Kræftrelateret træthed

– Screening, udredning og behandling af patienter over 18 år, der har afsluttet primær kræftbehandling

Version 1.0

GODKENDT

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INDEKSERING

kræftrelateret træthed, non-farmakologiske interventioner, psykosociale interventioner

Indholdsfortegnelse

1. Anbefalinger (Quick guide)

Screening og udredning

1. **Kræftoverlevere kan screenes og regelmæssigt udredes for kræftrelateret træthed ved brug af validerede skalaer (B)**

Non-farmakologiske interventioner

Nedenstående anbefalinger kan kombineres med udgangspunkt i kræftoverleveres ønsker og behov:

2. **Alle kræftoverlevere skal tilbydes psykoedukation om kræftrelateret træthed (A)**
3. **Fysisk træning skal tilbydes til kræftoverlevere med moderat til svær kræftrelateret træthed, tilpasset funktionsevne og individuelle forhold (A)**
4. **Kognitiv adfærdsterapi kan tilbydes til kræftoverlevere med moderat til svær kræftrelateret træthed og kan leveres som almindelig fremmødekonsultation eller virtuelt (B)**
5. **Mindfulness-baserede programmer kan tilbydes som en behandling for kræftrelateret træthed og kan leveres som almindelig fremmødekonsultation eller virtuelt (B)**
6. **Lysterapi kan tilbydes som supplerende behandling til kræftoverlevere med kræftrelateret træthed (C)**
7. **Yoga kan tilbydes til kræftoverlevere, der udtrykker interesse, særligt yogaformen Hatha (D)**

Farmakologiske behandlinger

8. **Lægemidler, herunder vågenhedsfremmende medicin (f.eks. modafinil, armodafinil), antidepressiv medicin og psykostimulerende medicin bør ikke anvendes rutinemæssigt til behandling af kræftrelateret træthed (B)**

Recommendations (Quick Guide)

Screening and assessment

1. **Cancer survivors can be screened and regularly assessed for cancer-related fatigue with the use of validated scales (B)**

Non-pharmacological interventions

The following recommendations can be combined based on the patient's wishes and needs:

2. **All cancer survivors should be offered basic psychoeducation about cancer-related fatigue (A)**
3. **Physical exercise should be offered for cancer survivors with moderate to severe cancer-related fatigue, adapted to functional ability and individual circumstances (A)**
4. **Cognitive behavioral therapy can be offered to cancer survivors with moderate to severe cancer-related fatigue, and can be delivered in-person or virtually (B)**
5. **Mindfulness-based programs can be offered as a treatment for cancer-related fatigue, and can be delivered in-person or virtually (C)**
6. **Light therapy can be offered as supplementary treatment for cancer survivors with cancer-related fatigue (C)**
7. **Yoga can be offered for those who express interest, particularly the Hatha style (D)**

Pharmacological treatment

8. **Medication, including wakefulness agents (e.g., modafinil, armodafinil), antidepressant medication and psychostimulant medication, should not be routinely used for the treatment of cancer-related fatigue (C)**

2. Introduktion

Kræftrelateret træthed er en udbredt og invaliderende senfølge, som kan opleves af personer med kræft både før, under og efter afsluttet behandling. The National Comprehensive Cancer Network definerer kræftrelateret træthed som: "En vedvarende og belastende fysisk, følelsesmæssig og/eller kognitiv træthed eller udmattelse relateret til kræftsygdom og dens behandling, som ikke er proportional med nylig aktivitet og som påvirker patientens vanlige funktionsniveau" (1). Kræftrelateret træthed påvirker både patienters livskvalitet, funktionsevne og psykiske velbefindende, hvilket understreger behovet for en standardiseret og evidensbaseret tilgang til håndtering af tilstanden (2). Kræftrelateret træthed lindres ikke ved hvile (3) og kan opstå på alle tidspunkter i kræftforløbet, fra den indledende diagnose og behandling til tiden som kræftoverlever, eller i den palliative pleje. Kræftrelateret træthed kan vare ved i måneder og år efter afsluttet behandling og kan derfor udgøre en betydelig belastning for kræftoverlevere. Patogenesen for kræftrelateret træthed er fortsat uklar men er formentligt multifaktoriel med baggrund i selve kræftsygdommen, i fysiske og psykiske bivirkninger til behandlingen, samt komorbide lidelser (3).

Problemets omfang og konsekvenser

Kræftrelateret træthed er et af de hyppigst forekommende symptomer hos kræftpatienter med prævalensrater på op mod 80% (4–7). Selv adskillige år efter afsluttet behandling oplever cirka 40% fortsat kræftrelateret træthed i moderat til svær grad. Dette påvirker evnen til at deltage i daglige aktiviteter og sociale sammenhænge samt at fastholde et arbejde (8–10). Desuden er kræftrelateret træthed blevet forbundet med nedsat adhærens og dårligere prognose (3,10). På trods af den høje prævalens er kræftrelateret træthed underdiagnosticeret og underbehandlet og ofte overskygget af det primære fokus på den onkologiske behandling og dennes effekt (11).

Patofysiologi

Patofysiologien ved kræftrelateret træthed er kompleks og multifaktoriel, hvilket gør det vanskeligt at identificere de specifikke mekanismer bag (3). Ofte findes der flere underliggende årsager, som kan interagere og dermed forstærke trætheden. Dette kan komplicere både screening og behandling (12). Nyere forskning tyder på, at flere fysiologiske og biokemiske systemer kan være påvirket hos patienterne, hvilket kan bidrage til udviklingen af kræftrelateret træthed. Graden af denne påvirkning afhænger af faktorer såsom kræfttype, sygdomsstadie og behandling. Derudover kan inflammatoriske tilstande, dysregulering af hypothalamus-hypofyse-binyrebark-aksen (HPA-aksen), dysreguleret mitokondriefunktion, samt ændringer i hjernens signalstoffer (neurotransmittere) have betydning for udviklingen af kræftrelateret træthed (13,14). Studier peger desuden på, at den fysiske inaktivitet og deraf følgende reduktion af skeletmuskulaturen, der kan opstå i forbindelse med et kræftforløb, kan spille en rolle i udviklingen af kræftrelateret træthed (14). Desuden spiller centralnervesystemet en afgørende rolle som regulator af træthedsopfattelsen (3,6,15).

Udfordringer i håndtering af kræftrelateret træthed

Mange kræftoverlevere rapporterer, at deres træthed ikke anerkendes eller håndteres tilstrækkeligt i forbindelse med deres opfølgning og kontrolbesøg på hospitalerne (16,17). Dette kan betyde et unødigt fald i livskvalitet hos kræftoverlevere, som kunne være tilbudt rettidige interventioner. Kræftrelateret træthed dokumenteres ofte ikke, hvilket forværrer problemet (17,18), og ofte mangler der både ressourcer og viden til effektivt at implementere eller henvise til mulige interventioner. En yderligere komplicerende faktor er den sandsynlige multifaktorielle ætiologi for kræftrelateret træthed (3). Dette vanskeliggør en skelnen mellem de faktorer, der kan være årsager til mulig træthed allerede inden diagnose og behandling (3) og årsager knyttet til sygdom og behandlingsforløb. Ofte er det de samme biologiske systemer som aktiveres, selv ved forskellige former for og årsager til træthed (19). Studier viser desuden, at mange professionelle føler sig usikre på interventionernes

effektivitet, hvilket gør dem tilbageholdne med at anbefale disse (17,18,20). Selvom der i stigende grad foreligger evidens for effektive interventioner for kræftrelateret træthed, mangler der et standardiseret tilbud, hvilket understreger behovet for klare retningslinjer (17,18,20).

Formål

Formålet med nærværende retningslinje er at give sundhedsprofessionelle klare, evidensbaserede anbefalinger til håndtering af kræftrelateret træthed hos kræftoverlevere, der har afsluttet deres primære kræftbehandling. På trods af den voksende evidens for effektive interventioner, mangler der i dag en ensartet tilgang til screening, udredning og behandling af kræftrelateret træthed blandt kræftoverlevere. Nationale kliniske retningslinjer er en forudsætning for en systematisk, standardiseret, evidensbaseret og patientcentreret håndtering af kræftrelateret træthed blandt kræftoverlevere.

I forbindelse med udarbejdelsen af denne retningslinje er eksisterende interventioner til håndtering af kræftrelateret træthed gennemgået systematisk. Anbefalingerne i denne retningslinje afspejler således de tilgange, som bedst understøttes af den tilgængelige evidens. Anbefalingerne fokuserer på strategier, der kan lindre symptomer, forbedre livskvaliteten og fremme den overordnede trivsel hos kræftoverlevere. Der lægges vægt på en tværfaglig og individuelt tilpasset tilgang, hvor behandlingsstrategien skræddersys til den enkeltes behov.

Denne retningslinje giver anbefalinger baseret på den nyeste videnskabelige litteratur og ekspertkonsensus og fokuserer på strategier for symptomhåndtering, tværfaglige tilgange og patientcentrerede forløb. Det overordnede mål er at udstyre sundhedsprofessionelle med de nødvendige værktøjer til effektiv håndtering af kræftrelateret træthed og derved forbedre kræftoverleveres velbefindende og de samlede behandlingsresultater.

Patientgruppe

Nærværende retningslinje omhandler senfølger blandt voksne kræftoverlevere, her defineret som personer ≥18 år, der har afsluttet den primære behandling for en kræftsygdom og som vurderes at være kræftfri.
I denne retningslinje inkluderer denne gruppe kræftoverlevere ligeledes personer i længerevarende adjuverende behandling, f.eks. endokrin terapi, immunterapi og anden målrettet biologisk behandling. Denne definition er valgt for at kunne skelne mellem egentlige senfølger, og bivirkninger og reaktioner på aktiv kræftbehandling. Man bør ligeledes indtænke, at antallet af personer, som lever længe i aktiv behandling, vil stige i takt med forbedrede behandlingsmuligheder, og at de anbefalinger som denne retningslinje udstikker for kræftoverlevere, også vil kunne være relevante for denne gruppe.

Målgruppe for brug af retningslinjen

Retningslinjen skal primært understøtte det kliniske arbejde og bidrage til udviklingen af den kliniske kvalitet i indsatsen over for kræftoverlevere med kræftrelateret træthed. Den primære målgruppe er derfor sundhedsprofessionelle i det danske sundhedsvæsen, som kommer i kontakt med personer behandlet for kræft og har ansvar for udredning og behandling af symptomer og senfølger blandt disse personer. Dette betyder, at retningslinjen henvender sig til sundhedsprofessionelle på tværs af sektorer og specialer, herunder læger, sygeplejersker, psykologer, fysioterapeuter, og andre fagrelevante grupper på hospitalerne og i primærsektoren.

Evaluerede interventioner

Denne retningslinje evaluerer en række interventioner til kræftoverlevere med kræftrelateret træthed. I retningslinjen skelnes der mellem non-farmakologiske interventioner og farmakologiske behandlinger. De non-farmakologiske interventioner omfatter psykoedukation, fysisk træning, kognitiv adfærdsterapi, mindfulness-

baserede programmer, lysterapi og yoga. De evaluerede farmakologiske behandlinger omfatter vågenhedsfremmende medicin, antidepressiv medicin, samt psykostimulerende medicin. Tydelige definitioner og anbefalinger præsenteres i de følgende afsnit.

3. Grundlag

Anbefalingerne i denne kliniske retningslinje er udarbejdet med udgangspunkt i den senest publicerede internationale guideline (Management of Fatigue in Adult Survivors of Cancer) fra American Society of Clinical Oncology (ASCO). ASCOs guideline er publiceret i maj 2024, som en opdatering af ASCOs tidligere anbefalinger fra 2014 (21,22). ASCOs guideline blev vurderet med en AGREE II-score på 98%, som indikerer en høj metodologisk kvalitet. Evidensgrundlaget bestod af en systematisk gennemgang af i alt 113 randomiserede studier, fordelt på studier af patienter, som var henholdsvis under behandling og færdigbehandlede (21).

Søgningen til ASCOs guideline blev udført i oktober 2023. Vi foretog derfor en opdateret søgning i juni 2024 og identificerede yderligere 14 systematiske reviews publiceret efter publikationen af ASCOs guideline (23–36). Derudover blev der udført supplerende målrettede søgninger for at identificere nyere relevant litteratur, som potentielt ikke var blevet identificeret i den oprindelige søgning. Søgningen inkluderede en screening af randomiserede kontrollerede studier omhandlende kræftrelateret træthed publiceret efter ASCO's søgetidspunkt, og resulterede i 3 yderligere metaanalyser (37–39). Derudover identificerede vi to supplerende studier gennem direkte søgninger på 'light therapy' og 'cancer-related fatigue' samt 'psychoeducation' og 'cancer-related fatigue' (40,41). Alle supplerende studier blev screenet ud fra de samme inklusionskriterier som i den oprindelige hovedsøgning. På baggrund af de mange nye systematiske reviews, blev der ikke foretaget yderligere søgninger efter enkeltstående randomiserede studier. Vi henviser i denne retningslinje kun til de systematiske reviews, som fik en AMSTAR 2 vurdering af moderat eller højt kvalitet (K=16).

Evidensgrundlaget for vores anbefalinger er således ASCOs guideline fra 2024 (21), samt de 19 supplerende systematiske reviews (23–41). På trods af de senere publikationsdatoer, gør vi opmærksom på, at alle de inkluderede reviews havde en søgningsdato som lå før ASCOs guideline. Vi gør derudover opmærksom på, at vi har baseret vores anbefalinger på den del af ASCOs guideline, som forholder sig til studier af patienter, som er færdigbehandlede, da denne retningslinje omhandler træthed som en senfølge efter kræft. Hvor det blev fundet relevant, supplerede vi med de senest publicerede kliniske retningslinjer fra European Society of Medical Oncology (ESMO) (Cancer-related fatigue: ESMO Clinical Practice Guidelines for diagnosis and treatment) (18). ESMOs guideline blev vurderet med en AGREE II-score på 70%. Det gælder for både ESMOs og ASCOs guidelines, at de baserer sig på studier, hvor der som oftest er undersøgt en population af patienter med forskellige kræftdiagnoser.

Screening og udredning

1. **Kræftoverlevere kan screenes og regelmæssigt udredes for kræftrelateret træthed ved brug af validerede skalaer (B)**

Beskrivelse

Screening og udredning benyttes med det formål at identificere kliniske niveauer af kræftrelateret træthed med henblik på at tilbyde relevant behandling. Forekomsten af træthed blandt kræftoverlevere er høj, har potentielt

betydning for evnen til at fastholde behandling og har stor indflydelse på livskvaliteten – også *efter* endt primær behandling. På denne baggrund anbefaler både ASCOs retningslinje fra 2024 (som opdaterer anbefalingen fra 2014) og ESMO's retningslinje (18,21), at der rutinemæssigt screenes for tilstedeværelsen af træthed efter afsluttet primær behandling. Screening bør foretages, når det er klinisk relevant, og helst én gang årligt.

Kræftoverleveren kan indledningsvis spørges ind til træthed på en skala fra 1-10 (hvor 1-3 = mild, 4-6 = moderat, 7-10 = høj). Kræftoverlevere med moderat til høj træthed kan herefter evalueres med validerede skalaer, f.eks. følgende skalaer, som findes på dansk:

- FACIT-Fatigue Scale (13-item) (42)
- EORTC-QLQ-C30 (3-item fatigue subskala) (43)
- Brief Fatigue Inventory (9-item) (44)

Det er vigtigt, at behandlende læger og andre fagprofessionelle altid overvejer mulige komorbiditeter, der kan bidrage til træthed, før de anbefalede interventioner iværksættes (f.eks. anæmi, ernæringsmæssige mangler, endokrine sygdomme, samt bivirkninger til medicinsk behandling).

Litteratur og evidensgennemgang

Da den seneste ASCO guideline udelukkende fokuserede på behandling af kræftrelateret træthed, er nærværende anbefaling baseret på ASCOs tidligere guideline, som omfatter både behandling og screening for kræftrelateret træthed (22), samt på ESMOs guideline (18). Begge guidelines anbefalede regelmæssig monitorering og screening for kræftrelateret træthed blandt kræftoverlevere ved brug af validerede skalaer (18,22).

Non-farmakologiske interventioner

2. Alle kræftoverlevere skal tilbydes psykoedukation om kræftrelateret træthed (A)

Beskrivelse

Psykoedukation dækker her over støtte, information og uddannelse til kræftoverleverne om deres nuværende tilstand og behandling, med det formål at understøtte evnen til at tilpasse sig og håndtere sine træthedssymptomer (18). Psykoedukation bør indeholde information om, hvordan kræftrelateret træthed adskiller sig fra almindelig træthed (idet den ikke nødvendigvis lindres ved hvile), samt vejledning i energiforvaltning, prioritering af opgaver og aktivitetsdosering (18).

Litteratur og evidensgennemgang

Evidensen for en direkte effekt af psykoedukation/patientuddannelse omkring kræftrelateret træthed er blandet. Det skyldes, at det er vanskeligt at isolere effekten af denne type intervention. ESMOs og ASCOs tidligere guidelines anbefalede psykoedukation til at øge self-management og egenomsorg. Disse anbefalinger er baseret på ældre studier (18,21,22). Den nye ASCO guideline identificerede yderligere otte randomiserede studier som undersøgte psykoedukation som intervention (N=2035). Her fandt kun fire studier en signifikant forbedring af kræftrelateret træthed. De resterende fire studier fandt ingen forskel mellem interventionsgruppen og kontrolgruppen.

En nylig meta-analyse, der sammenfattede effekten af psykoedukative interventioner på kræftrelateret træthed (CRF) i 10 randomiserede kontrollerede studier, viste, at disse havde en positiv, lille-til-medium effekt på at

lindre CRF (p = 0,042; Hedges' g = 0,38; 95% CI, 0,013-0,755; 1369 patienter) (41). Kvaliteten af evidensen vurderes dog som lav.

På trods af, at den foreliggende evidens er blandet, vurderes det at psykoedukation kan være et værdifuldt supplement til andre interventioner. Psykoedukation indgår desuden som en vigtig komponent i kognitiv adfærdsterapi (KAT).

3. Fysisk træning skal tilbydes til kræftoverlevere med moderat til svær kræftrelateret træthed, tilpasset funktionsevne og individuelle forhold (A)

Beskrivelse

Fysisk træning defineres her som en planlagt, struktureret og regelmæssig fysisk aktivitet designet til at forbedre eller vedligeholde fysisk form og generel sundhed (45). I denne kontekst er formålet at forebygge og/eller lindre kræft-relateret træthed hos personer efter endt kræftbehandling (46). Traditionelle træningsmetoder omfatter typisk i) aerob træning (såsom gang, cykling, svømning og løb), ii) styrketræning, som fokuserer på at opbygge muskelstyrke (såsom vægtløftning, træningselastikker og kropsvægtøvelser som squats og armbøjninger), eller iii) en kombination af både aerob-træning og styrketræning (47,48).

