



Recommendations for the surveillance of mental health problems in childhood, adolescent, and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group

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Survivors of childhood, adolescent, and young adult (diagnosed when <25 years of age) cancer are at risk of mental health problems. The aim of this clinical practice guideline is to harmonise international recommendations for mental health surveillance in survivors of childhood, adolescent, and young adult cancer. This guideline was developed by a multidisciplinary panel of experts under the sponsorship of the International Guideline Harmonization Group. We evaluated concordance among existing survivorship clinical practice guidelines and conducted a systematic review following evidence-based methods. Of 7249 studies identified, 76 articles from 12 countries met the inclusion criteria. Recommendations were formulated on the basis of identified evidence in combination with clinical considerations. This international clinical practice guideline strongly recommends mental health surveillance for all survivors of childhood, adolescent, and young adult cancers at every follow-up visit and prompt referral to mental health specialists when problems are identified. Overall, the recommendations reflect the necessity of mental health surveillance as part of comprehensive survivor-focused health care.

Introduction

With contemporary therapy, the 5-year overall survival rate for childhood, adolescent, and young adult (diagnosed when <25 years) cancer is more than 80% in North America, Northern and Western Europe, and Australia,¹⁻⁴ leading to a growing population of survivors worldwide. Following the completion of treatment, survivors of childhood, adolescent, and young adult cancer are at risk of various physical and psychosocial late effects.^{5,6} Multiple international cohort studies have found that these childhood, adolescent, and young adult survivors are more likely to have clinically relevant impairments in mental health than are their counterparts without cancer or instrument norms.⁷⁻¹¹ Cohort studies have also documented that survivors who have mental health problems have poorer physical health and decreased healthy lifestyle behaviours than survivors without mental health problems.^{9,11-15} In addition to being essential for better quality of life, mental health support is fundamental to promoting the long-term physical health of survivors of childhood, adolescent, and young adult cancer.

Different clinical practice guidelines developed for North America and Europe¹⁶⁻¹⁸ recommend that survivors of childhood, adolescent, and young adult cancer receive long-term surveillance for mental health problems; however, these guidelines were developed independently from one another and thus differ in recommendations regarding risks, approaches to surveillance, and interventions to address mental health problems among survivors. The aim of this clinical practice guideline project, under the sponsorship of the International Late Effects of Childhood Cancer Guideline Harmonization

Group (appendix pp 9–11), was to harmonise the recommendations for mental health surveillance in survivors of childhood, adolescent, and young adult cancer.

Methods

Literature search and inclusion criteria

A detailed description of our search strategy is provided in the appendix (pp 12–13). Inclusion criteria for studies were (1) childhood, adolescent, and young adult cancer diagnosis, (2) 75% or more of participants were younger than 25 years when diagnosed, (3) 50% or more of participants were 2 years or more from diagnosis, (4) main outcome was mental health, and (5) a sample size of 200 or more participants for clinical questions 1a and 1b (appendix p 14).

Mental health problems were defined as depression and other mood disorders, anxiety, psychological distress (ie, global stress including negative affect and physiological reactivity),¹⁹ post-traumatic stress (inclusive of post-traumatic stress disorder [PTSD] and post-traumatic stress symptoms), suicidal ideation, behavioural problems and externalising symptoms (ie, anger, oppositional, or antisocial behaviour), and psychotic disorders. Studies investigating substance use, neurocognitive outcomes, somatisation, fear of cancer recurrence, post-traumatic growth, or quality of life as primary outcomes were not eligible for these surveillance recommendations.

The title, abstract, and full text of identified publications were independently screened for eligibility by two reviewers (JGM, SC, KB, JMCB, TMB, IE, EH, NSK-L, JWTK, JL, CJR, CEW, LW, JV, or JLL). Disagreements were resolved through discussion with a third reviewer (JGM, JV, or GM)

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For more on the clinical practice guidelines see <http://www.ighg.org/>

See Online for appendix

to find consensus. Data from included articles were extracted into standardised evidence tables. Evidence from mental health outcomes was organised by the control groups used (ie, siblings or general population) and measurement approaches taken in the included articles. For example, some articles evaluated differences in prevalence of mental health diagnoses or cases on the basis of a clinical cutoff (ie, categorical), and others assessed differences in the magnitude of mental health symptoms (ie, continuous).

