic factors) in survivors:** • Female (Ref. male): OR=2.1, 95%CI:1.6-2.7 • Congestive heart failure: Yes (Ref. No): OR=2.9, 95%CI:1.4-6.1 • Lung fibrosis: Yes (Ref. No): OR=2.9, 95%CI:1.5-5.4 • Hypothyroidism: Yes (Ref. No): OR=0.9, 95%CI:0.7-1.3 • Depressed: Yes (Ref. No): OR=7.5, 95%CI:5.1-10.9 • BMI 30+ kg/m^2: Yes (Ref. No): OR=1.3, 95%CI:0.9-1.7 • Marital status: Not married (Ref. Married): OR=2.7, 95%CI:2.0-3.6 • Employment status: Not working full time (Ref. working full time): OR=1.2, 95%CI:0.3-1.6 • Infant at home <6mo old: Yes (Ref. No): OR=1.9, 95%CI:0.7-5.0	Selection bias: 0 Survivors: response rate 72%; Oversampling of Hodgkin disease survivors due to reports of excessive fatigue in this population → no Controls: response rate 73.8% → no Attrition bias: 1 Outcome for all included survivors → yes Detection bias: 0 Assessors were not blinded → no Confounding: 1 Adjusted comparison of mean fatigue scores and multivariate analyses → yes **Total quality 2/4** **Remarks:** To dichotomize the scales, we classified the lowest 10th percentile of the sibling scores on the FACIT-Fatigue as fatigued.

1. What is the **risk and what are risk factors for suffering from Fatigue** in CAYA survivors?				
Aksnes et al. Young survivors of malignant bone tumours in the extremities: a comparative study of quality of life, fatigue and mental distress. 2007				
Study Design **Treatment era** **Years of follow-up** **Fatigue measurement**	**Participants**	**Treatment**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Cross-sectional quantitative study **Treatment era:** Not stated **Years of follow-up:** At least 5 years after end of primary treatment, years since diagnosis is only reported stratified by type of diagnosis and sex (mean years since diagnosis around 9-14 years for all subgroups Male EBT survivors 14 years (SD 4.5) Female EBT survivors 11 years (SD 4.8) **Fatigue measurement:** **The Fatigue Questionnaire** **Country:** Norway	**Sample size:** N= 57 with matched controls (TC and HD) **Diagnoses:** • Extremity bone tumor (EBT) n=57 Controls: • Testicular cancer n= 62 • Hodgkin's n=89 **Age at diagnosis:** Males EBT survivors mean 20 years (SD 8.2) Females EBT survivors mean 16 years (SD 4.5) **Age at study:** Male EBT survivors 34 years (SD 9.4) Female EBT survivors 27 years (SD 4.8) **Controls:** Hodgkin n=89 Testicular cancer n=89 Norm population: five randomly chosen gender- and age-adjusted cases for each EBT survivor (n=285)	Not clear, they had treatment according to one of the osteosarcoma or Ewing tumor protocols of the Scandinavian Sarcoma Group (SSG)	**Risk:** No significant differences in the fatigue scores were observed between the survivor groups. The hypothesis that the EBT survivors, because of more extensive treatment, would display more fatigue than HD survivors and TC survivors, and gender- and age-matched individuals from the general population was not confirmed because EBT survivors hardly differed from HD survivors, TC survivors or NORMs except in the physical dimensions of QoL. EBT survivors had a significantly higher Total fatigue score (p=0.003) compared to their NORMs Total fatigue, mean: EBT: 13.2 (SD 3.8), NORMs: 11.8 (SD 3.9), p=0.003; HD survivors 13.4 (SD 4.8), TC survivors 13.4 (SD 4.7), both p=0.95 compared to EBT Chronic fatigue: n=8 (14%) of EBT, n=27 (10%) of NORMs, p=0.30; n=19 (21%) of HD survivors; n=10 (16%) of TC survivors, both p=0.49 compared to EBT **Risk factors:** No risk factors for fatigue were analyzed.	Selection bias: 0 Unclear if this is a Population-based study Attrition bias: 1 n= 75 received questionnaire 58 responded (77%) No difference between responders and non responders on age, sex, type of treatment or time since diagnoses Detection bias: 0 Questionnaire survey, no blinding possible. Confounding bias: 1 Multivariable analysis were used. **Total quality: 2-3/4**

1. What is the **risk and what are risk factors for suffering from Fatigue** in CAYA survivors?				
Meeske et al. Prevalence and Correlates of Fatigue in Long-Term Survivors of Childhood Leukemia. 2005				
Study Design **Treatment era** **Years of follow-up** **Fatigue measurement**	**Participants**	**Treatment**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Cross sectional, single centre study **Treatment era:** 1975-1995 **Years of follow-up:** Average time from end of therapy was 13.9 years (range 4-23 years) **Fatigue measurement:** -The Revised–Piper Fatigue Scale (R-PFS) -Profile of Mood State fatigue inertia subscale (POMS) - Rand SF-36 (SF-36) vitality subscale -Symptom Distress Scale (SDS). **Country:** USA	**Sample size:** N=161 **Diagnoses:** • Acute lymphoblastic leukemia (ALL) **Age at diagnosis:** 0-18 Average age at diagnosis was 7.4 years **Age at study:** 18-41 **Controls:**	Cranial irradiation n=103 (65%) Anthracycline n=104 (66%) BMT n=12 (7%)	**Risk:** Prevalence of fatigue (30%) fell within the general population normal limits (n=48 (30%) were classified as fatigued). Fatigue was the most frequently reported symptom (61%) on the SDS. Distress levels were higher for fatigue than for any other symptom. Survivors' average POMS fatigue-inertia score was 7.2 (standard deviation [SD], 6.3), which is within the normal range reported for college students. Survivors' SF-36 vitality mean score was 63.4 (SD 23.2), which is slightly higher (more energy) than the norms for the general population (61.3; SD 20.2). **Risk factors from multivariate logistic regression (a best-fitting multivariable logistic regression model was obtained through stepwise elimination): final model** • Married vs. not married: OR=0.11, 95%CI:0.02-0.50 • Children vs. no children: OR=5.80, 95%CI:1.30-25.82 • Sleep problems: OR=6.15; 95%CI:2.33-16.22 • Pain: OR=5.56; 95%CI:2.13-14.48 • Obesity: OR=3.80; 95%CI:1.41-10.26 • Neuro-cognitive impairment: OR=2.56; 95%CI:1.02-6.38 • Exercise-induced symptoms: OR=2.98, 95%CI:1.11-8.02 **Risk factors from multivariate logistic regression: Significantly associated with fatigue (data not shown)** • Not working or attending school • Being married (included in final model) • Having children (included in final model) • Relapse • Neurocognitive impairments (included in final model) • Obesity (included in final model) • Sleep problems (included in final model) • Pain (included in final model) It's unclear which other variables were included in the multivariable models but were not statistically significant.	Selection bias: 0 Low response rate Attrition bias: 1 Detection bias: 0 Questionnaire survey, no blinding possible. Confounding bias: 1 Multivariable analysis were used. **Total quality: 2/4**

1. What is the **risk and what are risk factors for suffering from Fatigue** in CAYA survivors?				
Langeveld et al. No excess fatigue in young adult survivors of childhood cancer. 2003				
Study Design **Treatment era** **Years of follow-up** **Fatigue measurement**	**Participants**	**Treatment**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Cross-sectional study **Treatment era:** Not mentioned **Years of follow-up:** mean time since completion of therapy: 15.5 years (SD 5.9) **Fatigue measurement:** Multidimensional Fatigue Inventory (MFI-20). The questionnaire consist of 20 items on a five point scale. Items are combined to form five scales: general fatigue, physical fatigue, mental fatigue, reduced activity and reduced motivation. Higher scores indicate higher levels of fatigue. **Country:** The Netherlands	**Sample size:** N=416 **Diagnoses:** Leukaemia/non-hodgkin lymphoma without CRT: n=116 (28%) Leukaemia/non-hodgkin lymphoma with CRT: n=87 (21%) Solid tumor: n=183 (44%) Brain/CNS tmour: n=30 (7%) **Age at diagnosis:** Mean age at diagnosis: 8 years (SD 4.7) **Age at study:** Mean age at follow-up: 24 years (SD 5.2) **Controls:** n=1026, recruited via survivors GPs. They were asked to help in selecting sex and age matched controls.	Chemotherapy (with or without surgery): n=197 (47%) Radiotherapy (with or without surgery): n=29 (7%) Combination therapy (chemotherapy and radiotherapy with or without surgery): n= 190 (46%)	**Risk:** "Survivors scored significantly lower (i.e. reflecting less fatigue) for general fatigue (P <0.05, effect size -0.14) and reduced motivation (P <0.05, effect size -0.19), but statistically higher (i.e. reflecting worse fatigue) for mental fatigue (P <0.05, effect size 0.15) than controls." Mean scores on the MFI-20 for General fatigue: survivors 7.5 (SD 4.3), controls 8.8 (SD 3.8), p<0.001 **Risk factors for fatigue from multivariable regression analysis (Full model):** General fatigue: **Female versus male: Beta coefficient 0.19, p<0.001** Age at follow-up: Beta coefficient 0.01, NS Married vs not married: Beta coefficient 0.04, NS Higher education level vs lower: Beta coefficient 0.03, NS Student/homemaker vs unemployed: Beta coefficient -0.12, NS **Employed vs unemployed: Beta coefficient -0.20, p<0.05** Age at diagnosis: Beta coefficient 0.06, NS **Leukaemia/non-hodgkin lymphoma with CRT vs without CRT: Beta coefficient -0.16, p<0.05** Solid tumor vs Leukaemia/NHL without CRT: Beta coefficient 0.02, NS Brain/CNS tumor vs Leukaemia/NHL without CRT: Beta coefficient -0.08, NS Duration of treatment: Beta coefficient 0.02, NS Years since completion of therapy: Beta coefficient 0.02, NS **Late effects/health problems: Beta coefficient 0.14, p<0.05** Radiation therapy* vs chemotherapy*: Beta coefficient 0.01, NS Combination therapy* vs chemotherapy*: Beta coefficient 0.04, NS **Depression: Beta coefficient 0.54, p<0.001**	Selection bias: 0 Hospital based study with patients from one hospital, but not clear whether that's population based. Attrition bias: 1 study group n=459. Included and outcome assessed n=416 (90.6%) Detection bias: 0 Questionnaire survey, no blinding possible. Confounding: 1 Prognostic factors are taken into account. Descriptive for risk (stratified for gender and age at assessment). And included in the full model. **Total quality: 2/4** **Remarks:** *With or without surgery

1. What is the **risk and what are risk factors for suffering from Fatigue** in CAYA survivors?				
Zebrack et al. Quality of life in childhood cancer survivors. 2002				
Study Design **Treatment era** **Years of follow-up** **Fatigue measurement**	**Participants**	**Treatment**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Cross-sectional (aim to validate a QoL questionnaire in young people diagnosed with cancer in childhood) **Treatment era:** Not mentioned **Years of follow-up:** Mean years since diagnosis 13.3 (SD 5.7) range 3-27 years **Fatigue measurement:** Quality of Life-Cancer survivors. 41 item scale composed of four subscales. Each item is scored on a 0 (lowest or worst QoL) to 10 (highest or best QoL) scale. Fatigue is one of the items of the 8 item physical subscale. **Country:** USA	**Sample size:** n=176 **Diagnoses:** Leukemia: n=53 Brain/CNS: n=19 Lymphoma: n=37 Wilm's Tumor: n=18 Sarcomas: n=28 Other (including neuroblastoma and retinoblastoma): n=20 **Age at diagnosis:** Mean 8.5 (SD 5.1) range 0-22 years **Age at study:** Mean 21.8 (SD 3.3) range 16-28 years **Controls:** No	Not mentioned	**Risk:** Mean score on the fatigue item was 7.32. It was the symptom with the lowest score in the physical subscale of the Quality of Life-Cancer Survivors. Thus indicating most problematic relative to other symptoms. **Risk factors:** No regression analyses with fatigue as outcome.	Selection bias: 0 original cohort n=493 eligible participants n= 335 participated/sample size n=176 Attrition bias: 0 study group n=335 sample size n= 176 (53%) Detection bias: 0 Questionnaire survey, no blinding possible Confounding: 0 For the fatigue part, only descriptive statistics were used. **Total quality: 0/4**

1. What is the **risk and what are risk factors for suffering from Fatigue** in CAYA survivors?				
Zeltzer et al. Comparison of Psychologic outcome in adult survivors of childhood acute lymphoblastic leukemia versus sibling controls: a cooperative children's cancer group and national institutes of health study. 1997				
Study Design **Treatment era** **Years of follow-up** **Fatigue measurement**	**Participants**	**Treatment**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Cross-sectional study **Treatment era:** Diagnosed in 1970 or after 1970 **Years of follow-up:** Not mentioned. In the method section it is stated that 95% of the survivors had survived for at least 5 years after diagnosis. **Fatigue measurement:** Profile of Mood State (POMS). 65 item self-report questionnaire to meausure six mood states, including fatigue. Individual items are scored on a scale from 0 to 4. Higher scores on the fatigue subscale suggest persons with low energy. **Country:** USA	**Sample size:** n=580 **Diagnoses:** Acute lymphoblastic leukemia **Age at diagnosis:** Not mentioned. **Age at study:** Mean 22.6 years (SD3.2) range 18.02-33.25 **Controls:** Sibling controls: n=396	Not mentioned	**Risk:** High score on the POMS indicates low energy/high fatigue Fatigue mean score in survivors: 7.87 (SD 5.58); n=552 Fatigue mean score in controls: 8.36 (SD 5.83); n=394 Results of t-test (p=0.19) and regression analyses (p=0.20) showed no significant difference between survivors and controls in level of fatigue. **Risk factors:** No regression analyses to identify possible risk factors for fatigue subscale.	Selection bias: 1 Original cohort n=731 Participated: n=593 Completed both POMS and interview n=580 (79%) Attrition bias: 1 Particpated = 593 included in analysis: n=580 Fatigue assessed = 552 (resp. 93% and 95%) Detection bias: 0 Questionnaire survey, blinding not possible. Confounding: 1 analyses for difference between survivors and controls, was controlled for age, sex, and survivor-sex interaction. **Total quality: 3/4**

1. What is the **risk and what are risk factors for suffering from Fatigue** in CAYA survivors?				
Vannatta et al. A controlled study of peer relationships of children surviving brain tumors: teacher, peer, and self ratings.1998				
Study Design **Treatment era** **Years of follow-up** **Fatigue measurement**	**Participants**	**Treatment**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Case-control **Treatment era:** Not mentioned **Years of follow-up:** Average time since diagnosis: 36 months (SD 13; range 18-62 months) **Fatigue measurement:** Revised Class Play (RCP). Descriptive matching instrument on which children or teachers are asked to cast classmates into different roles. Role about fatigue is described as "someone who is tired a lot". Scores are standardized with a mean of 0 and SD of 1. **Country:** USA	**Sample size:** n=28 **Diagnoses:** Brain tumors: Astrocytomas: n=9 Primitive neuroectodermal tumors: n=6 Oligodendrogliomas: n=5 Craniopharyngiomas: n=4 Ependymomas: n=2 Hypothalamic glioma: n=1 Brain stem glioma: n=1 **Age at diagnosis:** not mentioned **Age at study:** Mean age 11.2 years (SD 2.8) **Controls:** Classroom Comparison Peers (COMP): n=28 (for each survivor a classmate is selected for comparison based on race, gender and closest in date of birth)	Surgery alone: n=14 surgery and radiotherapy: n=7 surgery, radiotherapy and chemotherapy: n=7	**Risk:** RCP score for "Tired a lot" of Brain tumor survivors 0.90 (SD 1.24) RCP score for "Tired a lot" of COMP -0.24 (SD 0.81) This difference was statistically significant p<0.001 (two-tailed) "For the RCP supplementary roles related to illness, fatigue, and missing school, peers nominated the children surviving brain tumors significantly more often than COMP." **Risk factors:** No multivariable risk factor analysis performed.	Selection bias: 0 Unclear what the original cohort is. Attrition bias: 1 Eligible: n=28 Sample size: n=28 (100%) Detection bias: 0 Blinding not possible Confounding: 1 Comparison classmate is selected based on age, race and gender **Total quality: 2/4** Note: Fatigue standardized score is based on peer ratings.