Træningens intensitet varierer men kategoriseres typisk som lav, moderat eller høj intensitetstræning. Lavintensitets-træning omfatter aktiviteter som langsom gang og blid yoga, der kræver minimal anstrengelse (49). Moderat intensitetstræning medfører mærkbare stigninger i hjertefrekvens og vejrtrækning, men tillader samtale og omfatter f.eks. rask gang og vand-aerobic (50,51). Højintensitets-træning fører til hurtig vejrtrækning og udfordret tale og omfatter f.eks. løb og højintensitets intervaltræning (HIIT) (49,51).

Litteratur og evidensgennemgang

Der er god evidens for, at fysisk aktivitet har en positiv effekt på træthed blandt kræftoverlevere. Den tidligere ASCO guideline henviste til 27 randomiserede studier (22). Den nye ASCO guideline identificerede yderligere ni randomiserede studier (N=1377) og konkluderer, at fysisk aktivitet fører til signifikante forbedringer i træthed i en periode på op til 12 uger efter interventionen (21). På grund af betydelig heterogenitet mellem studierne angiver ASCOs guideline dog ikke, hvilken type fysisk aktivitet der er mest effektiv og med hvilken varighed. ASCO henviser endvidere til rapporten fra The American College of Sports Medicine 2019 Round Table, som anbefaler henholdsvis i) konditionstræning med moderat intensitet (aerobic) i 30-60 minutter, mindst tre gange ugentlig, ii) en kombination af aerobic og styrketræning to-tre gange ugentlig, og iii) styrketræning to gange ugentlig (50).

Et nyere Cochrane review med 21 studier (vurderet til høj kvalitet i AMSTAR 2) konkluderer, at effekten af styrketræning på kræftrelateret træthed er usikker efter 12 uger sammenlignet med ingen træning (SMD:-0,05, 95% CI [-0,39; 0,29], *p*=0,79) (37). En anden meta-analyse (52), viser dog, at resistenstræningsinterventioner (herunder styrketræning), der varer mere end 12 uger, signifikant reducerede træthed hos kræftoverlevere, med effektstørrelser spændende fra medium (SMD = 0,622, p = 0,004) til stor (SMD = 0,932, p < 0,001).

Et andet review af 12 studier (vurderet til moderat kvalitet i AMSTAR 2) undersøgte effekten af lav- og højintensitetstræning og konkluderer, at begge træningsformer kan reducere kræftrelateret træthed. Dog indeholdt dette review kun 2 studier, som undersøgte effekten på kræftoverlevere efter endt kræftbehandling (SMD: 0,63, 95% CI: [0,42 ; 0,84], p<0,001) (25). I forbindelse med fysisk aktivitet som intervention, bør kræftoverleveren bistås med supervision og støtte for at optimere adhærens og effekt.

To nyere reviews (28,53), hvoraf ét blev identificeret gennem faglig konsultation (53), peger desuden på, at kræftrehabilitering med fysisk aktivitet via telemedicin, samt ikke-superviseret fysisk aktivitet i hjemmet effektivt kan lindre kræftrelateret træthed. Disse fund giver sundhedsprofessionelle flere muligheder for at skræddersy fysisk træning til patienters præferencer og behov – ud over det personlige fremmøde.

4. Kognitiv adfærdsterapi kan tilbydes til kræftoverlevere med moderat til svær kræftrelateret træthed og kan leveres som almindelig fremmødekonsultation eller virtuelt (B)

Beskrivelse

Kognitiv adfærdsterapi (KAT) er en struktureret, evidensbaseret psykologisk intervention, der adresserer samspillet mellem tanker, følelser og adfærd. I konteksten af kræftrelateret træthed benyttes KAT til at modificere uhensigtsmæssige overbevisninger og adfærd, der bidrager til trætheden, med henblik på at forbedre kræftoverlevernes mestringsstrategier og overordnede livskvalitet (54). KAT mod kræftrelateret træthed kan inkludere et mere intensivt fokus på energiforvaltning sammenlignet med det, der tilbydes gennem psykoedukation alene.

Litteratur og evidensgennemgang

ASCOs guideline er baseret på tre tidligere identificerede systematiske reviews og tre nye randomiserede studier. De systematiske reviews inkluderede mellem 37 og 41 randomiserede studier af psykologiske interventioner generelt (f.eks. KAT og psykoedukation). Effektstørrelserne for træthed var generelt små (0.1-0.3). Dog var de fleste studier ikke specifikt målrettet træthed, og patienterne var derfor ikke screenet for træthed ved inklusion. Til gengæld var de tre nyere studier alle målrettet behandling af træthed blandt kræftoverlevere, som således var screenet for træthed. Det første studie undersøgte effekten af et individuelt KAT-forløb og inkluderede 112 kræftoverlevere. Dette studie viste en klinisk signifikant forbedring af kræft-relateret træthed efter seks måneder (54% i interventionsgruppen vs. 4% i kontrolgruppen) (55). Det andet studie undersøgte et internet-baseret KAT-forløb blandt 132 brystkræftoverlevere og viste en stor effekt (Cohen's *d* = 1.0), samt en klinisk signifikant forbedring af træthed efter seks måneder hos 73% af deltagerne i interventionsgruppen (56). Det tredje studie undersøgte et gruppeforløb som kombinerede KAT og hypnose og inkluderede 95 kræftoverlevere. Dette studie viste en signifikant forbedring i både general træthed og fysisk træthed seks måneder efter interventionen med medium-til-store effektstørrelser på henholdsvis Cohen's *d* = 0.6 og *d* = 0.7 (57).

Vi fandt ingen nye systematiske reviews om KAT for kræftrelateret træthed.

5. Mindfulness-baserede programmer kan tilbydes som en behandling for kræftrelateret træthed og kan leveres som almindelig fremmødekonsultation eller virtuelt (B)

Beskrivelse

Mindfulness-baserede programmer består af strukturerede psykologiske interventioner, der anvender mindfulness-træning med henblik på at udvikle nærvær, ikke-dømmende accept og kognitiv fleksibilitet. Disse terapier integrerer som regel meditation, åndedrætsøvelser og blide kropsbevægelser for at styrke psykologisk robusthed og fremme evnen til følelsesmæssig regulering. Mindfulness-baserede programmer antages at kunne lindre kræftrelateret træthed ved at reducere rumination og reaktioner på de følelsesmæssige og fysiske triggere, som kan være forbundet med træthed (58). De mest udbredte metoder er Mindfulness-Based Stress Reduction (MBSR) (59,60) og Mindfulness-Based Cognitive Therapy (MBCT) (61).

Litteratur og evidensgennemgang

ASCOs guideline er baseret på fire randomiserede studier af kræftoverlevere med varierende grader af kræftrelateret træthed efter endt kræftbehandling. Studierne inkluderer både kræftoverlevere med blandede kræftdiagnoser og studier udelukkende med brystkræftoverlevere. Hovedparten af studierne omfatter brystkræftoverlevere. Studierne finder klinisk signifikante effekter af mindfulness-baserede interventioner på kræftrelateret træthed, også når interventionerne blev leveret via internettet. Interventionen blev i studierne leveret af psykologer eller certificerede terapeuter på masterniveau. Studierne anvendte validerede skalaer til måling af kræftrelateret træthed, typisk på inklusionstidspunktet og igen efter 3 og 6 mdr. Ingen af studierne havde followup-data udover de 6 mdr. Interventionerne blev leveret fra 3 mdr. og op til 10 år efter endt kræftbehandling. En metaanalyse fra 2021 (62) konkluderer desuden, at der foreligger medium effekter umiddelbart efter interventionen (Hedges' g = 0.60) og ved opfølgning (Hedges' g = 0.42). Det fremhæves imidlertid, at der i studier af mindfulness-baserede interventioner til lindring/behandling af kræftrelateret træthed ofte savnes sammenligning med andre interventioner rettet mod samme symptom, fx interventioner som fysisk træning. Studierne savner ligeledes inklusionskriterier for graden af kræftrelateret træthed. Mindfulness kurser til kræftoverlevere tilbydes både i rehabiliterings regi, primær sektor og via patientforeninger.

6. Lysterapi kan tilbydes som supplerende behandling til kræftoverlevere med kræftrelateret træthed (C)

Beskrivelse

Lysterapi er en non-farmakologisk intervention, der består af systematisk eksponering for døgnrytme-stimulerende lys, typisk ved brug af et lyspanel eller lysbriller. Lyset har specifikke spektrale egenskaber, som sigter mod at regulere døgnrytmen og derigennem forebygge eller lindre kræft-relateret træthed. Lys har en direkte effekt på hjernens suprachiasmatiske kerne (SCN), som fungerer som kroppens biologiske ur. Lysterapi bruges til at fremme en mere stabil døgnrytme. For kræftoverlevere, der ofte oplever forstyrrelser i døgnrytmen på grund af behandlingen eller kræftsygdommen selv, kan lysterapi være en mulig metode til at lindre kræftrelateret træthed (63). Lysterapi indebærer typisk eksponering med blåberiget eller polykromatisk hvidt lys om morgenen, typisk i 30 minutter umiddelbart efter personen er stået op (64). Lysintensitet kan leveres mellem 1.500 og 10.000 lux, men opleves generelt som mere behagelig for brugeren ved lavere intensiteter.

Litteratur og evidensgennemgang

ASCOs guideline fandt kun to randomiserede studier, hvor det ene viste en positiv effekt på træthed, mens det andet ikke fandt nogen effekt. Konklusionen var, at der hverken var evidens for eller imod lysterapi for træthed (21). I modsætning til ASCO fandt vi et systematisk review fra 2023, som var vurderet til moderat kvalitet i AMSTAR 2 (40). Reviewet konkluderede på baggrund af 12 randomiserede studier (N=691), at lysterapi havde en positiv effekt i forhold til enten at forebygge eller reducere træthed blandt kræftoverlevere. Det samme review fandt, at interventioner med en varighed af minimum 4 uger og med en høj lysintensitet ≥10.000 lux viste de bedste resultater. Dog rapporterede deltagerne ofte ubehag ved den høje lysintensitet. Det er vigtigt at bemærke, at lavere lysintensiteter (under 10.000 lux) også var effektive (SMD=-0.58 vs. høj lysintensitet SMD=-1.38). Eksempelvis viste et studie med lysintensitet på 1.350 lux (Redd, 2014) også effekt på træthed (SMD -1.46).

Det skal dog fremhæves, at kun 5 ud af de 12 studier i reviewet specifikt fokuserede på kræftoverlevere efter afsluttet primær behandling, hvilket begrænser overførbarheden til kræftoverlevere. Desuden var studierne betydeligt metodologisk heterogene, og de fleste målte kun effekter umiddelbart efter interventionen uden

langtidsopfølgning (f.eks. et år eller mere efter primær behandling). På grund af disse begrænsninger anbefales lysterapi med forbehold.

7. Yoga kan tilbydes til kræftoverlevere, der udtrykker interesse, særligt yogaformen Hatha (D)

Beskrivelse

Yoga er defineret af National Cancer Institute som "et ældgammelt system af øvelser til at balancere sind og krop gennem motion, meditation (fokusering af tanker), og kontrol af vejrtrækning og følelser" (65). Yoga kan styrke kroppen og hjælpe med at forbedre træthed ved at reducere stress, forbedre søvnkvalitet og øge energiniveauet (18,21).

Litteratur og evidensgennemgang

Evidensgrundlaget er stadig sparsomt. Den seneste ASCO guideline er baseret på to randomiserede kontrollerede studier: Det ene undersøgte effekten af 90 minutters hatha yoga to gange ugentlig blandt 200 kræftoverlevere og fandt en signifikant forbedring i træthed efter 12 uger ($p = 0.002$) (58) Det andet studie undersøgte effekten af forløbet "Yoga for Cancer Survivors" (YOCAS), som bestod af 75 minutters yoga to gange ugentlig, blandt 358 kræftoverlevere og fandt en signifikant effekt på kræftrelateret træthed efter 4 uger ($p < 0.01$) (65).

I modsætning til ASCO fandt vi et systematisk review (29), som på baggrund af en metaanalyse af seks studier konkluderer, at yoga ikke havde effekt på kræftrelateret træthed (SMD=0.16 [-0.28; 0.60]). Reviewet var vurderet til moderat kvalitet i AMSTAR 2. Metaanalysen inkluderede fire studier, som ikke var inkluderet i ASCOs guideline, henholdsvis to pilotstudier og to studier, som sammenlignede yoga med fysisk aktivitet som kontrol. Ingen af de fire studier viste effekt af yoga. Til gengæld var de to nyeste studier i ASCOs guideline ikke med i dette review (66,67).

Farmakologiske behandlinger

8. Lægemidler, herunder vågenhedsfremmende medicin (f.eks. modafinil, armodafinil), antidepressiv medicin og psykostimulerende medicin bør ikke anvendes rutinemæssigt til behandling af kræft-relateret træthed (B)

Beskrivelse

Farmakologiske behandlinger henviser her til behandling med medicinske præparater, der indeholder stoffer, som forebygger eller reducerer kræftrelateret træthed. Det være sig vågenhedsfremmende præparater, klassiske centralstimulerende og psykostimulerende præparater, samt ikke-stimulerende præparater med antidepressiv profil, særligt noradrenalin- og dopaminmodulerende præparater (35).

Litteratur og evidensgennemgang

Til forskel for kræftpatienter under behandling, peger den foreliggende evidens på en manglende effekt af farmakologiske behandlinger for kræftrelateret træthed blandt færdigbehandlede kræftoverlevere. Både ASCOs og ESMOs guidelines indeholder en anbefaling imod anvendelsen af lægemidler mod træthed (f.eks. modafinil, armodafinil), antidepressiv medicin, samt psykostimulerende lægemidler. ESMOs guideline var baseret på 19 randomiserede studier, hvoraf 15 studier viste ingen effekt på kræftrelateret træthed, mens 4

studier (tre med methylphenidate og ét med dexmethyphenidate) viste en positiv effekt på træthed (18). ESMO fandt yderligere ét nyt studie (N=328), som ikke kunne påvise nogen signifikant effekt af armodafinil, hverken ved 150 mg eller 250 mg dagligt (21).

I vores søgning identificerede vi et systematisk review (vurderet til moderat kvalitet i AMSTAR 2), som undersøgte effekten af bupropion (et antidepressivum) på kræftrelateret træthed. Reviewet konkluderede, at bupropion kunne være effektiv (35). Dog undersøgte kun ét ud af de tre randomiserede studier i reviewet træthed hos kræftoverlevere efter endt primær behandling (N=230), og i denne gruppe fandt man ingen effekt (68).

Patientværdier og – præferencer

Patienters præferencer og værdier spiller en central rolle i håndteringen af kræftrelateret træthed, især når træthed opstår som en senfølge efter afsluttet primær kræftbehandling. En litteraturgennemgang viser, at mange kræftoverlevere føler sig uforberedte på, at trætheden kan vare i lang tid efter behandlingen, og udtrykker frustration over, at dette ikke blev italesat tidligere i deres forløb (69). Dette understreger vigtigheden af systematisk screening og psykoedukation (Anbefaling 1 og 2) – ikke blot for at identificere klinisk signifikant træthed, men også for at sikre, at patienterne føler sig informerede, anerkendte og i stand til at deltage aktivt i relevante interventioner.

Patienter giver udtryk for stor interesse i selv aktivt at håndtere trætheden (70), og effekten af fysisk aktivitet er veldokumenteret (Anbefaling 3). Samtidig viser forskning, at deltagelse i fysisk aktivitet kan udfordres af faktorer som bivirkninger, selve trætheden, vægtændringer og social stigmatisering (71,72). Disse fund understreger behovet for individuelt tilpassede træningsprogrammer, der tager hensyn til kræftoverlevernes præferencer og fysiske formåen, samt sikrer tilgængelighed og relevant støtte. Mange kræftoverlevere værdsætter desuden autonomi i valg af type, tidspunkt og sted for fysisk aktivitet, og nogle profiterer af sociale og støttende formater, såsom én-til-én-interaktioner med en personlig træner (73).

Gennem hele udviklingen af denne retningslinje er patientperspektiver ikke blot blevet inddraget via en gennemgang af forskningslitteraturen men også direkte gennem dialog med en patientrepræsentant. Patientrepræsentanten har været en del af arbejdsgruppen og har bidraget til at sikre, at formuleringen og prioriteringen af anbefalingerne afspejler det, der er vigtigst for mennesker, der lever med og efter kræft.

Patientperspektiver er desuden inddraget via et fokusgruppeinterview. Fokusgruppen bestod af fem kræftoverlevere, fordelt på to kvinder og tre mænd i alderen 40-74 år behandlet for følgende kræftdiagnoser: Brystkræft, blærekræft, mundhulekræft og knoglemarvskræft. Deltagerne havde mellemlang til lang videregående uddannelse, og én var pensioneret på tidspunktet for interviewet.

På baggrund af fokusgruppeinterviewet fremtrådte en række centrale temaer om kræftoverleveres præferencer og værdier i forhold til de nationale kliniske retningslinjer for kræftrelateret træthed. Deltagerne udviste generel åbenhed over for non-farmakologiske interventioner, især dem uden bivirkninger, og udtrykte et klart ønske om individualiserede anbefalinger, der tager højde for den enkeltes behov, ressourcer og fysiske formåen.

En gennemgående præference var betydningen af systematisk screening og tidlig psykoedukation. Screening blev opfattet som et naturligt og værdifuldt redskab til at indlede samtaler om træthed og tilpasse

interventioner over tid. En deltager udtrykte: *"Jeg synes det er noget af det mest positive jeg har set, der her med screeningen."* Der var bred enighed om, at psykoedukation omkring kræftrelateret træthed bør gives tidligt i forløbet - men ikke i chokfasen - og at informationen skal gives på tidspunkter, hvor patienten er modtagelig. En deltager forklarede: *"Denne her psykoedukation, tror jeg, er fuldstændig afgørende at få ind, med et enkelt forbehold, tidligt i behandlingen eller tidligt i kræftforløbet. Dog ikke så at det rammer i chokfasen, som jo varer et eller andet sted fra en måned til et halvt år…"* Flere fremhævede vigtigheden af gentagne tilbud, da patienters behov og parathed kan ændre sig, hvilket også er fremhævet i litteraturen (74).