The development of this clinical practice guideline followed the International Guideline Harmonization Groups' methods, as previously described by Kremer and colleagues.²⁰ A multidisciplinary international working group consisting of 21 experts in psychology, psychiatry, paediatric oncology, radiation oncology, health sciences, epidemiology, and guidelines methodology prepared the surveillance recommendations. The recommendations were discussed with a wider group of 15 additional experts and critically reviewed by five survivor stakeholders. The membership of the total guidelines group represented 11 countries and three continents (appendix pp 9–11). These guidelines are intended for international use by health-care professionals providing long-term follow-up care for survivors of childhood, adolescent, and young adult cancer.

Comparison of existing guidelines

We first evaluated the concordances and discordances among the existing clinical practice guidelines from the Children's Oncology Group, the Dutch Childhood Oncology Group,¹⁶ the Scottish Intercollegiate Guidelines Network,¹⁷ and the United Kingdom Children's Cancer Study Group Late Effects Group,¹⁸ regarding their recommendations for the surveillance of childhood, adolescent, and young adult survivors' mental health. Then, we developed clinical questions for mental health surveillance to address the identified discordances.

Classifying the strength of the evidence and the recommendations

We assessed the quality of included articles using evidence-based methods provided by Cochrane Childhood Cancer (appendix p 15). For every clinical question, we formulated and classified a conclusion that represented the evidence, on the basis of an adapted version of the American Heart Association's classification criteria (appendix p 16).^{21,22} The quality of the total body of evidence was graded across three categories: level A, representing high-quality evidence; level B representing moderate-quality evidence; and level C, representing low-quality evidence. If there was evidence from more than one study that was based on data from the same underlying cohort (eg, the Childhood Cancer Survivor Study),^{7,11,13–15} we applied a conservative approach of counting repeated cohort studies as evidence from one study for the purpose of evaluation.

Translating evidence into recommendations

The panel of experts formulated recommendations on the basis of the gathered scientific evidence in combination with other considerations, such as clinical factors, potential financial costs, benefits versus harms of the recommendations, and the need to promote feasibility of application across different health-care systems. We classified the strength of the recommendations according to previously published methods (appendix p 16).²¹ Recommendation decisions were made through iterative group discussions and consensus. The harmonised recommendations were decided by consensus among the 21 working group members, 15 additional experts, and five survivors' representatives (appendix pp 9–11) via teleconference, and the wording was finalised via electronic communications. Final recommendations, the strength of the recommendations, and the quality of evidence informing each recommendation were supported unanimously.

Results

The existing survivorship clinical practice guidelines concordantly identified all survivors of childhood, adolescent, and young adult cancer at risk for poor mental health but were discordant in all other areas (appendix pp 17–18).^{16–18} From this, we formulated clinical questions to investigate the evidence in more detail: (1) who needs surveillance, (2) timing and frequency of surveillance, (3) method of surveillance, and (4) recommendations for responding to problems identified by surveillance (appendix p 19). We divided clinical question 1 into two parts to evaluate who among childhood, adolescent, and young adult cancer survivors needs surveillance. We sought to characterise childhood, adolescent, and young adult cancer survivors' prevalence of, and risk for, mental health disorders or symptoms compared with control groups and instrument controls (clinical question 1a) and to identify the key risk factors survivors of childhood, adolescent, and young adult cancer might have that are associated with mental health disorders (clinical question 1b). Of the 7249 articles identified by our searches, 1065 full-text articles were assessed, and 76 articles were eligible for the mental health surveillance recommendations (figure 1; appendix pp 2–8). The 76 original studies were done in 12 different countries in Asia (n=5), Europe (n=19), and North America (n=52). Several of the included studies came from large cohort studies: the Childhood Cancer Survivor Study (n=30), the Swiss Childhood Cancer Survivors Study (n=3), the St Jude LIFE Cohort (n=3), the PETALE Cohort (n=3), and the now closed Children's Cancer Group (n=2).

The evidence and detailed conclusions of evidence are presented in the appendix (pp 20–264). Overall conclusions of evidence and the seven recommendations are presented in table 1, table 2, and panel 1. When summarising evidence on risk factors, we only describe risk factors that constitute at least level B evidence

(table 2). A complete list of all identified risk factors is available (appendix pp 271–73). An overview of studies analysing risk factors for the different mental health outcomes is also shown (appendix pp 274–75).

