Conclusions of evidence tables cancer-related fatigue surveilance

1. What is the risk for suffering from cancer-related fatigue (CRF) in CAYA survivors?	
Conclusion single studies	
Chalder Fatigue Questionnaire (FQ) Widely used questionnaire for assessment of fatigue severity and for case detection in clinical and epidemiological studies; 4-point Likert scoring for all 11 items, total fatigue defined by simple addition with higher scores implying higher levels of fatigue; two additional items ask for the duration and extent of fatigue; for the definition of *chronic fatigue* scores are dichotomized (0,0,1,1) and *chronic fatigue* is defined by a sum score of ≥4 for all 11 dichotomized items and a duration of ≥6 months.	
30.6% of childhood lymphoma survivors* reported chronic fatigue. *n=124; median 33 years at study; median 20 years of observation time	*Johannsdottir et al. 2017*
Survivors* with CF had a mean FQ total score of 20.0, survivors without CF a mean FQ total score of 10.5 (p<0.001). *n=62; Lymphoma, ALL; mean age at study 34.05 years; median 25.3 years of follow-up; follow-up study with all 62 survivors also participating in the ***Hamre et al. 2013a***	*Zeller et al. 2014*
Survivors* were significantly more fatigued than controls**: OR=4.5 (p<0.001) for having chronic fatigue. **28% of survivors had chronic fatigue (CF)**, 8% of controls had chronic fatigue. *Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), acute lymphoblastic leukemia (ALL); n=290; median age at diagnosis 9.5 years; median age at study 29.6 years; **Norwegian population sample; n=1405, median age at study 34.0 years	*Hamre et al. 2013a*
28% of survivors* had CF. *n=232; n=117 ALL, n=68 HL, n=47 NHL, median age at diagnosis: 9.6 years, median age at study: 29.7 years; same sample as ***Hamre et al. 2013a***	*Hamre et al. 2013b*
Total fatigue in survivors*: mean=13.9 (SD 5.3). **Cases of chronic fatigue: 27%** (n=76) SF-36 domain «Vitality»: Survivors mean=51.1 (SD 21.6), controls mean=60.1 (SD 19.3) (p<0.001) *n=285; diagnoses: n=91 Hodgkin lymphoma (HL), n=45 Non-Hodgkin (NHL), n=149 Acute lymphoblastic leukemia (ALL); median age at diagnosis: 10 years; Median age at study: 30 years; same sample as ***Hamre et al. 2013a;*** Age matched controls from the general population of Norway.	*Kanellopoulos et al. 2013*
11% of the survivors* had CF. CF was significantly more prevalent in the older group (OG; 13.6%) than in the younger group (YG; 6.8%, p<0.05). The OG also had a higher occurrence of CF relative to the general population (GP; 5.9%, p<0.001). * n=398; acute myeloid leukemia (AML)>astrocytoma>Wilms tumor (WT); age at diagnosis range 1-18 years; younger group (YG) 13-18 years at study; older group (OG) ≥19 years at study; Comparison group for OG from general population (GP; n=763)	*Johannsdottir et al. 2012*
Survivors of malignant extremity bone tumors (EBT; total N=57, mean age at diagnosis male/female: 20/16 years; mean years since diagnosis male/female: 14/11) were compared with Hodgkin's disease (HD; n=89) survivors, testicular cancer (TC; n=62) survivors and the general population (NORM; n=285). **14% of EBT, 21% of HD and 16% of TC survivors suffered from chronic fatigue**, compared to 10% of NORMS (p=0.30). No significant differences in the fatigue scores were observed between EBT and the other survivor groups, but EBT survivors had a **significantly higher total fatigue score compared to NORMs** (13.2 (SD 3.8) vs. 11.8 (SD 3.9), p=0.003).	*Aksnes et al. 2007*
EORTC-QLQ-30 30 items: global quality of life (2 items), five functional scales (social function (2 items), cognitive function (2 items), emotional function (4 items), role function (2 items), physical function (5 items)), three symptom scales (fatigue (3 items), nausea and vomiting (2 items), pain (2 items)) and six single items (financial problems, diarrhea, constipation, lack of appetite, insomnia, dyspnea). Scores of 0-100 for every scale or single item. Global quality of life, functional scales: high values = high QOL; symptom scales & single items: high values = low QOL → **Fatigue: higher values mean higher symptoms of fatigue**	
Survivors of childhood-onset craniopharyngioma* with no hypothalamic involvement (HI) have a median score of **21**, survivors with HI a median score of **37**. *n=108; median age at diagnosis: 8.1 years; median follow-up time: 16.3 years	*Sterkenburg et al. 2015*
Survivors of Hodgkin's disease* compared to controls**: male survivors had mean scores of **19.02** (SD 21.7) vs. controls 7.85 (SD 14.6) female survivors had mean scores of **26.57** (SD 24.8) vs. controls 14.02 (SD 20.09) (survivors had significantly more fatigue than controls, p<0.001) *n=725; mean age at diagnosis: 13.63 years; mean time since diagnosis: 15.26 years; **age-adjusted sample of the German norm population	*Calaminus et al. 2014*
The mean fatigue score of the study population* was **26.6** (SD 20.1), no control group was present. Mean fatigue score was the second highest score of the four symptom scales used in this study (eg. drowsiness, communication deficit and insomnia). *n=104, mean age at diagnosis 13.3 years, mean age at study 26.8 years, brain tumor survivors	*Sato et al. 2014*
Lower extremity bone tumor survivors* were significantly less fatigued (**sample mean 18.65** (SD 20.30)) than the control population (cancer survivors under the age of 50; sample mean of 33.9 (SD 26.1); p<0.001). *n=28; mean age at diagnosis 11.6 years	*Barrera et al. 2012*
Survivors of deep-seated low-grade gliomas* have a mean score of **28**, the normal population 28.8 (difference not statistically significant). *n=28; age at radiosurgery: median 8.3 years; years of follow-up: 134 months=11.17 years	*Korinthenberg et al. 2011*

Fatigue subscale of the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue) 13-item scale; validated in cancer patients; measure of physical and functional consequences of fatigue; reverse 4-point Likert scale, ranging from 0 to 52, lower scores indicate more fatigue; for dichotomization: lowest 10th percentile of the sibling scores classified as *fatigued*.	
26.7% of teenage and young adult cancer survivors* reported clinically significant levels of fatigue (scores>22**). Mean fatigue score in off-treatment survivors (n=135) was 15.56** (SD=10.98). *mixed diagnoses; n=202; age at study 13-24 years; **this study did not reverse code the FACIT-Fatigue scale; the scale ranges from 0-52, but lower scores indicate less fatigue	*Fortmann et al. 2018*
17% of Hodgkin's lymphoma survivors* reported elevated fatigue (total score ≤30). *Survivors of the childhood cancer survivor study (CCSS; n=751; 42.5% aged 11-15 years at diagnosis; at least 5 years since diagnosis)	*Rach et al. 2017*
13.8% of survivors* showed fatigue (cutoff score of ≤ lowest 10% of siblings was used). *CCSS; mixed diagnoses; n=1426; mean age at diagnosis 11.9 years; mean age at study 35.9 years	*Clanton et al. 2011*
Survivors* had a mean fatigue score of 40.56 (SD 10.40) was significantly lower than the siblings' mean of 45.19 (SD 6.88; p=0.02), indicating more significant problems with fatigue among survivors. **16% of survivors** had fatigue scores in the clinically significant range (scores<30), compared to 3.1% in siblings, but the difference only approached statistical significance (p=0.067). *n=55, mixed diagnoses; median age at diagnosis: 8 years; median current age: 56 years	***Kenney et al. 2010***
Survivors* were significantly more likely to be fatigued than their siblings**. The **prevalence of fatigue was 19.2%** in survivors (cutoff score of ≤ lowest 10% of siblings was used). *CCSS; n=1897; mixed diagnoses; diagnosed before the age of 21 years; at least 5 years from diagnosis; **nearest-age siblings n=369; mean 40.8 vs. 42.0	*Mulrooney et al. 2008*
PedsQL (Pediatric Quality of Life Inventory) Multidimensional Fatigue Scale This validated scale comprises six items about general fatigue, six items about sleep/rest fatigue, another six items about cognitive fatigue, and finalizing into a sum score of all 18 items. Age-categorized versions for the parent proxy report (age: 4, 5-7, 8-12 and 13-18 years) of the PedsQL were administered in this study. Higher scores indicate less fatigue, i.e. better fatigue-related QoL.	
Survivors of childhood acute lymphoblastic leukemia* reported greater fatigue compared with the general population. Cognitive fatigue survivors mean**: -0.75 (SD 1.2) vs. 0 (SD 1.0) expected in the general population, p=0.0003. General fatigue survivors mean*: -0.61 (SD 1.2), p=0.0003. Sleep-rest fatigue survivors mean*: -0.27 (SD 1.2), p=0.07). *n=70; 1.2-17.7 years at diagnosis; mean 7.4 years since diagnosis; **fatigue scores were transformed into age-adjusted Z-scores (mean=0, SD=1.0)	*Cheung et al. 2017*
85% of survivors of adolescent and young adult cancer experienced fatigue during the preceding month. The fatigued survivors had a mean MFS level of 44.3 (SD=20.5). *n=80; mixed diagnoses; mean 18.9 years at diagnosis; mean 22.1 years at survey	*Spathis et al. 2017*
Survivors of hematopoietic stem cell transplant (HSCT) in childhood*: Mean levels of fatigue was 69.21 (SD 20.14) for self-report and 72.15 (SD 20.79) for parent-report, indicating moderately elevated fatigue symptoms. 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). *n=76; <22 years at transplant; mean 17.8 years at study; mean 7.8 years since HSCT; ** 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.	*Graef et al. 2016*
13.8% of childhood and adolescent cancer survivors* were considered fatigued**. This did not statistically differ from the 16% (43 cases) that would have been expected based on community sample data for the MFS (p=0.467) *n=268; median age at diagnosis: 6.4 years; mean time since diagnosis 13.1 years; median age at study 21.4 years; Leukemia>HL>NL>Bone tumors>soft tissue sarcoma>neuroblastoma>wilms tumor>other; **MFS score ≥1 SD below means for non-cancer patients of similar age	*Frederick et al. 2016*
Survivors of brain tumors*: Mean total MFS score 70.67 (SD 18.72). 42 of the 142 study participants had clinically significant fatigue** (**29.5%**). No control group was present. *n=142, age at diagnosis mean 9.72 years (SD 4.87), mean age at study 20.24 years; **defined as MFS score >1 SD below the mean for normative samples	*Brand et al. 2016*
Survivors*: Child/Parent report «Total fatigue»: 78.73/74.25. Controls**: Child/Parent report «Total fatigue»: 76.84/81.21. Parents rated 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. *Survivors of ALL (n=62; age at diagnosis 5-17 years; mean age at study: 9.7 yrs). **Controls: Dutch norm references.	*Gordijn et al. 2013*
Survivors*: Child/Parent report «Total fatigue»: **83.33/84.03**. Controls**: Child/Parent report «Total fatigue»: **80.56/83.33**. The controls reported significantly more total fatigue than the survivors (p<0.01). Survivors scored higher on fatigue when compared with their parent proxy scores, but not statistically significantly (p>0.05). *Survivors of extracranial childhood cancer (n=199; mean age at diagnosis: 3.6 years; mean age at study: 14.4 years). **Matched controls from the Finnish Population Registry.	*Mört et al. 2011*

Checklist individual strength (CIS) 20 items scored on a 7-point Likert scale; four subscales *subjective fatigue*, *concentration*, *motivation* and *physical activity*. Total score by summing up all items. Higher scores indicate more fatigue-related problems.	
Brain tumor survivors* had a higher total score of Fatigue (**63.23** (SD 21.80)) than controls** (51.76 (SD 21.88); p=0.01). *n=82; mean age at diagnosis: 6.87 years; mean time of follow-up: 6.98 years; **siblings	*De Ruiter et al. 2016*
Survivors* had a a higher mean score of **81.42** (SD 20.14) than controls** 47.39 (SD 19.06, p<0.001). **26.4% of survivors** had a VAS score (Visual Analogue Scale for chronic fatigue) of ≥70mm. *mixed diagnoses; n=46; median age at diagnosis: 8.1; median age at study: 29.8 years; **n=33 siblings or healthy peers as controls	*Blaauwbroek et al. 2009*
Multidimensional Fatigue Inventory (MFI-20) **The MFI-20 questionnaire measures fatigue in 5 dimensions: *general fatigue*, *physical fatigue*, *reduced activity*, *reduced motivation* and *mental fatigue*.** The domains of MFI-20 are measured by 20 questions that are scored on a scale from 1-5. The 5 domains can have a total score of 4-20, expressed as a percentage: the higher the score, the more fatigue the participant experiences.	
Survivors of pediatric differentiated thyroid carcinoma* reported **more mental fatigue** compared to controls** (9 vs. 7, p=0.012). There were no statistically significant differences for the two groups regarding general fatigue (survivors 10 vs. controls 9, p=0.075), physical fatigue (8 vs. 6, p=0.083), reduced activity (8 vs. 8, p=0.613), reduced motivation (6 vs. 6, p=0.879), and total fatigue (41 vs. 36, p=0.129). *n=67; median age at diagnosis was 15.8 years; median 17.8 years of follow-up; **n=56 controls: healthy peers	*Nies et al. 2017*
In comparison to the control group**, **survivors* scored significantly lower for general fatigue** and **reduced motivation** (p<0.05, effect size GF: -0.14, effect size RM: -0.19), **but significantly higher for mental fatigue** (p<0.05, effect size 0.15). *n=416; mean age at diagnosis 8 years; mean age at study 24 years; Leukemia/Lymphoma>Solid tumor>brain/CNS tumor, **n=1026; sex and age matched, recruited via survivors GPs	*Langeveld et al. 2003*
PROMIS V1.0 Pediatric Profile 25 Pediatric Profile 25 is a collection instrument of self-reporting short forms containing items from the PROMIS domains.26. Domains used in this study included fatigue, physical and functional mobility, and depressive symptoms; each included 4 items. Fatigue and depression are scored on a 5-point Likert scale where 0 = never to 4 = almost always; the higher scores represent higher levels of fatigue and depression. Subscales are scored by summing items, with a possible range of 0 to 16.	
Pediatric cancer survivors* reported normal levels of fatigue: mean 4.1 (SD 4.0), range 0-16 (no comparison group). 22 children (**15.3%**) reported elevated levels of fatigue. *n=144; mixed diagnoses; mean age at study 12.9 years, mean 5.9 years since diagnosis; no control group	*Karimi et al. 2019*
Fatigue-scale adolescent (FS-A) The FS-A is a 14-item questionnaire that asks adolescents (age 13 to 18 years), to evaluate their fatigue experience during the previous week. Responses are rated using a 5-point Likert scale ranging from 1 to 5 (1=not at all; 2= a little; 3=some; 4= quite a bit; 5= a lot). Total possible scores range from 14 to 70. Higher scores indicate higher levels of fatigue.	
Participants were adolescent survivors of childhood cancer (CCS) and adolescent cancer patients (ACP).* CCS had a mean level of fatigue **28.6** (SD 3.7), ACP 31.3 (SD 5.2), whereas healthy controls had a mean level of 22.1 (SD 4.8; p<0.001 compared to CCS). *CCS n=200/ ACP n=50; Leukemia>Lymphoma>Brain tumor; 62% >2 years since treatment completion)	*Ho et al. 2015*
Health Knowledge Inventory One question about fatigue	
40% of survivors of childhood cancer*reported fatigue problems, compared to 22% of controls**. When adjusted for age and income, survivors reported significantly more fatigue compared to controls (p=0.002). *n=154; Leukemia>Lymphoma>Solid tumors; ≤18 years at diagnosis; on average 12.29 years since diagnosis; mean age of 20.1 years at study; **n=170; healthy AYA controls; mean age 21.1 years at study	*Daniel et al. 2016*
POMS (Profile of Mood State) The POMS is a 65-item self-report questionnaire designed to measure six identifiable mood states (tension/anxiety, depression, anger, confusion, vigor and fatigue) with demonstrated reliability and validity. High scores on the fatigue subscale suggest persons with low energy. Subjects are asked to describe the extent to which the adjectives describe the way they had been feeling during the past week, on a scale that ranged from 0 (“not at all”) to 4 (“extremely”).	
POMS fatigue-inertia mean score was 8.13 (SD=5.99) for survivors of childhood cancer*. *n=104; diagnosed <18 years; average 8.4 years since diagnosis	*Lowe et al. 2016*
No significant difference in mean fatigue score between ALL survivors* and sibling controls was found (mean score 7.87 (SD 5.58) vs mean score 8.36 (SD 5.83), t-test p=0.19). *n=580; diagnosed <20 years; at least 2 years from diagnosis	*Zeltzer et al. 1997*