1. What is the **risk and what are risk factors for suffering from Fatigue** in CAYA survivors?				
Sato et al. Impact of late effects on health-related quality of life in survivors of pediatric brain tumors. 2014				
Study Design **Treatment era** **Years of follow-up** **Fatigue measurement**	**Participants**	**Treatment**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Cross-sectional design **Treatment era:** Not mentioned **Years of follow-up:** Mean time since completion of antitumor therapy 11.1 years (SD 8.3) **Fatigue measurement:** EORTC-QLQ-C30. Symptom fatigue scale (three items). Scored on 4 point likert scale. Score is linearly transformed on a 0-100 scale. Lower scores indicating beter QoL (less fatigue) **Country:** Japan	**Sample size:** n=104; >18 years: n=51 (see remarks) **Diagnoses:** Brain tumor: Germinoma: n=23 Other germ cell tumor: n=5 Medulloblastoma/PNET: n=5 Low-grade glioma: n=9 High-grade glioma: n=4 Others: n=5 **Age at diagnosis:** Mean 13.3 years (SD 3.5) **Age at study:** Mean 26.8 (SD7.6) **Controls:** No	Neurosurgery: n=47 Radiation treatment: n=44 Chemotherapy: n=34	**Risk:** Mean fatigue score: 26.6 (SD 20.1) **Risk factors for fatigue (unclear from what analysis, impact represents the extent to which each late effect influences the scores of fatigue):** Motility disturbance of limbs: impact -5.5, p = 0.308 Seizure: impact -7.9, p = 0.158 Ocular/vision impairment: impact 5.9, p = 0.315 Endocrine abnormality: impact 12.9, p = 0.20 Higher brain dysfunction: impact 15.2, p=0.004 Analysis were adjusted for possible confounders: age, gender, age at diagnosis, hydrocephalus at diagnosis, tumor pathology, tumor location, neurosurgery, radiation treatment, chemotherapy, tumor recurrence and time since completion of antitumor therapy. A positive impact indicates that the late effect deteriorates the aspects of HRQOL; a negative impact indicates improvement	Selection bias: 0 Unclear how large the original cohort was. Only eligible patients are mentioned. Attrition bias: 1 Study group >18 years: n=66Sample size/ included >18 years: n=51 (77%) Detection bias: 0 Questionnaire survey, blinding not possible. Confounding: 1 Important factors were taken into account in the risk factor analysis. **Total quality: 2/4** Remarks: only results of the respondents aged >18 years are collected. Fatigue was not assessed in respondents aged 12-17.

1. What is the **risk and what are risk factors for suffering from Fatigue** in CAYA survivors?				
Brand et al. Screening for fatigue in adolescent and young adult pediatric brain tumor survivors: accuracy of a single-item screening measure. 2016				
Study Design **Treatment era** **Years of follow-up** **Fatigue measurement**	**Participants**	**Treatment**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Cross-sectional **Treatment era:** Not mentioned **Years of follow-up:** Mean time since diagnosis 10.55 years (SD 5.57; range 2-27 years) **Fatigue measurement:** Fatigue Thermometer (FT): Visual scale labeled from 0 (no fatigue) to 10 (worst fatigue imaginable). Pediatric Quality of life inventory multidimensional fatigue scale (MFS) : 18 items rated on 5 point Likert scale. Higher scores indicate fewer symptoms of fatigue. **Country:** USA	**Sample size:** n=142 **Diagnoses:** Brain tumor: Low-grade glioma: n=80 Embryonal tumor: n=29 Ependymoma: n=14 Craniopharyngioma: n=8 Germ cell: n=8 Choroid plexus: n=2 High-grade glioma: n=1 **Age at diagnosis:** Mean 9.72 (SD 4.87; range 4 months-22 years) **Age at study:** Mean 20.24 (SD 4.81; range 12-32 years) **Controls:** No	Not specified	**Risk:** MFS: Mean total MFS score: 70.67 (SD 18.72; range 22.22-100) Clinically significant fatigue (defined as MFS score >1 SD below the mean for normative samples): n=42 (/142=29.57%) FT: No fatigue (score 0): n=35 Mild fatigue (score 1-3): n=51 Moderate fatigue (score 4-6): n=27 Severe fatigue (score 7-10): n=18 **Risk factors:** No multivariable risk factor analysis performed.	Selection bias: 0 Original cohort brain tumor survivor project REACH: n= 245 Eligible for this study: n=191 (77%) Included: n=142 (58%) Attrition bias: 1 Detection bias: 0 Questionnaire survey, blinding not possible. Confounding: 1 **Total quality: 2/4**

1. What is the **risk and what are risk factors for suffering from Fatigue** in CAYA survivors?				
Adams et al. Cardiovascular Status in Long-Term Survivors of Hodgkin's Disease Treated With Chest Radiotherapy. 2004				
Study Design **Treatment era** **Years of follow-up** **Fatigue measurement**	**Participants**	**Treatment**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Cross sectional study **Treatment era:** After 1969 **Years of follow-up:** Median 14.3 years since diagnosis (range 5.9-27.5) **Fatigue measurement:** "General health status form" designed for this study **Country:** USA	**Sample size:** N=48 **Diagnoses:** • Hodgkin's disease **Age at diagnosis:** Median 16.5 years (range 6.3-25.0) **Age at study:** Median 31.9 years (range 18.7-49.5) **Controls:**	• Chemotherapy n=21 (43.8%) • Anthracycline n=4 (8.3%) • Mediastinal irradiation n=48 (100%) Total mediastinal dose, including emergency dose, Gy: median 40 (range 27.0-51.7)	**Risk:** • 67% [n=32 of 48] reported feeling tired/fatigued • 35% [n=17 of 48] stated that it was a moderate to severe problem (≥2 on a 0 to 4 scale) **Risk factors:** Data on risk factors was not extracted, because no multivariable analyses were done.	Selection bias: 1 Yes, all patients fulfilling the inclusion criteria were contacted. Attrition bias: 1 All participants were included in the analysis. Detection bias: 0 Questionnaire survey, no blinding possible. Confounding: 0 No multivariate analyses were used. **Total quality: 2/4**

1. What is the **risk and what are risk factors for suffering from Fatigue** in CAYA survivors?				
Enskär et al. Prevalence of aspects of distress, coping, support and care among adolescents and young adults undergoing and being off cancer treatment. 2007				
Study Design **Treatment era** **Years of follow-up** **Fatigue measurement**	**Participants**	**Treatment**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Cross sectional study **Treatment era:** n.a. **Years of follow-up:** n.a. **Fatigue measurement:** Life Situation Scale for Adolescents (LSS-A) **Country:** Sweden	**Sample size:** N=54 (n=15 on treatment; n=39 off treatment) **Diagnoses:** • Leukaemia n=18 • Lymphoma n=8 • Brain tumor n=7 • Sarcoma n=7 • Other tumors n=14 **Age at diagnosis:** n.a. **Age at study:** Mean 16.0 years (SD 2.1; range 13-22) **Controls:** n.a.	n.a.	**Risk:** "Fatigue was experienced by 67% of the adolescents and young adults off treatment." **Risk factors:** No risk factor analysis.	Selection bias: 0 Only survivors coming into hospital for FU consultations were recruited. Attrition bias: 1 Response rate 84% Detection bias: 0 Questionnaire survey, no blinding possible. Confounding: 0 No multivariate analyses were used. **Total quality: 2/4**

1. What is the **risk and what are risk factors for suffering from Fatigue** in CAYA survivors?				
Frederick et al. Fatigue in adolescent and adult survivors of non-CNS childhood cancer: a report from project REACH. 2016				
Study Design **Treatment era** **Years of follow-up** **Fatigue measurement**	**Participants**	**Treatment**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Cross sectional study **Treatment era:** **Years of follow-up:** Mean time since diagnosis was 13.1 years 2-9 years: n=80 10-14 years: n=74 15-19 years: n=52 20-24 years: n=24 25-29 years: n=17 30+ years: n=21 **Fatigue measurement:** **PedsQL Multidimensional Fatigue scale (MFS)** **Country:** USA	**Sample size:** N=268 **Diagnoses:** • Leukemia: n=94 (35.1%) • Hodgkin Lymphoma: n=41 (15.3%) • Non-Hodgkin Lymphoma: n=24 (9.0%) • Bone Tumors: n=25 (9.3%) • Soft tissue sarcoma: n=20 (7.5%) • Neuroblastoma: n=27 (10.1%) • Wilms Tumor: n=20 (7.5%) • Other: n=17 (6.3%) **Age at diagnosis:** Median age at diagnosis: 6.4 years 0-4 years: n=112 5-9 years: n=53 10-14 years: n=55 15+ years: n=46 **Age at study:** Range 12-49 years, median age of 21.4 years 12-15 years: n=74 16-19 years: n=45 20-29 years: n=83 30-39 years: n=48 40-49 years: n=18	Chemotherapy: Yes: n=239 Doxorubicin: Yes: n=74 Any Radiation therapy: Yes: n=171 CNS directed radiation therapy: Yes: n=84 Surgery: Yes: n=117 Bone Marrow Transplant: Yes: n=33	**Risk:** "Based on comparison with published data for the MSF in community samples, 37 survivors (13.8 %) were considered fatigued (MDF score ≥1 standard deviation below means for non-cancer patients of similar age) which is not statistically different from the 16 % (43 cases) that would have been expected based on community sample data [15, 16, 14] for the MFS (z= −0.727, p=0.467)." **Risk factors for fatigue caseness** (20% of participants with lowest scores on the MFS) **from multivariate logistic regression analysis:** Ethnicity, diagnosis, age at diagnosis, recurrence, chemotherapy, doxorubicin, any radiation therapy, CNS directed radiation therapy, surgery, bone marrow transplant were not statistically significantly associated with CRF in univariate analysis, and therefore not included in the multivariable model • Gender: Female (Ref. Male) OR=1.39 (95%CI:0.69-2.81), p=0.348 • Age at survey: 16-19 years (Ref. 12-15 years) OR=0.27 (95%CI:0.05-1.39) • Age at survey: 20-29 years (Ref. 12-15 years) OR=1.36 (95%CI:0.54-3.47) • Age at survey: 30-39 years (Ref. 12-15 years) OR=2.06 (95%CI:0.58-7.27) • Age at survey: 40-49 years (Ref. 12-15 years) OR=3.68 (95%CI:0.49-27.49) • Household income: Less than $49,999 (Ref. $100,000 and greater) OR=1.29 (95%CI:0.52-3.19) • Household income: $50-99,999 (Ref. $100,000 and greater) OR=2.16 (95%CI:0.98-4.76) • Survival time: 10-14 years (Ref. 2-9 years) OR=0.83 (95%CI:0.32-2.18) • Survival time: 15-19 years (Ref. 2-9 years) OR=1.33 (95%CI:0.45-3.91) • Survival time: 20-24 years (Ref. 2-9 years) OR=0.55 (95%CI:0.14-2.15) • Survival time: 25-29 years (Ref. 2-9 years) OR=0.34 (95%CI:0.05-2.17) • Survival time: 30+ years (Ref. 2-9 years) OR=0.83 (95%CI:0.14-5.16) • Chronic conditions: 1-2 (Ref. 0) OR=1.23 (95%CI:0.55-2.74) • **Chronic conditions: 3 or more (Ref. 0) OR=4.27 (95%CI:1.52-11.99)**	Selection bias: 1 301 were eligible, 268 participated. However, participants were drawn from a larger cohort followed up in a survivorship clinic, thus probably not representative for all CCS. Attrition bias: 1 268 evaluated Detection bias: 0 Not applicable Confounding: 1 Multivariable analyses performed **Total quality: 3/4**