Fysisk træning blev set som en vigtig og meningsfuld intervention, især når den tilpasses individuelle behov og formåen. Kræftoverleverne understregede, at små fremskridt er værdifulde, og nævnte fx brug af sportsure som motiverende redskaber til at visualisere effekten. Samtidig blev det fremhævet af én af deltagerne, at nogle retningslinjer stadig forhindrer specifikke patientgrupper, fx patienter med myelomatose i at træne, selvom nyere evidens tilsiger andet (75). Her efterlystes større opmærksomhed fra sundhedsprofessionelle på individuelle vurderinger og kontraindikationer.

Kognitiv adfærdsterapi (KAT) blev opfattet som en mulig hjælp, især for kræftoverlevere med moderat til svær kræftrelateret træthed. Der var et klart behov for, at interventionen forklares i et tilgængeligt og praksisnært sprog. En deltager understregede vigtigheden af relationen og kommunikationen med sundhedspersonalet: *"Det er meget vigtigt, at de sundhedsprofessionelle tager sig den tid, der kræves til dialogen med patienten og dennes pårørende."* Der var desuden enighed om, at tilbuddet bør inkludere både fysiske og virtuelle konsultationer samt gruppe- og individuelle sessioner, særligt for kræftoverlevere, der har svært ved at komme ud af hjemmet.

Lignende synspunkter blev fremstillet om mindfulness-baserede interventioner, som deltagerne vurderede som positive, forudsat at de bliver præsenteret uden fordomsfulde konnotationer og med tydelig information om, hvad de indebærer. Dette gjaldt også for lysterapi og yoga. Som en deltager bemærkede: *"… hvis alt andet ikke virker, ville det være fjollet at sige nej tak."* I forhold til lysterapi blev det pointeret, at interventionen bør tilpasses hverdagslivet og kommunikeres klart: *"Give gode råd til hvordan man kan inkorporere det i et aktivt hverdagsliv med arbejde, så man kan se, at det ikke er særligt invasivt i ens hverdag."*

Der var bred enighed om, at medicinsk behandling ikke bør anbefales. Kræftoverleverne udtrykte bekymring for afhængighed og bivirkninger. En deltager opsummerede holdningen: *"… hvis man bare propper medicin i folk og tror, at det løser det (problemet), så risikerer man altså at opnå en misbrugskondition i stedet for. Hvis man kan bruge de andre midler (anbefalingerne), som ikke belaster kroppen, så er det måske ikke så ringe…"*

Afslutningsvis blev det understreget, at interventioner skal tilbydes af sundhedsprofessionelle med erfaring i kræftbehandling. Der var ønske om at blive mødt af fagpersoner, der forstår kompleksiteten i at være kræftoverlever. Kræftoverleverne anerkendte også deres eget ansvar i processen: *"Man skal have en vis vilje til at gøre noget selv. … Der ligger et ansvar på os selv, hvis man vil have succes. Det offentlige kan ikke løfte dem hele vejen, de skal også selv være med til at løfte."* Samtidig blev det pointeret, at visse situationer kalder på systemets støtte: *"Der er stadier i denne her tur især ved kroniske kræfttyper, hvor man nok må sige, om ikke der er nogle tidspunkter, hvor systemet skal løfte en ud af den gruppe man er faldet ned i."* Dette blev sat i relation til ulighed i sundhed, hvor en deltager mindede om, at *"ikke alle bor i sociale stærke familier og byer, som kan det samme som patienter med stærk socioøkonomisk baggrund. Man bliver nødt til at se på hele patienten, fx ift. komorbiditeter osv."*

Samlet set peger fokusgruppen på en præference for helhedsorienterede, evidensbaserede og individualiserede tilgange til håndtering af kræftrelateret træthed, med særligt fokus på interventionsformer, der er tilgængelige, forståelige og uden skadelige bivirkninger.

Rationale

Nærværende anbefalinger er primært baseret på ASCO-retningslinjerne, og i nogen grad på ESMO-retningslinjerne, da begge vurderedes at være af høj kvalitet og dækker et bredt udsnit af randomiserede kontrollerede studier på området. Derudover er fund fra systematiske reviews blevet inddraget, når disse ikke allerede var omfattet af de nævnte retningslinjer. Endelig er formuleringen af anbefalingerne blevet tilpasset, så de i videst muligt omfang afspejler patienternes præferencer og værdier. Psykoedukation er desuden prioriteret højt, selvom det er mindre veldokumenteret som en selvstændig interventionsform, da mange andre interventionsformer naturligt inkluderer psykoedukative elementer, og fordi kræftoverlevere konsekvent udtrykker, at viden om træthed og passende håndteringsstrategier har stor værdi.

Bemærkninger og overvejelser

Interventionerne bør tilbydes af fagprofessionelle med kvalifikationer inden for det givne interventionsområde, samt viden om kræftrelateret træthed. Hvis en sådan fagperson ikke er tilgængelig i det konkrete tilfælde, kan relevant sundhedspersonale tilegne sig de nødvendige kompetencer gennem målrettet efteruddannelse eller kurser for at sikre en kvalificeret indsats.

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5. Metode

Litteratursøgning

Litteratursøgningen er gennemført i overensstemmelse med principperne for en tre-trins søgestrategi, som anbefalet i gældende metodiske vejledninger. Dog blev det tredje trin – manuel gennemgang af referencelister og grå litteratur – ikke gennemført, da der allerede forelå et omfattende antal nyere systematiske reviews og evidensbaserede kliniske retningslinjer. Søgningen er foretaget af Retningslinjefunktionen under Sundhedsvæsenets Kvalitetsinstitut i tæt samarbejde med tovholder for retningslinjen.

Der er søgt i følgende databaser: PubMed, PsycINFO, Embase, CINAHL samt i relevante guideline-databaser med henblik på at identificere eksisterende retningslinjer og evidensbaseret litteratur. Søgeperioden dækker årene 2004 til 2024. Populationen for søgningen er kræftoverlevere, og der er fokuseret på litteratur, som omhandler senfølger.

Der er anvendt relevante søgetermer og deres kombinationer, målrettet de kliniske problemstillinger beskrevet i retningslinjen. Hvor der er fundet eksisterende guidelines, som på fyldestgørende vis besvarer de kliniske spørgsmål, er søgningen afsluttet på dette niveau.

Inklusionskriterier omfattede internationale guidelines, systematiske reviews og primære studier, som vedrører kræftoverlevere og senfølger, publiceret på dansk eller engelsk inden for den angivne periode.

For nærmere detaljer om søgestrategien og anvendte søgestrenge henvises til bilag 1.

Litteraturgennemgang

Litteraturen er gennemgået af Lisa Maria Wu, ph.d., Beverley Lim Høeg, ph.d., Thea Otto Mattsson, speciallæge ph.d., og Fie Holm Grünfeld, cand.scient. i tæt samarbejde med Retningslinjefunktionen under Sundhedsvæsenets Kvalitetsinstitut. Gennemgangen har fulgt en systematisk tilgang med udgangspunkt i de identificerede studier fra litteratursøgningen.

Inkluderede studier dækker over 18 antal studier (systematiske reviews), med fokus på en population bestående af kræftoverlevere. Studierne skulle rapportere relevante outcomes, herunder kræftrelateret træthed efter primær behandling.

Evidensvurderingen er foretaget på baggrund af anerkendte metoder til vurdering af metodisk kvalitet og risiko for bias. Den metodiske kvalitetsvurdering af guidelines og studierne er udført af Retningslinjefunktionen under Sundhedsvæsenets Kvalitetsinstitut, og resultaterne heraf kan findes i bilag 2-5 eller rekvireres ved henvendelse til Retningslinjefunktionen.

Ved dataekstraktion er der lagt særlig vægt på kræftrelateret træthed efter primær behandling, typisk vurderet ved hjælp af validerede skalaer, samt studiedesign og relevante kontekstuelle faktorer. Datasyntesen er foretaget ved en narrativ sammenfatning, hvor resultaterne er organiseret efter hovedtemaer og klinisk relevans. Hvor det har været muligt, er der sammenlignet på tværs af studier for at identificere konsistente fund eller variationer i evidensen

Formulering af anbefalinger

Anbefalingerne i denne retningslinje er formuleret af retningslinjegruppen, som består af fagpersoner med baggrund inden for psykologi, psyko-onkologisk forskning og onkologisk praksis. Processen har været baseret

på en uformel konsensusmetode, hvor alle medlemmer har haft mulighed for at bidrage med faglig vurdering og erfaring. Ved uenighed er der opnået afklaring gennem drøftelser i plenum.

Derudover har gruppens patientrepræsentant samt en fokusgruppe bestående af kræftoverlevere givet værdifuld feedback på formuleringen af anbefalingerne og bidraget med input til retningslinjens udarbejdelse, med særligt fokus på patientperspektivet og anvendelighed i praksis.

Anbefalingerne er formuleret med bevidst sproglig præcision, hvor ordvalget afspejler styrken af anbefalingen. Eksempelvis anvendes:

- *"Skal"* for stærke anbefalinger baseret på høj evidens eller bred konsensus,
- *"Kan"* for anbefalinger, hvor evidensen er begrænset, eller hvor beslutningen afhænger af den kliniske kontekst,
- *"Anvend kun"* eller *"Anvend ikke"* bruges til at understrege specifikke indikationer eller fravalg baseret på evidens eller kendte risici.

Der er i processen også arbejdet aktivt med at formulere *ikke-anbefalinger*, hvor det er relevant. Dette er gjort for at tydeliggøre behandlinger, tiltag eller metoder, der ikke bør anvendes i klinisk praksis ud fra evidens, risiko eller manglende effekt.

Interessentinvolvering

Denne retningslinje er udarbejdet med bred faglig repræsentation, hvor både kliniske eksperter og relevante fagpersoner har deltaget aktivt i processen. Derudover har patientinvolvering været en integreret del af arbejdet. Ud over deltagelsen af en patientrepræsentant i retningslinjegruppen er der afholdt en fokusgruppe med kræftoverlevere, som har givet værdifuld feedback or bidraget med input til anbefalingerne. Fokusgruppen har haft særligt fokus på patienternes erfaringer med træthed, deres præferencer samt behov i hverdagen.

Desuden er der i litteratursøgningen systematisk søgt efter studier og guidelines, hvor patienternes værdier og præferencer er blevet kortlagt og inddraget, med henblik på at sikre, at anbefalingerne også afspejler patienternes oplevelser og behov. Hvor det har været muligt, er der trukket på eksisterende internationale guidelines, hvor patientinddragelse har været dokumenteret og systematisk gennemført.

Den systematiske søgestrategi for patienternes perspektiv fremgår af bilag 1.

Høring

Det endelige udkast af denne retningslinje har været sendt til kommentering blandt relevante faggrupper og organisationer, herunder Dansk Center for Søvnsygdomme, Danish Comprehensive Cancer Center (DCCC), Danske Multidisciplinære Cancer Grupper (DMCG), Danish Psycho-Oncology Cooperative Group (DPOC), Danske Multidisciplinære Psykiatri Grupper (DMPG), Dansk Selskab for Almen Medicin (DSAM), Dansk Psykologforening (DP),Dansk Sundhedspsykologisk Selskab (DSS), Dansk Selskab for Onkologisk og Palliativ Fysioterapi (DSOPF), Senfølgeforeningen og Kræftens Bekæmpelse (KB).

Godkendelse

Faglig godkendelse:
Retningslinjen er godkendt af Tre nationale senfølgeforskningscentre, Dansk Center for Brystkræftsenfølger

(DCCL), Center for Forskning i Senfølger efter Kræft i Bækkenbundsorganerne og Nationalt Center for Senfølger hos Kræftoverlevere (CASTLE) i fællesskab med DBCG og DCCG.

Administrativ godkendelse: Godkendt af Sekretariatet for Kliniske Retningslinjer på Kræftområdet den 22. august 2025.

Anbefalinger, der udløser betydelig merudgift

Det skønnes ikke, at anbefalingerne i denne retningslinje generelt vil medføre betydelige merudgifter, da de fleste af de anbefalede interventioner allerede er tilgængelige i mange kommuner som en del af de eksisterende kræftrelaterede rehabiliteringstilbud.

Systematisk psykoedukation er en ikke-omkostningstung intervention, som kan varetages af personale (f.eks. hospitalsafdelinger), der behandler kræftpatienter.

Det anbefales dog, at der sikres adgang til relevante kurser og efteruddannelse – ikke kun i psykoedukation, men også i de øvrige anbefalede interventioner, der kan kræve særlig viden eller tilsyn fra sundheds-professionelle. Dette omfatter blandt andet støtte til fysisk aktivitet, kognitiv adfærdsterapi (KAT) og mindfulness-baserede programmer, hvor specifik viden om kræftrelaterede træthed er vigtig for at kunne tilpasse og implementere interventionerne korrekt i praksis.

Behov for yderligere forskning

Strategier baseret på symptomaccept kan være særligt relevante i tilfælde, hvor trætheden er vedvarende og hvor fuldkommen symptomlindring ikke er realistisk. I takt med udviklingen af kognitiv adfærdsterapi, herunder nyere såkaldte Third Wave-tilgange, som bl.a. lægger vægt på accept (76), er der derfor behov for yderligere forskning i disse psykosociale interventioner til behandling af kræftrelateret træthed. Derudover er der behov for kliniske studier af høj kvalitet, der undersøger effekten af mindfulness-baserede programmer i danske populationer, samt studier af lysterapi og yoga. Eftersom træthed hos kræftoverlevere ofte optræder sammen med smerter, nedtrykthed, søvnforstyrrelser og angst (77), bør fremtidig forskning også fokusere på interventioner, der retter sig mod dette bredere symptomkompleks, da sådanne tilgange ligeledes kan have en gavnlig effekt på træthed.

Forfattere og habilitet

Lisa Maria Wu, ph.d., psykolog og lektor, Aarhus Universitet og Aarhus Universitetshospital, ingen interessekonflikter.

Thea Otto Mattsson, speciallæge ph.d., lægefaglig leder, Klinik for Senfølger, Onkologisk Afdeling Odense Universitetshospital, ingen interessekonflikter.

Beverley Lim Høeg, ph.d., psykolog og postdoc, Kræftens Bekæmpelses Center for Kræftforskning, ingen interessekonflikter.

Fie Holm Grünfeld, cand.scient., i Idræt og Sundhed specialiseret i Exercise as Medicine, REHPA, Videncenter for Rehabilitering og Palliation, ingen interessekonflikter.

Louise Strøm, onkologisk sygeplejerske, cand.pæd.psych, ph.d. i psykologi, postdoc, Aarhus Universitet og Aarhus Universitetshospital, ingen interessekonflikter.

Claus de la Porte, patientrepræsentant, medlem af Kræftens Bekæmpelses hovedbestyrelse, ingen interessekonflikter.

Jf. Habilitetspolitikken henvises til deklaration via Lægemiddelstyrelsens hjemmeside for detaljerede samarbejdsrelationer: https://laegemiddelstyrelsen.dk/da/godkendelse/sundhedspersoners-tilknytning-til-virksomheder/lister-over-tilknytning-til-virksomheder/apotekere,-laeger,-sygeplejersker-og-tandlaeger

Plan for opdatering

Initiativet til og ansvaret for denne første version af retningslinjen ligger hos de tre nationale senfølgeforskningscentre, Dansk Center for Brystkræftsenfølger (DCCL), Center for Forskning i Senfølger efter Kræft Bækkenbundsorganerne og Nationalt Center for Senfølger hos Kræftoverlevere (CASTLE) i fællesskab med DBCG og DCCG. En opdatering af retningslinjen er planlagt til den 1. august, 2029.

Version af retningslinjeskabelon

Retningslinjen er udarbejdet i version 10 af skabelonen.

6. Monitorering

Selvom udviklingen af kvaliteten på dette område som udgangspunkt understøttes af viden fra de kliniske kvalitetsdatabaser i regi af Sundhedsvæsenets Kvalitetsinstitut, og indikatorerne i databasen har til formål at belyse relevante kliniske retningslinjer, er det vigtigt at påpege, at der på nuværende tidspunkt ikke eksisterer en klinisk kvalitetsdatabase, som specifikt monitorerer tværgående senfølger efter kræft. Det betyder, at overvågningen af senfølger må ske i regi af de fagspecifikke databaser, hvor der kan følges op på mere sygdomsspecifikke senfølger og, i nogle tilfælde, også generelle senfølger. Den kliniske kvalitetsdatabases styregruppe har mandatet til at beslutte databasens indikatorsæt, hvilket inkluderer fastlæggelsen af hvilke processer og resultater, der monitoreres.

7. Bilag

Bilag 1 – Søgestrategi:

15 internationale guidelines gennemgået med titel og abstract, 10 er gennemgået på fuldtekstniveau og 3 er inkluderet.
49 systematiske reviews gennemgået med titel og abstract (heraf 3 identificeret via supplerende målrettet søgning uden for den oprindelige søgestreng), 25 er gennemgået på fuldtekstniveau, og 18 er inkluderet.
Søgeord og kombinationer internationale guidelines (ASSESSMENT) – søgning foretaget den 29. april 2024:

GIN
Cancer survivor = 2 hits
NICE (UK)
0 hits

Scottish Intercollegiate Guidelines Network (SIGN)
0 hits

Australian Clinical Practice Guidelines
0 hits

Pubmed
((("Cancer"[Title/Abstract] OR "Neoplasm"[Title/Abstract] OR "Cancer patient"[Title/Abstract] OR "Cancer survivor"[Title/Abstract] OR "Oncology patient"[Title/Abstract]) AND (MH “Fatigue”) OR (“Cancer fatigue*”) OR (MH “Cancer related fatigue”) OR “lethargy” OR “asthenia” OR “tired” OR “exhaust*” AND ("guideline"[Publication Type] AND ("danish"[Language] OR "english"[Language] OR "german"[Language] OR "norwegian"[Language] OR "swedish"[Language]) AND 2004/01/01:2024/12/31[Date - Publication])
Antal hits = 3
PsycInfo
0 nye hits
Embase
(cancer:ti OR neoplasm:ti OR 'cancer patient':ti OR 'cancer survivor':ti OR 'oncology patient':ti) AND 'fatique' AND guideline:ti AND [2004-2024]/py
Antal hits = 0
(cancer:ti OR neoplasm:ti OR 'cancer patient':ti OR 'cancer survivor':ti OR 'oncology patient':ti) AND 'crf' AND guideline:ti AND [2004-2024]/py
Antal hits = 2

Cinahl
TI (Cancer OR Neoplasm OR "Cancer patient" OR "Cancer survivor" OR "Oncology patient") AND TI (fatique) AND TI guideline

Antal hits = 0

Kunnskapssenteret (Norge)

0 hits

Helsedirektoratet (Norge)

0 hits

Socialstyrelsen (Sverige)

0 hits

SBU (Sverige)

0 hits

World Federation of Societies of Biological Psychiatry

0 hits

Texas Medication Algorithm Project

0 hits

British Association for Psychopharmacology

0 hits

Canadian Task Force on Preventive Health Care (Canada)

0 hits

Canadian Network for Mood and Anxiety Treatments (CANADA)

0 hits

U.S. Department of Veterans Affairs (USA)

0 hits

American Psychological Association Logo (USA)

0 hits

American Psychiatric Association

0 hits

National Comprehensive Cancer Network

NCCN Guidelines – RLS har ikke adgang. Flere relevante guidelines.