Quality of Life-Cancer survivors questionnaire Fatigue was measured as part of the physical subscale of the Qualtiy of Life-Cancer survivors questionnaire (scale 0(severe problem)-10(no problem))	
Participants were childhood cancer survivors*. Fatigue was the symptom with the lowest score in this subscale (mean score 7.32), which indicates that fatigue was experienced as the most problematic symptom relative to other symptoms included in the physical subscale (e.g. nausea, aches and pain, constipation, appetite changes, sleep changes and menstrual/fertility changes). No control group was present. *n=176; mean 8.5 years at dx; Leukemia>Lymphoma>Sarcomas; mean time since dx 13.3 years	*Zebrack et al. 2002*
Revised-Class Play (RCP)	
This study compared children who survived a brain tumor* with a peer control group. Peers nominated the children surviving a brain tumor significantly more often as fatigued than the control group (mean score for survivors 0.90 vs mean score of control group -0.24, p<0.001). *n=28; average time since diagnosis 36 months	*Vannatta et al. 1998*
Revised-Piper Fatigue Scale (R-PFS) The Piper Fatigue Scale is composed of 22 numerically scaled, 0-10 items that measure four dimensions of subjective fatigue: behavioral/severity (6 items), affective meaning (5 items), sensory (5 items), and cognitive/mood (6 items). These 22 items are used to calculate the four subscale/dimensional scores and the total fatigue scores. Subscales are scored by summing up items and dividing by number of items (0-10 subscale score). Total fatigue score is calculated by adding the 22 item scores together and divide by 22 (0-10 total score). Higher scores indicate higher levels of fatigue.	
Survivors of childhood leukemia (n=161; average age at diagnosis: 7.4 years; average time since end of treatment 13.9 years). Symptom distress scale (SDS): **Fatigue was the most frequently reported symptom (61%)**. POMS: Survivors' average **POMS fatigue-inertia score was 7.2** (SD 6.3), which is within the normal range reported for college students. SF-36: Survivors' **SF-36 vitality mean score was 63.4**, which is slightly higher (more energy) than the norms for the general population (61.3). R-PFS: **Prevalence of fatigue was 30%**.	*Meeske et al. 2005*
Non-standardized measurement tool	
29.7% of survivors of acute lymphoblastic leukemia* reported fatigue. *ALL; n=61; mean age at study 6.4 years; mean 2.6 years since treatment	*Arpaci & Kilicarslan Toruner 2016*
Survivors of Hodgkin Lymphoma* reported on four items**: "felt tired" mean 2.73, "had trouble finishing tasks because tired quickly" mean 3.46; "needed to sleep during the day" mean 3.25, "frustrated by being too tired to do things he/she wanted to do" mean 3.54, "needed to limit social activities because of fatigue" mean 3.68. *n=103; mean age at diagnosis 15.5 years; 36 months post therapy; **(0="very much so"-4"not at all")	*Macpherson et al. 2015*
Fatigue was determined in **21.6%** of childhood acute lymphoblastic leukemia survivors*. Of those, 60% Grade 1/mild, 31% Grade 2/moderate, 9% Grade 3/severe Fatigue. *n=162; median age at diagnosis: 3.9 years; median time from diagnosis: 10.2 years	*Khan et al. 2014*
25.78% of childhood cancer survivors* suffer from Fatigue. *n=225; hematologic cancers>solid or soft tissue tumors>CNS or brain tumors; mean age at diagnosis: 9.89 years; mean time since diagnosis 12.03 years	*Yi et al. 2014*
52% of childhood cancer survivors reported fatigue. Of those, 36% reported their fatigue was severe enough to limit work activities. *n=42; Leukemia>CNS>Lymphoma>Hodgkin's lymphoma; mean age at diagnosis 9.8 years; mean time of follow-up: 8.9 years	*Berg et al. 2013*
Overall incidence of fatigue in survivors* was **30%**, but brain tumor survivors reported 47%. *mixed diagnoses; n=271; Mean age at diagnosis: 10 years, mean age at survey: 24 years	*McClellan et al. 2013*
50% of craniopharyngioma survivors* reported fatigue *n=28; median age at diagnosis: 8 years; age at study: 29.7 years	*Manley et al. 2012*
12 items, 0-3 Likert scale (0= not at all; 3= every day; Total score 0-36) **Survivors* scored significantly lower than controls**** in total fatigue (9.8 vs. 11.4). Childhood leukemia survivors had equal or less fatigue compared with that of their age- and gender matched controls in multidimensional aspects of fatigue. *n=81, diagnoses: ALL and AML, age at diagnosis: mean 6.7 years; age at study: mean 14.1 years; **n=243 healthy controls	*Nagai et al. 2012*
24% of survivors* reported fatigue. *n=25; about half acute lymphoblastic leukemia; mean age at diagnosis 5.2 years; mean age at study 14.0 years	*Berg et al. 2009*
10.2% of childhood cancer survivors* suffered from Fatigue. Of those, 19% Grade 1, 75% Grade 2, 6% Grade 3/4/5. *n=1284; Leukemia>Lymphoma>Kidney/Wilms tumor>Soft tissue sarcoma; median follow-up time: 17 years	*Geenen et al. 2007*
67% of adolescents and young adults off treatment* experienced fatigue. *Leukemia>Lymphoma>Brain tumor; mean age at study 16 years	*Enskär et al. 2007*
67% of Hodgkin's disease survivors* reported feeling fatigued. 35% stated that it was a moderate to severe problem. *n=48; median age at diagnosis: 16.5 years; median 14.3 years	*Adams et al. 2004*
Overall conclusion	

Prevalence of CRF There is evidence that survivors of childhood, adolescent and young adult cancers are at risk for CRF. In 28 studies the prevalence of CRF in CAYACS ranged from 10 to 85%.	28 studies (24 samples) **Level A**
Prevalence of CRF in CAYACS versus controls Some evidence suggests that there is an increased risk for CRF in survivors of childhood, adolescent and young adult cancers as compared to controls. In 5 studies, there was a higher prevalence of CRF in survivors compared to controls with a difference ranging from 5 to 20%. One study reported lower prevalence of CRF in survivors compared to community norms.	6 studies **Level C**
Levels of CRF in CAYACS versus controls Evidence suggests that survivors of childhood, adolescent and young adult cancers have higher levels of CRF compared to controls. In 12 studies, survivors had significantly higher levels of CRF compared to controls. Two studies reported lower levels of CRF in survivors compared to controls.	18 studies **Level B**

1.1 What is the risk of CRF in CAYA cancer survivors **by sex**?	
Conclusion single studies	
Multivariable linear regression analysis* showed that females are at significantly higher risk for CRF: • **Female vs. male: β=0.19, p<0.001** Childhood cancer survivors (n=416; mean age at diagnosis 8 years; mean age at study 24 years; Leukemia/Lymphoma>Solid tumor>brain/CNS tumor); *adjusted for age at study, marital status, educational achievement, employment, age at diagnosis, diagnosis, treatment duration, follow-up time, late effects, treatment, and depression	*Langeveld et al. 2003*
Multivariable logistic regression* showed that females are at significantly higher risk for CRF: • **Female vs. male: RR=2.77 (95%CI:1.94-3.94)** Childhood cancer survivors (n=1284; Leukemia>Lymphoma>Kidney/WT>Soft tissue sarcoma; median follow-up time: 17 years; median age of 24.4 years); *adjusted for radiation, TBI, chemotherapy, surgery, follow-up duration, and age at diagnosis	*Geenen et al. 2007*
Multivariable logistic regression analysis* showed that females are at significantly higher risk for CRF: • **Female vs. male: OR=2.1 (95%CI:1.6-2.7)** Childhood cancer survivors (CCSS; n=1897; mixed diagnoses; diagnosed before the age of 21 years; at least 5 years from diagnosis); *adjusted for heart failure, lung fibrosis, hypothyroidism, depression, BMI, marital status, employment status, and infant at home	*Mulrooney et al. 2008*
Multivariable logistic regression analysis* showed no significant association between sex and total fatigue: • Female vs. male: β=2.99, p>0.05 Survivors of extracranial childhood cancer (n=199; mean age at diagnosis: 3.6 years; mean age at study: 14.4 years). **Lower scores of the effect measure indicate more fatigue.** *adjusted for age at study, diagnosis, treatment, follow-up time, additional diagnosis, remedial education, overall average grade, happiness, and HRQoL	*Mört et al. 2011*
Multivariable logistic regression analysis* showed no significant association between sex and CRF: • Female vs. male: OR=1.54 (95%CI:0.94-2.54) Childhood cancer survivors (only n=33 from older group (≥19 years) included for risk factor analysis); AML >astrocytoma>WT; age at diagnosis range 1-18 years;); *adjusted for age at study, educational achievement, marital status, employment, and receiving social benefits	*Johannsdottir et al. 2012*
Multivariable linear regression analysis* showed no significant association between sex and total fatigue: • Female (Ref. Male): β=0.35, p>0.05 Survivors of childhood leukemia (n=81, diagnoses: ALL and AML, age at diagnosis: mean 6.7 years; age at study: mean 14.1 years); *adjusted for age at study, diagnosis, cranial irradiation, TBI, and follow-up time	*Nagai et al. 2012*
Multivariable logistic regression analysis* showed no significant association between sex and CRF: • Female vs. male: OR=0.8 (95%CI:0.46-1.5), p=0.6 Childhood cancer survivors (n=290; HL, NHL, ALL; median age at diagnosis 9.5 years; median age at study 29.6 years); *adjusted for diagnosis, age at survey, treatment era, thyroid status, HADS (Hospital Anxiety and Depression scale) total score	*Hamre et al. 2013a*
Multivariable logistic regression analysis* showed no significant association between sex and CRF: • Female gender OR=1.09 (95%CI: 0.6-1.9), p=0.8 Childhood cancer survivors (n=232; HL, NHL, ALL; median age at diagnosis 9.6 years; median age at study 29.7 years; same sample as ***Hamre et al. 2013a***); *adjusted for age at survey, diagnosis, smoking, BMI, analgesics use, heart function, T-cell origin, CNS-irradiation, and B-symptoms at diagnosis	*Hamre et al. 2013b*
Multivariable logistic regression analysis* showed no significant association between sex and CRF: • Female vs. male: OR=1.39 (95%CI:0.69-2.81), p=0.348 Childhood and adolescent cancer survivors (n=268; median age at diagnosis: 6.4 years; mean time since diagnosis 13.1 years; median age at study 21.4 years; Leukemia>HL>NL>Bone tumors>soft tissue sarcoma>neuroblastoma>WT>other); *adjusted for age at study, income, survival time, and chronic conditions	*Frederick et al. 2016*
Multivariable logistic regression* showed that females were at higher risk for fatigue: • **Female (Ref. Male) OR=4.75 (95%CI:2.47-9.15), p<0.001** Hodgkin's lymphoma survivors of the childhood cancer survivor study (CCSS; n=751; 42.5% aged 11-15 years at diagnosis; at least 5 years since diagnosis); *adjusted for sex, emotional distress, employment, pain, physical function, and BMI	*Rach et al. 2017*
Hierarchical linear regression* showed no significant association between gender and CRF: • Gender: β=0.008, p=0.895 **Pediatric cancer survivors (n=144; mixed diagnoses; mean age at study 12.9 years, mean 5.9 years since diagnosis); *adjusted for age, sex, race, time since dia**gnosis, diagnosis, chemotherapy, radiation, depression, parent reported depression/anxiety, BMI, physical and function mobility	*Karimi et al. 2019*
Overall conclusion	
Some evidence suggests that **female sex** is associated with an **increased risk for CRF** in survivors of childhood, adolescent and young adult cancers.	10 studies (9 samples) **Level C**