1. What is the **risk and what are risk factors for suffering from Fatigue** in CAYA survivors?				
Cheung et al. Impact of Sleep, Fatigue, and Systemic Inflammation on Neurocognitive and Behavioral Outcomes in Long-Term Survivors of Childhood Acute Lymphoblastic Leukemia. 2017				
Study Design **Treatment era** **Years of follow-up** **Fatigue measurement**	**Participants**	**Treatment**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Cross-sectional study **Treatment era:** 2000-2010 **Years of follow-up:** Mean years from diagnosis 7.4 years (SD 1.9) **Country:** USA (treated at St. Jude Children's Research Hospital, SJCRH) **Fatigue measurement: PedsQL Multidimensional Fatigue Scale, domains assessed: general fatigue, sleep-rest fatigue and cognitive fatigue**	**Sample size:** N = 70 (male, n = 35) **Diagnoses:** Childhood Acute Lymphoblastic Leukemia **Age at diagnosis:** Male: mean 7.0 years (SD 4.8), range 1.2-16.5 years Female: mean 6.8 years (SD 4.5), range 1.9-17.7 years **Age at study:** Male: mean 14.8 years (SD 5.1), range 8.2-25.5 years Female: mean 13.9 years (SD 4.3), range 8.1-25.4 years **Controls:** No age-matched healthy comparison control group	All treated with chemotherapy only	**Risk:** Survivors self-reported more behavioral problems and greater fatigue compared with the general population (Supporting Information 3). Cognitive fatigue: All survivors mean -0.75 (SD 1.2) vs. expected population value (mean=0, SD=1), p=0.0003 Male mean -0.64 (SD 1.1) vs. female mean -0.85 (SD 1.3), p=0.61 General fatigue: All survivors mean -0.61 (SD 1.2) vs. expected population value (mean=0, SD=1), p=0.0003 Male mean -0.30 (SD .9) vs. female mean -0.88 (SD 1.4), p=0.19 Sleep-rest fatigue: All survivors mean -0.27 (SD 1.2) vs. expected population value (mean=0, SD=1), p=0.07 Male mean 0.16 (SD 1.0) vs. female mean -0.64 (SD 1.2), p=0.04 **Risk factors:** No risk factors for CRF were analyzed.	Selection bias: 1 - Recruited from SJCRH (treatment) - Response rate overall: 83% Attrition bias: 1 - Complete: 70 Detection bias: 0 Not possible, questionnaire study Confounding: 0 - Fatigue as a predictor, not as an outcome **Total quality: 2/4** Remarks: Neurocognitive testing, behavioral ratings, self-reported symptoms of fatigue, parent-reported (8-12 years) or self-reported (13-21 years) sleep measures, and serum collection (5 mL of blood)

1. What is the **risk and what are risk factors for suffering from Fatigue** in CAYA survivors?				
Nies et al. Long-Term Quality of Life in Adult Survivors of Pediatric Differentiated Thyroid Carcinoma. 2017				
Study Design **Treatment era** **Years of follow-up** **Fatigue measurement**	**Participants**	**Treatment**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Cross-sectional study **Treatment era:** 1970-2013 **Years of follow-up:** Median 17.8 years, range 5-44.7 years) **Country:** The Netherlands **Fatigue measurement:** Multidimensional Fatigue Inventory-20 (MFI-20)	**Sample size:** N = 67 (males n = 9) **Diagnoses:** Pediatric Differentiated Thyroid Carcinoma (DTC) **Age at diagnosis:** Median 15.8 years, range 7.9-18.8 years **Age at study:** Median 34.2 years, range 18.8-61.7 years **Controls:** Peers without a medical history of malignancy approached by participants (+/- 5 years) N = 56 (males n = 7) Median age at evaluation 34.0 years, range 19.4-60.2 years	All survivors underwent a total thyroidectomy and 131-I was administered to 97.0%.	**Risk:** Mental fatigue scores were significantly higher in survivors (p=0.012; higher scores represent more fatigue). Scores from the other MFI-20 subscales did not differ significantly between survivors and controls. Survivors vs. controls (median (25th percentile, 75th percentile) General fatigue: survivors 10 (8, 15) vs. controls 9 (5, 12), p=0.075 Physical fatigue: survivors 8 (5, 12) vs. controls 6 (4, 10), p=0.083 Reduced activity: survivors 8 (5, 11) vs. controls 8 (5, 11), p=0.613 Reduced motivation: survivors 6 (4, 9) vs. controls 6 (4, 9), p=0.879 Mental fatigue: survivors 9 (5, 15) vs. controls 7 (4, 10), p=0.012 Total: survivors 41 (31, 57) vs. controls 36 (27, 54), p=0.129 **Risk factors:** No multivariable risk factor analyses for fatigue	Selection bias:1 - Recruited from nationwide follow-up study - Response rate overall: 89.3% Attrition bias: 1 - Included: n=67 Detection bias: 0 Not possible, questionnaire study Confounding: 0 - No multivariable analyses **Total quality: 2/4** Remarks: - No multivariable analysis - Survivors of the nationwide study and participating survivors differed in age at evaluation (median 19.1 vs. 34.2 years, p<0.001) and follow-up duration (median 2.8 vs. 17.8 years, p<0.001)

1. What is the **risk and what are risk factors for suffering from Fatigue** in CAYA survivors?				
Rach et al. Predictors of fatigue and poor sleep in adult survivors of childhood Hodgkin's lymphoma: a report from the Childhood Cancer Survivor Study. 2017				
Study Design **Treatment era** **Years of follow-up** **Fatigue measurement**	**Participants**	**Treatment**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Baseline (2000-2002) and follow-up (2003-2007) questionnaire **Treatment era:** n.a. **Years of follow-up:** >5 years **Country:** USA **Fatigue measurement:** The Functional Assessment of Chronic Illness Therapy- Fatigue (FACIT-F) Survivors with a total score of ≤30 were classified as having clinically significant fatigue.	**Sample size:** N = 751 (male n = 372) **Diagnoses:** Pediatric Hodgkin's lymphoma (HL) **Age at diagnosis:** 0-10: n=150 (20%) 11-15: n=319 (42.5%) 16-20: n=282 (37.5%) **Age at study:** Follow-up survey age 18-29: n=53 (7.1%) 30-34: n=154 (20.5) ≥35: n=544 (72.4%) **Controls:** No healthy comparison control group. Comparisons have only been made between HL survivors with clinical elevations of fatigue and sleep problems and HL survivors without elevated fatigue.	Radiation therapy - Chest RT<30Gy (n=230, 30.6%) - Chest RT≥30Gy (n=445, 59.3%) Chemotherapy (patients may receive multi chemotherapy so the percentage exceeds 100) - Anthracycline (n=158, 21%) - Alkylating agents (n=419, 55.8%) - Bleomycin (n=147, 19.6%) - Vinca alkaloids and heavy metals (n=418, 55.7%) - None (n=326, 43.4%)	**Risk:** The proportion of survivors endorsing elevated fatigue was 17%. **Risk factors from multivariable logistic regression analysis:** • Sex: Female (Ref. Male) OR=4.75 (95%CI:2.47-9.15, p<0.001) • Emotional distress: Impaired (Ref. not impaired) OR=8.38 (95%CI:4.28-16.42, p<0.001) • Work status: Unemployed (Ref. employed) OR=2.90 (95%CI:1.27-6.62, p<0.01) • Body pain: Impaired (Ref. not impaired) OR=3.73 (95%CI:2.09-6.67, p<0.001) • Physical function: Impaired (Ref. not impaired) OR=3.28 (95%CI:1.75-6.15, p<0.001) • BMI: Overweight (Ref. Normal) OR=0.95 (95%CI:0.50-1.79, n.s.) • BMI: Obese (Ref. Normal) OR=1.06 (95%CI:0.52-2.15, n.s.)	Selection bias: 1 - Survivors of HL randomly selected from Childhood Cancer Survivor Study (CCSS) - Response rate overall: 79% Attrition bias: 1 - Complete: 751 Detection bias: 0 Not possible, questionnaire study Confounding: 1 - Multivariable logistic regression analyses investigated the demographic, psychological, and physical variables **Total quality: 3/4**

1. What is the **risk and what are risk factors for suffering from Fatigue** in CAYA survivors?				
Arpaci & Kilicarslan Toruner. Assessment of problems and symptoms in survivors of childhood acute lymphoblastic leukaemia. 2016				
Study Design **Treatment era** **Years of follow-up** **Fatigue measurement**	**Participants**	**Treatment**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Cross-sectional questionnaire **Treatment era:** n.a. **Years of follow-up:** Mean = 2.55 years (SD 1.19), range 1-5 years **Country:** Turkey **Fatigue measurement:** Collection form developed by the researchers	**Sample size:** N = 91 **Diagnoses:** Acute lymphoblastic leukaemia **Age at diagnosis:** Mean = 6.38 years (SD 3.84), range 1-14 years **Age at study:** Mean = 11.66 years (SD 4.17), range 5-23 years **Controls:** No control group	Chemotherapy (CT): n=50 (54.9%) Chemotherapy and radiotherapy (CT+RT): n=37 (40.7%) Haematopoietic stem cell transplantation (HSCT): n=4 (4.4%)	**Risk:** In total 29.7% (n=27) had fatigue **Risk factors:** No risk factor analyses for fatigue.	Selection bias: 1 - Recruited from three hospitals located in Ankara - Response rate overall: 95% Attrition bias: 1 - Included: n=91 Detection bias: 0 Not possible, questionnaire study Confounding: 0 Multivariable analyses have not been performed **Total quality: 2/4** Remarks: The variables were investigated using the Mann–Whitney U and chi-square test.

1. What is the **risk and what are risk factors for suffering from Fatigue** in CAYA survivors?				
Graef et al. Sleepiness, Fatigue, Behavioral Functioning, and Quality of Life in Survivors of Childhood Hematopoietic Stem Cell Transplant. 2016				
Study Design **Treatment era** **Years of follow-up** **Fatigue measurement**	**Participants**	**Treatment**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Cross-sectional study **Treatment era:** n.a. **Years of follow-up:** Mean 7.76 years (SD 1.87), range 5-14 years post-HSCT **Country:** USA **Fatigue measurement:** Pediatric Quality of Life Inventory Multidimentional Fatigue Scale (PedsQL MFS)	**Sample size:** N = 76 (males n=45) **Diagnoses:** Acute myeloid leukemia (n=31, 40.8%) Acute lymphoblastic leukemia (n=22, 29.0%) Severe aplastic anemia or other conditions requiring HSCT (n=16, 21.0%) Chronic myeloid leukemia (n=7, 9.2%) **Age at diagnosis:** <22 years of age at the time of transplant **Age at study:** Mean = 17.84 years (SD 6.04), range 8-29 years • Child (<13 years): n=18 (23.68%) • Adolescent (13-18 years): n=24 (31.58%) • Young adult (>18 years): n=34 (44.74) **Controls:** No control group	Pediatric hematopoietic stem cell transplant (HSCT)	**Risk:** Mean levels of fatigue were 69.21 (SD 20.14) for self-report (n=65) and 72.15 (SD 20.79) by parent report (n=38), indicating moderately elevated fatigue symptoms (scores range from 0 to 100, with higher scores indicating less fatigue). Compared to ratings described in another study*, ratings of total fatigue in survivors of this study indicated more fatigue than in healthy peers ($p<0.001$), but no difference compared to children on and off treatment for cancer ($p>0.05$). **Risk factors:** No multivariable risk factor analyses for fatigue. * Varni, J. W., Burwinkle, T. M., Katz, E. R., Meeske, K., & Dickinson, P. (2002). The PedsQL in pediatric cancer: Reliability and validity of the Pediatric Quality of Life Inventory Generic Core Scales, Multidimensional Fatigue Scale, and Cancer Module. Cancer, 94, 2090–2106.	Selection bias: 1 - Recruited from St. Jude Children's Research Hospital (sample representative of those who receive allogeneic transplant in that hospital) - Response rate overall: 78.4% Attrition bias: 1 - Included (self-report): n=76 Detection bias: 0 Not possible, questionnaire study Confounding: 0 Fatigue as a predictor, not as an outcome **Total quality: 2/4** Remarks: Self-report measures were completed for patients >18 years of age, and both self-and parent-proxy measures were completed for patients 8-18 years. Clinical information was obtained from electronic medical records.

1. What is the **risk and what are risk factors for suffering from Fatigue** in CAYA survivors?				
Lowe et al. Distinct health behavior and psychosocial profiles of young adult survivors of childhood cancers: a mixed methods study. 2016				
Study Design **Treatment era** **Years of follow-up** **Fatigue measurement**	**Participants**	**Treatment**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Mixed methods: Mail-based survey and semi-structured interviews **Treatment era:** n.a. **Years of follow-up:** Average time since diagnosis: 8.42 years (SD 5.73) **Country:** USA **Fatigue measurement:** Profile of Mood States (POMS)	**Sample size:** N = 104 (male: n=53) **Diagnoses:** • Hodgkin's lymphoma: n=24, 23.1% • Non-Hodgkin's lymphoma: n=9, 8.7% • Burkitt's lymphoma: n=4, 3.8% • Acute lymphoblastic leukemia: n=17, 16.3% • Acute myelogenous leukemia: n=3, 2.9% • Blastoma: n=6, 5.8% • Sarcoma: n=11, 10.6% • Thyroid cancer: n=10, 9.6% • Other: n=20, 19.2% **Age at diagnosis:** <18 years **Age at study:** Mean 22.13 years (SD 3.18) **Controls:** No control group, only comparisons among risk clusters were made	• Chemotherapy: n=86, 82.7% • Surgery: n=81, 77.9% • Radiation: n=58, 55.8%	**Risk:** POMS, fatigue-inertia: mean 8.13 (SD 5.99) **Risk factors:** No systematic risk factor analyses.	Selection bias: 0 - Recruitment limited to survivors whose current address and telephone number were available - Response rate overall: 55.5% Attrition bias: 1 - Included: n=104 (98%) Detection bias: 0 Not possible, questionnaire study Confounding: 0 Multivariable analyses were not performed **Total quality: 1/4** Remarks: Only data concerning the quantitative study are reported here