Recommendation one: surveillance of all survivors of childhood, adolescent, and young adult cancer is recommended for depression and mood disorders, anxiety, psychological distress, post-traumatic stress, behavioural problems, and suicidal ideation (strong recommendation; level A–C evidence)

Our strong recommendation was based on the elevated risks and observed prevalence of mental health disorders and symptoms among childhood, adolescent, and young adult survivors (clinical question 1a, table 1), low risk for harm from screening, and high benefit, as perceived by patient-stakeholders and clinician-stakeholders, of identifying childhood, adolescent, and young adult survivors with mental health needs as an initial step towards referring them to appropriate mental health support services. Positive screening results will require follow-up assessment and additional resources, including staff availability to address the small proportion of survivors presenting with severe mental health symptoms that need urgent or emergency evaluation and intervention. However, we concluded that the benefits associated with identifying and supporting childhood, adolescent, and young adult survivors with mental health needs far outweigh these potential costs.

The prevalence of depression and other mood disorders ranged from 2% to 40% (clinical question 1a, table 1) across 25 studies (11 samples). There is evidence that survivors of childhood, adolescent, and young adult cancer are more likely to have depression and other mood disorders than their siblings and the general population are (both level A). Some evidence suggests that childhood, adolescent, and young adult survivors have increased symptoms of depression (definition not uniform across studies) compared with their siblings and the general population (both level C; clinical question 1a, table 1; appendix p 266). An increased risk for depression was found for childhood, adolescent, and young adult survivors with physical late effects (eg, cardiac, endocrine, or pulmonary conditions), pain, and lower educational status, and for survivors who were unmarried or single (all level B; table 2).

The prevalence of anxiety in survivors of childhood, adolescent, and young adult cancer ranged from 1% to 27% (clinical question 1a, table 1) across 24 studies (11 samples). There is evidence that survivors of childhood, adolescent, and young adult cancer are more likely to have clinically significant anxiety than their siblings and the general population are (both level A). Some evidence suggests that childhood, adolescent, and young adult survivors have increased symptoms of anxiety (definition not uniform across studies) compared with their siblings and the general population (both

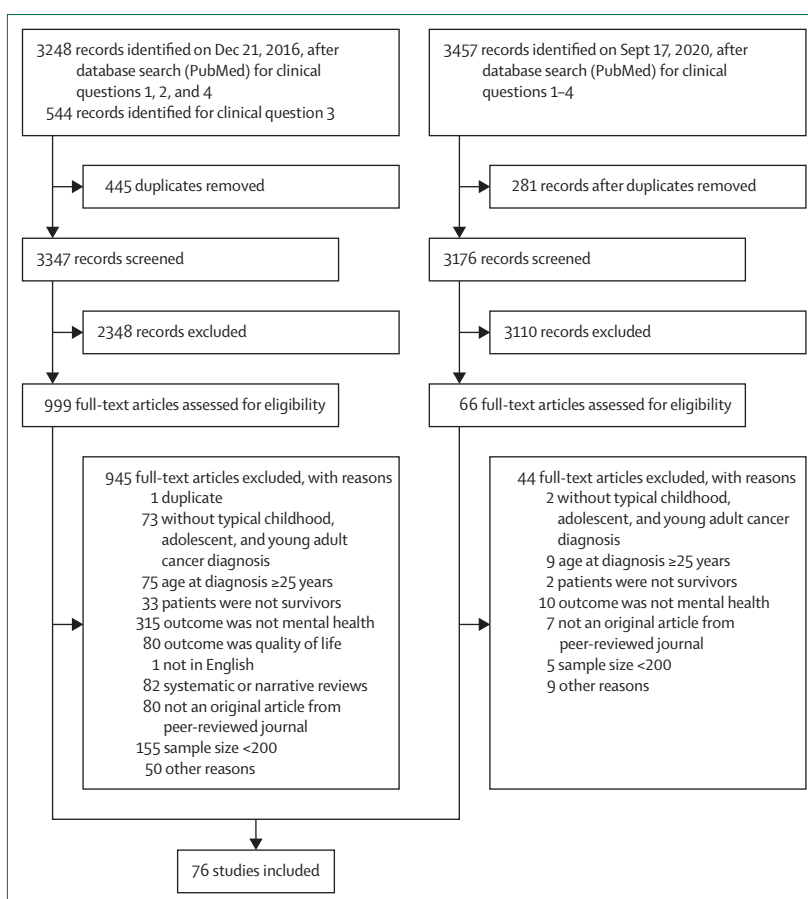


Figure 1: Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow chart

level C; clinical question 1a, table; appendix p 267). An increased risk of anxiety was found for survivors of childhood, adolescent, and young adult cancer with physical late effects or pain, and for survivors who are female, had lower educational status, were unemployed, or had a lower annual income compared with other survivors of childhood, adolescent, and young adult cancer (all level B; table 2).