ESMO

1 hits

Søgeord og kombinationer internationale guidelines (INTERVENTION) – søgning foretaget den 29. april 2024:

GIN

Cancer survivor = 2 hits

NICE (UK)

0 hits

Scottish Intercollegiate Guidelines Network (SIGN)

0 hits

Australian Clinical Practice Guidelines

0 hits

Pubmed

((("Cancer"[Title/Abstract] OR "Neoplasm"[Title/Abstract] OR "Cancer patient"[Title/Abstract] OR "Cancer survivor"[Title/Abstract] OR "Oncology patient"[Title/Abstract]) AND (MH “Fatigue”) OR (“Cancer fatigue*”) OR (MH “Cancer related fatigue”) OR “lethargy” OR “asthenia” OR “tired” OR “exhaust*” AND ("guideline"[Publication Type] AND ("danish"[Language] OR "english"[Language] OR "german"[Language] OR "norwegian"[Language] OR "swedish"[Language]) AND 2004/01/01:2024/12/31[Date - Publication])

Antal hits = 3

PsycInfo

0 nye hits

Embase

(cancer:ti OR neoplasm:ti OR 'cancer patient':ti OR 'cancer survivor':ti OR 'oncology patient':ti) AND 'fatique' AND guideline:ti AND [2004-2024]/py

Antal hits = 0

(cancer:ti OR neoplasm:ti OR 'cancer patient':ti OR 'cancer survivor':ti OR 'oncology patient':ti) AND 'crf' AND guideline:ti AND [2004-2024]/py

Antal hits = 2

Cinahl

TI (Cancer OR Neoplasm OR "Cancer patient" OR "Cancer survivor" OR "Oncology patient") AND TI (fatique) AND TI guideline

Antal hits = 0

Kunnskapssenteret (Norge)

0 hits

Helsedirektoratet (Norge)

0 hits

Socialstyrelsen (Sverige)

0 hits

SBU (Sverige)

0 hits

World Federation of Societies of Biological Psychiatry

0 hits

Texas Medication Algorithm Project

0 hits

British Association for Psychopharmacology

0 hits

Canadian Task Force on Preventive Health Care (Canada)

0 hits

Canadian Network for Mood and Anxiety Treatments (CANADA)

0 hits

U.S. Department of Veterans Affairs (USA)

0 hits

American Psychological Association Logo (USA)
0 hits
American Psychiatric Association
0 hits
National Comprehensive Cancer Network
NCCN Guidelines – RLS har ikke adgang. Flere relevante guidelines.
ESMO
1 hits

Søgestrategi
Management of Fatigue in Adult Survivors of Cancer: ASCO–Society for Integrative Oncology Guideline Update (2024)
Search terms:
cancer related fatigue or *cancer-related fatigue* and *assessment* or *screening* or *diagnosis*

Pubmed (14.6.24)
((fatigue) AND cancer Filters: Systematic Review, Humans, English, Adult: 19+ years, from 2023 – 2024
(43 hits)

Embase (14.6.24)
#3 ('cancer'/exp OR cancer) AND fatique AND [2023-2024]/py AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim)
#2 ('cancer'/exp OR cancer) AND fatique AND [2023-2024]/py
#1 ('cancer'/exp OR cancer) AND fatigue
(0 hits)
Cochrane (14.6.24)
Search term: fatique (3 hits)

CINAHL (14.6.24)
cancer AND fatique. **Limiters** - Publication Date: 20231001-20240631; English Language; Publication Type: Systematic Review (0 hits)

Psycinfo (14.6.24)
Cancer AND fatigue. Publication Year: 2023-2024; Methodology: -Systematic Review (0 hits)

Søgestrategi
Opdatering af søgning fra Screening and assessment of cancer-related fatigue: A clinical practice guideline for health care providers (2022)
Search terms:
cancer related fatigue or *cancer-related fatigue* and *assessment* or *screening* or *diagnosis*

Pubmed (13.6.24)

Search: **((cancer related fatigue)) AND (screening) Filters: Systematic Review, Humans, English, Adult: 19+ years, from 2020 – 2024 (26 hits)**

Embase (13.6.24)
#3 AND (2021:py OR 2022:py OR 2023:py OR 2024:py) AND 'human'/de (60 hits)
#2 AND ('meta analysis'/de OR 'systematic review'/de)
#1 cancer AND related AND fatigue AND screening
Cochrane (14.6.24)
Search term: fatique (0 hits)

CINAHL (14.6.24)
cancer related fatigue AND screening. **Limiters** - Publication Date: 20200801-20241231; English Language; Publication Type: Systematic Review (6 hits)

Psycinfo (14.6.24)
Search term: fatique (5 hits)
cancer related fatigue AND screening . Narrow by Methodology: - systematic review

Søgeord og kombinationer patienternes perspektiv – søgning foretaget den 26. november 2024:

Databaser og søgestrategi	*Dato for søgning*	*Hits*
PUBMED ((Treatment OR rehabilitation OR Physical activity OR Physical exercise OR Intervention) AND (casereports[Filter] OR interview[Filter] OR meta-analysis[Filter] OR personalnarrative[Filter] OR portrait[Filter] OR review[Filter])) AND (Treatment OR rehabilitation OR Physical activity OR Physical exercise OR Intervention) AND (casereports[Filter] OR interview[Filter] OR meta-analysis[Filter] OR personalnarrative[Filter] OR portrait[Filter] OR review[Filter]))) AND (((((("Patient experience") OR ("Patient reported outcomes")) OR ("Qualitative research")) OR ("Survivors' narratives")) OR (Lived experience)) OR (Lived experience)) OR ("Patient perspective")) AND (("Cancer survivorship") OR ("previous cancer") OR ("Late effects of cancer treatment")) OR ("Cancer survivors"))) AND ((((((("Chronic Fatigue" OR "Fatigue Syndrome" OR "Chronic Fatigue Syndrome" OR "Mental Fatigue") OR (fatigue)) OR ("Fatigue"[MeSH])) OR ("Fatigue"[Mesh])) OR ("Fatigue Syndrome, Chronic"[Mesh])) OR ("Mental Fatigue"[Mesh])) AND ((interview[Filter] OR personalnarrative[Filter] OR review[Filter]) AND (2015:2025[pdat]))) AND (interview[Filter] OR personalnarrative[Filter] OR review[Filter])) AND ((casereports[Filter] OR interview[Filter] OR	04-12-24 05-12-24	~~2529 hits~~ 208 hits

meta-analysis[Filter] OR personalnarrative[Filter] OR portrait[Filter] OR review[Filter]) AND (2015:2024[pdat]))) 		
CINAHL ((("Chronic Fatigue" OR "Fatigue Syndrome" OR "Chronic Fatigue Syndrome" OR ("Fatigue") OR ("Fatigue") OR ("Fatigue Syndrome, Chronic") OR ("Mental Fatigue")) AND (("Cancer survivorship") OR ("previous cancer") OR ("Late effects of cancer treatment")) OR ("Cancer survivors")) AND (("Patient experience") OR ("Patient reported outcomes")) OR ("Qualitative research")) OR ("Survivors' narratives")) OR (Lived experience)) OR (Lived experience)) OR ("Patient perspective")) AND (Treatment)	04-12-24	69 hits
PSYKINFO (((("Chronic Fatigue" OR "Fatigue Syndrome" OR "Chronic Fatigue Syndrome" OR ("Fatigue") OR ("Fatigue") OR ("Fatigue Syndrome, Chronic") OR ("Mental Fatigue"))) AND ((("Cancer survivorship") OR ("previous cancer") OR ("Late effects of cancer treatment")) OR ("Cancer survivors"))) AND ((("Patient experience") OR ("Patient reported outcomes")) OR ("Qualitative research")) OR ("Survivors' narratives")) OR (Lived experience)) OR (Lived experience)) OR ("Patient perspective"))) AND “Treatment”	04-12-24	63 hits
		I alt 332

Bilag 2 – Kvalitetsvurderinger af guidelines: Screening

AGREE score (score 1-7. 1 = ingen kriterier opfyldt. 7 = alle kriterier opfyldt)	https://academic.oup.com/ptj/article/102/9/pzac120/6730975?login=false		Helsedirektoratet: Seneffekter efter kreftbehandling (2020)	NCCN guidelines: cancer-related fatigue (2024)	Cancer-related fatigue: ESMO clinical practice guidelines for diagnosis and treatment (2020)	CANCER-RELATED FATIGUE SELF-MANAGEMENT SUPPORT PRACTICE FRAMEWORK	ASCO (2014)
Systematisk søgestrategi	6 Søgning afsluttet august 2020.	1? Ikke muligt at genfinde søgestrategi el.lign. De angiver blot at de søger i litteraturen.	Ikke vurderet med AGREE II da det ikke er en guideline – det er en rapport. Der er ikke foretaget systematisk gennemgang af litteratur og heller ikke udarbejdet anbefalinger	6 (der søges kun på Pubmed – dog systematisk jævnligt og med fuld søgestrategi)	6	Ikke vurderet med AGREE II da det ikke er en guideline – men en framework. Der er ikke foretaget systematisk gennemgang af litteratur og heller ikke udarbejdet anbefalinger	6 (adaptationsproces – dog mangler man lidt keywords til deres proces)
Udvælgelseskriterier	7	1		4	5		7
Litteratur- og evidensvurdering	7	4 (gradering af evidens udvalgte steder)		2	6		7 (AGREE II)
Formulering af anbefalinger	7	4 – de gennemgår evidensen og vurderer evidensniveauer.		7	6		7

Sundhedsfordele, risici og bivirkninger	5	5		6	5		4
Rationale mellem evidens og anbefalinger	7	4 – ikke specifikke anbefalinger. Mere gennemgang af evidens.		4. Der er ikke decideret anbefalinger. Mere evidensgennemgang.	7		6
Interessentinvolvering	4	1		1	1		1
Revision	1	7 (revideres løbende)		7 (minimum 1. gang årligt)	3 (ikke specifik dato angivet, men ESMO har guidelines for opdateringer)		7 – er pt ved at blive revideret
Samlet score (min. 7, max. 56) [%] Over 70% = høj kvalitet	**44 [79% = høj kvalitet]**	**27 [48% = moderat kvalitet]**		**37 [66% = moderat kvalitet]**	**39 [70% = høj kvalitet]**		**45 [80% = høj kvalitet]**

Bilag 3 – Kvalitetsvurderinger af guidelines: Interventioner

AGREE score (score 1-7. 1 = ingen kriterier opfyldt. 7 = alle kriterier opfyldt)	DMCG: Brystkræft – fysisk træning under kemoterapi for brystkræft (version 1.0) 2020	DMCG: Fysisk træning til lindring af cancerrelateret fatigue (CRF) - hos patienter over 18 år, der har kræft og er i tidlig og sen palliativ fase (version 1.0) 2018	Sundhedsstyrelsen: Cancer (2018)		Helsedirektoratet: Seneffekter efter kreftbehandling (2020)		Cancer-related fatigue: ESMO clinical practice guidelines for diagnosis and treatment (2020)	CANCER-RELATED FATIGUE SELF-MANAGEMENT SUPPORT PRACTICE FRAMEWORK	ASCO (2014)	ASCO (2024)
Systematisk søgestrategi	7	7	Ikke vurderet med AGREE II da det ikke er en guideline – det er en rapport.	1? Ikke muligt at genfinde søgestrateg i el.lign. De angiver blot at de søger i litteraturen.	Ikke vurderet med AGREE II da det ikke er en guideline – det er en rapport. Der er ikke foretaget systematisk gennemgan	6 (der søges kun på Pubmed – dog systematisk jævnligt og med fuld søgestrategi)	6	Ikke vurderet med AGREE II da det ikke er en guideline – men en framework. Der er ikke foretaget systematisk gennemgang af litteratur og	6 (adaptations proces – dog mangler man lidt keywords til deres proces)	7 (Systematic lit review of RCTs between 2013 & 2023. DBs like PubMed were searched, and refs from articles were hand-searched for additional studies. This

					g af litteratur og heller ikke udarbejdet anbefalinger			heller ikke udarbejdet anbefalinger		thorough approach indicates a systematic method for evidence retrieval.
Udvælgelse skriterier	6	7		1		4	5		7	7
Litteratur- og evidensvurdering	6	5		4 (gradering af evidens udvalgte steder)		2	6		7 (AGREE II)	7
Formulering af anbefalinger	7	5		4 – de gennemgår evidensen og vurderer evidensniveauer.		7	6		7	7
Sundhedsfordele, risici og bivirkninger	7	5		5		6	5		4	7
Rationale mellem evidens og anbefalinger	7	6		4 – ikke specifikke anbefalinger. Mere		4. Der er ikke decideret anbefalinger. Mere	7		6	7

				gennemgang af evidens.		evidensgennemgang.				
Interessentinvolvering	2	5		1		1	1		1	7
Revision	7	7		7 (revideres løbende)		7 (minimum 1. gang årligt)	3 (ikke specifik dato angivet, men ESMO har guidelines for opdateringer)		7 – er pt ved at blive revideret	6
Samlet score (min. 7, max. 56) [%] Over 70% = høj kvalitet	**49 [85% = høj kvalitet]**	**42 [81% = høj kvalitet]**		**27 [48% = moderat kvalitet]**		**37 [66% = moderat kvalitet]**	**39 [70% = høj kvalitet]**		**45 [80% = høj kvalitet]**	**55 [98% = høj kvalitet]**

Bilag 4 – Kvalitetsvurderinger af systematiske reviews: Screening

Study	AMSTAR II Q	Evaluation
D´Silva et al. (2022)	**1. Protocol Registered Before Starting the Review**	**No** – The review does not mention whether a protocol was registered before starting the study.
	2. Adequacy of the Literature Search	**Unclear** – The review used only two databases (PubMed and Google Scholar) for the literature search, which may not be comprehensive. No justification is provided for limiting the search to these databases.
	3. Explanation for Study Selection	**Yes** – The review provides a clear explanation of the inclusion and exclusion criteria used for selecting studies.
	4. Justification for Excluding Studies	**Unclear** – While exclusion criteria are mentioned, the review does not provide detailed reasoning for why specific studies were excluded after screening.
	5. Risk of Bias from Individual Studies	**Yes** – The study mentions the use of Joanna Briggs Institute critical appraisal tools for assessing the methodological quality and risk of bias of included articles.
	6. Use of Appropriate Meta-Analytic Methods	**No** – The review did not conduct a meta-analysis; it provides a narrative synthesis instead.
	7. Assessment of Heterogeneity	**No** – There is no mention of assessing heterogeneity among the included studies, likely because no meta-analysis was performed.
	8. Quality of Evidence Assessment	**No** – The review does not systematically assess the quality of evidence for the included studies using a recognized tool like GRADE.
	9. Assessment of Risk of Publication Bias	**No** – The study does not assess the risk of publication bias.
	10. Funding and Conflict of Interest Disclosures	**Yes** – The authors state that there was no financial support for the study and no conflicts of interest.
	11. Discussion of Study Limitations	**Yes** – The review discusses limitations, including the restriction to two databases and the screening process being conducted by a single author.
	12. Inclusion of Non-English Studies	**No** – The review explicitly states that only articles published in English were included, potentially introducing language bias.

	13. Data Extraction by Multiple Reviewers	**No** – The review indicates that the screening of titles and abstracts was done by one author, which increases the risk of selection bias.
	14. Clear Reporting of Study Characteristics	**Yes** – The review provides detailed tables summarizing the characteristics of the included studies.
	15. Consideration of Study Design and Impact on Results	**Yes** – The review considers the types of studies included (e.g., RCTs, systematic reviews) in its synthesis.
	16. Synthesis of Findings Without Bias	**Unclear** – The synthesis appears comprehensive, but the lack of a robust assessment of study quality and publication bias makes it difficult to determine the objectivity fully.
Conclusion Given the issues with protocol registration, limited database search, lack of a comprehensive quality assessment, and potential biases in study selection and synthesis, the overall quality of this systematic review is rated **Low**. This rating reflects significant concerns about the reliability and comprehensiveness of the review's findings.		

Study	**AMSTAR II Q**	**Evaluation**
Song et al. (2021)	**1. Protocol Registered Before Starting the Review**	**No -** The study does not mention any pre-registration of the review protocol, which is a critical aspect to minimize bias and ensure transparency.
	2. Adequacy of the Literature Search	**Yes -** The study conducted a comprehensive search across multiple databases, including both English and Chinese sources, covering relevant keywords related to cancer-related fatigue (CRF), chemoradiotherapy, and exercise
	3. Explanation for Study Selection	**Yes -** The study clearly outlines the inclusion and exclusion criteria for selecting studies, explaining the rationale for including systematic reviews, guidelines, and evidence summaries relevant to the topic.

	4. Justification for Excluding Studies	**Yes -** The study provides reasons for excluding certain studies, such as those where less than 50% of patients were undergoing chemoradiotherapy or where CRF was not a primary focus.
	5. Risk of Bias from Individual Studies	**Unclear -** The study mentions that included systematic reviews were evaluated for quality, but it is unclear if a detailed assessment of bias was performed for each individual study within those reviews.
	6. Use of Appropriate Meta-Analytic Methods	**No -** The study does not appear to perform a meta-analysis, as it is more of a systematic review and evidence synthesis. Thus, this criterion does not apply, but if meta-analytic methods were used, they are not detailed
	7. Assessment of Heterogeneity	**Unclear -** The study does not explicitly mention the assessment of heterogeneity among the included studies, which is important for understanding the variability in the results.
	8. Quality of Evidence Assessment	**Yes -** The study uses recognized tools such as AGREE II and JBI for assessing the quality of guidelines and systematic reviews, indicating a structured approach to evaluating evidence quality.
	9. Assessment of Risk of Publication Bias	**No -** There is no mention of an assessment of publication bias, which is crucial for ensuring the validity of the synthesized evidence.
	10. Funding and Conflict of Interest Disclosures	**Yes -** The study includes a section on funding sources and declares no conflicts of interest, which enhances the credibility of the review.
	11. Discussion of Study Limitations	**Yes -** The study discusses the limitations, such as the subjective nature of CRF assessment and potential bias in the original studies, providing a balanced interpretation of the results.
	12. Inclusion of Non-English Studies	**Yes .** The literature search included non-English studies, specifically Chinesestudies, which is important for a comprehensive review in a global context.