1. What is the **risk and what are risk factors for suffering from Fatigue** in CAYA survivors?				
Fortmann et al. Sleep Quality, Fatigue, and Quality of Life Among Teenage and Young Adult Cancer Survivors. 2018				
Study Design **Treatment era** **Years of follow-up** **Fatigue measurement**	**Participants**	**Treatment**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Cross-sectional survey study **Treatment era:** n.a. **Years of follow-up:** Time since active treatment in the off-treatment group: ≤3 months: 14% 4-11 months: 20% 1-5 years: 45.2% >5 years: 3.7% On active surveillance: 12.6% **Country:** United Kingdom **Fatigue measurement:** 13-item fatigue subscale of the Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-F) Scores above 22 were considered as clinically significant fatigue*. * Reeves WC, Lloyd A, Vernon SD, et al. Identification of ambiguities in the 1994 chronic fatigue syndrome research case definition and recommendations for resolution. BMC Health Serv Res. 2003;3(1):25.	**Sample size:** N = 202 (male: n=71; on treatment: n=67, off treatment: n=135, n=8: treatment status not known) **Diagnoses:** Leukemia n=55 Lymphoma n=66 Bone tumor n=16 Soft tissue tumor n=15 Carcinoma n=6 Germ cell tumor n=5 CNS tumor n=3 Melanoma n=2 Other n=31 **Age at diagnosis:** On treatment: mean 17.8 years (SD 3.3) Off treatment: mean 16.3 years (SD 4.3) **Age at study:** 13-24 years at study (inclusion criterion) On treatment: mean 19.6 years (SD 3.1) Off treatment: mean 20.2 years (SD 2.9) **Controls:** n.a.	Chemotherapy or radiotherapy • On treatment: n=64 (95.52%) • Off treatment: n=128 (94.81%) No chemotherapy or radiotherapy • On treatment: n=3 (4.48%) • Off treatment: n=7 (5.19%)	**Risk:** Mean fatigue score in off-treatment TYA survivors was 15.56 (SD=10.98) 26.67% of TYAs off treatment reported clinically significant levels of fatigue. **Risk factors:** No systematic risk factor analyses for fatigue.	Selection bias: 0 - TYA were recruited regardless of their date of diagnosis and treatment status - Response rate overall: n.a. (number of eligible participants not specified) Attrition bias: 1 - Incomplete responses were excluded Detection bias: 0 Not possible, questionnaire study Confounding: 1 Even though fatigue was an independent variable in the analysis, they controlled for age at survey, age at diagnosis, gender and ethnicity **Total quality: 2/4**

1. What is the **risk and what are risk factors for suffering from Fatigue** in CAYA survivors?				
Spathis et al. Cancer-Related Fatigue in Adolescents and Young Adults After Cancer Treatment: Persistent and Poorly Managed. 2017				
Study Design **Treatment era** **Years of follow-up** **Fatigue measurement**	**Participants**	**Treatment**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Cross-sectional study **Treatment era:** n.a. **Years of follow-up:** Months since diagnosis: mean 31 months (inter-quartile range (IQR) 18-49 mths) Months since last treatment: mean 18 months (IQR 10-32 mths) **Country:** United Kingdom **Fatigue measurement:** PedsQL Multidimensional Fatigue Scale (MFS)	**Sample size:** N = 80 (male: n=26) **Diagnoses:** Leukemia: n=20 (25%) Lymphoma: n=35 (44%) Osteosarcoma/Ewing's: n=6 (8%) Brain neoplasm: n=1 (1%) Other: n=18 (23%) **Age at diagnosis:** Mean 18.9 years (SD 3.1) range 12-24 years **Age at study:** Mean 22.1 years (SD 2.7) range 17-27 years **Controls:** n.a.	n.a.	**Risk:** 68 respondents (85%) experienced fatigue during the preceding month. The mean fatigue severity of the *fatigued participants* was 44.3 (SD=20.5). Fatigue severity was worse more than 1 year after cancer treatment (M=39, SD=19.7) compared to <1 year (M=53.8, SD=19.7; independent samples t-test, t(56)=2.8, p=0.007). Fatigue was worse in females (M=39.6, SD=19.3) than males (M=55.6, SD=19.6; t(66)=3.1, p=0.003), but was not associated with other demographic variables, including cancer type or treatment duration. **Risk factors:** No systematic multivariable risk factor analyses for fatigue.	Selection bias: 0 - Recruited from three teenage and young adult principal treatment centers (TYA PTCs) in the UK - Response rate overall: 41% Attrition bias: 1 - Included: n=80 Detection bias: 0 Not possible, questionnaire study Confounding: 0 **Total quality: 1/4** Remarks: Demographic data were collected for both respondents and non-respondents. Only data related to respondents was reported.

1. What is the **risk and what are risk factors for suffering from Fatigue** in CAYA survivors?				
Johannsdottir et al. Adverse Health Outcomes and Associations with Self-Reported General Health in Childhood Lymphoma Survivors. 2017				
Study Design **Treatment era** **Years of follow-up** **Fatigue measurement**	**Participants**	**Treatment**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Cross-sectional study with clinical examinations **Treatment era:** 1970-2000 **Years of follow-up:** Median 20 years (range: 7-37 years) **Country:** **Norway** **Fatigue measurement:** **Fatigue Questionnaire (FQ)**	**Sample size:** N = 124 (male: n=58) **Diagnoses:** Non-Hodgkin lymphoma (n=43) Hodgkin lymphoma (n=81) **Age at diagnosis:** Median 15 years (range: 2-18 years) **Age at study:** Median 33 years (range: 19-54 years) **Controls:** General health was compared with 478 individuals from the Norwegian general population, aged 30-39 years	Chemotherapy only (n=38) Radiotherapy only (n=14) Chemotherapy and radiotherapy (n=72) 10 participants received also stem cell transplantation in combination with total body radiation (n=5) or chemotherapy as conditioning regimen (n=5)	**Risk:** Grade 0: Asymptomatic (no) fatigue; n=86 (/124=69.4%) Grade 2: Chronic fatigue (i.e. substantial fatigue (≥4; with duration of at least 6 months); n=38 (/124=30.6%) **Risk factors:** No systematic risk factor analyses for fatigue.	Selection bias: 1 - Identified through the Norwegian cancer registry - Response rate overall: 56% Attrition bias: 1 - Complete questionnaires: 124 Detection bias: 0 Not possible, questionnaire study Confounding: 0 No multivariable analysis **Total quality: 2/4** Remarks: Psychosocial adverse health outcomes (AHOs) were assessed by the survivor's competition of validated instruments as the Hospital Anxiety and Depression Scale (HADS) and the fatigue questionnaire

1. What is the **risk and what are risk factors for suffering from Fatigue** in CAYA survivors?				
Karimi et al. Fatigue, Physical and Functional Mobility, and Obesity in Pediatric Cancer Survivors. 2019				
Study Design **Treatment era** **Years of follow-up** **Fatigue measurement**	**Participants**	**Treatment**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Cross-sectional study **Treatment era:** n.a. **Years of follow-up:** Time since diagnosis mean 5.9 years (SD 4.5) **Country:** USA **Fatigue measurement:** PROMIS V1.0 Pediatric Profile 25: among others 4 items on fatigue, 5-point likert scale (0-4), higher scores represent higher levels of fatigue. Scored by summing items, possible range of 0-16.	**Sample size:** N=144 **Diagnoses:** ALL/AML n=64 (44.5%) Brain tumor n=23 (16.0%) Lymphoma n=13 (9.0%) Solid tumor n=38 (26.4%) Neurocutaneous syndrome n=2 (1.4%) Other n=4 (2.8%) **Age at diagnosis:** n.a. **Age at study:** Mean 12.9 years (SD 3.0) **Controls:** No control group.	Bone marrow transplant n=7 (4.9%) Stem cell transplant: Allotransplantation n=6 (4.2%) Autotransplantation n=5 (3.4%) Chemotherapy n=135 (93.8%) Radiation therapy n=50 (34.7%) Surgery n=90 (62.5%)	**Risk:** Children reported normal levels of fatigue (mean 4.1 (SD 4.0); range 0-16). 22 children (/144=15.3%) reported elevated levels of fatigue* **Risk factors for fatigue from hierarchical linear regression** (adjusted for age, sex, race, time since diagnosis, diagnosis, chemotherapy, radiation, depression, parent reported depression/anxiety, BMI, physical and function mobility): Shorter time since diagnosis, more depression symptoms, and more difficulty with mobility predicted higher levels of fatigue. • Age at survey: β=-0.005, p=0.935 • Gender**: β=0.008, p=0.895 • **Race**: β=-0.123, p=0.047** • **Time since diagnosis: β=-0.154, p=0.019** • Diagnosis**: β=-0.045, p=0.464 • Chemotherapy: β=0.097, p=0.121 • Radiation: β=-0.030, p=0.625 • **Depression: β=0.396, p<0.001** • Parent-reported depression/anxiety: β=0.117, p=0.095 • BMI: β=-0.036, p=0.560 • **Physical and function mobility: β=-0.427, p<0.001**	Selection bias: 1 Review of medical charts, ≥80% gave consent Attrition bias: 1 All analyzed Detection bias: 0 No blinding possible Confounding: 1 Analyses adjusted for important confounders **Total quality: 3/4** Remarks: *definition of fatigue caseness is not clear from the manuscript ** reference categories not specified, variable therefore not included in the overall conclusions

4. Does the risk of developing Fatigue change over time in CAYA survivors?				
Macpherson et al. Exercise and Fatigue in Adolescent and Young Adult Survivors of Hodgkin Lymphoma: A Report from the Children's Oncology Group. 2015				
Study Design **Treatment era** **Years of follow-up** **Fatigue measurement**	**Participants**	**Treatment**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Retrospective cohort study with data from a RCT **Treatment era:** Not available **Years of follow-up:** End of therapy, 12 and 36 months post-therapy measurements. **Fatigue measurement:** No standardized measurement **Country:** USA	**Sample size:** N=103 **Diagnoses:** • Hodgkin Lymphoma **Age at diagnosis:** Mean age at dx: 15.46 years (13-21 years) **Age at study:** Not available **Controls:** No controls.	Protocol treatment arm: Rapid early responders: **Rapid early responders:** • ABVE-PC x 4, <CR, IFRT n=47 (45.6%) • ABVE-PC x 4, CR, IFRT n=15 (14.6%) • ABVE-PC x 4, CR, NO IFRT n=26 (25.2%) **Slow early responders:** • ABVE-PC x 4 + IFRT + DECA x 2 n= 10 (9.7%) • ABVE-PC x 4 + IFRT n=5 (4.9%)	Five items (Scale 0 "very much so" to 4 "not at all"), measured at end of therapy, 12 months post-therapy and 36 months post-therapy: "Felt tired": No significant changes at 12-month or 36-month assessment compared to baseline "Had trouble finishing tasks because tired quickly": No significant changes at 12-month or 36-month assessment compared to baseline "Needed to sleep during the day": No significant changes at 12-month or 36-month assessment compared to baseline "Frustrated by being too tired to do things he/she wanted to do": No significant changes at 12-month or 36-month assessment compared to baseline "Needed to limit social activities because of fatigue": Slight improvement at 12-month assessment ($p<0.045$), but no significant change at 36-month assessment compared to baseline.	Selection bias: 0 Secondary analysis of data collected as a randomized controlled trial. There's no information on how the randomization was done. One inclusion criterion is "completed a self-report survey at end of treatment, 12 and 36 months" → then it's rather not representative Attrition bias: 1 N=93/103 responded fatigue questions at 36 months → 90.3% Detection bias: 0 Questionnaire survey, no blinding possible. Confounding: 1 Multivariable logistic regression was used to evaluate association with exercise. **Total quality 2/4**

4. Does the risk of developing Fatigue change over time in CAYA survivors?				
Zeller et al. Chronic Fatigue in Long-term Survivors of Childhood Lymphomas and Leukemia: Persistence and Associated Clinical Factors. 2014				
Study Design **Treatment era** **Years of follow-up** **Fatigue measurement**	**Participants**	**Treatment**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Case-control study **Treatment era:** 1970-2002 **Years of follow-up:** Median 25.3 years (range 11.3-39.9) **Fatigue measurement:** **Fatigue Questionnaire (FQ)** **Country:** Norway	**Sample size:** Total n=62/102 **Diagnoses:** • Lymphoma n=33 • Acute lymphoblastic leukemia (ALL) n=29 **Age at diagnosis:** Not mentioned. **Age at study:** Mean 34.05 years **Years of follow-up:** Mean 23.5 years Controls did not differ from "cases" (with chronic fatigue (CF)) in sex, age at study, diagnosis, therapy, follow-up time	Radiation therapy: • CF: 43% • Controls: 57% Cum. Anthracycline dose (mg): • CF: mean 166.2 (SD 139.9) • Controls: 170.0 (SD 127.6)	1. Fatigue assessment: 79/290 (27.2%) survivors were fatigued [≥5 years since diagnosis] 2. Fatigue assessment at a median of 2.7 years later (1-4.3 years) [mean follow-up time of 23-24 years]: case-control study (no prevalence measure possible). **Persistent fatigue:** 32 of 53 former CF cases (60.4%) were still fatigued. **Persistently non-fatigued:** 40 of 49 former non-CF cases (81.6%) were still not fatigued **Converters:** 21 of 53 former CF cases (39.6%) were no longer fatigued 9 of 49 former non-CF cases (18.4%) were now fatigued	Selection bias: 0 Original cohort was 430 survivors, only 102 were included for this study. Attrition bias: 0 62/102 were analyzed. Detection bias: 0 Questionnaire survey, no blinding possible. Confounding: 1 Multivariate statistics were used. **Total quality: 1/4**