1.2 What is the **risk of CRF** in CAYA cancer survivors **by age at follow-up**?	
Conclusion single studies	
Multivariable regression analysis* showed no significant association between age at follow-up and CRF: • Age at follow-up: β=0.01, p>0.05 Childhood cancer survivors (n=416; mean age at diagnosis 8 years; mean age at study 24 years; Leukemia/Lymphoma>Solid tumor>brain/CNS tumor); *adjusted for sex, marital status, educational achievement, employment, age at diagnosis, diagnosis, treatment duration, follow-up time, late effects, treatment, and depression	*Langeveld et al. 2003*
Multivariable regression analysis* showed that older age at follow-up was significantly associated with an increased risk of total fatigue: • **Age at study: β= -1.87, p<0.001** Survivors of extracranial childhood cancer (n=199; mean age at diagnosis: 3.6 years; mean age at study: 14.4 years). **Lower scores of the effect measure indicate more fatigue**. *adjusted for sex, diagnosis, treatment, follow-up time, additional diagnosis, remedial education, overall average grade, happiness, and HRQoL	*Mört et al. 2011*
Multivariable logistic regression analysis* showed that older age at follow-up was significantly associated with an increased risk of CRF: • **Age at assessment: OR=1.08 (95%CI:1.01-1.16)** Childhood cancer survivors (only n=33 from older group (≥19 years) included for risk factor analysis); AML >astrocytoma>WT; age at diagnosis range 1-18 years;); *adjusted for sex, educational achievement, marital status, employment, and receiving social benefits	*Johannsdottir et al. 2012*
Multivariable logistic regression analysis* showed that older age at follow-up was significantly associated with an increased risk of total fatigue: • **Present age (years): β=0.24, p<0.05** Childhood cancer survivors (n=81, diagnoses: ALL and AML, age at diagnosis: mean 6.7 years; age at study: mean 14.1 years); *adjusted for sex, diagnosis, cranial irradiation, TBI, and follow-up time	*Nagai et al. 2012*
Multivariable logistic regression analysis* showed no significant association between age at follow-up and CRF: • Age at survey: OR=1.05 (95%CI:1.0-1.1), p=0.1 Childhood cancer survivors (n=290; HL, NHL, ALL; median age at diagnosis 9.5 years; median age at study 29.6 years); *adjusted for diagnosis, treatment era, sex, thyroid status, HADS (Hospital Anxiety and Depression scale) total score	*Hamre et al. 2013a*
Multivariable logistic regression analysis* showed that older age at survey was associated with an increased risk for CRF: • **Age: OR=1.04 (95% CI: 1.00–1.1) p=0.03** Childhood cancer survivors (n=232; HL, NHL, ALL; median age at diagnosis 9.6 years; median age at study 29.7 years; same sample as ***Hamre et al. 2013a***); *adjusted for sex, diagnosis, smoking, BMI, analgesics use, heart function, T-cell origin, CNS-irradiation, and B-symptoms at diagnosis	*Hamre et al. 2013b*
Multivariable logistic regression analysis* showed no significant association between age at follow-up and CRF: • 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) Childhood and adolescent cancer survivors (n=268; median age at diagnosis: 6.4 years; mean time since diagnosis 13.1 years; median age at study 21.4 years; Leukemia>HL>NL>Bone tumors>soft tissue sarcoma>neuroblastoma>WT>other); *adjusted for sex, income, survival time, and chronic conditions	*Frederick et al. 2016*
Hierarchical linear regression* showed no significant association between age at survey and CRF: • Age at survey: β=-0.005, p=0.935 Pediatric cancer survivors (n=144; mixed diagnoses; mean age at study 12.9 years, mean 5.9 years since diagnosis); *adjusted for age, sex, race, time since diagnosis, diagnosis, chemotherapy, radiation, depression, parent reported depression/anxiety, BMI, physical and function mobility	*Karimi et al. 2019*
Overall conclusion	
Evidence suggests that **older age at follow-up** is associated with an **increased risk for CRF** in survivors of childhood, adolescent and young adult cancers.	8 studies (7 samples) **Level B**

1.3 What is the **risk of CRF** in CAYA cancer survivors **by age at diagnosis**?	
Conclusion single studies	
Multivariable regression analysis* showed no significant association between age at diagnosis and CRF: • Age at diagnosis: β=0.06, not significant Childhood cancer survivors (n=416; mean age at diagnosis 8 years; mean age at study 24 years; Leukemia/Lymphoma>Solid tumor>brain/CNS tumor); *adjusted for sex, age at study, marital status, educational achievement, employment, diagnosis, treatment duration, follow-up time, late effects, treatment, and depression	*Langeveld et al. 2003*
Multivariate logistic regression analysis* showed no significant association between age at diagnosis and CRF: • 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) Survivors (CCSS; n=1897; mixed diagnoses; diagnosed before the age of 21 years; at least 5 years from diagnosis); *adjusted for age at diagnosis, radiation, and chemotherapy	*Mulrooney et al. 2008*
Univariable logistic regression showed no significant association between age at diagnosis and CRF (variable was therefore not included in the multivariable model): • Age at diagnosis: not significant Childhood and adolescent cancer survivors (n=268; median age at diagnosis: 6.4 years; mean time since diagnosis 13.1 years; median age at study 21.4 years; Leukemia>HL>NL>Bone tumors>soft tissue sarcoma>neuroblastoma>WT>other).	*Frederick et al. 2016*
Overall conclusion	
Evidence suggests that **age at diagnosis** is **not significantly associated** with the risk for **CRF** in survivors of childhood, adolescent and young adult cancers.	3 studies **Level B**

1.4 What is the **risk of CRF** in CAYA cancer survivors **by time since diagnosis**?	
Conclusion single studies	
Multivariable regression analysis* showed no significant association between years since completion of therapy and CRF: • Years since completion of therapy: β=0.02, p>0.05 Childhood cancer survivors (n=416; mean age at diagnosis 8 years; mean age at study 24 years; Leukemia/Lymphoma>Solid tumor>brain/CNS tumor); *adjusted for sex, age at study, marital status, educational achievement, employment, age at diagnosis, diagnosis, treatment duration, late effects, treatment, and depression	*Langeveld et al. 2003*
Multivariable regression analysis* showed no significant association between follow-up time and total fatigue: • Length of survival: More than 10 years (Ref. 10 years or less) β= -3.6, p>0.05 Survivors of extracranial childhood cancer (n=199; mean age at diagnosis: 3.6 years; mean age at study: 14.4 years). **Lower scores of the effect measure indicate more fatigue**. *adjusted for age at study, sex, diagnosis, treatment, additional diagnosis, remedial education, overall average grade, happiness, and HRQoL	*Mört et al. 2011*
Multiple regression analysis* showed that longer duration after completion of treatment was significantly associated with a decreased risk of CRF: • **Duration after completion of treatment (years): β= -0.45, p<0.05** Survivors (n=81, diagnoses: ALL and AML, age at diagnosis: mean 6.7 years; age at study: mean 14.1 years); *adjusted for age at study, sex, diagnosis, cranial irradiation, and TBI	*Nagai et al. 2012*
Multivariable logistic regression* showed no significant association of survival time with risk for CRF: • 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) Childhood and adolescent cancer survivors (n=268; median age at diagnosis: 6.4 years; mean time since diagnosis 13.1 years; median age at study 21.4 years; Leukemia>HL>NL>Bone tumors>soft tissue sarcoma>neuroblastoma>WT>other); *adjusted for sex, age at study, income, and chronic conditions	*Frederick et al. 2016*
Hierarchical linear regression* showed that shorter time since diagnosis was associated with higher levels of CRF: • **Time since diagnosis: β=-0.154, p=0.019** Pediatric cancer survivors (n=144; mixed diagnoses; mean age at study 12.9 years, mean 5.9 years since diagnosis); *adjusted for age, sex, race, time since diagnosis, diagnosis, chemotherapy, radiation, depression, parent reported depression/anxiety, BMI, physical and function mobility	*Karimi et al. 2019*
Overall conclusion	
Some evidence suggests that **longer time since diagnosis** is associated with a **decreased risk for CRF** in survivors of childhood, adolescent and young adult cancers.	5 studies **Level C**

1.5 What is the **risk of CRF** in CAYA cancer survivors by **ethnicity**?	
Conclusion single studies	
Univariable logistic regression showed no significant association of ethnicity and risk for CRF (variable was therefore not included in the multivariable model): • Ethnicity: not significant Childhood and adolescent cancer survivors (n=268; median age at diagnosis: 6.4 years; mean time since diagnosis 13.1 years; median age at study 21.4 years; Leukemia>HL>NL>Bone tumors>soft tissue sarcoma>neuroblastoma>WT>other).	*Frederick et al. 2016*
Overall conclusion	
Some evidence suggests that **ethnicity** is **not significantly associated** with the risk for **CRF** in survivors of childhood, adolescent and young adult cancers.	2 studies **Level C**

1.6 What is the **risk of CRF** in CAYA cancer survivors **by partnership status**?	
Conclusion single studies	
Multivariable regression analysis* showed no significant association of marital status and CRF: • Married vs. not married: β=0.04, p>0.05 Childhood cancer survivors (n=416; mean age at diagnosis 8 years; mean age at study 24 years; Leukemia/Lymphoma>Solid tumor>brain/CNS tumor); *adjusted for sex, age at study, educational achievement, employment, age at diagnosis, diagnosis, treatment duration, follow-up time, late effects, treatment, and depression	*Langeveld et al. 2003*
Multivariable logistic regression* showed that being married is associated with a lower risk for CRF: • **Married vs. not married: OR=0.11, 95%CI:0.02-0.50** Survivors of childhood leukemia (n=161; average age at diagnosis: 7.4 years; average time since end of treatment 13.9 years); *adjusted for having children, sleep problems, pain, obesity, neuro-cognitive impairment, exercise-induced symptoms, unemployment, and relapse	*Meeske et al. 2005*
Multivariable logistic regression analysis* showed that not being married was associated with an increased risk of CRF: • **Marital status: Not married (Ref. Married): OR=2.7, 95%CI:2.0-3.6** Childhood cancer survivors (CCSS; n=1897; mixed diagnoses; diagnosed before the age of 21 years; at least 5 years from diagnosis); *adjusted for sex, heart failure, lung fibrosis, hypothyroidism, depression, BMI, employment status, and infant at home	*Mulrooney et al. 2008*
Multivariable logistic regression analysis* showed no significant association of marital status/cohabiting and CRF: • **Married/cohabiting: Yes (vs. No): OR=1.09 (95%CI:0.64-1.85)** Childhood cancer survivors (only n=33 from older group (≥19 years) included for risk factor analysis); AML >astrocytoma>WT; age at diagnosis range 1-18 years;); *adjusted for age at study, sex, educational achievement, employment, and receiving social benefits	*Johannsdottir et al. 2012*
Univariable logistic regression analysis showed no significant association between partnership and CRF (variable was therefore not included in the multivariable model): • Partnership: p>0.05 Childhood cancer survivors (n=290; HL, NHL, ALL; median age at diagnosis 9.5 years; median age at study 29.6 years).	*Hamre et al. 2013a*
Overall conclusion	
Some evidence suggests that **not being married** is associated with an **increased risk for CRF** in survivors of childhood, adolescent and young adult cancers.	5 studies **Level C**

1.7 What is the **risk of CRF** in CAYA cancer survivors **who have children?**	
Conclusion single studies	
Multivariable logistic regression analysis* showed that having children was associated with an increased risk for CRF: • **Children (vs. no children): OR=5.80 (95%CI:1.30-25.82)** Survivors of childhood leukemia (n=161; average age at diagnosis: 7.4 years; average time since end of treatment 13.9 years). *adjusted for marital status, sleep problems, pain, obesity, neuro-cognitive impairment, exercise-induced symptoms, unemployment, and relapse	*Meeske et al. 2005*
Multivariable logistic regression analysis* showed no significant association of having an infant at home and CRF: • Infant at home <6 months old: Yes (Ref. No): OR=1.9 (95%CI:0.7-5.0) Childhood cancer survivors (CCSS; n=1897; mixed diagnoses; diagnosed before the age of 21 years; at least 5 years from diagnosis); *adjusted for sex, heart failure, lung fibrosis, hypothyroidism, depression, BMI, marital status, and employment status	*Mulrooney et al. 2008*
Overall conclusion	
Some evidence suggests that **having children** is associated with an **increased risk for CRF** in survivors of childhood, adolescent and young adult cancers.	2 studies **Level C**

1.8 What is the **risk of CRF** in CAYA cancer survivors **by education**?	
Conclusion single studies	
Multivariable regression analysis* showed no significant association of education level and CRF: • Higher education level (vs. lower): β=0.03, p>0.05 Childhood cancer survivors (n=416; mean age at diagnosis 8 years; mean age at study 24 years; Leukemia/Lymphoma>Solid tumor>brain/CNS tumor); *adjusted for sex, age at study, marital status, employment, age at diagnosis, diagnosis, treatment duration, follow-up time, late effects, treatment, and depression	*Langeveld et al. 2003*
Multivariate regression* showed no significant association between educational outcomes and total fatigue: • Remedial education: No (Ref. Yes) β= -1.43, p>0.05 • Overall average grade: β=2.47, p>0.05 Survivors of extracranial childhood cancer (n=199; mean age at diagnosis: 3.6 years; mean age at study: 14.4 years). **Lower scores of the effect measure indicate more fatigue**. *adjusted for age at study, sex, diagnosis, treatment, follow-up time, additional diagnosis, happiness, and HRQoL	*Mört et al. 2011*
Multivariable logistic regression analysis* showed no significant association between academic education and CRF: • Academic education: Yes (vs. No): OR 0.63 (95% CI 0.36-1.12) Childhood cancer survivors (only n=33 from older group (≥19 years) included for risk factor analysis); AML >astrocytoma>WT; age at diagnosis range 1-18 years;); *adjusted for age at study, sex, marital status, employment, and receiving social benefits	*Johannsdottir et al. 2012*
Univariable logistic regression analysis showed no significant association of level of education and CRF (variable was therefore not included in the multivariable model): • **Education: p>0.05** Childhood cancer survivors (n=290; HL, NHL, ALL; median age at diagnosis 9.5 years; median age at study 29.6 years).	*Hamre et al. 2013a*
Overall conclusion	
Evidence suggests that **level of education, overall average grade and remedial education** are **not significantly associated** with the risk for **CRF** in survivors of childhood, adolescent and young adult cancers.	4 studies **Level B**