The prevalence of clinically significant psychological distress ranged from 2% to 35% (clinical question 1a, table 1) across 25 studies (12 samples). We graded the level of evidence as level C due to the inconsistency of findings and heterogeneity of measures used to assess psychological distress across studies. Some evidence suggests that survivors of childhood, adolescent, and young adult cancer are more likely to have clinically significant psychological distress and increased symptoms of psychological distress than their siblings are (level C). Evidence was conflicting regarding both the prevalence and symptoms of psychological distress in childhood, adolescent, and young adult cancer survivors compared with the general population (clinical question 1a, table 1; appendix p 268). An increased risk for psychological distress was found

for unemployed survivors of childhood, adolescent, and young adult cancer or those without health-care insurance (both level A), and for survivors experiencing

late effects, unmarried survivors, female survivors, and survivors with lower educational status or annual income compared with other childhood, adolescent,

	Prevalence or level of evidence
1a: What is the risk of mental health disorders or symptoms in survivors of childhood, adolescent, and young adult cancer?*	
Psychiatric health care use	
Prevalence of psychiatric health care use in survivors	
Survivors of cancer use psychiatric care	2–10%*
Prevalence of psychiatric health care use in survivors vs comparisons	
Increased prevalence of psychiatric health care use in survivors vs comparisons	Level B*
Depression and other mood disorders ^{8,9,12,14,23–29*}	
Prevalence of depression and other mood disorders in survivors	
Survivors are at risk for depression and other mood disorders	2–40% ^{8,9,12,23–26,28*}
Prevalence of depression and other mood disorders in survivors vs comparisons	
Survivors are more likely to experience clinically significant depression and mood disorders vs siblings	Level A ^{24,26–28*}
Survivors are more likely to experience clinically significant depression vs general population norms	Level A ^{8,9*}
Symptoms of depression in survivors vs comparisons	
Survivor have increased symptoms of depression vs siblings	Level C ^{12,14*}
Survivors have increased symptoms of depression vs general population norms	Level C ^{9,12,29*}
Anxiety ^{8,9,11,12,14,27,28,30,35,40*}	
Prevalence of anxiety in survivors	
Survivors are at risk for anxiety	1–27% ^{8,9,11,12,23,25,28*}
Prevalence of anxiety in survivors vs comparisons	
Survivors are more likely to experience clinically significant anxiety vs siblings	Level A ^{28*}
Survivors are more likely to experience clinically significant anxiety vs general population norms	Level A ^{8,9*}
Symptoms of anxiety in survivors vs comparisons	
Survivor have increased symptoms of anxiety vs siblings	Level C ^{12,14*}
Survivors have increased symptoms of anxiety vs general population norms	Level C ^{9,12,29,30*}
Psychological distress ^{8,9,11,12,14,23,25,29*}	
Prevalence of psychological distress in survivors	
Survivors are at risk for psychological distress	2–35% ^{8,9,11,12,14,23,25,29*}
Prevalence of psychological distress in survivors vs comparisons	
Survivors of are more likely to experience clinically significant psychological distress vs siblings	Level C ^{11*}
Conflicting evidence regarding prevalence of psychological distress in survivors vs general population norms	Conflicting evidence ^{9,29}
Symptoms of psychological distress in survivors vs comparisons	
Survivors have increased symptoms of psychological distress vs siblings	Level C ^{12,14*}

(Table 1 continues in next column)