	13. Data Extraction by Multiple Reviewers	**Yes -** The study mentions that data extraction was performed independently by multiple reviewers, which helps to reduce errors and bias.
	14. Clear Reporting of Study Characteristics	**Yes -** The study provides detailed descriptions of the included studies, including their design, population, and interventions, allowing for a clear understanding of the evidence base.
	15. Consideration of Study Design and Impact on Results	**Yes -** The study considers the design of included studies, particularly noting the prevalence of randomized controlled trials (RCTs) and their implications for evidence strength.
	16. Synthesis of Findings Without Bias	**Yes -** The synthesis appears to be conducted systematically, with evidence drawn from high-quality sources and summarized without apparent bias.
Conclusion The review is thorough in many aspects, such as the comprehensiveness of the literature search and the assessment of evidence quality. However, the lack of protocol registration, unclear bias assessment, and absence of publication bias analysis limit its strength. The study could be improved by addressing these areas to ensure greater transparency and rigor. Overall quality: Low		

Study	**AMSTAR II Q**	**Evaluation**
Fisher et al. (2022)	**1. Protocol Registered Before Starting the Review**	No - There is no mention of a registered protocol before the review. Registration is crucial for transparency and preventing selective reporting bias
	2. Adequacy of the Literature Search	Yes - The study conducted a comprehensive search across multiple databases, including PubMed, CINAHL, and Cochrane, with clear search terms and strategies. The search was updated multiple times to include recent studies

	3. Explanation for Study Selection	Yes - The study provides a clear explanation of the inclusion and exclusion criteria used to select studies. The process was rigorous, involving multiple reviewers to ensure accuracy
	4. Justification for Excluding Studies	Yes - The exclusion of studies is justified based on the criteria such as relevance to cancer-related fatigue (CRF), non-cancer populations, and studies focused on treatment rather than screening or assessment
	5. Risk of Bias from Individual Studies	Yes - The study employed standardized tools like the Scottish Intercollegiate Guideline Network (SIGN) and the Consensus-Based Standards for the Selection of Health Status Measurement Instruments (COSMIN) to assess the risk of bias, ensuring a systematic evaluation of each included study
	6. Use of Appropriate Meta-Analytic Methods	No - A meta-analysis was not conducted. Given the nature of the study, a meta-analysis could have provided a more quantitative synthesis of the evidence
	7. Assessment of Heterogeneity	Unclear - The study does not provide a detailed assessment of heterogeneity among the included studies. This is a limitation as understanding variability across studies is important for interpreting the results
	8. Quality of Evidence Assessment	Yes - The study uses the Oxford Centre for Evidence-Based Medicine levels of evidence and the APTA CPG process manual to assess the quality of evidence, providing a structured and transparent approach
	9. Assessment of Risk of Publication Bias	No - The study does not explicitly address publication bias. This is a significant omission, as publication bias can affect the validity of the findings
	10. Funding and Conflict of Interest Disclosures	Yes - The study discloses funding sources (APTA) and follows a structured guideline development process, reducing potential conflicts of interest

	11. Discussion of Study Limitations	Yes - The study discusses the limitations related to the available evidence, including the lack of responsiveness measures and the limited scope of some tools, providing a balanced view of the findings
	12. Inclusion of Non-English Studies	No - The review only included studies published in English, which introduces a language bias and limits the generalizability of the findings
	13. Data Extraction by Multiple Reviewers	Yes - Data extraction was conducted by multiple reviewers, with a third reviewer resolving any disagreements, ensuring accuracy and reducing bias
	14. Clear Reporting of Study Characteristics	Yes - The study characteristics, including the type of cancer, stage, and the specific tools used, are clearly reported, allowing for an understanding of the context in which the tools were evaluated
	15. Consideration of Study Design and Impact on Results	Yes - The study design of each included study was considered in the quality assessment, and the impact of these designs on the results was discussed
	16. Synthesis of Findings Without Bias	Yes - The synthesis of findings was thorough, with recommendations based on the strength and quality of evidence. The authors used a structured approach to derive their recommendations, reducing the potential for bias
Conclusion The study demonstrates many strengths, including a comprehensive literature search, clear reporting, and a systematic approach to evidence assessment. However, it lacks protocol registration, an explicit assessment of publication bias, and a meta-analysis, which are critical components for a high-quality review. Given these factors, the study is of low quality.		

Study	**AMSTAR II Q**	**Evaluation**
Walker et al. (2020)	**1. Protocol Registered Before Starting the Review**	No - The document does not mention a protocol registration before the review started. This omission is a significant limitation since preregistration improves transparency and helps prevent bias

	2. Adequacy of the Literature Search	Yes - The literature search is described as comprehensive, including multiple databases like CINAHL, MEDLINE, PubMed, and more. The search strategy included specific keywords, and the search continued until saturation was reached
	3. Explanation for Study Selection	Yes - The document provides clear inclusion and exclusion criteria for study selection, which are explicitly mentioned. The selection process followed these criteria strictly
	4. Justification for Excluding Studies	Yes - Exclusions were justified based on the criteria such as language (only English), availability of full text, and relevance to fatigue measurement
	5. Risk of Bias from Individual Studies	Yes - The review used the GRADE system to assess the quality of the evidence, considering factors like study limitations, consistency, and precision
	6. Use of Appropriate Meta-Analytic Methods	No - This review does not include a meta-analysis. The use of meta-analytic methods would have been appropriate to synthesize the findings quantitatively, but this was not pursued.
	7. Assessment of Heterogeneity	Unclear - While different studies were reviewed, the document does not provide an explicit assessment of heterogeneity among the included studies, which is necessary to understand the variability in study outcomes
	8. Quality of Evidence Assessment	Yes - The GRADE approach was used to assess the quality of the evidence, categorizing it as high, moderate, low, or very low based on predefined criteria
	9. Assessment of Risk of Publication Bias	No - The document does not explicitly address the risk of publication bias, which is important in systematic reviews to ensure that all relevant data, published or unpublished, are considered
	10. Funding and Conflict of Interest Disclosures	No - The review does not provide information on funding sources or potential conflicts of interest, which is a critical aspect to assess potential bias in the review process

	11. Discussion of Study Limitations	Yes - The limitations of the included studies and the review process are discussed, particularly the reliance on cross-sectional studies and the absence of a consensus on the best assessment tool for CRF
	12. Inclusion of Non-English Studies	No - The review excluded non-English studies, which could introduce language bias and limit the comprehensiveness of the review
	13. Data Extraction by Multiple Reviewers	Unclear - It is not explicitly mentioned whether multiple reviewers were involved in the data extraction process, which is important to reduce bias and ensure the accuracy of the extracted data
	14. Clear Reporting of Study Characteristics	Yes - The characteristics of the included studies are clearly reported, including the types of fatigue assessment tools used and study design details
	15. Consideration of Study Design and Impact on Results	Yes - The study design of each included study was considered in the quality assessment, particularly in how it might impact the reliability and applicability of the results
	16. Synthesis of Findings Without Bias	Yes - The findings are synthesized without a meta-analysis, with a narrative summary provided for the different tools and guidelines reviewed. The GRADE system was applied appropriately to contextualize these findings
Conclusion The study has several strengths, including a comprehensive literature search and appropriate quality assessment using the GRADE system. However, it falls short in areas such as protocol registration, addressing publication bias, and inclusion of non-English studies. The absence of meta-analysis and explicit heterogeneity assessment also limits the robustness of the review. Therefore, the study is assessed as being of low quality.		

Bilag 5 – Kvalitetsvurderinger af systematiske reviews: Interventioner

Study	AMSTAR II Q	Evaluation
Belloni et al. (2023) *A Systematic Review of Systematic Reviews and a Pooled Meta-Analysis on Complementary and Integrative Medicine for Improving Cancer-Related Fatigue*	**1. Protocol Registered Before Starting the Review**	**Yes** – The protocol was registered on PROSPERO (CRD42020194254).
	2. Adequacy of the Literature Search	**Yes** – The search was comprehensive, covering multiple databases and manual searches.
	3. Explanation for Study Selection	**Yes** – Inclusion criteria were clearly defined using the PICOS framework.
	4. Justification for Excluding Studies	**Partial** – Exclusion reasons were given, but details were less explicit.
	5. Risk of Bias from Individual Studies	**Yes** – The ROBIS tool was used to assess risk of bias in systematic reviews, though not explicitly for primary studies.
	6. Use of Appropriate Meta-Analytic Methods	**Yes** – Random effects models were used to account for heterogeneity.
	7. Assessment of Heterogeneity	**Yes** – Heterogeneity was evaluated and subgroup analyses were conducted.
	8. Quality of Evidence Assessment	**No Clear Mention** – The study does not explicitly mention the use of the GRADE approach or another framework to assess the overall quality of evidence.
	9. Assessment of Risk of Publication Bias	**No Clear Mention** – No mention of publication bias assessment is found in the provided sections.
	10. Funding and Conflict of Interest Disclosures	**No Clear Mention** – No explicit mention of funding sources or conflicts of interest in the provided sections.
	11. Discussion of Study Limitations	**Partial** – Some limitations were discussed, but a broader discussion across different studies was not provided.
	12. Inclusion of Non-English Studies	**Yes** – Studies in multiple languages were considered.
	13. Data Extraction by Multiple Reviewers	**Yes** – Two reviewers independently conducted data extraction, with disagreements resolved by consensus

	14. Clear Reporting of Study Characteristics	**Yes** – Study characteristics were reported clearly using structured methods.
	15. Consideration of Study Design and Impact on Results	**Partial** – The study could have further explored how study designs impacted results, particularly with respect to bias assessments.
	16. Synthesis of Findings Without Bias	**Yes** – The synthesis appeared robust, with statistical methods used to minimize bias.
Conclusion The systematic review by Belloni et al. meets many of the key AMSTAR II criteria, including pre-registration, explicit inclusion criteria, duplicate data extraction, and comprehensive literature searching. However, there are gaps in reporting regarding funding of included studies and the assessment of publication bias. Based on AMSTAR II, the study would rank as moderate quality but with some limitations.		

Study	**AMSTAR II Q**	**Evaluation**
Maunick et al. (2023)	**1. Protocol Registered Before Starting the Review**	**Yes -** The study protocol was registered on PROSPERO on July 12, 2022.
	2. Adequacy of the Literature Search	**Yes -** The authors conducted a comprehensive search across multiple databases (MEDLINE, EMBASE, CINAHL, PsycINFO, Cochrane Library, US National Library of Medicine Clinical Trial Register) and reference lists of relevant papers.
	3. Explanation for Study Selection	**Yes -** The review clearly explained the inclusion criteria, focusing on RCTs that implemented ACT interventions and measured fatigue in adults with chronic health conditions.
	4. Justification for Excluding Studies	**Partial -** Exclusion reasons are mentioned, but a comprehensive explanation for each excluded study is not provided.
	5. Risk of Bias from Individual Studies	**Yes -** The review used the Cochrane Risk of Bias Version 1 tool to assess the risk of bias in the included studies, with two reviewers independently assessing and a third reviewer resolving conflicts.

	6. Use of Appropriate Meta-Analytic Methods	**Yes -** The review used inverse-variance random effect models with restricted maximum likelihood estimation (REML) to calculate the standardized mean difference (SMD) for fatigue post-intervention.
	7. Assessment of Heterogeneity	**Yes -** Heterogeneity was assessed using the I^2 statistic, with values representing low, moderate, and high levels of heterogeneity.
	8. Quality of Evidence Assessment	**Yes -** The review assessed the quality of evidence, considering the risk of bias in the included studies.
	9. Assessment of Risk of Publication Bias	**Yes -** Publication bias was tested using Kendall's Tau for funnel plot asymmetry, Egger's regression test for funnel plot asymmetry, and Rosenthal's Failsafe N.
	10. Funding and Conflict of Interest Disclosures	**Yes -** The review reported that there were no conflicts of interest.
	11. Discussion of Study Limitations	**Yes -** The review discussed the limitations of the included studies and the review itself
	12. Inclusion of Non-English Studies	**Not explicitly stated -** The review does not mention whether non-English studies were included or excluded.
	13. Data Extraction by Multiple Reviewers	**Yes -** Data extraction was performed by two authors, with discrepancies reviewed by a third independent reviewer.
	14. Clear Reporting of Study Characteristics	**Yes -** The review provides details about the included studies, such as the number of participants, interventions, and outcomes measured.
	15. Consideration of Study Design and Impact on Results	**Yes -** The review considered the design of the included studies and their impact on the results.
	16. Synthesis of Findings Without Bias	**Yes -** The review synthesized the findings appropriately, considering the risk of bias and heterogeneity.
Conclusion Overall, the review meets many of the AMSTAR II criteria but lacks explicit statements on some aspects such as list of excluded studies and inclusion of non-English studies. However, these are not considered of high importance while this review is ranked as high quality.		

Study	AMSTAR II Q	Evaluation
Batalik et al. (2023)	**1. Protocol Registered Before Starting the Review**	**Yes** - The review protocol was registered in PROSPERO (CRD42023395521), fulfilling this criterion.
	2. Adequacy of the Literature Search	**Partial -** The study conducted a comprehensive literature search in PubMed and Web of Science up to March 2023. However, there is no mention of the search being conducted in additional databases like Cochrane or Embase, potentially limiting the comprehensiveness.
	3. Explanation for Study Selection	**Yes -** The authors clearly outlined their selection criteria using the PICOS framework, detailing population, intervention, comparison, outcomes, and study design.
	4. Justification for Excluding Studies	**Yes -** The authors provided clear criteria for excluding studies, including quasi-experimental studies, conference abstracts, and articles unavailable after contacting authors.
	5. Risk of Bias from Individual Studies	**Yes -** The authors used the Cochrane Risk of Bias Tool 2.0 to assess the risk of bias in included studies, addressing multiple bias domains, though some concerns remained regarding randomization and selective reporting.
	6. Use of Appropriate Meta-Analytic Methods	**Yes -** Meta-analytic methods were appropriate, using tools like Review Manager 5.3 for data pooling and conducting sensitivity analyses to handle heterogeneity.
	7. Assessment of Heterogeneity	**Yes -** The study assessed heterogeneity using I^2 and τ^2 statistics. For example, cardiorespiratory fitness showed moderate heterogeneity (I^2 = 42%).
	8. Quality of Evidence Assessment	**No -** While the review assessed quality using various statistical measures, it did not employ a formal quality assessment tool like GRADE, which would be needed to fully meet this criterion.

	9. Assessment of Risk of Publication Bias	**Yes -** The study conducted funnel plot analysis to evaluate the risk of publication bias, which was reported as low.
	10. Funding and Conflict of Interest Disclosures	**Yes -** The funding source was disclosed (Ministry of Health of the Czech Republic), and the authors declared no competing interests.
	11. Discussion of Study Limitations	**Yes -** The review discusses several limitations, including language bias, small sample sizes in some studies, and heterogeneity in telehealth interventions.
	12. Inclusion of Non-English Studies	**No -** The review was limited to studies published in English, which introduces language bias.
	13. Data Extraction by Multiple Reviewers	**Yes -** Data extraction was performed independently by two reviewers, with disagreements resolved by a third reviewer.
	14. Clear Reporting of Study Characteristics	**Yes -** The review clearly reported study characteristics, including sample size, intervention types, and outcomes.
	15. Consideration of Study Design and Impact on Results	**Yes -** The review focused exclusively on RCTs, ensuring a high level of study design consideration.
	16. Synthesis of Findings Without Bias	**Unclear -** While the synthesis of findings was thorough, there were some concerns about study heterogeneity and the lack of reporting on adverse events in some studies.
Conclusion The review meets most of the criteria, but limitations such as language bias and the absence of a formal quality assessment tool like GRADE slightly reduce its overall quality. Overall ranking: Moderate		

Study	**AMSTAR II Q**	**Evaluation**
Garcia-Munuz et al. (2023)	**1. Protocol Registered Before Starting the Review**	**Yes**: The study protocol was registered on the Open Science Framework before the review started

	2. Adequacy of the Literature Search	**Yes**: The study conducted a comprehensive search across multiple databases (CINAHL, Embase, PubMed, SPORTDiscus) without language or document type restrictions
	3. Explanation for Study Selection	**Yes**: The study clearly explained the criteria for selecting studies based on the PICOS framework
	4. Justification for Excluding Studies	**Unclear**: Although the study mentions excluding non-English and non-Spanish studies, there is no detailed explanation for the specific studies excluded during the review process
	5. Risk of Bias from Individual Studies	**Yes**: The study used the Cochrane Risk of Bias Tool version 2 to assess the risk of bias in individual studie
	6. Use of Appropriate Meta-Analytic Methods	**Yes**: Meta-analysis was conducted using appropriate methods with random-effects models and various sensitivity analyses
	7. Assessment of Heterogeneity	**Yes**: Heterogeneity was assessed using I-square, Tau-square, and Q-test. The study also used prediction intervals and meta-regressions to explore sources of heterogeneity
	8. Quality of Evidence Assessment	**Yes**: The GRADE approach was used to assess the quality of evidence, categorizing it from low to very low for different outcomes
	9. Assessment of Risk of Publication Bias	**Yes**: Egger's test and funnel plot symmetry were used to assess publication bias
	10. Funding and Conflict of Interest Disclosures	**Yes**: Funding sources and potential conflicts of interest were disclosed
	11. Discussion of Study Limitations	**Yes**: The study discusses its limitations, including the high risk of bias in several included studies and weaknesses in reporting
	12. Inclusion of Non-English Studies	**No**: The study explicitly excluded non-English and non-Spanish studies, which may introduce language bias
	13. Data Extraction by Multiple Reviewers	**Unclear**: It is not explicitly stated whether data extraction was conducted by multiple independent reviewers.
	14. Clear Reporting of Study Characteristics	**Yes**: Study characteristics are clearly reported in a comprehensive table

	15. Consideration of Study Design and Impact on Results	**Yes**: The study differentiates between RCTs and feasibility/pilot RCTs, and this is factored into their analysis
	16. Synthesis of Findings Without Bias	**Yes**: The study used meta-regression and sensitivity analysis to ensure unbiased synthesis of findings
Conclusion The study meets most of the AMSTAR 11 criteria but has some unclear elements, particularly regarding justification for excluding studies and whether data extraction was conducted by multiple reviewers. The review ranking a moderate quality.		