1.9 What is the **risk of CRF** in CAYA cancer survivors **by household income**?	
Conclusion single studies	
Multivariable logistic regression* showed no significant association between household income and CRF: • 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) Childhood and adolescent cancer survivors (n=268; median age at diagnosis: 6.4 years; mean time since diagnosis 13.1 years; median age at study 21.4 years; Leukemia>HL>NL>Bone tumors>soft tissue sarcoma>neuroblastoma>wilms tumor>other); *adjusted for sex, age at study, survival time, and chronic conditions	*Frederick et al. 2016*
Overall conclusion	
Some evidence suggests that **household income** is **not significantly associated** with the risk for **CRF** in survivors of childhood, adolescent and young adult cancers.	1 study **Level C**

1.10 What is the **risk of CRF** in CAYA cancer survivors **by employment status**?	
Conclusion single studies	
Multivariable regression analysis* showed that being employed was significantly associated with a decreased risk of CRF and found no significant association between being a student or homemaker and CRF: • Student/homemaker vs. unemployed: β= -0.12, p>0.05 • **Employed vs. unemployed: β= -0.20, p<0.05** Childhood cancer survivors (n=416; mean age at diagnosis 8 years; mean age at study 24 years; Leukemia/Lymphoma>Solid tumor>brain/CNS tumor); *adjusted for sex, age at study, marital status, educational achievement, age at diagnosis, diagnosis, treatment duration, follow-up time, late effects, treatment, and depression	*Langeveld et al. 2003*
Survivors of childhood leukemia (n=161; average age at diagnosis: 7.4 years; average time since end of treatment 13.9 years). Multivariate logistic regression (adjusted for marital status, having children, sleep problems, pain, obesity, neuro-cognitive impairment, exercise-induced symptoms, and relapse) showed that not working or attending school was significantly associated with an increased risk of CRF: • **Not working or attending school: p<0.05 (effect measure not reported)**	*Meeske et al. 2005*
Childhood cancer survivors (CCSS; n=1897; mixed diagnoses; diagnosed before the age of 21 years; at least 5 years from diagnosis). Multivariate logistic regression analysis (adjusted for sex, heart failure, lung fibrosis, hypothyroidism, depression, BMI, marital status, and infant at home) showed no significant association between employment status and CRF: • Not working full time (Ref. working full time): OR=1.2 (95%CI:0.3-1.6)	*Mulrooney et al. 2008*
Multivariable logistic regression analysis (adjusted for age at study, sex, educational achievement, marital status, and receiving social benefits) showed no significant association between being gainfully employed and CRF: • Gainfully employed: Yes (vs. No): OR=1.18 (95%CI:0.67-2.07) Childhood cancer survivors (only n=33 from older group (≥19 years) included for risk factor analysis); AML >astrocytoma>WT; age at diagnosis range 1-18 years;);	*Johannsdottir et al. 2012*
Hodgkin's lymphoma survivors of the childhood cancer survivor study (CCSS; n=751; 42.5% aged 11-15 years at diagnosis; at least 5 years since diagnosis). Multivariable logistic regression (adjusted for sex, emotional distress, employment, pain, physical function, and BMI) showed that **unemployed was associated with an increased risk for CRF:** • **Unemployed (Ref. employed) OR=2.90 (95%CI:1.27-6.62, p<0.01)**	*Rach et al. 2017*
Overall conclusion	
Evidence suggests that **being employed** or attending school is associated with a **decreased risk of CRF** in survivors of childhood, adolescent and young adult cancers.	5 studies **Level B**

1.11 What is the **risk of CRF** in CAYA cancer survivors **by social benefits**?	
Conclusion single studies	
Multivariable logistic regression analysis (adjusted for age at study, sex, educational achievement, marital status, and employment) showed no significant association between receiving social benefits and CRF: • Receiving social benefits: Yes (vs. No): OR=1.79 (95%CI:0.61-5.26) Childhood cancer survivors (only n=33 from older group (≥19 years) included for risk factor analysis); AML >astrocytoma>WT; age at diagnosis range 1-18 years;);	*Johannsdottir et al. 2012*
Overall conclusion	
Some evidence suggests that **receiving social benefits** is **not significantly associated** with the risk of **CRF** in survivors of childhood, adolescent and young adult cancers.	1 study **Level C**

1.12 What is the **risk of CRF** in CAYA cancer survivors **by amount of exercise**?	
Conclusion single studies	
Multiple logistic regression analysis* showed no significant association between number of steps per day and CRF: • Number of steps per day: p>0.05 (effect measure not reported) Childhood cancer survivors (n=62; Lymphoma, ALL; mean age at study 34.05 years; median 25.3 years of follow-up; follow-up study with all 62 survivors also participating in the ***Hamre et al. 2013a***); *adjusted for insomnia, PHQ9 score, pain, and depressive symptoms	*Zeller et al. 2014*
Generalized estimation equation* showed no significant association between amount of exercise and CRF: • "[…] amount of exercise was not predictive of fatigue at end of therapy or at 12 or 36 months post-therapy (p>0.05)." Survivors of Hodgkin Lymphoma (n=103; mean age at diagnosis 15.5 years; 36 months post therapy); *adjusted for sex, age at diagnosis, stage at diagnosis and protocol treatment arm	*Macpherson et al. 2015*
Overall conclusion	
Evidence suggests that **amount of exercise** is **not significantly associated** with the risk of **CRF** in survivors of childhood, adolescent and young adult cancers.	2 studies **Level B**

1.13 What is the **risk of CRF** in **overweight/obese** CAYA cancer survivors?	
Conclusion single studies	
Multivariable logistic regression* showed that obesity was significantly associated with an increased risk for CRF: • **Obesity: OR=3.80 (95%CI:1.41-10.26)** Survivors of childhood leukemia (n=161; average age at diagnosis: 7.4 years; average time since end of treatment 13.9 years); *adjusted for marital status, having children, sleep problems, pain, neuro-cognitive impairment, exercise-induced symptoms, unemployment, and relapse	*Meeske et al. 2005*
Multivariate logistic regression analysis* showed no significant association between obesity and CRF: • BMI 30+ kg/m^2: Yes (Ref. No): OR=1.3 (95%CI:0.9-1.7) Childhood cancer survivors (CCSS; n=1897; mixed diagnoses; diagnosed before the age of 21 years; at least 5 years from diagnosis); *adjusted for sex, heart failure, lung fibrosis, hypothyroidism, depression, marital status, employment status, and infant at home	*Mulrooney et al. 2008*
Univariable logistic regression showed no significant association between BMI and CRF (variable was therefore not included in the multivariable model): • BMI: not significant Childhood cancer survivors (n=290; HL, NHL, ALL; median age at diagnosis 9.5 years; median age at study 29.6 years).	*Hamre et al. 2013a*
Multivariable logistic regression analysis* showed no significant association between BMI and CRF: • BMI OR=1.1 (95%CI:1.0-1.1), p=0.1 Childhood cancer survivors (n=232; HL, NHL, ALL; median age at diagnosis 9.6 years; median age at study 29.7 years; same sample as ***Hamre et al. 2013a***); (adjusted for age at study, sex, diagnosis, smoking, analgesics use, heart function, T-cell origin, CNS-irradiation, and B-symptoms at diagnosis)	*Hamre et al. 2013b*
Multivariable logistic regression* showed no significant association between overweight/obesity and CRF: • 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.) Hodgkin's lymphoma survivors of the CCSS (n=751; 42.5% aged 11-15 years at diagnosis; at least 5 years since diagnosis); *adjusted for sex, emotional distress, employment, pain, physical function, and BMI	*Rach et al. 2017*
Hierarchical linear regression* showed no significant association between BMI and CRF: • BMI: β=-0.036, p=0.560 Pediatric cancer survivors (n=144; mixed diagnoses; mean age at study 12.9 years, mean 5.9 years since diagnosis); *adjusted for age, sex, race, time since diagnosis, diagnosis, chemotherapy, radiation, depression, parent reported depression/anxiety, BMI, physical and function mobility	*Karimi et al. 2019*
Overall conclusion	
Some evidence suggests that higher **BMI or obesity** is associated with an **increased risk for CRF** in survivors of childhood, adolescent and young adult cancers.	6 studies (4 samples) **Level C**

1.14 What is the **risk of CRF** in CAYA cancer survivors who **smoke**?	
Conclusion single studies	
Multivariable logistic regression analysis* showed no significant association between smoking and CRF: • Smoking OR=1.34 (95%CI=0.7-2.5), p=0.3 Childhood cancer survivors (n=232; HL, NHL, ALL; median age at diagnosis 9.6 years; median age at study 29.7 years; same sample as ***Hamre et al. 2013a***); *adjusted for age at study, sex, diagnosis, BMI, analgesics use, heart function, T-cell origin, CNS-irradiation, and B-symptoms at diagnosis	*Hamre et al. 2013b*
Overall conclusion	
Some evidence suggests that **smoking** is **not significantly associated** with the risk of CRF in survivors of childhood, adolescent, and young adult cancers.	1 study **Level C**

1.15 What is the **risk of CRF** in CAYA cancer survivors **with sleep problems**?	
Conclusion single studies	
Multivariate logistic regression analysis* showed that having sleep problems was significantly associated with an increased risk of CRF: • **Sleep problems: OR=6.15 (95%CI:2.33-16.22)** Survivors of childhood leukemia (n=161; average age at diagnosis: 7.4 years; average time since end of treatment 13.9 years); *adjusted for marital status, having children, pain, obesity, neuro-cognitive impairment, exercise-induced symptoms, unemployment, and relapse	*Meeske et al. 2005*
Multiple logistic regression analysis* showed no significant association between insomnia and CRF: • Insomnia present vs. insomnia absent: not significant (effect measure not reported) Childhood cancer survivors (n=62; Lymphoma, ALL; mean age at study 34.05 years; median 25.3 years of follow-up; follow-up study with all 62 survivors also participating in the ***Hamre et al. 2013a***); *adjusted for PHQ9 score, pain, number of steps, and depressive symptoms	*Zeller et al. 2014*
Overall conclusion	
Some evidence suggests that **sleep problems** are associated with an **increased risk for CRF** in survivors of childhood, adolescent and young adult cancers.	2 studies **Level C**

1.16 What is the **risk of CRF** in CAYA cancer survivors **by quality of life (QoL)?**	
Conclusion single studies	
Multivariable regression analysis* showed that better health-related quality of life was significantly associated with a decreased risk of total fatigue: • **HRQoL score: β= 0.87, p<0.001** Survivors of extracranial childhood cancer (n=199; mean age at diagnosis: 3.6 years; mean age at study: 14.4 years). **Lower scores of the effect measure indicate more fatigue**. *adjusted for age at study, sex, diagnosis, treatment, follow-up time, additional diagnosis, remedial education, overall average grade, and happiness	*Mört et al. 2011*
Overall conclusion	
Some evidence suggests that better **health-related quality of life** is associated with a **decreased risk for CRF** in survivors of childhood, adolescent and young adult cancers.	1 study **Level C**

1.17 What is the **risk of CRF** in CAYA cancer survivors **by happiness**?	
Conclusion single studies	
Multivariate regression analysis* showed no significant association of self-rated happiness and total fatigue. • Self-rated happiness: No (Ref. Yes) β= -1.13, p>0.05 Survivors of extracranial childhood cancer (n=199; mean age at diagnosis: 3.6 years; mean age at study: 14.4 years). **Lower scores of the effect measure indicate more fatigue**. *adjusted for age at study, sex, diagnosis, treatment, follow-up time, additional diagnosis, remedial education, overall average grade, and HRQoL	*Mört et al. 2011*
Overall conclusion	
Some evidence suggests that self-rated **happiness** is **not significantly associated** with the risk of **CRF** in survivors of childhood, adolescent and young adult cancers.	1 study **Level C**

1.18 What is the **risk of CRF** in CAYA cancer survivors **with late effects or health problems**?	
Conclusion single studies	
Multivariable regression analysis* showed that suffering from late effects/health problems was significantly associated with an increased risk of CRF: • **Late effects/health problems: β= 0.14, p<0.05** Childhood cancer survivors (n=416; mean age at diagnosis 8 years; mean age at study 24 years; Leukemia/Lymphoma>Solid tumor>brain/CNS tumor); *adjusted for sex, age at study, marital status, educational achievement, employment, age at diagnosis, diagnosis, treatment duration, follow-up time, treatment, and depression	*Langeveld et al. 2003*
Multivariable regression analysis* showed no significant association of an additional non-cancer diagnosis and total fatigue: • Additional diagnosis: No (Ref. Yes) β=2.2, p>0.05 Survivors of extracranial childhood cancer (n=199; mean age at diagnosis: 3.6 years; mean age at study: 14.4 years). **Lower scores of the effect measure indicate more fatigue**. *adjusted for age at study, sex, diagnosis, treatment, follow-up time, remedial education, overall average grade, happiness, and HRQoL	*Mört et al. 2011*
Multivariable logistic regression* showed that 3 or more chronic conditions was significantly associated with an increased risk of CRF: • 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)** Childhood and adolescent cancer survivors (n=268; median age at diagnosis: 6.4 years; mean time since diagnosis 13.1 years; median age at study 21.4 years; Leukemia>HL>NL>Bone tumors>soft tissue sarcoma>neuroblastoma>wilms tumor>other); *adjusted for sex, age at study, income, and survival time	*Frederick et al. 2016*
Multivariable logistic regression* showed that impaired physical function was associated with an increased risk for CRF: • **Physical functioning limitations (Ref. no limitations) OR=3.28 (95%CI:1.75-6.15, p<0.001)** Hodgkin's lymphoma survivors of the childhood cancer survivor study (CCSS; n=751; 42.5% aged 11-15 years at diagnosis; at least 5 years since diagnosis); *adjusted for sex, emotional distress, employment, pain, physical function, and BMI	*Rach et al. 2017*
Hierarchical linear regression* showed that problems with physical and function mobility was associated with increased levels of CRF: • **Physical and function mobility: β=-0.427, p<0.001** Pediatric cancer survivors (n=144; mixed diagnoses; mean age at study 12.9 years, mean 5.9 years since diagnosis); *adjusted for age, sex, race, time since diagnosis, diagnosis, chemotherapy, radiation, depression, parent reported depression/anxiety, BMI, physical and function mobility	*Karimi et al. 2019*
Overall conclusion	
Evidence suggests that **late effects or health problems** are associated with an **increased risk for CRF** in survivors of childhood, adolescent and young adult cancers.	5 studies **Level B**