	Prevalence or level of evidence
(Table 1 continued from previous column)	
Conflicting evidence regarding symptoms of psychological distress in survivors vs general population norms	Conflicting evidence ^{9,12,29*}
PTSD, SRMD, and PTSS ^{24,26,27*}	
Prevalence of PTSD, SRMD, and PTSS in survivors	
Survivors are at risk for PTSD, SRMD, and PTSS	1–18% for PTSD; cumulative incidence for all SRMD diagnoses was 18%; 12–71% for PTSS ^{18,30–32*}
Prevalence of PTSD, SRMD, and clinically significant PTSS in survivors vs comparisons	
Survivors are more likely to meet partial or full criteria for PTSD or SRMD vs comparisons	Level B ^{28,30,32*}
Externalising problems ^{24,26,27*}	
Prevalence of externalising problems in survivors	
Survivors are at risk for externalising behavioural problems	12–22% ^{24,26*}
Prevalence of externalising problems in survivors vs comparisons	
Survivors are at risk for externalising behaviour problems	12–22%; ^{24,26*} level C ^{24,26,27}
Symptoms of externalising problems in survivors vs comparisons	
Survivors have increased symptoms of anger vs siblings	Level C*
Suicidal ideation and death by suicide ^{8*}	
Prevalence of suicidal ideation and death by suicide in survivors	
Survivors are at risk for suicidal ideation, attempted suicide, and death by suicide	5–12% for suicidal ideation; 1–4% for attempted suicide; 0.1–1.6% for death by suicide ^{8*}
Prevalence of suicidal ideation and death by suicide in survivors vs comparisons	
Survivors are more likely to experience suicidal ideation vs comparisons	Level C ^{8*}
Survivors are more likely to experience death by suicide vs comparisons	Level C*
Other mental disorders and symptoms ^{8,9*}	
Prevalence of other mental disorders and symptoms in survivors	
Survivors are at risk for obsessive compulsive symptoms	10.5% ⁹
Survivors are at risk for attention-deficit hyperactivity disorder	13%*
Survivors are at risk for panic	7% ⁸
Prevalence and symptoms of other mental health disorders and symptoms in survivors vs comparisons	
Survivors are more likely to experience schizophrenia and psychotic disorder vs comparisons	Level C*
Survivors are more likely to experience personality disorders vs comparisons	Level C*

(Table 1 continues in next column)

	Prevalence or level of evidence
(Table 1 continued from previous column)	
Survivors are equally likely to experience obsessive-compulsive symptoms vs comparisons, but more likely to report fewer symptoms	Level C ⁹
Survivors are more likely to experience attention-deficit hyperactivity disorders vs the general population	Level C*
Survivors are more likely to experience panic vs the general population	Level C ⁹
2: Does the risk of developing poor mental health change over time in survivors of childhood, adolescent, and young adult cancer?	
The risk of anxiety and depression does not change over time in most survivors of childhood, adolescent, and young adult cancer; however, there is also a suggestion that the risk of anxiety and depression might increase over time for 10–12% of survivors or decrease for 15–16% of survivors; additionally, persistent or increasing symptoms of depression and anxiety were more prevalent in survivors than siblings	Level C ^{34,35}
3: How sensitive are commonly used diagnostic tools for self-reported outcomes, parent-reported outcomes, different age groups, format, and different clinical issues?	
Adult measures	
There is evidence that the Brief Symptom Inventory-18 is a reliable and valid measure of clinically significant emotional distress in adult survivors of childhood, adolescent, and young adult cancers	Level A ³⁷⁻⁴⁰
Some evidence suggests that the Distress Thermometer with a cutoff of ≥ 3 can be used as a screening measure for psychological distress in adult survivors of childhood, adolescent, and young adult cancers; the score was associated with anxiety, positive and negative affect, but not with depression	Level C ^{38,42,43}
Some evidence suggests that the post-Traumatic Stress Response Diagnostic Scale is a valid measure of clinically significant distress in adult survivors of childhood, adolescent, and young adult cancers, but is not able to reliably identify clinically significant functional impairment	Level C ⁴¹
Youth measures	
Some evidence suggests that the Distress Rating Scale or the Distress Thermometer are not ideal to identify psychological distress in paediatric and adolescent survivors of cancer; differences in agreement between parents' and children's ratings on the Distress Rating Scale were negligible to small in paediatric and adolescent survivors of cancer; the Distress Thermometer score was associated with negative affect, but not with depression, or positive affect in paediatric and adolescent survivors of cancer	Level B ^{30,45}
(Table 1 continues in next column)	