5. What is the most reliable and valid diagnostic tool to diagnose Fatigue in CAYA survivors?				
Ho et al. Psychometric properties of the Chinese version of the fatigue scale-adolescent. 2015				
Study Design **Treatment era** **Years of follow-up** **Diagnostic tool**	**Participants**	**Diagnostic tool**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Cross-sectional study **Treatment era:** n.a. **Years of follow-up:** 62% (n=124) have ≥25 months since treatment completed; n=37 (18.5%) 13-24 months; n=39 (19.5%) 6-12 months. **Fatigue measurement:** **Fatigue-scale adolescent (FS-A)** **Country:** Hong Kong, China	**Sample size:** N=200 adolescent cancer survivors (ACS) N=50 adolescent cancer patients (ACP) **Diagnoses:** • Leukemia n=91 (45.5%) • Lymphoma n=57 (28.5%) • Brain tumor n=33 (16.5%) • Osteosarcoma n=9 (4.5%) • Kidney tumor n=4 (2.0%) • Germ-cell tumor n=6 (3.0%) **Age at diagnosis:** Not available **Age at study:** N=200 CCS: 13-14 years: n=48 (24%) 15-16 years: n=70 (35%) 17-18 years: n=82 (41%) N=50 ACP: 13-14 years: n=13 (26%) 15-16 years: n=18 (36%) 17-18 years: n=19 (38%) **Controls:** N=50 healthy controls (HC; age at study): 13-14 years: n=15 (30%) 15-16 years: n=18 (36%) 17-18 years: n=17 (34%)	Chinese version of the Fatigue Scale for Adolescents (FS-A) **Cases of Fatigue:** Levels of fatigue ACS:28.6 (SD 3.7) ACP: 31.3 (SD 5.2) HC: 22.1 (SD 4.8)	**Reliability:** "The test-retest reliability coefficient of the Chinese version of the FS-A at a 2-week interval was 0.85 (ICCvalue), indicating a reliability of 0.80 or higher, which is acceptable for an instrument to be used in research." After deletion of items 6 and 10, Cronbach's alpha was 0.89. **Validity:** - Semantic equivalence was high (94%). - Content validity index was 82%, after omission of items 6 and 10 even higher (92%), indicating good content validity. - The known-groups validity (ACS, ACP, HC) was supported, mean FS-A score of the ACS was significantly lower than that of the ACP, but significantly higher than that of the HC. - The discriminant validity of the FS-A was supported: There was a strong positive correlation between scores on the FS-A and CES-DC (r=0.53, n=200, P<0.01), indicating that adolescents with higher levels of fatigue were associated with more depressive symptoms. In addition, there was a strong negative correlation between scores on the FS-A and PedsQL (r=−0.58, n=200, P<0.01), indicating that higher levels of fatigue were to be associated with lower quality of life.	Selection bias: 0 Convenience sample of 200 survivors. Attrition bias: 1 All answered the fatigue questionnaire. Detection bias: 0 Questionnaire survey, no blinding possible. Confounding: 0 Multivariable analysis were not used. **Total quality: 1/4**

5. What is the most reliable and valid diagnostic tool to diagnose Fatigue in CAYA survivors?				
Nascimento et al. High validity and reliability of the PedsQL Multidimensional Fatigue Scale for Brazilian children with cancer. 2015				
Study Design **Treatment era** **Years of follow-up** **Diagnostic tool**	**Participants**	**Diagnostic tool**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Cross-sectional study **Treatment era:** n.a. **Years of follow-up:** any stage (outpatient, hospitalized, palliative care); >50% still in active treatment **Country:** Brazil	**Sample size:** N=42 children (8-12 years) N=68 teenagers (13-17 years) N=106 caregivers **Diagnoses:** Leukemias and lymphomas 45.9% CNS tumor 21.6% Sarcomas 14.4% Other 18% **Age at diagnosis:** n.a. **Age at study:** See above **Treatment:** Chemo 39.6% Chemo and surgery 27.9% Chemo and radio 11.7% Chemo, radio and surgery 9.9% Surgery 5.4% Other 5.4%	PedsQL MFS-Brazilian version **Cases of Fatigue:** n.a.	**Reliability:** "[…] overall scale reliability was acceptable, as Cronbach's alpha statistic values varied between 0.70 and 0.90 for all dimensions, self and proxy versions. The only exception was the self-reported dimension sleep/rest fatigue, for which a Cronbach's alpha of 0.55 was observed." "Overall, the results showed acceptable levels of reliability, except for the self-reported sleep/rest fatigue dimension." **Validity:** "[…] in all cases linear correlation coefficients were greater than 0.40 for the dimension to which the item belonged (convergent validity). Adjustment values of 100% for all dimensions for both the proxy and self-reported versions (divergent validity) were also observed." "Root mean square error of approximation values were also within acceptable limits (0.08-0.10), with 0.098 and 0.095 for the self-report and proxy versions, respectively. These values indicate that the factorial structure of the construct is maintained in the model adapted for Brazil." "The comparative fit index for children and teenagers was lower than the expected threshold of 0.90 (0.699 and 0.847, for the self and proxy versions, respectively)." "The results of this study demonstrate acceptable reliability and validity of the Brazilian version of the scale for use in children with cancer."	Selection bias: 0 Convenience sample Attrition bias: 1 Outcome was assessed for >75% of remaining Detection bias: 0 No blinding Confounding: 1 Total 2/4

5. What is the most reliable and valid diagnostic tool to diagnose Fatigue in CAYA survivors?				
Baptista et al. Psychometric properties of the multidimensional fatigue inventory in Brazilian Hodgkin's lymphoma survivors. 2012				
Study Design **Treatment era** **Years of follow-up** **Diagnostic tool**	**Participants**	**Diagnostic tool**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Cross sectional study **Treatment era:** 1996-2004 **Years of follow-up:** Median follow-up was seven years (range 3.6-12.7 years) **Country:** Brazil	**Sample size:** N=200 **Diagnoses:** Hodgkin's lymphoma **Age at diagnosis:** n.a. **Age at study:** Median age 29 years (range 16-77 years) **Treatment:** n.a.	Brazilian version of the Multidimensional Fatigue Inventory **Cases of Fatigue:** n.a.	**Reliability:** Overall Cronbach's alpha: "The overall Cronbach's alpha coefficient for the 20 items was 0.84, and the Cronbach's alpha of each of the five scales ranged from 0.59 to 0.81." "Cronbach's alpha coefficient was higher than 0.7 in all dimensions, indicating a fairly good reliability, except for "reduced motivation"." **Validity:** Construct validity: "The factor analysis yielded a five-factor solution that explained 65% of the variance, which is consistent with the multidimensional concept of fatigue." "The present findings support the reliability and validity of the Brazilian Portuguese version, which can be used to assess fatigue in clinical and epidemiological studies; […]"	Selection bias: 0 Only 229/335 were contacted = 68.4% Attrition bias: 1 Outcome was assessed for >75% of remaining Detection bias: 0 No blinding Confounding: 1 Total 2/4

5. What is the most reliable and valid diagnostic tool to diagnose Fatigue in CAYA survivors?				
Robert et al. Feasibility, reliability, and validity of the Pediatric Quality of Life Inventory generic core scales, cancer module, and multidimensional fatigue scale in long-term adult survivors of pediatric cancer. 2012				
Study Design **Treatment era** **Years of follow-up** **Diagnostic tool**	**Participants**	**Diagnostic tool**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Cross-sectional study **Treatment era:** n.a. **Years of follow-up:** 25.2 years (range 5-43) **Country:** USA	**Sample size:** N=64 **Diagnoses:** Solid tumor 51.6% Leukemia 17.2% Lymphoma 17.2% CNS tumor 14.1% **Age at diagnosis:** Mean 9.6 years (range 1-21) **Age at study:** Mean 34.5 years (range 25-53) **Treatment:** n.a.	PedsQL Multidimensional Fatigue Scale (adaptation to 18-25 year olds)	**Reliability:** PedsQL Multidimensional Fatigue Scale: Total Fatigue Score had a Cronbach's alpha of 0.95; all subscales >0.88 **Validity:** n.a.	Selection bias: 0 Convenience sample Attrition bias: 0 Outcome was assessed for <75% of remaining Detection bias: 0 No blinding Confounding: 1 Total 1/4

5. What is the most reliable and valid diagnostic tool to diagnose Fatigue in CAYA survivors?				
Nagai et al. Fatigue in survivors of childhood acute lymphoblastic and myeloid leukemia in Japan. 2012				
Study Design **Treatment era** **Years of follow-up** **Diagnostic tool**	**Participants**	**Diagnostic tool**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Cross-sectional study **Treatment era:** n.a. **Years of follow-up:** Mean time after completion of treatment: 5.8 years (SD 3.8) **Country:** Japan	**Sample Size:** n = 81 **Diagnoses:** ALL 77.8% and AML 22.2% **Age at diagnosis:** Mean 6.7 years (SD 3.5) **Age at study:** Mean 14.1 years (SD 5.7) **Treatment:** Chemo only 55.6% Chemo + radiation 9.9% Chemo + SCT 12.3% Chemo + radiation + SCT 22.2%	Devised their own 12-item fatigue questionnaire	**Validity:** "Cronbach's alpha for the total and each of the three fatigue dimension scores was between 0.75 and 0.88 in both the patient and control groups. These values (i.e. >0.7) are considered to indicate good internal consistency." **Reliability:** "We evaluated the reliability of the questionnaire by comparing total fatigue scores in the control subjects with the subscales in the Chalder scale. The correlation coefficient between the questionnaire and the Chalder scale was 0.89, supporting the construct validity of the questionnaire." "We developed our own questionnaire consisting of 12 items, and it demonstrated good validity and reliability."	Selection bias: 0 Participants were recruited at follow-up appointment, unclear whether convenience sample or population based Attrition bias: 1 81/90 included & analyzed Detection bias: 0 No blinding possible Confounding: 1 Total 2/4

5. What is the most reliable and valid diagnostic tool to diagnose Fatigue in CAYA survivors?				
Bektas et al. Developing scales for the assessment of fatigue in Turkish pediatric oncology patients aged 13-18 and their parents. 2014				
Study Design **Treatment era** **Years of follow-up** **Diagnostic tool**	**Participants**	**Diagnostic tool**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Cross-sectional study **Treatment era:** n.a. **Years of follow-up:** n.a. **Country:** Turkey	**Sample size:** N=184 **Diagnoses:** 57.6% leukemia **Age at diagnosis:** n.a. **Age at study:** Average age 14.6+/-1.4 **Treatment:** 59.8% only chemotherapy	Scale for the Assessment of Fatigue in Pediatric Oncology Patients Aged 13-18 Scale for the Assessment of Fatigue in Pediatric Oncology Patients Aged 13-18 for Parents	**Sensitivity:** Child form: 1.00 (cutoff 75.5 points) Parent form: 1.00 (cutoff 73 points) **Specificity:** Child form: 0.06 (cutoff 75.5 points) Parent form: 0.06 (cutoff 73 points) **Reliability:** Cronbach's alpha=0.99 in total for the scale **Validity:** Parent Form: "The Kaiser-Meyer-Olkin coefficient (KMO) was determined as 0.799" "The total variance being explained is 90.5%." Known group comparison: "a statistically significant difference was determined between the score averages" Child Form: "the KMO was determined as 0.777" "The total variance being explained is 89.4%." Known group comparison: "a statistically significant difference was determined between the score averages" "This study suggests that the Scale for the Assessment of Fatigue in Pediatric Oncology Patients Aged 13-18 and the Scale for the Assessment of Fatigue in Pediatric Oncology Patients Aged 13-18 for Parents are valid and reliable instruments in assessing the fatigue symptoms of children in Turkey."	Selection bias: 0 Convenience sample Attrition bias: 1 Outcome was assessed for >75% of remaining Detection bias: 0 No blinding Confounding: 1 Total 2/4

5. What is the most reliable and valid diagnostic tool to diagnose Fatigue in CAYA survivors?				
Brand et al. Screening for fatigue in adolescent and young adult pediatric brain tumor survivors: accuracy of a single-item screening measure. 2016				
Study Design **Treatment era** **Years of follow-up** **Diagnostic tool**	**Participants**	**Diagnostic tool**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Cross-sectional **Treatment era:** Not mentioned **Years of follow-up:** Mean time since diagnosis 10.55 years (SD 5.57; range 2-27 years) **Country:** USA	**Sample size:** n=142 **Diagnoses:** Brain tumor: Low-grade glioma: n=80 Embryonal tumor: n=29 Ependymoma: n=14 Craniopharyngioma: n=8 Germ cell: n=8 Choroid plexus: n=2 High-grade glioma: n=1 **Age at diagnosis:** Mean 9.72 (SD 4.87; range 4 months-22 years) **Age at study:** Mean 20.24 (SD 4.81; range 12-32 years) **Controls:** No	Fatigue Thermometer (FT): Visual scale labeled from 0 (no fatigue) to 10 (worst fatigue imaginable). Pediatric Quality of life inventory multidimensional fatigue scale (MFS) : 18 items rated on 5 point Likert scale. Higher scores indicate fewer symptoms of fatigue.	"The AUC for the FT was 0.822, indicating the FT had good diagnostic utility relative to the gold standard of the total MFS." "No possible cutoff scores for the FT could be chosen that resulted in a sensitivity and specificity meeting the a priori criteria (sensitivity of >0.90 and specificity of >0.75)." "Results from this study suggest that a single-item screening measure for fatigue is not able to reliably identify clinically significant fatigue in AYA brain tumor survivors."	Selection bias: 0 Original cohort brain tumor survivor project REACH: n= 245 Eligible for this study: n=191 (77%) Included: n=142 (58%) Attrition bias: 1 81/90 included & analyzed Detection bias: 0 No blinding possible Confounding: 1 Total 2/4

5. What is the most reliable and valid diagnostic tool to diagnose Fatigue in CAYA survivors?				
Kudubes et al. Developing a scale for the assessment of fatigue in pediatric oncology patients aged 7-12 for children and parents. 2014				
Study Design **Treatment era** **Years of follow-up** **Diagnostic tool**	**Participants**	**Diagnostic tool**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Cross sectional study **Treatment era:** n.a. **Years of follow-up:** n.a. **Country:** Turkey	**Sample size:** N=204 **Diagnoses:** Leukemia 49% **Age at diagnosis:** **Age at study:** Aged 7-12 years **Treatment:** Only chemo 51% Chemo and radio and surgery 25% Radiotherapy head-neck 18.1%	Scale for the Assessment of Fatigue in Pediatric Oncology Patients Aged 7-12 Scale for the Assessment of Fatigue in Pediatric Oncology Patients Aged 7-12 for Parents	**Sensitivity:** Child form: 0.73 **Specificity:** Child form: 0.93 **Reliability:** Cronbach's alpha=0.98 in total for the scale **Validity:** Parent Form: "the Kaiser-Meyer-Olkin coefficient (KMO) was determined as 0.791 […] The total variance being explained is 85.7%." Known group comparison: "a statistically significant difference was determined between the score averages" Child Form: "the KMO was determined as 0.863 […] The total variance being explained is 84.7%" Known group comparison: "a statistically significant difference was determined between the score averages" "This study suggests that our scales for the assessment of fatigue in pediatric oncology patients aged 7-12 and their parents are valid and reliable instruments."	Selection bias: 0 Convenience sample Attrition bias: 1 Outcome was assessed for >75% of remaining Detection bias: 0 No blinding Confounding: 1 Total 2/4 **Remarks:**