1.19 What is the **risk of CRF** in CAYA cancer survivors **with neuro-cognitive impairment**?	
Conclusion single studies	
Multivariate logistic regression* showed that neuro-cognitive impairment was significantly associated with an increased risk of CRF: • **Neuro-cognitive impairment: OR=2.56 (95%CI:1.02-6.38)** Survivors of childhood leukemia (n=161; average age at diagnosis: 7.4 years; average time since end of treatment 13.9 years).; *adjusted for marital status, having children, sleep problems, pain, obesity, exercise-induced symptoms, unemployment, and relapse	*Meeske et al. 2005*
Overall conclusion	
Some evidence suggests that **neuro-cognitive impairment** is associated with an **increased risk for CRF** in survivors of childhood, adolescent and young adult cancers.	1 study **Level C**

1.20 What is the **risk of CRF** in CAYA cancer survivors **with higher brain dysfunction**?	
Conclusion single studies	
Multivariable regression analysis* showed that higher brain dysfunction was associated with an increased risk of CRF. • **Higher brain dysfunction: Impact= 15.2, p=0.004** Childhood brain tumor survivors (n=104, mean age at diagnosis 13.3 years, mean age at study 26.8 years). A positive impact **indicates more fatigue; a negative impact less fatigue.** *adjusted for age, sex, age at diagnosis, hydrocephalus at diagnosis, tumor pathology, tumor location, neurosurgery, radiation treatment, chemotherapy, tumor recurrence and time since completion of antitumor therapy	*Sato et al. 2014*
Overall conclusion	
Some evidence suggests that **higher brain dysfunction** is associated with an **increased risk for CRF** in survivors of childhood, adolescent and young adult cancers.	1 study **Level C**

1.21 What is the **risk of CRF** in CAYA cancer survivors **with seizures**?	
Conclusion single studies	
Multivariable regression analysis* showed no significant association between seizures and CRF: • Seizure: Impact= -7.9, p=0.158 Childhood brain tumor survivors (n=104, mean age at diagnosis 13.3 years, mean age at study 26.8 years, brain tumors) . A positive impact **indicates more fatigue; a negative impact less fatigue.** *adjusted for age, sex, age at diagnosis, hydrocephalus at diagnosis, tumor pathology, tumor location, neurosurgery, radiation treatment, chemotherapy, tumor recurrence and time since completion of antitumor therapy	*Sato et al. 2014*
Overall conclusion	
Some evidence suggests that **seizures** are **not significantly associated** with the risk for **CRF** in survivors of childhood, adolescent and young adult cancers.	1 study **Level C**

1.22 What is the **risk of CRF** in CAYA cancer survivors **with heart problems**?	
Conclusion single studies	
Multivariate logistic regression analysis* showed that congestive heart failure was significantly associated with an increased risk of CRF: • **Congestive heart failure: Yes (Ref. No): OR=2.9 (95%CI:1.4-6.1)** Childhood cancer survivors (CCSS; n=1897; mixed diagnoses; diagnosed before the age of 21 years; at least 5 years from diagnosis); *adjusted for sex, lung fibrosis, hypothyroidism, depression, BMI, marital status, employment status, and infant at home	*Mulrooney et al. 2008*
Multivariable logistic regression analysis* showed no significant association between reduced heart function and CRF: • Reduced heart function OR=1.8 (95%CI:1.0-3.3), p=0.06 Childhood cancer survivors (n=232; HL, NHL, ALL; median age at diagnosis 9.6 years; median age at study 29.7 years; same sample as ***Hamre et al. 2013a***); *adjusted for age at study, sex, diagnosis, smoking, BMI, analgesics use, T-cell origin, CNS-irradiation, and B-symptoms at diagnosis	*Hamre et al. 2013b*
Overall conclusion	
Some evidence suggests that a **heart problem** is associated with an **increased risk for CRF** in survivors of childhood, adolescent and young adult cancers.	2 studies **Level C**

1.23 What is the **risk of CRF** in CAYA cancer survivors **with exercise-induced symptoms**?	
Conclusion single studies	
Multivariate logistic regression* showed that exercise-induced symptoms are associated with an increased risk of CRF: • **Exercise-induced symptoms: OR=2.98 (95%CI:1.11-8.02)** Survivors of childhood leukemia (n=161; average age at diagnosis: 7.4 years; average time since end of treatment 13.9 years); *adjusted for marital status, having children, sleep problems, pain, obesity, neuro-cognitive impairment, unemployment, and relapse	*Meeske et al. 2005*
Overall conclusion	
Some evidence suggests that **exercise-induced symptoms** are associated with an **increased risk for CRF** in survivors of childhood, adolescent and young adult cancers.	1 study **Level C**

1.24 What is the **risk of CRF** in CAYA cancer survivors **with motility disturbance of limbs**?	
Conclusion single studies	
Multivariable regression analysis* showed no significant association between motility disturbance of limbs and CRF: • Motility disturbance of limbs: Impact= -5.5, p=0.308 Childhood brain tumor survivors (n=104, mean age at diagnosis 13.3 years, mean age at study 26.8 years) . A positive impact **indicates more fatigue; a negative impact less fatigue.** *adjusted for age, sex, age at diagnosis, hydrocephalus at diagnosis, tumor pathology, tumor location, neurosurgery, radiation treatment, chemotherapy, tumor recurrence and time since completion of antitumor therapy	*Sato et al. 2014*
Overall conclusion	
Some evidence suggests that **motility disturbance of limbs** is **not significantly associated** with the risk for **CRF** in survivors of childhood, adolescent and young adult cancers.	1 study **Level C**

1.25 What is the **risk of CRF** in CAYA cancer survivors **with ocular/vision impairment**?	
Conclusion single studies	
Multivariable regression analysis* showed no significant association between ocular/vision impairment and CRF: • Ocular/vision impairment: impact 5.9, p=0.315 Childhood brain tumor survivors (n=104, mean age at diagnosis 13.3 years, mean age at study 26.8 years, brain tumors). A positive impact **indicates that more fatigue; a negative impact less fatigue.** *adjusted for age, sex, age at diagnosis, hydrocephalus at diagnosis, tumor pathology, tumor location, neurosurgery, radiation treatment, chemotherapy, tumor recurrence and time since completion of antitumor therapy	*Sato et al. 2014*
Overall conclusion	
Some evidence suggests that **ocular/vision impairment** is **not significantly associated** with the risk for **CRF** in survivors of childhood, adolescent and young adult cancers.	1 study **Level C**

1.26 What is the **risk of CRF** in CAYA cancer survivors **by thyroid status**?	
Conclusion single studies	
Multivariate logistic regression analysis* showed no significant association between hypothyroidism and CRF: • Hypothyroidism: Yes (Ref. No): OR=0.9 (95%CI:0.7-1.3) Childhood cancer survivors (CCSS; n=1897; mixed diagnoses; diagnosed before the age of 21 years; at least 5 years from diagnosis); *adjusted for sex, heart failure, lung fibrosis, depression, BMI, marital status, employment status, and infant at home	*Mulrooney et al. 2008*
Multivariable logistic regression analysis* showed no significant association between hypothyroidism and CRF: • Present hypothyroidism (vs. Thyroid status normal): OR=1.4 (95%CI:0.7-3.0), p=0.4 Childhood cancer survivors (n=290; HL, NHL, ALL; median age at diagnosis 9.5 years; median age at study 29.6 years); *adjusted for diagnosis, age at survey, treatment era, sex, HADS (Hospital Anxiety and Depression scale) total score	*Hamre et al. 2013a*
Overall conclusion	
Evidence suggests that **thyroid status** is **not significantly associated** with the risk for **CRF** in survivors of childhood, adolescent and young adult cancers.	2 studies **Level B**

1.27 What is the **risk of CRF** in CAYA cancer survivors **with endocrine abnormalities?**	
Conclusion single studies	
Multivariable regression analysis* showed no significant association between endocrine abnormalities and CRF: • Endocrine abnormality: impact 12.9, p=0.20 Childhood brain tumor survivors (n=104, mean age at diagnosis 13.3 years, mean age at study 26.8 years). A positive impact **indicates that more fatigue; a negative impact less fatigue.** *adjusted for age, sex, age at diagnosis, hydrocephalus at diagnosis, tumor pathology, tumor location, neurosurgery, radiation treatment, chemotherapy, tumor recurrence and time since completion of antitumor therapy	*Sato et al. 2014*
Overall conclusion	
Some evidence suggests that **endocrine abnormality** is **not significantly associated** with the risk for **CRF** in survivors of childhood, adolescent and young adult cancers.	1 study **Level C**

1.28 What is the **risk of CRF** in CAYA cancer survivors **with lung fibrosis**?	
Conclusion single studies	
Multivariate logistic regression analysis* showed that lung fibrosis was significantly associated with an increased risk of CRF: • **Lung fibrosis: Yes (Ref. No): OR=2.9 (95%CI:1.5-5.4)** Childhood cancer survivors (CCSS; n=1897; mixed diagnoses; diagnosed before the age of 21 years; at least 5 years from diagnosis); *adjusted for sex, heart failure, hypothyroidism, depression, BMI, marital status, employment status, and infant at home	*Mulrooney et al. 2008*
Overall conclusion	
Some evidence suggests that **lung fibrosis** is associated with an **increased risk for CRF** in survivors of childhood, adolescent and young adult cancers.	1 study **Level C**

1.29 What is the **risk of CRF** in CAYA cancer survivors **with pain**?	
Conclusion single studies	
Multivariate logistic regression analysis* showed that pain was significantly associated with an increased risk of CRF: • **Pain: OR=5.56 (95%CI:2.13-14.48)** Survivors of childhood leukemia (n=161; average age at diagnosis: 7.4 years; average time since end of treatment 13.9 years); *adjusted for marital status, having children, sleep problems, obesity, neuro-cognitive impairment, exercise-induced symptoms, unemployment, and relapse	*Meeske et al. 2005*
Multiple logistic regression analysis* showed no significant association between the pain severity score and CRF: • Pain severity score: not significant (effect measure not reported) Childhood cancer survivors (n=62; Lymphoma, ALL; mean age at study 34.05 years; median 25.3 years of follow-up; follow-up study with all 62 survivors also participating in the ***Hamre et al. 2013a***); *adjusted for insomnia, PHQ9 score, number of steps, and depressive symptoms	*Zeller et al. 2014*
Multivariable logistic regression analysis* showed no significant association between regular use of analgesics and CRF: • Regular use of analgesics OR=1.6 (95%CI:0.7-3.7), p=0.2 Childhood cancer survivors (n=232; HL, NHL, ALL; median age at diagnosis 9.6 years; median age at study 29.7 years; same sample as ***Hamre et al. 2013a***); *adjusted for age at study, sex, diagnosis, smoking, BMI, heart function, T-cell origin, CNS-irradiation, and B-symptoms at diagnosis	*Hamre et al. 2013b*
Multivariable logistic regression* showed that body pain was associated with an increased risk for CRF: • **Elevated body pain (Ref. subclinical pain) OR=3.73 (95%CI:2.09-6.67, p<0.001)** Hodgkin's lymphoma survivors of the childhood cancer survivor study (CCSS; n=751; 42.5% aged 11-15 years at diagnosis; at least 5 years since diagnosis); *adjusted for sex, emotional distress, employment, pain, physical function, and BMI	*Rach et al. 2017*
Overall conclusion	
Some evidence suggests that **pain** is associated with an **increased risk for CRF** in survivors of childhood, adolescent and young adult cancers.	4 studies (3 samples) **Level B**

1.30 What is the **risk of CRF** in CAYA cancer survivors **by cytokine levels**?	
Conclusion single studies	
Multivariable logistic regression analysis* showed no significant association between cytokine levels and CRF (OR, 95%CI, p-value): IL-1ra OR=0.9 (95%CI:0.6-1.3, p=0.5) IL-6 OR=1.0 (0.5-2.4, p=0.9) IL-7 OR=2.1 (0.02-224, p=0.7) IL-8/CXCL8 OR=32.2 (0.2-5346, p=0.2) IL-9 OR=1.0 (0.8-1.2, p=0.9) IL-10 OR=0.5 (0.06-3.3, p=0.4) IL-12 OR=0.7 (0.2-2.0, p=0.5) FGF OR=5.2 (0.6-43.6, p=0.1) Eotaxin/CCL11 OR=1.0 (0.9-1.1, p=0.5) IP-10/CXCL10 OR=1.0 (0.9-1.1, p=0.3) MCP-1/CCL2 OR=1.7 (0.3-8.5, p=0.5) MIP-1 β/CCL4 OR=1.8 (0.8-4.1, p=0.2) RANTES/CCL5 OR=1.0 (1.0-1.0, p=0.3) PDGF OR=1.0 (1.0-1.0, p=0.3) VEGF OR=0.8 (0.5-1.3, p=0.4) IFN-γ OR=0.7 (0.4-1.3, p=0.3) Childhood cancer survivors (n=232; HL, NHL, ALL; median age at diagnosis 9.6 years; median age at study 29.7 years; same sample as ***Hamre et al. 2013a***); *adjusted for diagnosis, age, sex, BMI, and reduced heart function	*Hamre et al. 2013b*
Overall conclusion	
Some evidence suggests that **cytokine levels** are **not significantly associated** with the risk for **CRF** in survivors of childhood, adolescent and young adult cancers.	1 study **Level C**