	Prevalence or level of evidence
(Table 1 continued from previous column)	
Some evidence suggests that the Distress Screening Tool (self-report and caregiver report) is a reliable and valid measure to screen for distress in paediatric and adolescent survivors of cancer	Level C ⁴⁶
Some evidence suggests that the Benefit and Burden Scale for Children is a reliable and valid measure of psychological adjustment to potentially traumatic experiences in child and adolescent survivors of cancer	Level C ⁴⁴
Some evidence suggests that the Beck Youth Inventories-II is a reliable measure of anxiety and depression in child and adolescent survivors of cancer; however, differences in agreement between parents' and children's ratings on the Beck Youth Inventories were medium	Level C ^{37,45}
4: What is the effect of any intervention in the treatment of mental health symptoms for survivors of childhood, adolescent, and young adult cancer?*	
Effect of cognitive behavioural therapy	
Cognitive behavioural therapy can be useful in the treatment of anxiety, depression, and post-traumatic stress symptoms among survivors	Level B ^{48,49}
Effect of group social skills training	
No effect of social skills training in improving mental health symptoms in paediatric and adolescent survivors of cancer	Level C*
Effect of family group intervention for PTSD	
A family group intervention can be useful in the treatment of post-traumatic arousal symptoms in paediatric and adolescent survivors of cancer	Level C ⁵⁰
Effect of participating in musical training	
Some evidence suggests that participating in weekly musical training can be useful in the treatment of depression in paediatric and adolescent survivors of cancer.	Level C ⁵¹
For clinical question 1b, see table 2. Level A: high-quality evidence; level B: moderate-quality evidence; level C: low-quality evidence. PTSD=post-traumatic stress disorder. SRMD=stress-related mental disorders. PTSS=post-traumatic stress symptoms. * Full reference list included in the appendix (pp 2–8).	
Table 1: Overall conclusions of the evidence of mental health problems in survivors of childhood, adolescent, and young adult cancer	

and young adult cancer survivors and controls (all level B; table 2).

The prevalence of PTSD, stress-related mental disorders, and post-traumatic stress symptoms varied across 14 studies (ten samples) as a function of how post-traumatic stress was operationalised (eg, full vs partial

diagnostic criteria; with or without accompanying impairment). The prevalence of PTSD diagnosis ranged from 1% to 18% and stress-related mental disorder diagnoses was 18% (clinical question 1a, table 1). By contrast, the prevalence of moderate to severe post-traumatic stress symptoms ranged from 12.5% to 40.0%, and the prevalence of mild post-traumatic stress symptoms ranged from 64.3% to 71.0%. Evidence suggests that survivors of childhood, adolescent, and young adult cancer are more likely to have PTSD or stress-related mental disorders than control groups and controls from instrument norms (level B). Survivors were more likely to meet full or partial diagnostic criteria for PTSD than their siblings and the general population, and they were more likely to have stress-related mental disorder diagnoses compared with children without

	Depression	Anxiety	Psychological distress	PTSD, PTSS, and SRMD	Suicidal ideation
Clinical risk factors					
Age at diagnosis	No (level B evidence) ^{36,27*}	No for PTSS (level A evidence) ^{30*}	..
Longer time since diagnosis (definition not uniform across studies)	No (level B evidence) ^{30*}	..
Primary cancer diagnosis	No (level B evidence) ^{12*}
Tumour location	..	No (level B evidence)*
Late effects of cancer treatment	Yes; increased risk (level B evidence) ^{12,14,23,27,28*}	Yes; increased risk (level B evidence) ^{11,12,14,23,28*}	Yes; increased risk (level B evidence) ^{9,11,12,14,23*}	Yes; increased risk (level B evidence) ^{28*}	..
Pain	Yes; increased risk (level B evidence) ²⁸	Yes; increased risk (level B evidence) ^{28*}
Seizures	Yes; increased risk (level B evidence)*
History of depression	Yes; increased risk (level A evidence)*
Mental health disorders	Yes; increased risk (level B evidence) ^{31*}	..
Demographic risk factors					
Female	..	Yes; increased risk (level B evidence) ^{8,11,12,28*}	Yes; increased risk (level B evidence) ^{9,11,12,14*}	Yes; increased risk (level B evidence) ^{28,30*}	No (level B evidence) ^{9*}
Older age at study (definition not uniform across studies)	Conflicting ^{2,12,26*}	No (level B evidence) ^{9*}
Lower educational status	Yes; increased risk (level B evidence) ^{5,14*}	Yes; increased risk (level B evidence) ^{8,11*}	Yes; increased risk (level B evidence) ^{11*}	Yes; increased risk (level A evidence)*	..
Unemployment	..	Yes; increased risk (level B evidence) ^{8,14*}	Yes; increased risk (level A evidence)*	Yes; increased risk (level B evidence)*	..
Marital status	Yes; increased risk in unmarried survivors ^{8,8,14*}	..	Yes; increased risk in unmarried survivors (level B evidence) ^{6*}	Yes; increased risk in unmarried survivors (level B evidence)*	Yes; decreased risk in married or divorced survivors (level B evidence) ^{8*}
Lower annual income	..	Yes; increased risk (level B evidence) ^{8,11,14*}	Yes; increased risk (level B evidence) ^{11,14*}
Health insurance status	No (level B evidence)*	No (level B evidence)*	Yes; increased risk with no insurance (level A evidence)*
Race, ethnicity, or immigration status	No (level B evidence) ^{26*}	..	–	No (level B evidence) ^{30*}	..
Treatment-related risk factors					
Surgery	..	No ^{8,12*}
Radiotherapy	Conflicting ^{12,26–27*}	No (level B evidence) ^{12,28*}	No (level B evidence) ^{12*}