5. What is the most reliable and valid diagnostic tool to diagnose Fatigue in CAYA survivors?				
Gerceker et al. Reliability and validity of Turkish versions of the child, parent and staff cancer fatigue scales. 2012				
Study Design **Treatment era** **Years of follow-up** **Diagnostic tool**	**Participants**	**Diagnostic tool**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Cross-sectional study **Treatment era:** **Years of follow-up:** still in active treatment **Country:** Turkey	**Sample size:** N=52 children N=86 parents N=43 nurses **Diagnoses:** Leukemia 59.6% Lymphoma 11.5% Other 28.9% **Age at diagnosis:** 7-12 years **Age at study:** 7-12 years; Mean age 9.67 years (SD1.89) **Treatment:** Corticosteroid treatment 44.2% Radiotherapy treatment 21.2% Surgery treatment 25.0%	Child Fatigue Scale-24 Hours Parent Fatigue Scale-24 Hours Staff Fatigue Scale-24 Hours **Cases of Fatigue:**	**Reliability:** "The Cronbachs Alpha coefficient for internal consistency was ascertained for the CFS-24 hours as 0.83; for the PFS-24 hours as 0.77 and for the SFS-24 hours as 0.72." **Validity:** Content Validity was tested by assessing the appropriateness of all items by ten academics working in the field of pediatrics and oncology. The items that needed improvements were reviewed once again and changes were made. "[…] the Turkish versions of CFS-24 hours, SFS-24 hours and PFS-24 hours were reaffirmed as valid and reliable in evaluating cancer related fatigue."	Selection bias: 0 Convenience sample Attrition bias: 1 Outcome was assessed for >75% of remaining Detection bias: 0 No blinding Confounding: 1 Total 2/4

5. What is the most reliable and valid diagnostic tool to diagnose Fatigue in CAYA survivors?				
Tomlinson et al. Psychometric properties of instruments used to measure fatigue in children and adolescents with cancer: a systematic review. 2013				
Study Design **Treatment era** **Years of follow-up** **Diagnostic tool**	**Participants**	**Diagnostic tool**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Systematic review **Treatment era:** n.a. **Years of follow-up:** n.a.	**Sample size:** N=25 articles		The most commonly used instruments were: 1. Fatigue Scale-Child (FS-C) and Fatigue Scale-Adolescent (FS-A) and the proxy versions for parents (Fatigue Scale-Parents) and staff (Fatigue Scale-Staff) and 2. PedsQL Multidimensional Fatigue Scale (MFS) self-report and parent proxy versions. Four other CRF instruments also had psychometric properties reported (Pediatric Functional Assessment of Chronic Illness Therapy-Fatigue; Memorial Symptom Assessment Scale (MSAS); Daily Fatigue Report Scale; and McCorkle Symptom Distress Scale (SDS). The FS-C is recommended for children aged 7-12 years, the FS-A for adolescents aged 13-18 years. The FS generally has good internal consistency, inter-rater reliability and responsiveness. Known group validity is more variable. The PedsQL MFS child report has versions for three age ranges (5-7, 8-12 and 13-18 years), the parent report includes a forth age group (2-4 years). In general, this instrument has good internal consistency and responsiveness. Similar to the Fatigue Scale, known group validity is inconsistent. “In conclusion, our findings demonstrate that either the Fatigue Scale or the PedsQL MFS can be incorporated into clinical trials as endpoints when the intention of the study is to evaluate fatigue or the effects of an intervention on fatigue in a population of children or adolescents with cancer.”	Remark: “[…] fatigue is primarily a subjective experience; child self-report should be the primary source of information for fatigue intensity where possible, based on age, cognitive and communicative abilities, and situational factors.”

5. What is the most reliable and valid diagnostic tool to diagnose Fatigue in CAYA survivors?				
Hinds et al. PROMIS pediatric measures in pediatric oncology: valid and clinically feasible indicators of patient-reported outcomes. 2013				
Study Design **Treatment era** **Years of follow-up** **Diagnostic tool**	**Participants**	**Diagnostic tool**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Cross-sectional study **Treatment era:** n.a. **Years of follow-up:** Active treatment (received disease-directed therapy within the past 45 days) or survivorship group (completed cancer treatment, disease-free, in follow-up care) **Country:** USA	**Sample size:** N=200 (n=107 survivors; n=93 in active treatment) **Diagnoses:** Leukemia or lymphoma n=120 (60.0%) Brain tumor N=22 (11.0%) Solid tumor n=58 (29.0%) **Age at diagnosis:** <17 years **Age at study:** 8-12y 45.5% 13-17y 54.5% Mean age 12.9 years (SD 2.9) **Treatment:** n.a.	Eight PROMIS pediatric measures: 1. Physical Functioning-Mobility 2. Physical Functioning-Upper Extremity 3. Pain Interference 4. Fatigue 5. Depression 6. Anxiety 7. Peer Relationships 8. Anger	**Sensitivity:** n.s **Specificity:** n.s. **Reliability:** n.s. **Validity:** Known-group validity: children in the active treatment group had significantly higher (worse) scores on the PROMIS fatigue outcome measure (short form): Active treatment: 52.9 (SD 13.5) vs. Survivorship care: 43.8 (SD 11.8), p<0.001 This remained so even after controlling for demographic variables, tumor type, and presence/absence of other health problems. Acceptability and feasibility of the PROMIS measures was high. Known-groups validity was supported by the findings.	Selection bias: 1 200/203 participated Attrition bias: 1 195/200 analyzed Detection bias: 0 Blinding not possible Confounding: 1 Controlled for main confounders Total 3/4

5. What is the most reliable and valid diagnostic tool to diagnose Fatigue in CAYA survivors?				
Mandrell et al. Psychometric and Clinical Assessment of the 13-Item Reduced Version of the Fatigue Scale-Adolescent Instrument. 2011				
Study Design **Treatment era** **Years of follow-up** **Diagnostic tool**	**Participants**	**Diagnostic tool**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Cross-sectional study **Treatment era:** 2011 **Years of follow-up:** Assessed during active treatment **Country:** USA	**Sample size:** N=138 **Diagnoses:** ALL 37.7% AML 2.9% HL/Lymphoma 37.7% Solid tumor 18.1% Germ cell tumor 3.6% **Age at diagnosis:** See below. **Age at study:** Mean age of 15.51 years **Treatment:**	Fatigue Scale-Adolescent (13-18 year old)	**Reliability:** "13-item FS-A achieved an internal consistency coefficient (Cronbach alpha) of 0.87." "Confirmatory factor analysis suggested a reasonable fit of the 4-factor structure: The goodness-of-fit index was 0.8551, and the root mean square residual was 0.080. The Spearman correlation coefficient between the FS-A and FS-P was 0.347 (p=0.0033) in the 75 patient/parent dyads." "According to the Youden index, the cut score of the 13-item FS-A was 31, sensitivity was 66.6%, and specificity was 82.6%. The AUC was 0.797." "The 13-item FS-A has acceptable psychometric properties and is able to identify adolescent oncology patients with high fatigue."	Selection bias: 0 Unclear how the participants were recruited in the 9 studies. Attrition bias: 0 Unclear Detection bias: 0 No blinding possible Confounding: 1 Total 1/4

5. What is the most reliable and valid diagnostic tool to diagnose Fatigue in CAYA survivors?				
Ho et al. The Psychometric Properties of the Chinese Version of the Fatigue Scale for Children. 2016				
Study Design **Treatment era** **Years of follow-up** **Diagnostic tool**	**Participants**	**Diagnostic tool**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Cross-sectional design **Treatment era:** n.a. **Years of follow-up:** Mean time of recovery was 4.2 years **Country:** China, Hong Kong	**Sample size:** N=200 cancer survivors (CS) N=50 cancer children (CC) N=50 healthy children (HC) **Diagnoses:** Leukemia 33.5% Lymphoma 23.0% Brain tumor 17.5% Osteosarcoma 13.0% Kidney tumor 7.5% Germ cell tumor 5.5% **Age at diagnosis:** <12 years (not specified) **Age at study:** Median slightly below 9 years (not specified) **Treatment:** Chemotherapy 44.5% Surgery 8% BMT 8% Chemo and BMT 15% Surgery and chemo 10.5% Chemo and radio 7.5% Radio and surgery 6.5%	Chinese Version of the Fatigue Scale for Children (FS-C), **Cases of Fatigue:** Levels of Fatigue: CS 27.0 (SD 8.3; p=0.02 compared to HC) CC 30.4 (SD 7.2; p<0.001 compared to HC) HC 22.6 (SD 5.0)	**Reliability:** "A Cronbach's alpha of 0.88 confirmed the internal consistency of the Chinese version of the FS-C (14 items), thus supporting its use for research purposes." "All of the items were highly correlated with the scale except item 8, which had a correlation of 0.20. After a thorough discussion among the panel members, it was removed from the scale. Cronbach's alpha for the remaining 13 items was 0.91." **Validity:** "The semantic equivalence for items ranged from 83% to 100%, indicating that the meanings of the translated items were equivalent to those of the original items." "After removing item 8 from the analysis, the content validity index was 0.83 for scale and ranged from 0.83 to 1.00 for items." "The convergent validity and discriminant validity of the scales are […] supported." "The mean level of fatigue reported by the survivors was significantly lower than that of the children currently receiving cancer treatment, but statistically significantly higher than that of the healthy comparison group, with P < .05 for both. This supports the Chinese version of the FS-C having good known-group validity."	Selection bias: 0 unclear Attrition bias: 1 Outcome was assessed for >75% of remaining Detection bias: 0 No blinding Confounding: 1 Total 2/4

5. What is the most reliable and valid diagnostic tool to diagnose Fatigue in CAYA survivors?				
Macpherson et al. Comparison of Legacy Fatigue Measures With the PROMIS Pediatric Fatigue Short Form. 2018				
Study Design **Treatment era** **Years of follow-up** **Diagnostic tool**	**Participants**	**Diagnostic tool**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Longitudinal study **Treatment era:** n.a. **Years of follow-up:** During treatment **Country:** USA	**Sample size:** N=96 **Diagnoses:** Lymphoma or ALL n=56 Solid tumor n=35 Brain tumor n=5 **Age at diagnosis:** n.a. **Age at study:** 8-12 years: n=40 13-18 years: n=56 **Treatment:** n.a.	PROMIS Pediatric Fatigue Short Form Fatigue Scale-Adolescent Fatigue Scale-Child Symptom Distress Scale fatigue item	**Sensitivity:** n.a. **Specificity:** n.a. **Reliability:** Over the three time points, Cronbach's Alpha was 0.93-0.94 for FS-A, 0.96 for PROMIS-completed by adolescents, 0.83-0.94 for FS-C, and 0.93-0.94 for PROMIS-completed by children **Validity:** Correlations between PROMIS and FS-A were consistently strong (r=0.85-0.9), and moderate to strong for FS-C (r=0.65-0.88). The area under the curve (AUC) was 0.84-0.93 for the FS-A, 0.82-0.87 for the PROMIS-completed by adolescents, 0.84-0.87 for the FS-C, and 0.72-0.86 for the PROMIS-completed by children. Differences between the measures were not statistically significant.	Selection bias: 0 Response rate not clear Attrition bias: 1 At least 84/96 (87.5%) responded at all timepoints Detection bias: 0 Blinding not possible Confounding: 0 No multivariable analyses Total 1/4 **Remarks:** T1: beginning of a course of chemotherapy T2: count nadir, on average 11.1 days after T1 (SD=3.2) T3: just before the beginning of the next course of chemotherapy, on average 18.4 days after T2 (SD=10.7) and 28.6 days after T1 (SD=10.8) Same sample as Hinds et al. 2019

5. What is the most reliable and valid diagnostic tool to diagnose Fatigue in CAYA survivors?				
Lai et al. Computerized Adaptive Testing in Pediatric Brain Tumor Clinics. 2017				
Study Design **Treatment era** **Years of follow-up** **Diagnostic tool**	**Participants**	**Diagnostic tool**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Cross-sectional study **Treatment era:** n.a. **Years of follow-up:** Years since diagnosis: mean 5.2 yrs (SD=4.6) Years since last treatment: mean 3.7 yrs (SD=3.4) **Country:** USA	**Sample size:** N=161 **Diagnoses:** Brain tumors Embryonal tumors medulloblastoma 23.0% Ganglioma 18.3% Pilocytic astrocytoma 13.5% Astrocytoma (diffuse, infiltrative, fibrillary) 11.1% **Age at diagnosis:** n.a. **Age at study:** Mean 13.9 yrs (SD=3.7) **Treatment:** Chemotherapy 77.5% Radiotherapy 54.2% Surgery 69.9% Surgery, chemotherapy, and radiation 20.3% No surgery, chemotherapy and radiation 5.3%	PROMIS pediatric fatigue measure: computerized adaptive testing (CAT) and short form (SF)	**Sensitivity:** n.a. **Specificity:** n.a. This study compared PROMIS CAT to PROMIS SF measures. Correlations between CAT and SF fatigue scores were strong: Pearson r=0.976 Correlations were acceptable when comparing CAT and SF fatigue scores by T-score groups (<45 r=0.88, p<0.001; 45-55 r=0.79, p=0.128; >55 r=0.90, p=0.080) Differences between CAT and SF fatigue scores were significantly different (CAT T-score mean 43.7 (SD=12.9) vs. SF T-score mean 44.8 (SD=11.6)), but effect size was 0.08 indicating this difference was negligible. The authors recommend use of the dynamic CATs, as they enable a more individualized assessment (floor effects were observed for the PROMIS fatigue SF). However, they need more infrastructure (access to a computer). If no computer is available, fixed-length SFs can be used. PROMIS CATs and SFs produce comparable scores for children with a brain tumor.	Selection bias: 0 Unclear how many were recruited. Attrition bias: 1 At least n=147 analyzed (>75%) Detection bias: 0 Blinding not possible Confounding: 0 No multivariable analyses. Total 1/4 **Remarks:** Participants were classified into three groups based on their T-scores: <45 (1/2 standard deviation [SD] below norm), 45-55 (1/2 SD within the norm), and >55 (1/2 SD above the norm). Higher scores represent worse Fatigue.