1.31 What is the **risk of CRF** in CAYA cancer survivors **with psychological distress**?	
Conclusion single studies	
Multivariable regression analysis* showed that depression was significantly associated with an increased risk of CRF: • **Depression: β=0.54, p<0.001** Childhood cancer survivors (n=416; mean age at diagnosis 8 years; mean age at study 24 years; Leukemia/Lymphoma>Solid tumor>brain/CNS tumor); *adjusted for sex, age at study, marital status, educational achievement, employment, age at diagnosis, diagnosis, treatment duration, follow-up time, late effects, and treatment	*Langeveld et al. 2003*
Multivariate logistic regression analysis* showed that depression was significantly associated with an increased risk of CRF: • **Depressed: Yes (Ref. No): OR=7.5 (95%CI:5.1-10.9)** Childhood cancer survivors (CCSS; n=1897; mixed diagnoses; diagnosed before the age of 21 years; at least 5 years from diagnosis); *adjusted for sex, heart failure, lung fibrosis, hypothyroidism, BMI, marital status, employment status, and infant at home	*Mulrooney et al. 2008*
Multivariable logistic regression analysis* showed that depression was significantly associated with an increased risk of CRF: • **HADS (Hospital Anxiety and Depression Scale) total score: OR=1.15 (95%CI:1.1-1.2), p<0.001** Childhood cancer survivors (n=290; HL, NHL, ALL; median age at diagnosis 9.5 years; median age at study 29.6 years); *adjusted for diagnosis, age at survey, treatment era, sex, and thyroid status	*Hamre et al. 2013a*
Multiple logistic regression analysis* showed that depression (measured by PHQ8) was significantly associated with an increased risk of CRF: • **Level of depressive symptoms (PHQ8 score): OR 1.3 (95%CI:1.1-1.7), p=0.014** • PHQ9 score (patient health questionnaire-9, assesses degree of depression): not significant (effect measure not reported) Childhood cancer survivors (n=62; Lymphoma, ALL; mean age at study 34.05 years; median 25.3 years of follow-up; follow-up study with all 62 survivors also participating in the ***Hamre et al. 2013a***); *adjusted for insomnia, pain, and number of steps	*Zeller et al. 2014*
Multivariable logistic regression* showed that emotional distress was associated with an increased risk for CRF: • **Emotional distress (Ref. no emotional distress) OR=8.38 (95%CI:4.28-16.42, p<0.001)** Hodgkin's lymphoma survivors of the childhood cancer survivor study (CCSS; n=751; 42.5% aged 11-15 years at diagnosis; at least 5 years since diagnosis); *adjusted for sex, emotional distress, employment, pain, physical function, and BMI	*Rach et al. 2017*
Hierarchical linear regression* showed that self-reported depression symptoms were associated with increased levels of CRF: • **Depression: β=0.396, p<0.001** • Parent-reported depression/anxiety: β=0.117, p=0.095 Pediatric cancer survivors (n=144; mixed diagnoses; mean age at study 12.9 years, mean 5.9 years since diagnosis); *adjusted for age, sex, race, time since diagnosis, diagnosis, chemotherapy, radiation, depression, parent reported depression/anxiety, BMI, physical and function mobility	*Karimi et al. 2019*
Overall conclusion	
There is evidence that **psychological distress** is associated with an **increased risk for CRF** in survivors of childhood, adolescent and young adult cancers.	6 studies (5 samples) **Level A**

1.32 What is the **risk of CRF** in CAYA cancer survivors **by primary cancer diagnosis**?	
Conclusion single studies	
Multivariable regression analysis* showed no significant association between primary cancer diagnosis (solid tumor vs. leukemia/NHL, brain tumor vs. leukemia/NHL) and CRF: • Solid tumor vs Leukaemia/NHL without CRT: β=0.02, p>0.05 • Brain/CNS tumor vs Leukaemia/NHL without CRT: β= -0.08, p>0.05 Childhood cancer survivors (n=416; mean age at diagnosis 8 years; mean age at study 24 years; Leukemia/Lymphoma>Solid tumor>brain/CNS tumor); *adjusted for sex, age at study, marital status, educational achievement, employment, age at diagnosis, treatment duration, follow-up time, late effects, treatment, and depression	*Langeveld et al. 2003*
Multivariate logistic regression analysis* showed no significant association between primary cancer diagnosis (CNS malignancy, Hodgkin disease, soft tissue sarcoma or bone cancer (all vs. ALL)) and CRF: • 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) Childhood cancer survivors (CCSS; n=1897; mixed diagnoses; diagnosed before the age of 21 years; at least 5 years from diagnosis); *adjusted for age at diagnosis, radiation, and chemotherapy	*Mulrooney et al. 2008*
Multivariate regression analysis* showed no significant association between sarcoma survivors (vs. leukemia) and CRF: • **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** Survivors of extracranial childhood cancer (n=199; mean age at diagnosis: 3.6 years; mean age at study: 14.4 years). **Lower scores of the effect measure indicate more fatigue**. *adjusted for age at study, sex, treatment, follow-up time, additional diagnosis, remedial education, overall average grade, happiness, and HRQoL	*Mört et al. 2011*
Multiple regression analysis* showed no significant association between primary cancer diagnosis and CRF. • AML (Ref. ALL): β= -0.02, p>0.05 Childhood cancer survivors (n=81, diagnoses: ALL and AML, age at diagnosis: mean 6.7 years; age at study: mean 14.1 years). *adjusted for age at study, sex, cranial irradiation, TBI, and follow-up time	*Nagai et al. 2012*
Multivariable logistic regression analysis* showed no significant association between primary cancer diagnosis (lymphoma vs. leukemia) and CRF: • NHL (vs. ALL): OR=1.5 (95%CI:0.6-3.4), p=0.4 • HL (vs ALL): OR=1.7 (95%CI:0.8-3.5), p=0.2 Childhood cancer survivors (n=290; HL, NHL, ALL; median age at diagnosis 9.5 years; median age at study 29.6 years); *adjusted for age at survey, treatment era, sex, thyroid status, and HADS (Hospital Anxiety and Depression scale) total score	*Hamre et al. 2013a*
Multivariable logistic regression analysis* showed no significant association between diagnosis and CRF, but T-cell origin was significantly associated with an increased risk for CRF: • 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 • **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 • 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 Childhood cancer survivors (n=232; HL, NHL, ALL; median age at diagnosis 9.6 years; median age at study 29.7 years; same sample as ***Hamre et al. 2013a***); *adjusted for age at survey, sex, smoking, BMI, analgesics use, heart function, and CNS-irradiation	*Hamre et al. 2013b*
Univariable logistic regression analysis showed no significant association between primary cancer diagnosis and CRF (variable was therefore not included in the multivariable model): • Diagnosis: not significant Childhood and adolescent cancer survivors (n=268; median age at diagnosis: 6.4 years; mean time since diagnosis 13.1 years; median age at study 21.4 years; Leukemia>HL>NL>Bone tumors>soft tissue sarcoma>neuroblastoma>WT>other).	*Frederick et al. 2016*
Hierarchical linear regression* showed no significant association between diagnosis and CRF: • Diagnosis: β=-0.045, p=0.464 Pediatric cancer survivors (n=144; mixed diagnoses; mean age at study 12.9 years, mean 5.9 years since diagnosis); *adjusted for age, sex, race, time since diagnosis, diagnosis, chemotherapy, radiation, depression, parent reported depression/anxiety, BMI, physical and function mobility	*Karimi et al. 2019*
Overall conclusion	
Evidence suggests that primary cancer **diagnosis** is **not significantly associated** with the risk for CRF in survivors of childhood, adolescent and young adult cancer survivors.	8 studies (7 samples) **Level B**

1.33 What is the **risk of CRF** in CAYA cancer survivors **with a relapse**?	
Conclusion single studies	
Multivariable logistic regression analysis* showed that relapse was significantly associated with an increased risk of CRF: • **Relapse p<0.05 (effect measure not reported)** Survivors of childhood leukemia (n=161; average age at diagnosis: 7.4 years; average time since end of treatment 13.9 years); *adjusted for marital status, having children, sleep problems, pain, obesity, neuro-cognitive impairment, exercise-induced symptoms, and unemployment	*Meeske et al. 2005*
Multivariable logistic regression analysis* showed that history of leukemia relapse was significantly associated with an increased risk of CRF: • **History of leukemia relapse (vs. none): OR=8.35 (95%CI:1.16-59.93), p<0.03** Childhood acute lymphoblastic leukemia survivors (n=162; median age at diagnosis: 3.9 years; median time from diagnosis: 10.2 years); *unclear what other variables were included in the model	*Khan et al. 2014*
Univariable logistic regression analysis showed no significant association between recurrence and CRF (variable was therefore not included in the multivariable model): • Recurrence: not significant Childhood and adolescent cancer survivors (n=268; median age at diagnosis: 6.4 years; mean time since diagnosis 13.1 years; median age at study 21.4 years; Leukemia>HL>NL>Bone tumors>soft tissue sarcoma>neuroblastoma>Wilms tumor>other).	*Frederick et al. 2016*
Overall conclusion	
Evidence suggests that a **relapse** is associated with an **increased risk for CRF** in survivors of childhood, adolescent and young adult cancers.	3 studies **Level B**

1.34 What is the **risk of CRF** in CAYA cancer survivors who were treated with **CNS/brain irradiation**?	
Conclusion single studies	
Multivariable regression analysis* showed that treatment with CRT (leukemia/NHL) was significantly associated with a decreased risk of CRF (vs. without CRT): • **Leukemia/Non-hodgkin lymphoma with CRT vs without CRT: β= -0.16, p<0.05** Childhood cancer survivors (n=416; mean age at diagnosis 8 years; mean age at study 24 years; Leukemia/Lymphoma>Solid tumor>brain/CNS tumor); *adjusted for sex, age at study, marital status, educational achievement, employment, age at diagnosis, diagnosis, treatment duration, follow-up time, late effects, and depression	*Langeveld et al. 2003*
Multivariable logistic regression analysis* showed that radiotherapy including craniospinal radiation (vs. none) was significantly associated with an increased risk of CRF: • **Radiotherapy to head and/or neck vs. none: RR=1.76 (95%CI:1.14-2.71)** • **Radiotherapy to head and/or neck and thorax and/or abdomen including craniospinal vs. none: RR=2.43 (95% CI 1.54-3.82)** Childhood cancer survivors (n=1284; Leukemia>Lymphoma>Kidney/Wilms tumor>Soft tissue sarcoma; median follow-up time: 17 years; median age of 24.4 years); *adjusted for sex, TBI, chemotherapy, surgery, follow-up duration, and age at diagnosis	*Geenen et al. 2007*
Multiple regression analysis* showed no significant association between cranial irradiation and total fatigue: • Cranial irradiation: β= -0.04, p>0.05 Childhood cancer survivors (n=81, diagnoses: ALL and AML, age at diagnosis: mean 6.7 years; age at study: mean 14.1 years); *adjusted for age at study, sex, diagnosis, TBI, and follow-up time	*Nagai et al. 2012*
Univariable logistic regression analysis showed no significant association between CNS directed radiation therapy and CRF (variable was therefore not included in the multivariable model): • CNS directed radiation therapy: not significant Childhood and adolescent cancer survivors (n=268; median age at diagnosis: 6.4 years; mean time since diagnosis 13.1 years; median age at study 21.4 years; Leukemia>HL>NL>Bone tumors>soft tissue sarcoma>neuroblastoma>wilms tumor>other).	*Frederick et al. 2016*
Multivariable logistic regression analysis* showed no significant association between CNS-irradiation and CRF: • **CNS-irradiation OR=0.9 (95%CI:0.3-2.9), p=0.9** Childhood cancer survivors (n=232; HL, NHL, ALL; median age at diagnosis 9.6 years; median age at study 29.7 years; same sample as ***Hamre et al. 2013a***); *adjusted for age at survey, sex, diagnosis, smoking, BMI, analgesics use, heart function, T-cell origin, and B-symptoms at diagnosis	*Hamre et al. 2013b*
Overall conclusion	
There is conflicting evidence on the association of **CNS/brain irradiation** and the risk for CRF in survivors of childhood, adolescent and young adult cancers.	5 studies **Conflicting evidence**

1.35 What is the **risk of CRF** in CAYA cancer survivors who were treated with **total body irradiation (TBI)**?	
Conclusion single studies	
Multivariable logistic regression analysis* showed no significant association between TBI and CRF: • **TBI vs. none: RR 1.67 (95% CI 0.62-4.47)** Childhood cancer survivors (n=1284; Leukemia>Lymphoma>Kidney/Wilms tumor>Soft tissue sarcoma; median follow-up time: 17 years; median age of 24.4 years); adjusted for sex, radiation, chemotherapy, surgery, follow-up duration, and age at diagnosis	*Geenen et al. 2007*
Multiple regression analysis* showed no significant association between TBI and: • Total body irradiation: β=2.72, p>0.05 Survivors (n=81; ALL and AML; age at diagnosis: mean 6.7 years; age at study: mean 14.1 years); *adjusted for age at study, sex, diagnosis, cranial irradiation, and follow-up time	*Nagai et al. 2012*
Overall conclusion	
Evidence suggests that **total body irradiation** is **not significantly associated** with the risk for **CRF** in survivors of childhood, adolescent and young adult cancer survivors.	2 studies **Level B**