Only risk factors with at least level B evidence are presented. Please see appendix (pp 271–73) for all risk factors identified. No risk factors of at least level B evidence identified for behavioural problems, mental health-care visit, panic, suicide, or first severe mental health event. Conflicting=conflicting evidence. No=no association. Yes=statistically significant association. PTSD=post-traumatic stress disorder. PTSS=post-traumatic stress symptoms. SRMD=stress-related mental disorder. *Full reference list included in the appendix (pp 2–8).

Table 2: Clinical question 1b: what are the key risk factors for developing mental disorders in survivors of childhood, adolescent, and young adult cancer?

cancer (clinical question 1a, table 1; appendix p 269). We graded the evidence as level B due to the inconsistency in measurement of post-traumatic stress and its potential impact on findings across studies. An increased risk for PTSD, stress-related mental disorders, or post-traumatic stress symptoms was found for survivors with lower educational status (level A), physical late effects, other mental health problems, female survivors, or survivors who were unemployed or unmarried compared with

other childhood, adolescent, and young adult cancer survivors (all level B; table 2).

The prevalence of externalising behavioural problems was 12% to 22%, antisocial behaviour was 12·3% to 14·6%, and headstrong behaviour (eg, has a strong temper or argues often) was 13·2% to 22·8% (clinical question 1a, table 1) across three studies (two samples). We graded the evidence as level C due to the paucity of data investigating behavioural problems and externalising

Panel 1: Surveillance recommendations for mental disorders and symptoms in survivors of childhood, adolescent, and young adult cancer

Who needs surveillance?

Health-care providers and survivors of childhood, adolescent, and young adult cancer should be aware that survivors are at risk for mental disorder symptoms. For all survivors, surveillance is recommended for:

- Depression and mood disorders (level A–C evidence)
- Anxiety (level A–C evidence)
- Psychological distress (level C evidence)
- Post-traumatic stress (level B evidence)
- Behavioural problems (level C evidence)
- Suicidal ideation (level C evidence)

The main risk factors* for mental disorders and symptoms in survivors of childhood, adolescent, and young adult cancer are unemployment†, lower educational status‡, late effects§, experiencing pain¶, and female sex||** (strong recommendation, based on level A–C evidence).

At what age or time from exposure should surveillance be initiated?

Health-care providers should be aware that mental disorders and symptoms can be present at diagnosis or arise during treatment for childhood, adolescent, and young adult cancer. Mental health surveillance is important for patients throughout treatment for childhood, adolescent, and young adult cancer (strong recommendation; expert opinion).

Mental health surveillance is recommended for survivors of all ages to begin at the first follow-up visit and continue throughout the lifespan (strong recommendation; level C evidence).

At what frequency should surveillance be done?

Mental health surveillance is recommended for all survivors of childhood, adolescent, and young adult cancers at every follow-up visit (or at general medical health checks; strong recommendation; level C evidence).

What surveillance method should be used?

A medical history focused on survivors' mental health is recommended during follow-up care visits (strong recommendation; expert opinion).

Suggested questions to screen for mental health problems:

"Have you [has your child††] ..."

- "been feeling sad, angry, or less interested in things than usual?"

- "been feeling worried, tense, stressed, or overwhelmed?"
- "had trouble coping with thoughts, memories, or reminders of the cancer experience?"
- "had thoughts of harming yourself or ending your life?"
- "considered connecting with a health-care provider to support your mental health?"