5. What is the most reliable and valid diagnostic tool to diagnose Fatigue in CAYA survivors?				
Al-Gamal et al. The psychometric properties of an Arabic version of the PedsQL Multidimensional Fatigue Scale tested for children with cancer. 2017				
Study Design **Treatment era** **Years of follow-up** **Diagnostic tool**	**Participants**	**Diagnostic tool**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Cross-sectional study **Treatment era:** n.s. **Years of follow-up:** During active treatment **Country:** Jordan	**Sample size:** N=70 **Diagnoses:** Leukemia n=34 (46%) Lymphoma n=4 (5.7%) Other types of cancer n=32 (48.3%) **Age at diagnosis:** **Age at study:** Range 5-18 years Mean 10.17 years (SD=3.4 yrs) **Treatment:** n.s.	Paediatric Quality of Life (PedsQL) Multidimensional Fatigue Scale (child report)-Arabic Version Compared to PedsQL TM 4.0 Generic Core scale (existing Arabic version)	**Sensitivity:** Not reported **Specificity:** Not reported **Reliability:** Internal consistency was good or excellent for total scale (α=0.90), general fatigue subscale (α=0.94), and cognitive fatigue subscale (α=0.87). Internal consistency was questionable for sleep/rest subscale (α=0.67). The effect of individual items on the reliability of their subscale was tested using the Alpha if item deleted approach. Removing any individual items on all three subscales resulted in minimal changes in Cronbach's alpha, indicating that all items should be retained. **Validity:** To measure construct validity, correlation of PedsQL MFS and PedsQL TM 4.0 Generic Core scale was tested. PedsQL MFS total components and PedsQL TM 4.0 Generic Core subscales were significantly positively correlated: Higher scores on the PedsQL MFS (fewer problems) were associated with higher scores on the PedsQL TM 4.0 Generic Core subscales (better overall HRQoL). The authors conclude that the PedsQL Multidimensional Fatigue Scale-Arabic Version is useful to measure fatigue in Arabic children with cancer. They state that reliability was good for the total PedsQL MFS (α=0.90), and that the PedsQL Multidimensional Fatigue Scale-Arabic Version is a valid instrument.	Selection bias: 0 Unclear Attrition bias: 1 All n=70 assessed. Detection bias: 0 No blinding possible. Confounding: 0 Analyses not controlled for confounders. Total 1/4

5. What is the most reliable and valid diagnostic tool to diagnose Fatigue in CAYA survivors?				
Hinds et al. PROMIS pediatric measures validated in a longitudinal study design in pediatric oncology. 2019				
Study Design **Treatment era** **Years of follow-up** **Diagnostic tool**	**Participants**	**Diagnostic tool**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Longitudinal study (three time points) **Treatment era:** n.a. **Years of follow-up:** During chemotherapy. Mean time since diagnosis was 0.7 years **Country:** USA	**Sample size:** N=96 **Diagnoses:** ALL/Lymphoma n=56 (58.3%) Brain tumor n=5 (5.2%) Solid tumor n=35 (36.5%) **Age at diagnosis:** n.a. **Age at study:** 8-12 years: n=40 (41.7%) 13-18 years: n=56 (58.3%) **Treatment:** n.a.	PROMIS pediatric short-form fatigue Symptom Distress Scale (SDS)	**Sensitivity:** n.a. **Specificity:** n.a. **Reliability:** n.a. **Validity:** Construct validity: PROMIS fatigue scores increased (got worse) from T1 to T2, but decreased (improved) at T3. PROMIS fatigue scores correlated with PROMIS performance measures (mobility, peer relationship, and upper extremity function; r=(-0.3)-(-0.68), all p<0.01). Results suggest reasonable construct validity of the PROMIS fatigue measure. Concurrent validity: Correlations of the PROMIS fatigue measure with the corresponding items of the SDS were highly significant (p<0.0001). Correlation coefficients are not presented separately for the different PROMIS symptom measures. Results suggest concurrent validity of the PROMIS fatigue measure. **Responsiveness to change:** The standardized response mean (SRM) was small for fatigue (0.29). In terms of within-child analyses (short-term responsiveness), fatigue worsened slightly but not significantly from T1 to T2, then improved significantly from T2 to T3. For long-term responsiveness (T1 to T3) and using generalized estimating equation (GEE; controlling for age, sex, hemoglobin, and time since diagnosis) fatigue scores improved significantly as predicted. Importantly, the cancer-specific SDS was not as responsive across time as the PROMIS pediatric measures.	Selection bias: 0 Unclear how many participants were contacted Attrition bias: 1 All analyzed Detection bias: 0 No blinding possible Confounding: 1 Controlled for important confounders Total 2/4 **Remarks:** T1: time of stability, between 7 days before the start of a new course of chemotherapy T2: during course of chemotherapy treatment when adverse effects were predictably present; average 11.1 days after T1 T3: after the course of chemotherapy, when stability was predictably achieved; average 18.4 days after T2

5. What is the most reliable and valid diagnostic tool to diagnose Fatigue in CAYA survivors?				
Hinds et al. Validity and Reliability of a New Instrument to Measure Cancer-Related Fatigue in Adolescents. 2007				
Study Design **Treatment era** **Years of follow-up** **Diagnostic tool**	**Participants**	**Diagnostic tool**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: 4 studies: 1. Measuring Fatigue in Childhood Cancer (MFCC): longitudinal (2 timepoints) 2. Sleep, Fatigue, and Dexamethasone in Childhood ALL (SLEEP): longitudinal (4 timepoints) 3. Sleep, Fatigue, and Enhanced Physical Activity in Hospitalized Pediatric Oncology Patients (SLEEP2; 2-4 timepoints) 4. Symptom Clusters in Pediatric Oncology (CLUSTERS; 3 timepoints) **Treatment era:** n.a. **Years of follow-up:** In treatment **Country:** USA	**Sample size:** A total of n=64 adolescents in the 4 studies (and n=61 parents, and n=18 staff) **Diagnoses:** ALL n=39 (60.9%) AML n=3 (4.7%) Hodgkin's disease/lymphoma n=6 (9.4%) Solid tumor n=16 (25.0%) **Age at diagnosis:** n.a. **Age at study:** Mean age 15.3 years (SD 1.52); range 12.75-18.26 years **Treatment:** n.a.	Fatigue Scale-Adolescent (FS-A), with parent and staff versions Reynolds Depression Scale (RDS)	**Sensitivity:** n.a. **Specificity:** n.a. **Internal consistency:** For 11 of the 13 data-collection points, the FS-A had strong coefficient alpha estimates, Cronbach-if-deleted coefficients ranged from 0.597 to 0.956. Two items (9 and 10) diminished reliability. Item to scale correlation ranged from 0.24 to 0.92, except for item 10 (r=-0.088 at one time point). Standardized Cronbach's Alpha coefficient was between 0.70 and 0.95 for 10/13 timepoints (FS-A), 10/13 timepoints (FS-P), 2/5 timepoints (FS-S). For the MFCC study, Cronbach's Alpha was 0.81 (FS-A), 0.75 (FS-P), and 0.85 (FS-S) at T1. **Validity:** Exploratory factor analysis revealed four factors of the FS-A, all items loaded onto these four factors and correlation coefficients were 0.353-0.758. Correlation between total scale scores of RDS and FS-A were strong (r=0.71, p<0.001) Known-group comparison: anemic patients scored higher than non-anemic patients by parent-report (p=0.04) **Responsiveness:** Across the four studies, the FS-A scores increased significantly between the two designated time points (p=0.01), but FS-P scores did not.	Selection bias: 0 Unclear how many participants were contacted Attrition bias: 1 All analyzed Detection bias: 0 No blinding possible Confounding: 1 Controlled for important confounders Total 2/4 **Remarks:** T1: time of stability, between 7 days before the start of a new course of chemotherapy T2: during course of chemotherapy treatment when adverse effects were predictably present; average 11.1 days after T1 T3: after the course of chemotherapy, when stability was predictably achieved; average 18.4 days after T2

6. What is the **effect of individual cognitive behavioral therapy** in the treatment of CRF in CAYA cancer survivors?				
Boonstra et al. Cognitive Behavior Therapy for Persistent Severe Fatigue in Childhood Cancer Survivors: A Pilot Study. 2018				
Study Design **Treatment era** **Years of follow-up** **Diagnostic tool**	**Participants**	**Intervention**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Intervention study **Treatment era:** n.a. **Years of follow-up:** Time since diagnosis mean: 13.0 years (SD 7.3), range: 5-34 years **Country:** The Netherlands **Fatigue measurement:** Fatigue Severity Subscale of the Checklist Individual Strength (CIS); severe fatigue was defined as a score of ≥35 on the Fatigue Severity Subscale of the CIS and a duration of fatigue of at least 6 months.	**Sample size:** N=33 (males: n=8) **Diagnoses:** Leukemia: n=13 Lymphoma: n=7 Bone cancer: n=5 Solid cancer: n=4 Brain cancer: n=3 Other cancer: n=1 **Age at diagnosis:** Mean: 9.7 years (SD 4.4), range: 0-17 years **Age at study:** Mean: 23.1 years (SD 7.0), range 11-42 years **Treatment:** Chemotherapy: n=29 Surgery: n=13 Stem cell transplantation radiotherapy: n=4 Noncranial (spinal) radiotherapy: n=8 Cranial (spinal) radiotherapy: n=1	Patients suffering fatigue completed a questionnaire assessing fatigue severity and maintaining factors, demographic and health characteristics. Medical records provided data on the medical history. A face-to-face interview was conducted with the aim to screen for the presence of psychiatric disorders and psychological problems that might explain fatigue and eligible survivors were offered cognitive behavioral therapy (CBT). CBT consisted of 12 to 14 sessions over 6 to 8 months, covering 6 modules addressing different maintaining factors (coping with cancer, fear of recurrence, cognitions with regard to fatigue, social interactions, sleep-wake pattern, activity pattern regulation including a graded activity program).	Using intention-to-treat analyses, fatigue serverity decreased significantly from pretreatment to posttreatment (pretreatment mean 46.2 (SD 4.5) vs. posttreatment mean 28.9 (SD 13.7); mean difference -17.4 (95%CI:-22.1 to -12.7, p<0.001)) and the effect size was large (1.7 (95%CI: 1.1-2.3). In total, 23 of the 33 CCS (70%) showed a clinically significant improvement of fatigue. Of the CCSs who completed CBT (N =25), 22 (88%) survivors reported a clinically significant improvement. Of the 25 survivors who completed CBT, 5 CCS indicated that they were completely recovered (20%), 17 CCS reported a significant improvement (68%), and 3 CCS reported that fatigue levels had not changed (12%).	Selection bias: 1 - Response rate overall: 76% Attrition bias: 1 - Eligible: n=33 - Complete: n=25 (76%) Detection bias: 0 - No blinded outcome assessors Confounding: 0 - No multivariable analyses, no control group **Total quality: 2/4** Remarks: No control group

9. What is the effect of **any intervention** in the treatment of Fatigue in CAYA survivors?				
Chang et al. Systematic Review and Meta-Analysis of Nonpharmacological Interventions for Fatigue in Children and Adolescents With Cancer. 2013				
Study Design **Treatment era** **Years of follow-up** **Diagnostic tool**	**Participants**	**Intervention**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Systematic Review and Meta-Analysis **Treatment era:** n.a. **Years of follow-up:** All except one study on CAYA patients **Diagnostic tool:** • Fatigue-CIS-20 • Lansky play performance scale (PPS) • Child fatigue scale (CFS) • **Fatigue Scale (FS-C, FS-A, FS-P, FS-S)** • Pediatric Quality of Life Multidimensional Fatigue Scale (Peds QL-MFS) **Country:** 5x USA, 1x Taiwan	**Sample size:** 6 studies included **Diagnoses:** Acute lymphoblastic leukemia Acute myeloid leukemia Lymphoma Solid tumor **Age at diagnosis:** Dependent on the study **Age at study:** 1-18 years **Treatment:** • Dependent on the study	a. 12-week exercise training in survivors of ALL (n=9) b. 4-week massage therapy in patients (n=17) c. Enhanced physical activity in patients (n=29) d. 16-week physical activity in patients (n=10) e. Effective nursing interventions in patients (n=60) f. 6-week home-based aerobic exercise in patients (n=24)	The meta-analysis included 2 studies (d. & f.) and revealed a statistically significant effect of exercise interventions in reducing general fatigue (effect size = –0.76; 95% CI [–1.35–0.17]) in children and with cancer. 3 of the 6 studies with no change, the other 3 with significant differences: a. 12-week exercise training → n.s. differences b. 4-week massage therapy → n.s. differences between groups c. Enhanced physical activity → n.s. differences between groups d. 16-week physical activity → sign. differences short- & long-term e. Effective nursing interventions → sign. differences between groups The results indicate that fatigue in children with cancer can be reduced by implementing appropriate nursing interventions (education about fatigue and suggestions for activities that can reduce fatigue). f. 6-week home-based aerobic exercise → sign. differences between groups This study found that exercise interventions had no effect on reduction of total fatigue, sleep or rest fatigue, cognitive fatigue.	

9. What is the effect of **any intervention** in the treatment of Fatigue in CAYA survivors?				
Baumann et al. Clinical exercise interventions in pediatric oncology: a systematic review. 2013				
Study Design **Treatment era** **Years of follow-up** **Diagnostic tool**	**Participants**	**Intervention**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Systematic review **Treatment era:** Dependent on the study **Years of follow-up:** Dependent on the study, some studies on treatment, some not with cancer patients	**Sample size:** 17 studies included, 257 children with cancer **Diagnoses:** Mixed cancer types, but mainly ALL **Age at diagnosis:** 0-21 years **Age at study:** Dependent on the study **Treatment:** • Dependent on the study	Different exercise interventions: In-hospital endurance/strength training; home-based endurance exercise program; supervised group exercise and educational intervention; supervised and home-based exercise program	The findings confirm that clinical exercise interventions are feasible and safe, especially with acute lymphoblastic leukemia (ALL) patients and during medical treatment. No adverse effects have been reported. Regarding fatigue: two studies found no effect, whereas three studies found a positive effect of clinical exercise during medical treatment or survivorship. The authors conclude: “Relatively good evidence is given in terms of positive effects of supervised exercise programs during medical treatment on fatigue, muscle strength, and quality of life.	