1.36 What is the **risk of CRF** in CAYA cancer survivors who were treated with **radiation not further specified?**	
Conclusion single studies	
Multivariable regression analysis* showed no significant association between radiotherapy (compared to chemotherapy) and CRF: • Radiation therapy** vs chemotherapy**: β=0.01, not significant • Combination therapy** vs chemotherapy**: β=0.04, not significant Childhood cancer survivors (n=416; mean age at diagnosis 8 years; mean age at study 24 years; Leukemia/Lymphoma>Solid tumor>brain/CNS tumor); *adjusted for sex, age at study, marital status, educational achievement, employment, age at diagnosis, diagnosis, treatment duration, follow-up time, late effects, and depression; ** with or without surgery	*Langeveld et al. 2003*
Multivariate logistic regression analysis* showed that radiotherapy was significantly associated with an increased risk of CRF: • **Radiation: Yes (Ref. No): OR=1.7 (95%CI:1.3-2.3)** Childhood cancer survivors (CCSS; n=1897; mixed diagnoses; diagnosed before the age of 21 years; at least 5 years from diagnosis); *adjusted for diagnosis, age at diagnosis, and chemotherapy	*Mulrooney et al. 2008*
Multivariable regression analysis* showed no significant association between radiotherapy (compared to surgery alone) and CRF: • Radiation (Ref. surgery alone): β= -8.73, p>0.05 Survivors of extracranial childhood cancer (n=199; mean age at diagnosis: 3.6 years; mean age at study: 14.4 years). **Lower scores of the effect measure indicate more fatigue**. *adjusted for age at study, sex, diagnosis, follow-up time, additional diagnosis, remedial education, overall average grade, happiness, and HRQoL	*Mört et al. 2011*
Univariable logistic regression analysis showed no significant association between any radiation therapy and CRF (variable was therefore not included in the multivariable model): • Any radiation therapy: not significant Childhood and adolescent cancer survivors (n=268; median age at diagnosis: 6.4 years; mean time since diagnosis 13.1 years; median age at study 21.4 years; Leukemia>HL>NL>Bone tumors>soft tissue sarcoma>neuroblastoma>wilms tumor>other).	*Frederick et al. 2016*
Hierarchical linear regression* showed no significant association between radiation and CRF: • Radiation: β=-0.030, p=0.625 Pediatric cancer survivors (n=144; mixed diagnoses; mean age at study 12.9 years, mean 5.9 years since diagnosis); *adjusted for age, sex, race, time since diagnosis, diagnosis, chemotherapy, radiation, depression, parent reported depression/anxiety, BMI, physical and function mobility	*Karimi et al. 2019*
Overall conclusion	
Some evidence suggests that **treatment with radiation** is associated with an **increased risk for CRF** in survivors of childhood, adolescent and young adult cancers.	5 studies **Level C**

1.37 What is the **risk of CRF** in CAYA cancer survivors who were treated with **chemotherapy**?	
Conclusion single studies	
Multivariable logistic regression analysis* showed no significant association between chemotherapy and CRF. • **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) Childhood cancer survivors (n=1284; Leukemia>Lymphoma>Kidney/Wilms tumor>Soft tissue sarcoma; median follow-up time: 17 years; median age of 24.4 years); *adjusted for sex, radiation, TBI, surgery, follow-up duration, and age at diagnosis	*Geenen et al. 2007*
Multivariate logistic regression analysis* showed no significant association between chemotherapy and CRF: • Chemotherapy: Yes (Ref. No): OR=1.0 (95%CI:0.8-1.4) Survivors (CCSS; n=1897; mixed diagnoses; diagnosed before the age of 21 years; at least 5 years from diagnosis); *adjusted for diagnosis, age at diagnosis, and radiation	*Mulrooney et al. 2008*
Multivariate regression analysis* showed no significant association between chemotherapy (vs. surgery only) and CRF: • Treatment: Chemotherapy (Ref. surgery alone) β= -4.2, p>0.05 Survivors of extracranial childhood cancer (n=199; mean age at diagnosis: 3.6 years; mean age at study: 14.4 years). **Lower scores of the effect measure indicate more fatigue**. *adjusted for age at study, sex, diagnosis, follow-up time, additional diagnosis, remedial education, overall average grade, happiness, and HRQoL	*Mört et al. 2011*
Univariable logistic regression analysis showed no significant association between chemotherapy and CRF (variable was therefore not included in the multivariable model): • Chemotherapy: not significant • Doxorubicin: not significant Childhood and adolescent cancer survivors (n=268; median age at diagnosis: 6.4 years; mean time since diagnosis 13.1 years; median age at study 21.4 years; Leukemia>HL>NL>Bone tumors>soft tissue sarcoma>neuroblastoma>wilms tumor>other).	*Frederick et al. 2016*
Hierarchical linear regression* showed no significant association between chemotherapy and CRF: • Chemotherapy: β=0.097, p=0.121 Pediatric cancer survivors (n=144; mixed diagnoses; mean age at study 12.9 years, mean 5.9 years since diagnosis); *adjusted for age, sex, race, time since diagnosis, diagnosis, chemotherapy, radiation, depression, parent reported depression/anxiety, BMI, physical and function mobility	*Karimi et al. 2019*
Overall conclusion	
Evidence suggests that **chemotherapy** is **not significantly associated** with the risk for **CRF** in survivors of childhood, adolescent and young adult cancer survivors.	5 studies **Level B**

1.38 What is the **risk of CRF** in CAYA cancer survivors who were treated with **surgery**?	
Conclusion single studies	
Multivariable logistic regression analysis* showed no significant association between surgery and CRF: • Surgery yes vs. no: RR=1.09 (95%CI:0.76-1.58) Childhood cancer survivors (n=1284; Leukemia>Lymphoma>Kidney/Wilms tumor>Soft tissue sarcoma; median follow-up time: 17 years; median age of 24.4 years); *adjusted for sex, radiation, TBI, chemotherapy, follow-up duration, and age at diagnosis	*Geenen et al. 2007*
Univariable logistic regression analysis showed no significant association between surgery and CRF (variable was therefore not included in the multivariable model): • Surgery: not significant Childhood and adolescent cancer survivors (n=268; median age at diagnosis: 6.4 years; mean time since diagnosis 13.1 years; median age at study 21.4 years; Leukemia>HL>NL>Bone tumors>soft tissue sarcoma>neuroblastoma>wilms tumor>other).	*Frederick et al. 2016*
Overall conclusion	
Evidence suggests that **surgery** is **not significantly associated** with the risk for **CRF** in survivors of childhood, adolescent and young adult cancer survivors.	2 studies **Level B**

1.39 What is the **risk of CRF** in CAYA cancer survivors who were treated with **bone marrow / stem cell transplantation**?	
Conclusion single studies	
Multivariable regression analysis* showed no significant association between stem cell transplant (vs. surgery only) and CRF: • SCT (Ref. surgery alone): β= -3.17, p>0.05 Survivors of extracranial childhood cancer (n=199; mean age at diagnosis: 3.6 years; mean age at study: 14.4 years). **Lower scores of the effect measure indicate more fatigue**. *adjusted for age at study, sex, diagnosis, follow-up time, additional diagnosis, remedial education, overall average grade, happiness, and HRQoL	*Mört et al. 2011*
Univariable logistic regression analysis showed no significant association between bone marrow transplant and CRF (variable was therefore not included in the multivariable model): • Bone marrow transplant: not significant Childhood and adolescent cancer survivors (n=268; median age at diagnosis: 6.4 years; mean time since diagnosis 13.1 years; median age at study 21.4 years; Leukemia>HL>NL>Bone tumors>soft tissue sarcoma>neuroblastoma>WT>other).	*Frederick et al. 2016*
Overall conclusion	
Evidence suggests that **stem cell transplantation** is **not significantly associated** with the risk for **CRF** in survivors of childhood, adolescent and young adult cancer survivors.	2 studies **Level B**

1.40 What is the **risk of CRF** in CAYA cancer survivors **by treatment duration**?	
Conclusion single studies	
Multivariable regression analysis* showed no significant association between the duration of treatment and CRF: • Duration of treatment: β=0.02, NS Survivors of childhood cancer (n=416; mean age at diagnosis 8 years; mean age at study 24 years; Leukemia/Lymphoma>Solid tumor>brain/CNS tumor); *adjusted for sex, age at study, marital status, educational achievement, employment, age at diagnosis, diagnosis, follow-up time, late effects, treatment, and depression	*Langeveld et al. 2003*
Overall conclusion	
Some evidence suggests that **duration of treatment** is **not significantly associated** with the risk for **CRF** in survivors of childhood, adolescent and young adult cancer survivors.	1 study **Level C**

1.41 What is the **risk of CRF** in CAYA cancer survivors **by treatment era**?	
Conclusion single studies	
Multivariable logistic regression analysis* showed no significant association between treatment era and CRF: • Treatment 1970-1985 (vs. Treatment after 1985): OR=0.8 (95%CI:0.3-2.1), p=0.7 Childhood cancer survivors (n=290; HL, NHL, ALL; median age at diagnosis 9.5 years; median age at study 29.6 years); *adjusted for diagnosis, age at survey, sex, thyroid status, HADS (Hospital Anxiety and Depression scale) total score	*Hamre et al. 2013a*
Overall conclusion	
Some evidence suggests that **treatment era** is **not significantly associated** with the risk for **CRF** in survivors of childhood, adolescent and young adult cancers.	1 study **Level C**

2. What is the **risk** for suffering from Fatigue in CAYA cancer survivors who had received **pulmonary radiation vs. no pulmonary radiation**?	
Conclusion single studies	
No studies identified in survivors of childhood, adolescent and young adult cancers.	
Overall conclusion	
Risk after pulmonary radiation No studies reported on risk of CRF after pulmonary radiation in survivors of childhood, adolescent and young adult cancers.	0 studies **No studies**

3. What is the **latency time** to develop Fatigue in CAYA cancer survivors?	
Conclusion single studies	
No studies identified in survivors of childhood, adolescent and young adult cancers.	
Overall conclusion	
Latency time to develop CRF No studies reported on latency time to develop CRF in survivors of childhood, adolescent and young adult cancers.	0 studies **No studies**

4. Does the **risk** of developing Fatigue **change over time** in CAYA cancer survivors?	
Conclusion single studies	
In a cohort of Hodgkin Lymphoma survivors (CCSS; n=103), they found no significant changes in mean levels of fatigue from end of treatment until 36 months post-therapy.	*Macpherson et al. 2015*
In longitudinally followed survivors of childhood lymphoma and leukemia (n=102), 60.4% of former fatigue cases were persistently fatigued, 81.6% of former non-fatigue cases were persistently non-fatigued, 39.6% of former fatigue cases were no longer fatigued, 18.4% of former non-fatigue cases were fatigued a median of 2.7 years later (range 1-4.3 years).	*Zeller et al. 2014*
Overall conclusion	
Change of risk over time Evidence from longitudinal studies suggests that the risk of CRF does not change over time in the majority of CAYA cancer survivors. However, there is also a suggestion that the risk of CRF may increase or decrease over time. None of the studies reported the predictors for change, only risk factors for persistent CRF or persistent non-CRF were analyzed.	2 studies **Level B**

5. Which fatigue scales are **reliable and valid diagnostic tools to diagnose CRF** in CAYA cancer survivors?	
Conclusion single studies	
Systematic review Includes 25 articles that were published until April 2011	
In a systematic review of children and adolescents with cancer, the **Fatigue Scale-Child** (FS-C; 7-12 years) and **Fatigue Scale-Adolescent** (FS-A; 13-18 years) and its proxy versions (Fatigue Scale-Parents, Fatigue Scale-Staff), as well as the **PedsQL Multidimensional Fatigue Scale** (MFS; versions 5-7 years, 8-12 years, 13-18 years) self-report and parent proxy versions (additional version 2-4 years) have **good internal consistency and inter-rater reliability**, but known group validity is more variable. The authors recommend use of any of the two instruments for clinical trials in a CAYA cancer population.	*Tomlinson et al. 2013*
Fatigue Scale-Child, Fatigue Scale-Adolescent and proxy versions (FS-C, FS-A)	
In childhood cancer patients (CP; n=50) and survivors (CS; n=200), the **Chinese version of the Fatigue Scale for Children (FS-C)** was **reliable** (Cronbach's alpha = 0.91) and **valid:** semantic equivalence 83-100%. Content validity index 0.83 for scale. Known-group validity was good: CS scored significantly lower than CP, but statistically higher than HC. Discriminant validity was supported: strong correlation with CES-DC (r=0.53, p<0.01) and strong negative correlation with PedsQL (r=-0.54, p<0.01).	*Ho et al. 2016*
In adolescent cancer patients (ACP; n=50) and adolescent survivors (ACS; n=200), the **Chinese version of the Fatigue Scale for adolescents (FS-A)** was **reliable** (Cronbach's alpha = 0.89) and **valid**: Semantic equivalence was high: 94%. Content validity index was good: 0.92. Known groups validity was supported (ACS scored significantly lower than ACP, but higher than healthy controls). Discriminant validity was also supported: strong positive correlation with CES-DC (r=0.53, p<0.01) and strong negative correlation with PedsQL (r=-0.58, p<0.01).	*Ho et al. 2015*
In childhood cancer patients (n=52, n=86 parents and n=43 nurses), the **Turkish versions of the Child, Parent and Staff Fatigue Scale-24 Hours** was **reliable** (Cronbach's alpha: 0.83 (FS-C), 0.77 (FS-P), 0.72 (FS-S)) and **valid:** Language validity was confirmed by blind back-translation. Content validity was tested by ten academics working in the field of pediatrics and oncology and the versions adapted accordingly.	*Gerceker et al. 2012*
In adolescent cancer patients (n=138), the **Fatigue Scale-Adolescent** (13-18 years old) had acceptable psychometric properties and was able to reliably identify adolescent oncology patients with high fatigue (Cronbach's alpha was 0.87). Construct validity was acceptable: It was assessed with a confirmatory factor analysis and suggested a reasonable fit of the 4-factor structure (goodness-of-fit index was 0.855). Concurrent validity was acceptable: It was assessed with the Spearman correlation coefficient between FS-A and FS-P (0.347, p=0.0033). Cut score of 31 was used to identify fatigue: **sensitivity was 66.6%** and **specificity 82.6%**.	*Mandrell et al. 2011*
In adolescent cancer patients (n=64), the **Fatigue Scale-Adolescent** and its proxy versions (parents FS-P, and staff FS-S) had moderate to high internal consistency (Cronbach's alpha 0.81 (FS-A), 0.75 (FS-P), 0.85 (FS-S), was able to distinguish between known groups, and was able to measure change over time.	*Hinds et al. 2007*