Study	**AMSTAR II Q**	**Evaluation**
Lin et al. (2024)	**1. Protocol Registered Before Starting the Review**	**Yes**: The study protocol was registered with PROSPERO (CRD42022321471) before conducting the review
	2. Adequacy of the Literature Search	**Yes**: The study conducted a comprehensive literature search across multiple databases, including both English and Chinese-language databases, up to May 1, 2023
	3. Explanation for Study Selection	**Yes**: The inclusion and exclusion criteria were clearly defined according to the PICOS framework, and the selection process was well-documented
	4. Justification for Excluding Studies	**Yes**: The study provided clear reasons for excluding studies, such as non-experimental study designs or the combination of art-making with other psychological interventions
	5. Risk of Bias from Individual Studies	**Yes**: The risk of bias was assessed using the Cochrane Risk of Bias Tool (RoB 2.0) for RCTs and the ROBINS-I tool for quasi-experimental studies. However, many studies were judged to have a moderate level of bias

	6. Use of Appropriate Meta-Analytic Methods	**Yes**: Meta-analysis was conducted using appropriate statistical methods, including the use of standardized mean differences (SMD) and the application of random-effects models where appropriate
	7. Assessment of Heterogeneity	**Yes**: Heterogeneity was assessed using the I^2 statistic and χ^2 test. The study also explored sources of heterogeneity through subgroup analyses
	8. Quality of Evidence Assessment	**Yes**: The study used the GRADE approach to assess the quality of evidence, which was rated as low to very low due to high heterogeneity and methodological limitations in the included studies
	9. Assessment of Risk of Publication Bias	**Yes**: The study evaluated publication bias using funnel plots and Egger's tests to assess for asymmetry and potential bias
	10. Funding and Conflict of Interest Disclosures	**Yes**: Funding sources and potential conflicts of interest were disclosed, and there was a clear statement regarding the absence of any conflicts
	11. Discussion of Study Limitations	**Yes**: The study discussed its limitations, including the high risk of bias in several studies and the heterogeneity of the interventions and outcomes measured
	12. Inclusion of Non-English Studies	**Yes**: The review included non-English studies, specifically from Chinese-language databases, which strengthens its comprehensiveness
	13. Data Extraction by Multiple Reviewers	**Yes**: Data extraction was performed by one reviewer and verified by a second reviewer for 50% of the studies, with discrepancies resolved by a third reviewer
	14. Clear Reporting of Study Characteristics	**Yes**: Study characteristics were clearly reported in detailed tables, including participant demographics, intervention types, and study settings
	15. Consideration of Study Design and Impact on Results	**Yes**: The study considered the design of the included studies and how factors like the type and duration of art-making interventions might impact the results

	16. Synthesis of Findings Without Bias	**Yes**: The findings were synthesized without bias, with efforts made to address potential biases through subgroup and sensitivity analyses
Conclusion This systematic review and meta-analysis were conducted with high methodological rigor, meeting all AMSTAR 11 criteria. The quality of the underlying evidence was low, but the review process itself was thorough, transparent, and well-executed, justifying a high-quality ranking.		

Study	**AMSTAR II Q**	**Evaluation**
Correa-Morales et al. (2024)	**1. Protocol Registered Before Starting the Review**	**Yes -** The study mentions that the systematic review protocol was registered in PROSPERO (CRD42022349833).
	2. Adequacy of the Literature Search	**Yes -** The authors conducted searches in three databases: PubMed, EMBASE, and Medline. While they limited the search to these databases and included only English-language studies, the search seems adequate given the scope.
	3. Explanation for Study Selection	**Yes -** The study selection process is clearly outlined, with criteria specified for inclusion and exclusion, and the PRISMA diagram is provided to show the flow of studies through the review process.
	4. Justification for Excluding Studies	**Yes -** The reasons for excluding studies are mentioned, particularly the exclusion of gray literature, editorials, commentaries, and small case series.
	5. Risk of Bias from Individual Studies	**Yes -** The risk of bias in individual studies was assessed using the Cochrane Risk of Bias Tool for randomized trials, the Newcastle-Ottawa Scale for non-randomized studies, and Murad et al.'s tool for case series.
	6. Use of Appropriate Meta-Analytic Methods	**No -** A meta-analysis was not performed, even though it might have been possible for some outcomes. The authors justified this by citing the

		heterogeneity of the scales used, which is a valid concern but does limit the statistical synthesis of data.
	7. Assessment of Heterogeneity	**Unclear -** While the study discusses heterogeneity qualitatively, it does not employ statistical methods (such as I^2) to assess heterogeneity formally, which leaves this aspect somewhat unclear.
	8. Quality of Evidence Assessment	**Yes -** The quality of the included studies was assessed, with details provided about the methodological quality and risk of bias.
	9. Assessment of Risk of Publication Bias	**No -** The study does not mention any formal assessment of publication bias, such as using a funnel plot or Egger's test.
	10. Funding and Conflict of Interest Disclosures	**Yes -** The study clearly states that the authors have no conflict of interest and that no specific funding was received for the research.
	11. Discussion of Study Limitations	**Yes -** The study limitations are discussed, including the exclusion of gray literature, the small number of high-quality studies, and the short follow-up periods in included studies.
	12. Inclusion of Non-English Studies	**No -** The review was limited to English-language studies, which could lead to language bias.
	13. Data Extraction by Multiple Reviewers	**Yes -** Data extraction was performed by two independent reviewers, and any disagreements were resolved by discussion or third-party adjudication.
	14. Clear Reporting of Study Characteristics	**Yes -** The characteristics of the included studies are clearly reported in tables, detailing the population, scale, outcomes, and duration.
	15. Consideration of Study Design and Impact on Results	**Yes -** The study acknowledges the varying designs of the included studies (randomized, non-randomized, and case series) and discusses how these designs impact the robustness of the findings.
	16. Synthesis of Findings Without Bias	**Yes -** The findings are synthesized in a balanced way, with the authors acknowledging the limitations of the evidence and the need for further research.
Conclusion		

Based on the AMSTAR II criteria, this systematic review is of **moderate quality**. The strengths lie in the registration of the protocol, comprehensive search strategy, risk of bias assessment, and clear reporting. However, the review could be improved by including non-English studies, formally assessing heterogeneity and publication bias, and attempting a meta-analysis where appropriate.

Study	AMSTAR II Q	Evaluation
Belloni et al. (2024) *A Systematic Review of Systematic Reviews and Pooled Meta-Analysis on Psychosocial Interventions for Improving Cancer-Related Fatigue*	**1. Protocol Registered Before Starting the Review**	**Yes -** The study protocol was registered on PROSPERO (CRD42020194254), as mentioned in the article
	2. Adequacy of the Literature Search	**Yes -** The authors conducted a thorough search in PubMed, CINAHL, Cochrane Database of Systematic Reviews, PEDro, and PsycINFO from 2010 to 2022, and they applied the search strategy to multiple databases with no language restrictions
	3. Explanation for Study Selection	**Yes -** The study selection process is clearly described, including the use of the PRISMA flowchart to detail how studies were identified, screened, and selected
	4. Justification for Excluding Studies	**Yes -** The authors provided clear reasons for excluding studies, particularly focusing on the exclusion of systematic reviews that lacked a quantitative synthesis or contained only one effect size from a single study
	5. Risk of Bias from Individual Studies	**Yes -** The study used the ROBIS tool to assess the risk of bias in the included systematic reviews. Most reviews were rated as low risk, with only a few having unclear or high risk
	6. Use of Appropriate Meta-Analytic Methods	**Yes -** The meta-analytic methods were appropriate, with the use of random-effects models and the assessment of heterogeneity using I^2

		and Cochran's Q tests. They also controlled for overlapping studies to avoid overestimation of effects
	7. Assessment of Heterogeneity	**Yes -** e study assessed heterogeneity through the I^2 statistic and Cochran's Q test, reporting these results appropriately. High heterogeneity was acknowledged in certain analyses
	8. Quality of Evidence Assessment	**Yes -** The authors assessed the quality of the included systematic reviews using the ROBIS tool and discussed the implications of bias and the quality of evidence in their findings
	9. Assessment of Risk of Publication Bias	**No -** There was no mention of a formal assessment of publication bias, such as a funnel plot or statistical tests, in the study
	10. Funding and Conflict of Interest Disclosures	**Yes -** The study clearly disclosed that there were no conflicts of interest and did not receive specific funding
	11. Discussion of Study Limitations	**Yes -** The limitations of the study were discussed, including the high heterogeneity of interventions, variations in timepoints of assessments, and the small number of studies for certain analyses
	12. Inclusion of Non-English Studies	**Yes -** The study did not restrict the search by language, which increases the comprehensiveness of the review
	13. Data Extraction by Multiple Reviewers	**Yes -** Data extraction was performed by two independent reviewers, with disagreements resolved through consensus, ensuring reliability in the process
	14. Clear Reporting of Study Characteristics	**Yes -** the characteristics of the included studies are clearly reported, with detailed tables summarizing the interventions, populations, outcomes, and results
	15. Consideration of Study Design and Impact on Results	**Yes -** The study considered the designs of the included systematic reviews and discussed how these might influence the overall findings, particularly in relation to heterogeneity and the robustness of evidence
	16. Synthesis of Findings Without Bias	**Yes -** The synthesis of findings appears to be conducted without bias, with careful attention to the inclusion criteria, risk of bias assessment, and appropriate statistical methods for meta-analysis

Conclusion
Based on the AMSTAR II criteria, this systematic review is of **high quality.** It demonstrates a strong adherence to systematic review best practices, including protocol registration, comprehensive literature search, detailed risk of bias assessment, and appropriate meta-analytic methods. The primary limitation is the lack of formal assessment of publication bias, but this does not significantly detract from the overall quality of the review.

Study	**AMSTAR II Q**	**Evaluation**
Fan et al. (2024)	**1. Protocol Registered Before Starting the Review**	**Unclear -** There is no mention of a registered protocol for this systematic review, which makes it unclear whether the protocol was registered before the study began.
	2. Adequacy of the Literature Search	**Yes -** The authors conducted a comprehensive search across five databases (PubMed, Cochrane Library, Web of Science, CINAHL, and Elsevier). The search strategy seems thorough, covering a wide range of keywords and not being restricted by language, which is considered adequate.
	3. Explanation for Study Selection	**Yes -** The study provides a clear explanation of the selection process, including inclusion and exclusion criteria, and this process is illustrated using a PRISMA flow diagram.
	4. Justification for Excluding Studies	**Yes -** The reasons for excluding studies are provided, including the exclusion of studies that were not randomized controlled trials or did not meet the specific intervention criteria.
	5. Risk of Bias from Individual Studies	**Yes -** The risk of bias in the included studies was assessed using the Cochrane risk of bias tool, and the results are presented in a risk of bias summary figure.

	6. Use of Appropriate Meta-Analytic Methods	**Yes -** Meta-analytic methods were appropriately used, including the use of standardized mean differences (SMD) for effect size calculation and the use of random-effects models to account for heterogeneity. Sensitivity analyses and subgroup analyses were also conducted.
	7. Assessment of Heterogeneity	**Yes -** Heterogeneity was assessed using the I^2 statistic and Cochran's Q test. High levels of heterogeneity were acknowledged, and the study employed appropriate statistical methods to deal with it.
	8. Quality of Evidence Assessment	**No -** The study does not provide a formal assessment of the overall quality of evidence using tools like GRADE. This limits the ability to evaluate the strength of the evidence presented.
	9. Assessment of Risk of Publication Bias	**No -** Although the authors attempted to assess publication bias using funnel plots, they reported that this was not possible due to the small number of included studies. This means that publication bias was not formally assessed.
	10. Funding and Conflict of Interest Disclosures	**Yes -** The study clearly states that there were no conflicts of interest and no specific funding was received.
	11. Discussion of Study Limitations	**Yes -** The limitations of the study are discussed, including the high heterogeneity, differences in intervention content, duration, and delivery methods among included studies.
	12. Inclusion of Non-English Studies	**Yes -** The study did not restrict the search by language, which increases its comprehensiveness.
	13. Data Extraction by Multiple Reviewers	**Yes -** Data extraction was performed by two independent reviewers, and any discrepancies were resolved by discussion or a third reviewer, ensuring the reliability of the process.
	14. Clear Reporting of Study Characteristics	**Yes -** The study characteristics are clearly reported in tables, including information on the population, intervention, comparison groups, and outcomes.

	15. Consideration of Study Design and Impact on Results	**Yes -** The study design of the included studies was considered, and the authors discussed how variations in design might impact the results, especially in relation to heterogeneity.
	16. Synthesis of Findings Without Bias	**Yes -** The findings are synthesized in a balanced way, and the authors acknowledge the limitations and strengths of the evidence presented.
Conclusion Based on the AMSTAR II criteria, this systematic review is of **moderate quality.** While the study demonstrates strong methodology in terms of literature search, study selection, risk of bias assessment, and meta-analytic methods, it lacks a formal assessment of the quality of evidence (e.g., using GRADE) and does not adequately address publication bias. The absence of a registered protocol also detracts from its overall rigor.		

Study	**AMSTAR II Q**	**Evaluation**
Li et al. (2022)	**1. Protocol Registered Before Starting the Review**	Yes - The study mentions that it was registered with PROSPERO (CRD42022319731) before the review started, meeting the criterion for a pre-registered protocol
	2. Adequacy of the Literature Search	Yes - The literature search appears adequate, as it was conducted across multiple databases (PubMed, Embase, and Web of Science) and included supplementary hand searches of references from relevant reviews
	3. Explanation for Study Selection	Yes - The study provides clear inclusion and exclusion criteria, with explanations for selecting studies focused on randomized controlled trials involving exercise interventions in digestive system cancer patients
	4. Justification for Excluding Studies	Yes - The review explains why certain studies were excluded, such as those focusing on non-DSC cancers or those not reporting the relevant outcomes
	5. Risk of Bias from Individual Studies	Yes - The study assessed the risk of bias using the Cochrane risk-of-bias tool (RoB 2), which is a well-established method. However, the

		overall risk of bias was high in 28.13% of included studies, mostly due to issues with randomization and deviations from intended interventions
	6. Use of Appropriate Meta-Analytic Methods	Yes - The study uses a network meta-analysis with appropriate statistical methods, including random effects models to account for heterogeneity, and employs SUCRA values to rank the effectiveness of different exercise interventions
	7. Assessment of Heterogeneity	Yes - Heterogeneity was assessed using I^2 statistics, and the study acknowledges high heterogeneity in many comparisons, which is appropriately managed using random effects models
	8. Quality of Evidence Assessment	Yes - The study evaluated the quality of evidence through a structured risk-of-bias assessment (RoB 2), although it could benefit from a more explicit discussion of evidence quality across different outcomes
	9. Assessment of Risk of Publication Bias	Yes - Publication bias was assessed using Egger's test, which is appropriate for this type of analysis
	10. Funding and Conflict of Interest Disclosures	Yes - The study clearly discloses its funding sources and states that there are no competing interests, which adds to the transparency of the review
	11. Discussion of Study Limitations	Yes - The study thoroughly discusses its limitations, including the diversity of assessment tools used and the lack of studies focused solely on resistance exercise, which may affect the generalizability of results
	12. Inclusion of Non-English Studies	No - The review excluded studies not published in English, potentially introducing language bias
	13. Data Extraction by Multiple Reviewers	Yes - Data extraction was conducted independently by two reviewers, with discrepancies resolved by consensus, which is good practice for reducing bias
	14. Clear Reporting of Study Characteristics	Yes - The study provides detailed tables of the included studies, including information on participants, interventions, and outcomes, which are essential for transparency

	15. Consideration of Study Design and Impact on Results	Yes - The study considers the impact of different study designs on the results, discussing how variations in exercise types and durations may influence outcomes
	16. Synthesis of Findings Without Bias	Yes - The synthesis of findings appears balanced, with both positive and negative results being discussed. The network meta-analysis allows for the comparison of multiple interventions, and the study acknowledges the potential for bias in interpreting these results due to high heterogeneity
Conclusion Based on the AMSTAR II criteria, this systematic review and network meta-analysis can be classified as high quality. The review meets the majority of AMSTAR II criteria, with only minor issues related to the exclusion of non-English studies and the inherent challenges of high heterogeneity in the included studies. The methodology is rigorous, and the findings are presented transparently, making this a robust contribution to the literature on exercise interventions for digestive system cancers.		

Study	**AMSTAR II Q**	**Evaluation**
Anemoulis et al. (2023)	**1. Protocol Registered Before Starting the Review**	No - The study mentions that a review protocol was developed but not registered. This is a significant omission, as protocol registration is crucial for minimizing bias and enhancing transparency
	2. Adequacy of the Literature Search	Yes - The literature search was comprehensive, covering multiple databases including PubMed, CINAHL, Cochrane, Web of Science, and Scopus. The search terms were well-defined, targeting both intermittent fasting and breast cancer
	3. Explanation for Study Selection	Yes - The study provides a clear explanation of the inclusion and exclusion criteria for selecting studies. It included studies focused on intermittent fasting in breast cancer patients and provided sufficient data on relevant outcomes

	4. Justification for Excluding Studies	Yes - The study lists reasons for excluding certain studies, such as not being published in English, being non-human studies, or lacking relevant outcomes
	5. Risk of Bias from Individual Studies	Yes - The study assessed the risk of bias using the Mixed Methods Appraisal Tool (MMAT), which is appropriate for the diverse study designs included in the review. However, the discussion of how these biases impacted the findings is limited
	6. Use of Appropriate Meta-Analytic Methods	No - A meta-analysis was not conducted due to the heterogeneity of the included studies. While this is understandable, the absence of any quantitative synthesis limits the strength of the conclusions drawn
	7. Assessment of Heterogeneity	No - Heterogeneity was acknowledged but not quantitatively assessed. Given the diverse study designs and outcomes, a more detailed discussion or formal assessment of heterogeneity would have been beneficial
	8. Quality of Evidence Assessment	Unclear - The study mentions the use of the MMAT for quality assessment, but there is limited discussion on the overall quality of evidence across the included studies. A more explicit evaluation using a framework like GRADE would have provided clearer insights
	9. Assessment of Risk of Publication Bias	No - The study does not mention any assessment of publication bias, which is a notable omission given the potential for selective reporting in this field
	10. Funding and Conflict of Interest Disclosures	Yes - The study clearly states that it received no external funding and that there are no conflicts of interest, which enhances the credibility of the review【
	11. Discussion of Study Limitations	Yes - The study discusses several limitations, including the heterogeneity of fasting regimens, the small sample sizes, and the lack of control groups in many studies. These are important considerations that affect the generalizability of the findings

	12. Inclusion of Non-English Studies	No - The review excluded non-English studies, which could introduce language bias and limit the comprehensiveness of the review
	13. Data Extraction by Multiple Reviewers	Yes - Data extraction was performed independently by multiple reviewers, with discrepancies resolved by consensus. This is good practice to reduce the risk of bias during the data extraction process
	14. Clear Reporting of Study Characteristics	Yes - The study provides detailed tables summarizing the characteristics of the included studies, including sample sizes, fasting regimens, and outcomes
	15. Consideration of Study Design and Impact on Results	Yes - The study considers the impact of different study designs on the results, acknowledging that the heterogeneity of designs complicates the interpretation of findings
	16. Synthesis of Findings Without Bias	Yes - The synthesis appears balanced, with both positive and negative outcomes being reported. The authors are cautious in their conclusions, acknowledging the limitations of the available evidence
Conclusion Based on the AMSTAR II criteria, this systematic review is of low quality. While the literature search, study selection, and reporting are strong, the lack of a registered protocol, absence of meta-analytic methods, insufficient heterogeneity assessment, and failure to evaluate publication bias are significant weaknesses. These issues suggest that the findings should be interpreted with caution.		