9. What is the effect of **any intervention** in the treatment of Fatigue in CAYA survivors?				
Blaauwbroek et al. The effect of exercise counselling with feedback from a pedometer on fatigue in adult survivors of childhood cancer: a pilot study				
Study Design **Treatment era** **Years of follow-up** **Diagnostic tool**	**Participants**	**Intervention**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Intervention study **Treatment era:** **Years of follow-up:** Mean since diagnosis 21.8. range 14.7-28.9 **Fatigue measurement: Visual Analogue Scale for chronic fatigue (VAS fatigue)** **Country:** The Netherlands	**Sample size:** N=46 **Diagnoses:** • Leukemia n=22 (46.8%) • Malignant lymphoma n=6 (12.8) • Bone tumor n=4 (8.5) • Soft tissue sarcoma n=3 (6.4%) • Wilms tumor n=1(2.1%) • Langerhans cell histiocytosis n=2 (4.3%) • CNS tumor n=6 (12.8%) • Other n=3 (6.4%) **Age at diagnosis:** Mean age 8 years. Range 1.5-14.8 **Age at study:** Median age 29 years. Range 18-61 **Controls:** N=33 (recruited by the survivors among healthy siblings or peers)	10 week Home-based daily physical activity counselling programme—with feedback from a pedometer—on fatigue in adult survivors of childhood cancer was evaluated. A counsellor trained according to the COACH protocol visited the survivor and explained the use of pedometer and step diaries at **week 1**. They also filled in Checklist Individual Strength (CIS). Survivor wore the pedometer during two weeks to assess steps at baseline and in week 4 and 10 during the study. In the end of each day they record daily steps counts and duration in minuets in an online or posted diary. At 3, 6 and 9 weeks the counsellor phoned the survivor. At week 3 the use of pedometer were discussed and they were asked how many steps they could improve- Together with the counselor a goal were set. After this conversation, the survivor received a written summary of the conversation and wore the pedometer again. At week 6 the couselor and surv evaluated if the goal were reached if not, they explored barriers. Survivors were asked to plan a peak day were they walked as many steps as possible. Again, a written summary were received and asked to wear the pedometer on the peak day in week 7. At week 9 the counsellor and survivor evaluated the peak day and asked if they could adjust their goal to a higher steps per day. Written summary received of the conversation. And asked to wear pedometer for week 10 and fill out a questionnaire. They did the same in week 36.	The stimulation of daily physical activity using exercise counselling and a pedometer over 10 weeks leads to a significant decrease in fatigue in adult survivors of childhood cancer, and this improvement lasts for at least 36 weeks. Mean CIS scores ± SD of participants (81.42±20.14 at T1; 62.62±20.86 at T10 ($p<0.0005$); 63.67±23.12 at T 36 ($p<0.0005$ compared to T1)) and controls (47.39±19.06 at T1; 46.18±17.70 at T10; 42.57± 17.40 at T36) There was no statistically significant difference in the mean CIS scores of the controls during the study period.	Selection bias: 0 Attrition bias: 0 n= 486 eligible n=453 were sent questionnaire respons rate 56%. 46 were enrolled into the study but eight dropped out Detection bias: 0 Confounding bias: 0 Descriptive statistics and Linear regression used. **Total quality: 0/4**

9. What is the effect of **any intervention** in the treatment of Fatigue in CAYA survivors?			
Robinson et al. Guideline for the Management of Fatigue in Children and Adolescents with Cancer and Pediatric Hematopoietic Stem Cell Transplantation Recipients. 2018			
Study Design **Treatment era** **Years of follow-up** **Diagnostic tool**	**Participants**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Clinical practice guideline, based on systematic review & meta-analysis **Treatment era:** n.a. **Years of follow-up:** n.a. **Country:** n.a.	**Sample size:** They included 6 pediatric and 456 adult randomized trials **Diagnoses:** Mixed **Age at diagnosis:** n.a. **Age at study:** n.a. **Treatment:** n.a.	Recommendation 1: **Use physical activity**. They made a strong recommendation to use physical activity, preferably aerobic, neuromotor (incl. yoga and tai chi), or combination exercises. Quality of evidence was downgraded to moderate, as evidence was mostly from adults. Recommendation 2: **Do not routinely use pharmacological approaches**. They made a strong recommendation against erythropoietin use, and methylphenidate use. They made a strong recommendation that pharmacological agents should not be routinely used in the management of fatigue in children and adolescents. Recommendation 3: **Use relaxation or mindfulness, or both**. They made a strong recommendation for the use of relaxation, mindfulness or both (acupressure, mindfulness, relaxation techniques, massage therapy, energy therapies, energizing yogic breathing, and others). A challenge might be the implantation of these interventions in younger children and cranial irradiation survivors due to immaturity or cognitive ability. Recommendation 4: **Cognitive or cognitive behavioral therapies may be offered**. They made a weak recommendation to use cognitive behavioral therapy, due to higher costs of intervention and lack of randomized data in children. However, if trained professionals are available at an institution, or if physical activity, mindfulness and relaxation were not feasible or successful, cognitive behavioral therapy should be considered. Other interventions: Other interventions (e.g. symptom screening, nutrition-focused, music therapy, and cognitive rehabilitation training) were too heterogeneous to analyze and the authors did not formulate a recommendation. The authors conclude “Using the Grades of Recommendation Assessment, Development and Evaluation approach, strong recommendations were made for the use of physical activity, relaxation and mindfulness to reduce fatigue. Where these approaches are not feasible or were not successful, cognitive or cognitive behavioral therapies may be offered. Maturity and cognitive ability will influence intervention feasibility. Systemic pharmacological approaches should not be routinely used for the management of fatigue in children.”	

9. What is the effect of **any intervention** in the treatment of CRF in CAYA cancer survivors?				
Li et al. Adventure-based training to promote physical activity and reduce fatigue among childhood cancer survivors: A randomized controlled trial. 2018				
Study Design **Treatment era** **Years of follow-up** **Diagnostic tool**	**Participants**	**Intervention**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Randomized Control Trial (RCT) **Treatment era:** n.a. **Years of follow-up:** All completers (n=192): <25 months: n=112 (58.3%) 25-48 months: n=54 (28.1%) 37-60 months: n=40 (20.8%) >60 months: n=4 (2.1%) **Country:** Hong Kong, China **Fatigue measurement:** **Fatigue Scale-Child (FS-C)**	**Sample size:** N=222 (males: n=118) Experimental gr.: n=117 Completed: n=103 Dropped out: n=14 Control group: n=105 Completed: n=89 Dropped out: n=16 **Diagnoses (all completers n=192):** Leukaemia: n=81 (42.2%) Lymphoma: n=51 (26.6%) Brain tumor: n=25 (13.0%) Bone tumor: n=21 (10.9%) Neuroblastoma: n=14 (7.3%) **Age at diagnosis:** n.a. **Age at study:** Range 9-16 years Experimental (completers): mean 12.8 years (SD 2.6) Control (completers): mean 12.4 years (SD 2.6) **Treatment (all completers n=192):** Surgery: n=14 (7.3%) Chemotherapy: n=137 (71.4%) Radiotherapy: n=5 (2.6%) Mixed method: n=36 (18.8%)	The treatment group participated to 4 training days (2 weeks, 2, 4, 6 months after randomization respectively) of maximum 12 participants. Each session started with a 40-min briefing session. Then, participants take part in adventure activities (ice-breaking, team-building games, shuttle runs, rock climbing, rope courses, descending) with increasing levels of difficulty. After activities, physical fitness was assessed and a 75-min debriefing session was organized. Data were collected at baseline (T1), after 6 (T2) and 12 (T3) months. The **control group** received a placebo treatment including health talks, leisure activities, and museum visits, etc.	Participants in the experimental group reported significantly lower levels of fatigue than those in the control group at the 12-month follow-up. T1, mean (SD): Experimental group: 29.4 (4.2) Control group: 29.2 (4.1) p-value: 0.83 T2 mean (SD): Experimental group: 26.6 (4.9) Control group: 28.5 (4.2) p-value: 0.09 T3 mean (SD): Experimental group: 22.3 (4.2) Control group: 28.9 (4.9) p-value: <0.001 Mixed between-within-subjects ANOVA revealed a significant effect for time on cancer-related fatigue (CRF), reflecting a significant change in participants' CRF (Eta Squared=0.61, p<0.001). The effect for interaction on CRF was also significant (Eta Squared=0.55, p<0.001), indicating that the change in CRF over time in the experimental group differed from that in the control group. The effect for intervention on CRF was smaller, but also significant (Eta Squared=0.04, p=0.02); participants in the experimental group reported lower levels of CRF than those in the control group during the 12-month follow-up. Participants of the experimental group also reported higher levels of physical activity, self-efficacy, and better QoL than controls at the 12-month follow-up.	Selection bias: 1 - Random sample with respect to treatment Attrition bias: 1 - Complete experimental: n=103 - Complete control: n=89 Detection bias: 0 It is not mentioned that assessors were blinded Confounding: 1 - randomization of participants **Total quality: 3/4** **Remarks:** Data on diagnosis, age, treatment are provided only for participants who completed either treatment or control (n=192)

9. What is the effect of **any intervention** in the treatment of CRF in CAYA cancer survivors?				
Nunes et al. Interventions minimizing fatigue in children/adolescents with cancer: An integrative review. 2018				
Study Design **Treatment era** **Years of follow-up** **Diagnostic tool**	**Participants**	**Intervention**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Integrative review Studies published between January 2000 and December 2016 **Years of follow-up:** Patients and survivors **Country:** 6 studies from USA 2 from the Netherlands 1 each from Taiwan, Germany, Turkey, Canada, Iran & Canada **Instrument:** **5 PedsQL-MFS** **6 Fatigue Scales (FS-C, FS-A, FS-P)** 1 CIS-20 1 Visual Analog Scale 1 My Fatigue meter	**Sample size:** Median sample size was n=22; range 9-120 **Diagnoses:** Mixed diagnoses **Age at diagnosis:** Childhood & Adolescence	The studies tested six different types of interventions: 1. Exercise 2. Exercise plus leisure activities 3. exercise plus psychological training 4. Massage 5. Healing touch 6. Acupressure	Exercise (seven studies): Four (n=22/23/11/16) found a decrease of CRF in participants. Interventions used were home-based aerobic exercise, in-patient bicycle ergometer use, in-patient yoga sessions, weekly step goal with FitBitR tracker. Three studies (n=29/9/13) found no effect of exercise on CRF in participants. Interventions used were stationary bicycle-style exerciser, muscular strength/aerobic fitness/resistance range, yoga. Exercise plus leisure activities (one study): One study (n=60) found a decrease of CRF in participants after an intervention including exercise (15min) and leisure activities, such as drawing, reading, listening to music (45min). Exercise plus psychosocial intervention (one study): One study (n=30) found no effect of a physical exercise training, and additional psychosocial training (psychoeducation and cognitive-behavioral techniques). Healing touch (one study): One study (n=9) found a decrease of CRF in participants after an intervention of healing touch. Massage (two studies): Two studies (n=17/34) found no effect of massage to reduce CRF. Acupressure (one study): One study (n=60) found a decrease of CRF in participants after an intervention of acupressure (point ST36) compared to controls (point LI12). Positive effects were observed only immediately after intervention.	

9. What is the effect of **any intervention** in the treatment of CRF in CAYA cancer survivors?

Kudubes et al. The Effect of Fatigue-Related Education on Pediatric Oncology Patients' Fatigue and Quality of Life. 2018

Study Design **Treatment era** **Years of follow-up** **Diagnostic tool**	**Participants**	**Intervention**	**Main outcomes**	**Quality assessment** **Remarks**
Study Design: Controlled trial, non-randomized **Treatment era:** 2015-2017 **Years of follow-up:** In active treatment **Country:** Turkey **Fatigue measurement:** Scale for the Assessment of Fatigue in Pediatric Oncology Patients (Versions 7-12 years, and 7-12 years for Parents)**[56]** (scale ranges from 27-135, higher values indicate less fatigue) Data was collected at three timepoints: before the intervention (pretest), 3 months later (posttest 1), and 6 months later (posttest 2)	**Sample size:** N=80 (each n=40 in the experimental and control group) **Diagnoses (exp. vs. cont.):** Oncological disease: n=23 (57.5%) vs. n=21 (52.5%) Hematologic disease: n=17 (42.5%) vs. n=19 (47.5%) **Age at diagnosis:** Newly diagnosed **Age at study:** 9.4 years (SD=2.2) vs. 9.1 years (SD=1.7) **Treatment:** Chemotherapy: n=22 (55.0%) vs. n=25 (62.5%) Combination therapy: n=18 (45.0%) vs. n=15 (37.5%) Corticosteroid therapy: n=33 (82.5%) n=32 (80.0%)	Based on the literature, an educational pamphlet for children and parents was developed. Different experts were involved. An intervention including five modules, each consisting of one or two 45min sessions, was developed: 1. Opening and Basic information on Fatigue 2. Fatigue Coping Methods – Symptom Management 3. Fatigue Coping Methods – Energy Conservation and Activity (Exercise) Regulation 4. Fatigue Coping Methods – Ensuring adequate sleep and sleep quality 5. Fatigue Coping Methods – Stress Management/Stress Coping It's unclear in within what time frame the five modules were delivered, and whether all modules were delivered to patients before posttest 1.	Pretest: Patients in the experimental group had more fatigue than those in the control group (lower scores indicate more fatigue). Posttest 1: Mean level of fatigue for patients in the experimental group improved, while mean level of fatigue in the control group worsened. Posttest 2: Mean level of fatigue for patients in the experimental group improved again, while mean level of fatigue in the control group worsened again. |	Pretest (mean)	Posttest 1 (mean)	Posttest 2 (mean)
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Experimental	46.3	67.9	77.9
Control	65.4	50.5	29.5 | Multidimensional variance analysis was used: There was a statistically significant effect of group (F=40.6; p<0.001), indicating that patients in the experimental and control group differ in the total mean scores (fatigue). There was a statistically significant effect of time (F=4.2; p=0.017), indicating that patients' total mean scores (fatigue) differ over time. There was a statistically significant interaction of group*time (F=154.7; p<0.001), indicating that the effect of time depends on the group. No post-hoc tests were used to test which factor levels differ. Linear regression analysis to analyze associations with total mean score fatigue: Experimental group (Ref. control group) β=0.844 (p<0.001)	Selection bias: 0 Unclear how many were approached Attrition bias: 1 80/80 participants completed the intervention Detection bias: 0 No blinding Confounding: 0 No additional confounders controlled for; description of analysis partly unclear **Total quality: 1/4** **Remarks:** 1. Kudubes AA, Bektas M, Ugur O. Developing a scale for the assessment of fatigue in pediatric oncology patients aged 7-12 for children and parents. *Asian Pac J Cancer Prev.* 2014;15(23):10199-10207.