PedsQL Multidimensional Fatigue Scale (PedsQL MFS) Studies published after April 2011	
In childhood cancer patients (n=70), the **Arabic version of the PedsQL MFS** demonstrated good to excellent reliability (Cronbach's alpha between 0.87 and 0.94) for all scales except sleep rest subscale (α=0.67)). Validity was assessed by testing correlations of PedsQL MFS subscales to PedsQL TM 4.0 Generic Core scales (Arabic version), scales were consistently positively correlated (fewer problems with fatigue correlated with better overall HRQoL).	*Al-Gamal et al. 2017*
The psychometric properties of the **Brazilian version of the PedsQL MFS** was assessed in childhood cancer patients (n=42 children (8-12 years), n=68 teenagers (13-17 years). **Reliability was acceptable** (Cronbach's alpha between 0.70 and 0.90) for all dimensions except sleep/rest fatigue (Cronbach's alpha=0.55)) and **valid:** Convergent validity: all linear correlation coefficients were greater than 0.40 for the dimension to which the item belonged. Root mean square error of approximation values were within acceptable limits: 0.08-0.10, with 0.098 for self-report and 0.095 for proxy versions. This indicates that the factorial structure of the construct is maintained in the adapted Brazilian model. Comparative fit index was lower than the expected 0.90: 0.699 for self-report and 0.847 for proxy version.	*Nascimento et al. 2015*
In childhood cancer survivors (n=64) the **PedsQL MFS (adaptation to 18-25 year olds)** demonstrated high **reliability** (Cronbach's alpha for Total Fatigue Score=0.95, all subscales≥0.88). Validity was not assessed.	*Robert et al. 2012*
PROMIS Pediatric Fatigue measures Studies published after April 2011	
In childhood and adolescent cancer patients (n=96), the **PROMIS Pediatric Fatigue Short Form** was valid: PROMIS fatigue scores correlated significantly with PROMIS performance measures (construct validity; r=-0.68 to -0.3, p<0.01) and with corresponding items of the Symptom Distress Scale (SDS; concurrent validity; p<0.0001). Responsiveness: Fatigue worsened slightly, but not significantly from T1 to T2, then improved significantly to T3. The PROMIS pediatric measures were more responsive across time than the SDS.	*Hinds et al. 2019*
In childhood and adolescent cancer patients (n=96; same sample as ***Hinds et al. 2019***), the **PROMIS Pediatric Fatigue Short Form** was similarly **reliable** (Cronbach's Alpha 0.93-0.96 over all time points and participants) as the Fatigue Scale-Child and Fatigue Scale-Adolescent (0.83-0.94 and 0.93-0.94). **Validity**: PROMIS was correlated with FS-A (r=0.85-0.9) and FS-C (r=0.65-0.88). The area under the curve was 0.72-0.87 for PROMIS (0.84-0.93 for FS-A, 0.84-0.87 for FS-C; differences were not statistically significant). Because of its reliable and valid results, as well as broader applicability in age groups, the authors suggest to use the PROMIS measure for measuring fatigue in patients aged 7-18 years with cancer.	*Macpherson et al. 2018*
In childhood and adolescent brain tumor survivors (n=161; mean 13.9 years at study; mean 5.2 years since diagnosis), the **PROMIS Pediatric Fatigue Computerized Adaptive Testing** (CAT) was compared to the PROMIS Pediatric Fatigue Short Form (SF). Scores were strongly correlated (r=0.976). The authors recommend use of CATs because they enable a more individualized assessment and are less prone to floor or ceiling effects. However, if computers are not available, fixed-length SFs can be used. PROMIS CATs and SFs produced comparable scores for children with a brain tumor.	*Lai et al. 2017*
In childhood cancer patients (n=93) and survivors (n=107), the **PROMIS Pediatric Fatigue Short Form** was **valid**: Known-group validity: Children in the active treatment group had significantly worse scores than children in the survivor group (patients: mean 52.9, survivors: mean 43.8; p<0.001). This remained so even after controlling for demographic variables, tumor type and presence of other health problems. **Reliability** of the tool was not analyzed.	*Hinds et al. 2013*

Other measures of CRF in CAYA cancer patients or survivors Studies published after April 2011	
In adolescent and young adult brain tumor survivors (n=142), the **area under the curve (AUC)** of the **Fatigue Thermometer (FT)** as compared to the multidimensional fatigue scale (MFS, gold standard) to detect fatigue was **0.822**. 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).	*Brand et al. 2016*
In childhood cancer patients (n=204), the **Turkish Scale for the Assessment of Fatigue in Pediatric Oncology Patients Aged 7-12** was **reliable** (Cronbach's alpha= 0.98 in total for the scale) and **valid** (14 experts assessed content validity, coherence was 0.803; factor analysis explained 84.7% of the variance; statistically significant differences were found in known group comparison). Cut-off point 75 was chosen, **sensitivity was 0.73**, **specificity was 0.93**.	*Kudubes et al. 2014*
In childhood cancer patients (n=184), the **Turkish Scale for the Assessment of Fatigue in Pediatric Oncology Patients Aged 13-18** was **reliable** (Cronbach's alpha= 0.99 in total for the scale) and **valid** (14 experts assessed content validity, coherence was 0.803; factor analysis explained 89.4% of total variance; statistically significant differences were found between groups in known group comparison). Cut-off point 75.5 was chosen (75.4 or below are fatigue cases), **sensitivity was 1.00** and **specificity 0.06**.	*Bektas et al. 2014*
In survivors of Hodgkin's Lymphoma (n=200), the **Multidimensional Fatigue Inventory (MFI)-Brazilian Portuguese version** demonstrated **acceptable reliability** (Cronbach's alpha higher than 0.7 in all dimensions except reduced motivation). Construct validity was analyzed with a factor analysis and explained 65% of the variance.	*Baptista et al. 2012*
In childhood cancer survivors (n=81), a **12-item fatigue questionnaire** was **reliable** (Internal consistency: Cronbach's alpha for the total and each of the three fatigue dimension scores between 0.75 and 0.88) and **valid**: Correlation coefficient between the questionnaire and the Chalder fatigue scale was 0.89, supporting the construct validity of the questionnaire.	*Nagai et al. 2012*
Overall conclusion	
In patients of CAYA cancers, evidence suggests that the **Fatigue Scale-Child (FS-C)** and **Fatigue Scale-Adolescent** (FS-A) with its proxy versions (Fatigue Scale-Parents, Fatigue Scale-Staff) is a valid and reliable instrument to measure CRF.	1 systematic review, 5 studies **Level B**
In patients and survivors of CAYA cancers, evidence suggests that the **PedsQL Multidimensional Fatigue Scale** (5-7 years, 8-12 years, 13-18 years, 18-25 years) with its proxy versions (parent versions 2-4 years, 5-7 years) is a valid and reliable instrument to measure CRF.	1 systematic review, 3 studies **Level B**
In patients and survivors of CAYA cancers, evidence suggests that the **PROMIS Pediatric Fatigue measures** (short form, and computerized adaptive testing) is a valid and reliable instrument to measure CRF.	4 studies **Level B**
In patients and survivors of CAYA cancers, some evidence suggests that other measuring instruments, such as the Multidimensional Fatigue Inventory, and the Turkish Scale for the Assessment of Fatigue in Pediatric Oncology Patients (versions 7-12 years, 13-18 years) are valid and reliable instruments to measure CRF.	4 studies **Level C**
In AYA brain tumor survivors, some evidence suggests that a single-item screening measure for CRF (Fatigue Thermometer) is not able to reliably identify clinically significant CRF.	1 study **Level C**

6. What is the **effect of individual cognitive behavioral therapy** in the treatment of CRF in CAYA cancer survivors?	
This pilot study in survivors of childhood cancers (n=33; mixed diagnoses; mean 23.1 years at study; mean 13.0 years since diagnosis) found that cognitive behavior therapy was able to significantly **reduce fatigue severity** (Checklist Individual Strength; pretreatment mean 46.2 (SD 4.5) vs. posttreatment mean 28.9 (SD 13.7), p<0.001; large effect size 1.7 (95%CI:1.1-2.3)). 23 of the 33 CCS (70%) included in the study showed a clinically significant improvement, the improvement was even higher in completers of the CBT intervention (n=22/25; 88%). Of the 25 completers, 22 reported that their fatigue level improved significantly or that they were completely recovered.	*Boonstra et al. 2018*
Overall conclusion	
Effect of cognitive behavioral therapy Some evidence suggests that cognitive behavioral therapy can help to reduce CRF in survivors of childhood, adolescent and young adult cancers.	1 study **Level C**

7. What is the effect of **individual physiotherapy** in the treatment of CRF in CAYA cancer survivors?	
Conclusion single studies	
No studies identified in survivors of childhood, adolescent and young adult cancers.	
Overall conclusion	
Effect of individual physiotherapy No studies reported on the effect of individual physiotherapy in the treatment of CRF in patients or survivors of childhood, adolescent and young adult cancers.	0 studies **No studies**

8. What is the effect of **a revalidation program** in the treatment of CRF in CAYA cancer survivors?	
Conclusion single studies	
No studies identified in survivors of childhood, adolescent and young adult cancers.	
Overall conclusion	
Effect of a revalidation program No studies reported on the effect of a revalidation program in the treatment of CRF in patients or survivors of childhood, adolescent and young adult cancers.	0 studies **No studies**

9. What is the effect of **any intervention** in the treatment of CRF in CAYA cancer survivors?	
Conclusion single studies CAYA cancer survivors	
An **adventure-based training** for childhood cancer survivors (n=222; 9-16 years at intervention; 4 training days; 2 weeks, 2, 4, 6, months after randomization respectively; max. 12 participants; team-building games, shuttle runs, rock climbing, etc.) was able to significantly reduce CRF at the 12-month follow-up compared to those in the control group (Fatigue Scale-Child: Intervention Group mean 22.3 (SD 4.2) vs. Control Group mean 28.9 (SD 4.9), p<0.001).	*Li et al. 2018*
In a pilot study, an **exercise intervention** (10 week home-based daily physical activity counselling programme (n=46)) was **significantly** associated with **reduced fatigue** in adult survivors of childhood cancer that at least lasted for 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)); siblings/peers: 47.39±19.06 at T1; 46.18±17.70 at T10; 42.57± 17.40 at T36).	*Blaauwbroek et al. 2009*
Conclusion single studies CAYA cancer patients and survivors	
This intervention study investigated the effect of a fatigue education intervention in childhood cancer patients (n=80; each n=40 in the intervention and control group). The intervention consisted of five educational modules. The intervention and control group were not randomized, and differed regarding mean level of fatigue at baseline (controls having less fatigue). After 3 months, and 6 months the intervention group's mean fatigue scores had increased (indicating less fatigue), whereas the control group's mean fatigue scores had decreased (indicating more fatigue).	*Kudubes et al. 2018*
This was an integrative review including 13 studies in CAYA cancer patients and survivors (of which 4 studies were also included in the Baumann et al. 2013, and 4 in the Chang et al. 2013 review). 5/8 studies found that **exercise** (total n=72; in-patient aerobic exercise/bicycle ergometer, in-patient yoga, weekly step goal with FitBit tracker, exercise combined with quiet leisure activities (reading, listening to music)) reduced CRF in participants. 3/8 studies (total n=51; stationary bicycle exerciser, muscular strength/aerobic fitness, yoga) found no effect. Other interventions that resulted in a decrease in CRF were **healing touch** (1 study, n=9), and **acupressure** (1 study, n=60). Other interventions that found no effect on CRF were exercise plus psychosocial intervention (1 study, n=68; physical exercise plus psychoeducation and cognitive-behavioral techniques), and massage (2 studies; total n=51).	*Nunes et al. 2018*
In a systematic review including 17 studies (3 studies were also included in the Chang et al. 2013 review), **exercise interventions** (in-hospital endurance/strength training, group exercises, educational intervention, home-based exercise program) were associated with **reduced fatigue** in children with cancer, although two (of five) studies found no effect (no effect measure reported).	*Baumann et al. 2013*
In a systematic review including 6 studies (3 studies were also included in the Baumann et al. 2013 review), two **exercise interventions** (16-week physical activity (n=10) and 6-week home-based aerobic exercise (n=24)) were **significantly** associated with **reduced general fatigue** in children with cancer (effect size meta-analysis including 2 studies: -0.76 (95% CI -1.35-0.17)). These exercise interventions did not significantly reduce **total fatigue, sleep or rest fatigue, and cognitive fatigue** in children with cancer. In one study, a **nursing intervention** (education about fatigue and suggestions for activities that can reduce fatigue (n=60)) was associated with **reduced fatigue** in children with cancer (no effect measure reported).	*Chang et al. 2013*
Overall conclusion	
Effect of physical activity interventions Evidence suggests that physical activity can be useful in the treatment of CRF in survivors of childhood, adolescent, and young adult cancers.	4 studies **Level B**
Effect of education interventions Evidence suggests that education about fatigue can help to reduce CRF in childhood, adolescent and young adult cancer patients.	2 studies **Level B**
Effect of adventure-based training Some evidence suggests that an adventure-based training can help to reduce CRF in childhood, adolescent and young adult cancer patients.	1 study **Level C**
Effect of relaxation interventions Some evidence suggests that relaxation and mindfulness interventions (acupressure, healing touch, massage) can help to reduce CRF in childhood, adolescent and young adult cancer patients.	1 study **Level C**
Effect of combined physical activity and psychosocial interventions Some evidence suggests that exercise plus a psychosocial intervention does not decrease CRF in childhood, adolescent, and young adult cancer patients.	1 study **Level C**

Existing clinical practice guidelines CAYA cancer patients & survivors	
In this clinical practice guideline for CAYA cancer patients and survivors including 462 randomized trials (only n=6 in CAYA cancer patients or survivors), the use of **physical activity** (preferably aerobic, neuromotor (e.g. yoga, tai chi), or combination), **relaxation and mindfulness** (e.g. acupressure, mindfulness, relaxation techniques, massage therapy) are strongly recommended to reduce CRF. Where these approaches are not feasible or were not successful, **cognitive or cognitive behavioral therapies** may be offered. It was recommended that pharmacological interventions should not be routinely used.	*Robinson et al. 2018*
Overall conclusion	
Physical activity, relaxation and mindfulness can be used as interventions for CRF. Cognitive behavioral therapy may be used as an intervention for CRF. The evidence is insufficient about the usefulness and safety of pharmacological interventions.	**Existing guideline**