Study	**AMSTAR II Q**	**Evaluation**
Andersen et al. (2023)	**1. Protocol Registered Before Starting the Review**	Yes - The review mentions that an outline was registered with PROSPERO before the review started, which is the gold standard for systematic reviews.
	2. Adequacy of the Literature Search	Yes - The literature search was comprehensive, covering multiple databases such as PubMed, CINAHL, Embase, and others. The search strategy included relevant MeSH terms and keywords.

	3. Explanation for Study Selection	Yes - The criteria for including and excluding studies are clearly stated, focusing on interventions targeting coping skills in adults with hematologic malignancies and measuring fatigue as an outcome.
	4. Justification for Excluding Studies	Yes - The review provides reasons for excluding studies, such as not meeting the inclusion criteria (e.g., qualitative studies, observational research, and studies at the protocol stage).
	5. Risk of Bias from Individual Studies	Unclear - The review uses the Johns Hopkins Nursing Evidence-Based Practice Appraisal tool for quality assessment, but it does not thoroughly discuss how bias was assessed in individual studies.
	6. Use of Appropriate Meta-Analytic Methods	No - A meta-analysis was not performed due to the heterogeneity of the included studies, which is mentioned in the review. Instead, a narrative synthesis was used.
	7. Assessment of Heterogeneity	Yes - the review acknowledges the heterogeneity in study designs and methodologies, which justified the use of narrative synthesis over a meta-analysis.
	8. Quality of Evidence Assessment	Yes - The quality of the studies was assessed using the Johns Hopkins Nursing Evidence-Based Practice Appraisal tool, which provides a structured way to evaluate evidence quality.
	9. Assessment of Risk of Publication Bias	Unclear - The review does not explicitly mention whether or how publication bias was assessed, leaving this criterion unclear.
	10. Funding and Conflict of Interest Disclosures	No - There is no clear statement about the funding sources or conflicts of interest for the review itself, which is important for transparency.
	11. Discussion of Study Limitations	Yes - The review discusses limitations, including the heterogeneity of studies, small sample sizes, and varying study designs.
	12. Inclusion of Non-English Studies	No - The review only included studies published in English, potentially introducing language bias.
	13. Data Extraction by Multiple Reviewers	Yes - The review mentions that two authors independently assessed the articles for inclusion and quality, which reduces the risk of bias.

	14. Clear Reporting of Study Characteristics	Yes - The review mentions that two authors independently assessed the articles for inclusion and quality, which reduces the risk of bias.
	15. Consideration of Study Design and Impact on Results	Yes - The review differentiates between randomized controlled trials, quasi-experimental designs, and other study types, reflecting on how these designs impact the reliability of results.
	16. Synthesis of Findings Without Bias	Yes - The synthesis appears balanced, discussing both significant and non-significant findings across the included studies.
Conclusion Based on the AMSTAR II criteria, this systematic review can be classified as low/moderate quality. While the review has many strengths, such as a comprehensive literature search and clear reporting of study characteristics, some weaknesses exist, particularly in the areas of publication bias assessment, funding disclosures, and the exclusion of non-English studies.		

Study	**AMSTAR II Q**	**Evaluation**
Belloni et al. (2023) *Non-pharmacologic interventions for improving cancer-related fatigue (CRF): A systematic review of systematic reviews and pooled meta-analysis*	**1. Protocol Registered Before Starting the Review**	**Yes -** The study mentions that the review protocol was registered on PROSPERO (ID CRD42020194258), which is in line with good practice for systematic reviews
	2. Adequacy of the Literature Search	**Yes -** The literature search was conducted across multiple databases (e.g., PubMed, CINAHL, Cochrane Database of Systematic Reviews), which suggests a comprehensive search strategy. The use of specific filters and the re-run of the search before final analysis further strengthens this criterion
	3. Explanation for Study Selection	**Yes -** The study provides a clear description of the study selection process, using the PRISMA flowchart to outline the steps from initial search to final inclusion
	4. Justification for Excluding Studies	**Yes -** Reasons for excluding studies are documented, particularly focusing on studies that did not meet the eligibility criteria, such as those without control groups or with low methodological quality

	5. Risk of Bias from Individual Studies	**Yes** - The study used the ROBIS tool to assess the risk of bias in included systematic reviews, addressing concerns in areas such as study eligibility criteria, study appraisal, and data collection
	6. Use of Appropriate Meta-Analytic Methods	**Yes -** the study employed a meta-analysis of meta-analyses approach using a random-effects model, which is appropriate given the expected heterogeneity across studies. Heterogeneity was assessed using I^2 and Q statistics
	7. Assessment of Heterogeneity	**Yes -** Heterogeneity was rigorously assessed, with I^2 values provided for the overall analysis and subgroup analyses, indicating a thorough examination of variability among studies
	8. Quality of Evidence Assessment	**Yes -** The quality of evidence was evaluated using the ROBIS tool, and only studies with a low risk of bias were included in the final analysis, ensuring the robustness of the conclusions drawn
	9. Assessment of Risk of Publication Bias	**Yes -** The study explored publication bias using funnel plots and the Egger test for small-study effects, although it acknowledges the limitation due to a small number of studies in some analyses
	10. Funding and Conflict of Interest Disclosures	**Yes -** The study declares that it did not receive any specific funding and that there were no conflicts of interest, providing transparency in potential biases
	11. Discussion of Study Limitations	**Yes -** The study acknowledges several limitations, including high heterogeneity, variability in patient characteristics, and the descriptive nature of the meta-analysis of meta-analyses, which may affect the generalizability of the findings
	12. Inclusion of Non-English Studies	**No -** The review was limited to English-language publications, which could introduce language bias and potentially overlook relevant studies published in other languages
	13. Data Extraction by Multiple Reviewers	**Yes -** Data extraction was performed independently by two reviewers, with disagreements resolved through discussion or the involvement of a third reviewer, ensuring accuracy and reducing bias

	14. Clear Reporting of Study Characteristics	**Yes -** The study provides detailed characteristics of the included systematic reviews, including the number of studies, type of interventions, and outcomes measured, allowing for transparency and reproducibility
	15. Consideration of Study Design and Impact on Results	**Yes -** The study design was considered in the analysis, with appropriate subgroup analyses conducted to explore the impact of different types of interventions on outcomes
	16. Synthesis of Findings Without Bias	**Yes -** The synthesis of findings was conducted in a manner that aimed to minimize bias, with clear justification for the inclusion and exclusion of studies, and appropriate methods used to pool the data
Conclusion The study meets most of the AMSTAR II criteria, with a comprehensive and methodologically sound approach. The only notable limitation is the exclusion of non-English studies, which slightly affects the comprehensiveness of the literature search. Despite this, the overall quality of the review is assessed as high, as it provides a reliable and thorough synthesis of evidence on non-pharmacologic interventions for cancer-related fatigue.		

Study	**AMSTAR II Q**	**Evaluation**
Dong et al. (2023)	**1. Protocol Registered Before Starting the Review**	Yes - The study was registered in PROSPERO with the registration number CRD42022335764. This indicates that a protocol was established before the review commenced.
	2. Adequacy of the Literature Search	Yes - The study conducted an extensive literature search across seven electronic databases without language restrictions. This comprehensive search strategy suggests adequacy.
	3. Explanation for Study Selection	Yes - The study provides a clear explanation for study selection, including criteria for inclusion and exclusion based on the type of cancer, treatment stages, and interventions.

	4. Justification for Excluding Studies	Yes - The study includes a flowchart (FIGURE 1) showing the number of studies excluded and the reasons for exclusion, such as inability to extract data or inconsistent interventions.
	5. Risk of Bias from Individual Studies	Yes - The study used the Cochrane Risk-of-Bias tool to assess individual studies across several domains. However, several trials had unclear risks due to insufficient reporting on allocation concealment and other biases.
	6. Use of Appropriate Meta-Analytic Methods	Yes - The study uses both traditional pairwise meta-analysis and network meta-analysis (NMA), following PRISMA-NMA guidelines, which are appropriate for the research question.
	7. Assessment of Heterogeneity	Yes - The study assessed heterogeneity using I^2 statistics, confidence intervals, and p-values, indicating moderate to high heterogeneity in some analyses, which is appropriately reported.
	8. Quality of Evidence Assessment	Yes - The study used the GRADE approach to assess the certainty of the evidence. However, the certainty was rated as very low due to risks of bias, inconsistency, and imprecision.
	9. Assessment of Risk of Publication Bias	Yes - the study assessed publication bias using funnel plots and acknowledged the presence of bias due to asymmetrical plots. However, it was unclear whether this was due to publication bias or small-study effects.
	10. Funding and Conflict of Interest Disclosures	Yes - The study disclosed funding sources (National Natural Science Foundation of China) and stated that the authors had no financial conflicts of interest.
	11. Discussion of Study Limitations	Yes - The study discusses several limitations, including the small number of studies in some subgroups, potential publication bias, and the lack of direct comparisons between some interventions.
	12. Inclusion of Non-English Studies	Yes - The study did not restrict its search by language, implying that non-English studies were considered if they met inclusion criteria.

	13. Data Extraction by Multiple Reviewers	Yes - Data extraction was conducted independently by two reviewers, with discrepancies resolved by a third reviewer, indicating a robust process.
	14. Clear Reporting of Study Characteristics	Yes - The study provides detailed tables and descriptions of the included studies, including participant characteristics, intervention details, and outcomes.
	15. Consideration of Study Design and Impact on Results	Yes - The study considered study design impacts, especially in the context of risk of bias and heterogeneity, and accounted for these factors in the meta-analyses.
	16. Synthesis of Findings Without Bias	Yes - The synthesis appears systematic, and efforts were made to avoid bias in interpreting the results, although the presence of potential publication bias is acknowledged.
Conclusion Based on the AMSTAR II criteria, the study fulfills most requirements, with minor concerns related to potential bias. Thus, the study is of high quality.		

Study	**AMSTAR II Q**	**Evaluation**
Wang et al. (2023)	**1. Protocol Registered Before Starting the Review**	Yes - The study was registered with PROSPERO (CRD42022344923), indicating that a protocol was established before conducting the review
	2. Adequacy of the Literature Search	Yes - The literature search was thorough, covering multiple databases (PubMed, Cochrane, Web of Science, Scopus, ScienceDirect) up to January 2023. The search strategy is detailed, with MeSH terms specified
	3. Explanation for Study Selection	Yes - The study provides a clear explanation of the inclusion and exclusion criteria, focusing on randomized controlled trials (RCTs) involving HIIT and combined HIIT programs for cancer-related fatigue (CRF) and pain

	4. Justification for Excluding Studies	Yes - The study provides reasons for excluding certain studies, such as lack of relevant outcomes or non-comparable interventions. The PRISMA flowchart details the exclusion process
	5. Risk of Bias from Individual Studies	Yes - The study used the Cochrane Risk of Bias tool, assessing domains such as random sequence generation, allocation concealment, and blinding. However, some studies lacked adequate blinding, which introduces potential bias
	6. Use of Appropriate Meta-Analytic Methods	Yes - The study utilized appropriate meta-analytic methods, including the use of random-effects models to account for heterogeneity. Subgroup analyses were also conducted
	7. Assessment of Heterogeneity	Yes - Heterogeneity was assessed using the I^2 statistic. Moderate heterogeneity was observed for CRF, and a fixed-effects model was used for pain, reflecting appropriate methodological choices
	8. Quality of Evidence Assessment	No - While the study discusses the impact of the interventions, it does not explicitly mention the use of a formal evidence grading system like GRADE to assess the quality of evidence.
	9. Assessment of Risk of Publication Bias	Yes - Publication bias was assessed using Egger's regression test, and funnel plots were created for both CRF and pain, with no significant bias detected
	10. Funding and Conflict of Interest Disclosures	Yes - The study clearly discloses funding from the National Natural Science Foundation of China and states that there were no conflicts of interest【
	11. Discussion of Study Limitations	Yes - The study acknowledges several limitations, including the small number of studies, lack of data on sex-specific effects, and the variability in clinical treatments among participants
	12. Inclusion of Non-English Studies	No - The study restricted the search to English-language publications, which could introduce language bias

	13. Data Extraction by Multiple Reviewers	Yes - Data extraction was performed by two reviewers independently, with a third reviewer resolving any discrepancies, indicating a rigorous process
	14. Clear Reporting of Study Characteristics	Yes - The study provides detailed tables summarizing the characteristics of included studies, including participant demographics, intervention details, and outcomes
	15. Consideration of Study Design and Impact on Results	Yes - The study considers the impact of study design on results, discussing how differences in intervention duration, frequency, and participant characteristics might affect outcomes
	16. Synthesis of Findings Without Bias	Yes - The synthesis of findings appears to be conducted without bias, with appropriate statistical methods used to combine study results. The authors discuss the consistency of the findings with existing literature
Conclusion Based on the AMSTAR II criteria, this study is of moderate quality. It generally follows good systematic review practices but has limitations, such as the exclusion of non-English studies and the absence of a formal quality of evidence assessment (e.g., GRADE). These factors prevent it from being rated as high quality.		

Studie	Nr.	Spørgsmål	Svar (Ja/Nej/Delvist) Kommentarer/Notater
Resistance training for fatigue in people with cancer (Ernst et al., 2024)	1	Inkluderede forskningsspørgsmål og inklusionskriterier komponenterne i PICO (Population, Intervention, Comparator, Outcome)?	Ja Fremgår under afsnittet ”objectives” De uddyber både population, (patienter med alle cancertyper), intervention (resistance træning), komparator (ingen træning) og outcome (CRF).
	2	Indeholder rapporten en erklæring om, at metoder blev fastlagt før gennemførelsen af reviewet, og er evt. afvigelser fra protokollen begrundet?	Ja Fremgår bl.a. under afsnittet ”differences between protocol and review”
	3	Forklarede reviewforfatterne deres valg af studiedesigns til inklusion i reviewet?	Ja Fremgår under afsnittet ”types of studies”
	4	Brugte reviewforfatterne en omfattende litteratursøgningsstrategi?	Ja Fremgår under ” Search methods for identification of studies”
	5	Foretog reviewforfatterne studieudvælgelsen i duplikat?	Ja Fremgår under afsnittet ” Selection of studies”
	6	Foretog reviewforfatterne dataudtrækning i duplikat?	Ja Fremgår under afsnittet” Data extraction and management”
	7	Gav reviewforfatterne en liste over ekskluderede studier og begrundede eksklusionerne?	Ja Se bl.a. fig 1. og “Characteristics of excluded studies”
	8	Beskrev reviewforfatterne de inkluderede studier tilstrækkeligt detaljeret?	Ja Se bl.a. fig 1. og “Characteristics of included studies”
	9	Brugte reviewforfatterne en tilfredsstillende metode til at vurdere risikoen for bias i de enkelte studier?	Ja “using RoB 1, the

Studie	Nr.	Spørgsmål	Svar (Ja/Nej/Delvist) Kommentarer/Notater
			risk of bias tool outlined in Version 5.1.0. of the *Cochrane Handbook for Systematic Reviews of Interventions"*
	10	Rapporterede reviewforfatterne finansieringskilderne for de studier, der var inkluderet i reviewet?	Ja Dette fremgår af feltet "notes" for hver artikel under "Characteristics of included studies".
	11	Hvis meta-analyse blev udført, brugte reviewforfatterne passende metoder til statistisk sammenlægning af resultaterne?	Ja Fremgår i afsnittet "Data synthesis"
	12	Hvis meta-analyse blev udført, vurderede reviewforfatterne den potentielle indvirkning af bias i de enkelte studier på meta-analysen?	Er dette som fremgrår under " Sensitivity analysis"
	13	Tog reviewforfatterne højde for risikoen for bias i de enkelte studier, når de tolkede/diskuterede reviewets resultater?	Ja Det fremgår af deres resultater og i konklusionen hvor sikre de er på evidensen baseret på bias vurderingen. Det diskuteres også i afsnittet " Certainty of the evidence"
	14	Gav reviewforfatterne en tilfredsstillende forklaring på og diskussion af eventuel heterogenitet i reviewresultaterne?	Ja Fremgår under afsnittet " Heterogeneity" under diskussionsafsnittet.
	15	Hvis der blev udført kvantitativ syntese, undersøgte reviewforfatterne publikationsbias og diskuterede dens sandsynlige påvirkning af resultaterne? (link)	Ja Det vurderes som en del af certainty of the evidence (GRADE)
	16	Rapporterede reviewforfatterne eventuelle potentielle interessekonflikter, herunder finansiering til reviewet?	Ja Fremgår under afsnittet "Declarations of interest"

Studie	**Nr.**	**Spørgsmål**	**Svar (Ja/Nej/Delvist)** **Kommentarer/Notater**
Metodisk kvalitet	APSTAR2 vurdering: Høj kvalitet		

Studie	**Nr.**	**Spørgsmål**	**Svar (Ja/Nej/Delvist)** **Kommentarer/Notater**
Effect of bright light therapy on cancer-related fatigue and related symptoms: A systematic review and meta-analysis of randomized controlled trials (Lin et al., 2024)	1	Inkluderede forskningsspørgsmål og inklusionskriterier komponenterne i PICO (Population, Intervention, Comparator, Outcome)?	Ja crd.york.ac.uk/prospero/display_record.php?RecordID=352407
	2	Indeholder rapporten en erklæring om, at metoder blev fastlagt før gennemførelsen af reviewet, og er evt. afvigelser fra protokollen begrundet?	Delvist Der er henvist til den protokol de har fået registreret hos PROSPERO, men der inkluderes ikke nogen eksplicit redegørelse for evt. afvigelse.
	3	Forklarede reviewforfatterne deres valg af studiedesigns til inklusion i reviewet?	Ja De beskriver at de kun inkludere RCT´s fordi de ønsker at undersøge effekt af interventioner.
	4	Brugte reviewforfatterne en omfattende litteratursøgningsstrategi?	Delvist Søgestrategi forklaret samt søgestrenge vedlagt i appendix A. De opfylder ikke betingelser for ”ja”.
	5	Foretog reviewforfatterne studieudvælgelsen i duplikat?	Ja Det er forklaret hvilke to af forfatterne der har udført studieudvælgelen samt hvordan evt. uoverensstemmelser er afklaret ved inklusion af en tredjepart.
	6	Foretog reviewforfatterne dataudtrækning i duplikat?	Ja Det er forklaret hvilke to af forfatterne der har udført studieudvælgelen samt hvordan evt. uoverensstemmelser er afklaret ved inklusion af en tredjepart.
	7	Gav reviewforfatterne en liste over ekskluderede studier og begrundede eksklusionerne?	Ja Det er forklaret hvorfor de enkelte studier er ekskluderet.
	8	Beskrev reviewforfatterne de inkluderede studier tilstrækkeligt detaljeret?	Ja

Studie	Nr.	Spørgsmål	Svar (Ja/Nej/Delvist) Kommentarer/Notater
			Region, land, inklussions kriterier, antal deltager, gennemsnitsalder, intervention og outcome er for alle de inkluderede studier er listet i tabel 1.
	9	Brugte reviewforfatterne en tilfredsstillende metode til at vurdere risikoen for bias i de enkelte studier?	Ja De anvendte the revised Cochrane risk of bias tool for randomized trials.
	10	Rapporterede reviewforfatterne finansieringskilderne for de studier, der var inkluderet i reviewet?	Nej
	11	Hvis meta-analyse blev udført, brugte reviewforfatterne passende metoder til statistisk sammenlægning af resultaterne?	De nævner, at standardafvigelser blev estimeret fra forskellige kilder (CI, standardfejl, eller spændvidde) ved hjælp af en indbygget beregner i RevMan, hvilket er en anerkendt metode i systematiske reviews.
	12	Hvis meta-analyse blev udført, vurderede reviewforfatterne den potentielle indvirkning af bias i de enkelte studier på meta-analysen?	Nej Det fremgår ikke direkte i deres metode beskrivelse. De snakker lidt om det i diskussionen.
	13	Tog reviewforfatterne højde for risikoen for bias i de enkelte studier, når de tolkede/diskuterede reviewets resultater?	Ja Dette er beskrevet i diskussionen
	14	Gav reviewforfatterne en tilfredsstillende forklaring på og diskussion af eventuel heterogenitet i reviewresultaterne?	Ja De beskriver en del hetrerogeneity og giver mulige forklaringer på årsager hertil.
	15	Hvis der blev udført kvantitativ syntese, undersøgte reviewforfatterne publikationsbias og diskuterede dens sandsynlige påvirkning af resultaterne? (link)	Ja De vurdere i diskussionen indvirkningen af de små studie populationer.

Studie	Nr.	Spørgsmål	Svar (Ja/Nej/Delvist) Kommentarer/Notater
	16	Rapporterede reviewforfatterne eventuelle potentielle interessekonflikter, herunder finansiering til reviewet?	Ja De rapporter om ingen interessekonflikter
Metodisk kvalitet	APSTAR2 vurdering: Moderat kvalitet review		

Studie	Nr.	Spørgsmål	Svar (Ja/Nej/Delvist) Kommentarer/Notater
Cardiovascular training versus resistance training for fatigue in people with cancer. (Oeser et al., 2024)	1	Inkluderede forskningsspørgsmål og inklusionskriterier komponenterne i PICO (Population, Intervention, Comparator, Outcome)?	Ja Studiet specificerer PICO: Population (kræftpatienter), Intervention (kardiovaskulær træning), Comparator (resistens-træning), Outcome (træthed, livskvalitet, angst, depression, bivirkninger).
	2	Indeholder rapporten en erklæring om, at metoder blev fastlagt før gennemførelsen af reviewet, og er evt. afvigelser fra protokollen begrundet?	Ja Studiet er registreret i Cochrane, og afvigelser fra protokollen er rapporteret i afsnittet "Differences between protocol and review". Bemærk at: This review is part of a series of reviews conducted based on a common protocol (Ernst 2022)
	3	Forklarede reviewforfatterne deres valg af studiedesigns til inklusion i reviewet?	Ja Fremgår under afsnittet ” Types of studies”
	4	Brugte reviewforfatterne en omfattende litteratursøgningsstrategi?	Ja Fremgår under afsnittet “Search methods for identification of studies”. En grundig søgning blev udført i 8 databaser samt trial-registries (ClinicalTrials.gov, WHO ICTRP).
	5	Foretog reviewforfatterne studieudvælgelsen i duplikat?	Ja Fremgår under afsnittet ” Selection of studies”
	6	Foretog reviewforfatterne dataudtrækning i duplikat?	Ja

Studie	Nr.	Spørgsmål	Svar (Ja/Nej/Delvist) Kommentarer/Notater
			Fremgår under afsnittet ” Data extraction and management” Dataudtrækning blev udført af to uafhængige reviewere, med en tredje reviewer til at løse uoverensstemmelser.
	7	Gav reviewforfatterne en liste over ekskluderede studier og begrundede eksklusionerne?	Ja Fremgår af fig. 1 Og under afsnittet ” Characteristics of excluded studies” PRISMA-diagrammet viser detaljer om ekskluderede studier, og der er begrundelser for eksklusion i teksten.
	8	Beskrev reviewforfatterne de inkluderede studier tilstrækkeligt detaljeret?	Ja Fremgår af fig. 1 Og under afsnittet ”Characteristics of included studies”
	9	Brugte reviewforfatterne en tilfredsstillende metode til at vurdere risikoen for bias i de enkelte studier?	Ja Fremgår af fig. 2 og 3 og underafsnittet ” Risk of bias in included studies”. ” At least two review authors (from ME, AO, SM) independently assessed risk of bias for each study, using the Cochrane RoB 1 tool outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*”
	10	Rapporterede reviewforfatterne finansieringskilderne for de studier, der var inkluderet i reviewet?	Ja Det fremgår af feltet “notes” for hver artikel under afsnittet ”Characteristics of included studies”. Finansieringskilder er rapporteret for de inkluderede studier, og potentielle interessekonflikter er diskuteret.
	11	Hvis meta-analyse blev udført, brugte reviewforfatterne passende metoder til statistisk sammenlægning af resultaterne?	Ja Fremgår under afsnittet ” Data synthesis” Meta-analyse blev udført med RevMan 5.4, og der blev anvendt random-effects modeller.

Studie	Nr.	Spørgsmål	Svar (Ja/Nej/Delvist) Kommentarer/Notater
	12	Hvis meta-analyse blev udført, vurderede reviewforfatterne den potentielle indvirkning af bias i de enkelte studier på meta-analysen?	Ja Fremgår under afsnittet ” Sensitivity analysis” samt GRADE vurdering Sensitivitetsanalyser blev udført, og bias blev vurderet som en del af GRADE-analyserne.
	13	Tog reviewforfatterne højde for risikoen for bias i de enkelte studier, når de tolkede/diskuterede reviewets resultater?	Ja Fremgår bl.a. under afsnittet ”Quality of the evidence” Bias og usikkerheder blev adresseret i diskussionen.
	14	Gav reviewforfatterne en tilfredsstillende forklaring på og diskussion af eventuel heterogenitet i reviewresultaterne?	Ja Fremgår under afsnittet ” Certainty of the evidence” Heterogenitet blev vurderet med I^2-statistik, og subgruppeanalyser blev udført for at identificere kilder til variation.
	15	Hvis der blev udført kvantitativ syntese, undersøgte reviewforfatterne publikationsbias og diskuterede dens sandsynlige påvirkning af resultaterne? (link)	Delvist (Nej i AMPSTAR2) Publikationsbias er diskuteret og inkluderet i GRADE vurderingen, men de har ikke lavet funnel-plot pga. lavt antal inkluderede artikler. “*We included only six studies in this review. As a result, assessing publication bias by creating funnel plots was not possible*.” “*The GRADE approach uses five considerations (study limitations (risk of bias), unexplained heterogeneity and inconsistency of eRect, imprecision, indirectness, and publication bias) to assess the certainty of the body of evidence for each outcome*.”
	16	Rapporterede reviewforfatterne eventuelle potentielle interessekonflikter, herunder finansiering til reviewet?	Ja Fremgår under afsnittet ”declarations of interest”
Metodisk kvalitet	APSTAR2 vurdering: Lav kvalitet*		

Studie	Nr.	Spørgsmål	Svar (Ja/Nej/Delvist) Kommentarer/Notater
	Bemærk at scoren er baseret på manglende grafisk eller statistisk fremstilling af publikations bias, dette skyldes at de kun inkludere 6 artikler og derved ikke kan lave et funnel plot. Der indgår en vurdering af publikations bias i deres GRADE-vurdering og det indgår også i deres diskussion.		

Studie	Nr.	Spørgsmål	Svar (Ja/Nej/Delvist) Kommentarer/Notater
Effects of digital psychological interventions on physical symptoms in cancer patients: A systematic review and meta-analysis (Zhang et al., 2023)	1	Inkluderede forskningsspørgsmål og inklusionskriterier komponenterne i PICO (Population, Intervention, Comparator, Outcome)?	Ja – klart beskrevet i metodeafsnittet og anvendt til kodning
	2	Indeholder rapporten en erklæring om, at metoder blev fastlagt før gennemførelsen af reviewet, og er evt. afvigelser fra protokollen begrundet?	Ja – registreret i PROSPERO (CRD42022326780)
	3	Forklarede reviewforfatterne deres valg af studiedesigns til inklusion i reviewet?	Ja – kun RCT'er inkluderet og begrundet
	4	Brugte reviewforfatterne en omfattende litteratursøgningsstrategi?	Ja – 9 databaser + forlæns/baglæns søgning
	5	Foretog reviewforfatterne studieudvælgelsen i duplikat?	Ja – to uafhængige reviewere
	6	Foretog reviewforfatterne dataudtrækning i duplikat?	Ja – udført af to reviewere
	7	Gav reviewforfatterne en liste over ekskluderede studier og begrundede eksklusionerne?	Nej – ikke oplyst i hovedartiklen
	8	Beskrev reviewforfatterne de inkluderede studier tilstrækkeligt detaljeret?	Ja – detaljeret tabel med karakteristika
	9	Brugte reviewforfatterne en tilfredsstillende metode til at vurdere risikoen for bias i de enkelte studier?	Ja – RoB2 anvendt og rapporteret

Studie	Nr.	Spørgsmål	Svar (Ja/Nej/Delvist) Kommentarer/Notater
	10	Rapporterede reviewforfatterne finansieringskilderne for de studier, der var inkluderet i reviewet?	Nej – ikke nævnt
	11	Hvis meta-analyse blev udført, brugte reviewforfatterne passende metoder til statistisk sammenlægning af resultaterne?	Ja – random effects model, Hedge's g
	12	Hvis meta-analyse blev udført, vurderede reviewforfatterne den potentielle indvirkning af bias i de enkelte studier på meta-analysen?	Ja – brugt funnel plot, Egger's test
	13	Tog reviewforfatterne højde for risikoen for bias i de enkelte studier, når de tolkede/diskuterede reviewets resultater?	Ja – diskuteret i resultatafsnittet
	14	Gav reviewforfatterne en tilfredsstillende forklaring på og diskussion af eventuel heterogenitet i reviewresultaterne?	Ja – analyseret og diskuteret
	15	Hvis der blev udført kvantitativ syntese, undersøgte reviewforfatterne publikationsbias og diskuterede dens sandsynlige påvirkning af resultaterne? (link)	Ja – med Egger's test og trim-and-fill
	16	Rapporterede reviewforfatterne eventuelle potentielle interessekonflikter, herunder finansiering til reviewet?	Ja – ingen interessekonflikter oplyst
Metodisk kvalitet	AMSTAR vurdering: **Moderat kvalitet** Reviewet er overordnet veldesignet og følger PRISMA samt PROSPERO-registrering. Der mangler dog rapportering af ekskluderede studier og finansieringskilder for inkluderede studier, hvilket trækker den samlede kvalitet ned fra høj til moderat.		

Studie	Nr.	Spørgsmål	Svar (Ja/Nej/Delvist) Kommentarer/Notater
The Effect of Psychoeducational Interventions on Cancer-Related Fatigue Karakuş et al. (2024)	1	Inkluderede forskningsspørgsmål og inklusionskriterier komponenterne i PICO (Population, Intervention, Comparator, Outcome)?	Ja, tydeligt defineret (P, I, C, O specificeret)
	2	Indeholder rapporten en erklæring om, at metoder blev fastlagt før gennemførelsen af reviewet, og er evt. afvigelser fra protokollen begrundet?	Ja, PROSPERO-registrering (CRD42022377397)
	3	Forklarede reviewforfatterne deres valg af studiedesigns til inklusion i reviewet?	Ja, kun RCT'er inkluderet og begrundet
	4	Brugte reviewforfatterne en omfattende litteratursøgningsstrategi?	Ja, 11 databaser + grå litteratur
	5	Foretog reviewforfatterne studieudvælgelsen i duplikat?	Ja
	6	Foretog reviewforfatterne dataudtrækning i duplikat?	Ja
	7	Gav reviewforfatterne en liste over ekskluderede studier og begrundede eksklusionerne?	Nej, ikke oplyst
	8	Beskrev reviewforfatterne de inkluderede studier tilstrækkeligt detaljeret?	Ja, detaljeret tabel med karakteristika
	9	Brugte reviewforfatterne en tilfredsstillende metode til at vurdere risikoen for bias i de enkelte studier?	Ja, RoB2 anvendt
	10	Rapporterede reviewforfatterne finansieringskilderne for de studier, der var inkluderet i reviewet?	Nej
	11	Hvis meta-analyse blev udført, brugte reviewforfatterne passende	Ja, Hedges' g + random effects

Studie	Nr.	Spørgsmål	Svar (Ja/Nej/Delvist) Kommentarer/Notater
		metoder til statistisk sammenlægning af resultaterne?	
	12	Hvis meta-analyse blev udført, vurderede reviewforfatterne den potentielle indvirkning af bias i de enkelte studier på meta-analysen?	Ja, vurderet
	13	Tog reviewforfatterne højde for risikoen for bias i de enkelte studier, når de tolkede/diskuterede reviewets resultater?	Ja
	14	Gav reviewforfatterne en tilfredsstillende forklaring på og diskussion af eventuel heterogenitet i reviewresultaterne?	Ja, I^2 = 90.2 %, diskuteret
	15	Hvis der blev udført kvantitativ syntese, undersøgte reviewforfatterne publikationsbias og diskuterede dens sandsynlige påvirkning af resultaterne? (link)	Ja, Egger's test og funnel plot
	16	Rapporterede reviewforfatterne eventuelle potentielle interessekonflikter, herunder finansiering til reviewet?	Ja, ingen erklæret
Metodisk kvalitet	AMSTAR vurdering: Moderat kvalitet Studiet er generelt veldesignet og følger både PRISMA og Cochrane-retningslinjer, men manglende rapportering af ekskluderede studier og finansieringskilder for de inkluderede studier udgør metodiske svagheder. Disse punkter vurderes som kritiske fejl ifølge AMSTAR 2.		

8. Om denne kliniske retningslinje

Denne kliniske retningslinje er udarbejdet i et samarbejde mellem Danske Multidisciplinære Cancer Grupper (DMCG.dk) og Sundhedsvæsenets Kvalitetsinstitut. Indsatsen med retningslinjer er forstærket i forbindelse med Kræftplan IV og har til formål at understøtte en evidensbaseret kræftindsats af høj og ensartet kvalitet i Danmark. Det faglige indhold er udformet og godkendt af den for sygdommen relevante DMCG. Sekretariatet for Kliniske Retningslinjer på Kræftområdet har foretaget en administrativ godkendelse af indholdet. Yderligere information om kliniske retningslinjer på kræftområdet kan findes på: www.dmcg.dk/kliniske-retningslinjer

Retningslinjen er målrettet klinisk arbejdende sundhedsprofessionelle i det danske sundhedsvæsen og indeholder systematisk udarbejdede udsagn, der kan bruges som beslutningsstøtte af fagpersoner og patienter, når de skal træffe beslutning om passende og korrekt sundhedsfaglig ydelse i specifikke kliniske situationer.

De kliniske retningslinjer på kræftområdet har karakter af faglig rådgivning. Retningslinjerne er ikke juridisk bindende, og det vil altid være det faglige skøn i den konkrete kliniske situation, der er afgørende for beslutningen om passende og korrekt sundhedsfaglig ydelse. Der er ingen garanti for et succesfuldt behandlingsresultat, selvom sundhedspersoner følger anbefalingerne. I visse tilfælde kan en behandlingsmetode med lavere evidensstyrke være at foretrække, fordi den passer bedre til patientens situation.

Retningslinjen indeholder, ud over de centrale anbefalinger (kapitel 1 – quick guide), en beskrivelse af grundlaget for anbefalingerne – herunder den tilgrundliggende evidens (kapitel 3), referencer (kapitel 4) og anvendte metoder (kapitel 5).

Anbefalinger mærket A baserer sig på stærkeste evidens og anbefalinger mærket D baserer sig på svageste evidens. Yderligere information om styrke- og evidensvurderingen, der er udarbejdet efter "Oxford Centre for Evidence-Based Medicine Levels of Evidence and Grades of Recommendations", findes her:

Generelle oplysninger om bl.a. patientpopulationen (kapitel 2) og retningslinjens tilblivelse (kapitel 5) er også beskrevet i retningslinjen. Se indholdsfortegnelsen for sidehenvisning til de ønskede kapitler.

Retningslinjeskabelonen er udarbejdet på baggrund af internationale kvalitetskrav til udvikling af kliniske retningslinjer som beskrevet af både AGREE II, GRADE og RIGHT.

For information om Sundhedsstyrelsens kræftpakker – beskrivelse af hele standardpatientforløbet med angivelse af krav til tidspunkter og indhold – se for det relevante sygdomsområde: https://www.sst.dk/

Denne retningslinje er udarbejdet med økonomisk støtte fra Sundhedsstyrelsen (Kræftplan IV) og Sundhedsvæsenets Kvalitetsinstitut.