For survivors of childhood, adolescent, and young adult cancer with an indication for mental health problems from medical history:

Further testing with a validated parent-report or self-report measure‡‡ by a mental health professional (eg, psychologist, psychiatrist, or other suitable specialist) is recommended (strong recommendation; level A–C evidence; expert opinion).

What should be done if problems are identified?

Health-care providers and survivors of childhood, adolescent, and young adult cancers should be aware of standard recommended care (strong recommendation):

- Prompt referral of survivors reporting mental health symptoms to a mental health professional (eg, psychologist, psychiatrist, or other suitable specialist) for diagnostic and risk assessment (expert opinion)
- Immediate referral of survivors with severe mental health problems that might substantially interfere with their safety (eg, psychosis, severe depression, suicidal ideation, self-harming behaviours, or impulses) to a mental health professional (eg, psychiatrist, psychologist, or local mental health crisis services; expert opinion)
- Cognitive behavioural therapy for the treatment of survivors of childhood, adolescent, and young adult cancer with anxiety, depression, and post-traumatic stress symptoms (level B evidence)

*Risk factors with at least level B evidence. †Level A evidence for psychological distress; level B evidence for anxiety and post-traumatic stress. ‡Level A evidence for post-traumatic stress; level B evidence for depression, anxiety, and psychological distress. §Level B evidence for depression, anxiety, psychological distress, and post-traumatic stress. ¶Level B evidence for depression, and anxiety. **Level B evidence for anxiety, psychological distress, and post-traumatic stress. ††If parent report is indicated. ‡‡Recommended measures for children to assess mental health problems: Benefit and Burden Scale for Children, Beck Youth Inventories-II, Distress Screening Tool, and Strengths and Difficulties Questionnaire. Recommended measures for adults: Brief Symptom Inventory-18, Posttraumatic Stress Diagnostic Scale, Distress Thermometer, and General Health Questionnaire.

symptoms among survivors of childhood, adolescent, and young adult cancers. Some evidence suggests that survivors are more likely to have clinically significant behavioural problems and have increased symptoms of anger than their siblings (clinical question 1a, table 1; appendix p 269). There was no evidence for risk factors with at least level B evidence (table 2).

The prevalence of suicidal ideation ranged from 5% to 12% and recurrent suicidal ideation was 0.9% to 3.0%; the prevalence of attempted suicide was 1% to 4% and

death by suicide was 0.1% to 1.6% (clinical question 1a, table 1) across nine studies (eight samples). We graded the evidence as level C due to the inconsistency of findings across studies. Some evidence suggests that survivors of childhood, adolescent, and young adult cancer are more likely to have suicidal ideation, recurrent suicidal ideation, and death by suicide than control groups are (all level C; clinical question 1a, table 1; appendix p 270). An increased risk for suicidal ideation was found for survivors with a history of depression (level A) or seizures (level B)

compared with other childhood, adolescent, and young adult survivors. A decreased risk for suicidal ideation was found for married survivors compared with unmarried survivors (both level B; table 2). None of the studies identified risk factors for death by suicide.

Recommendation two: mental health surveillance is important for patients throughout treatment for childhood, adolescent, and young adult cancer (strong recommendation; expert opinion)

Although this clinical practice guideline is focused on the care of long-term survivors of childhood, adolescent, and young adult cancer, not patients during active treatment, the panel considers it important to raise awareness that mental health disorders and symptoms can be present at diagnosis, arise during treatment, or occur as late effects.^{33–35} Mental health surveillance is, therefore, important throughout the cancer continuum. This strong recommendation was based on expert opinion that considered the low risk for harm of beginning mental health screening at diagnosis and received unanimous stakeholder support.

Recommendation three: mental health surveillance is recommended for survivors of all ages, to begin at the first follow-up visit and continue throughout survivorship (strong recommendation; level C)

Our strong recommendation for surveillance beginning at the first survivor care visit for survivors of all ages was based on the observed risks for mental health problems among childhood, adolescent, young adult, and adult survivors, the low risk for harm, and stakeholder support.

We identified no studies reporting specifically on the latency time to develop mental health problems in survivors of childhood, adolescent, and young adult

cancer. However, studies investigating the time since diagnosis as a risk factor for mental health disorders and symptoms in survivors of childhood, adolescent, and young adult cancer found no effect for the time since diagnosis on post-traumatic stress (level B), depression (level C), or anxiety (level C). These studies also found that a longer time since diagnosis (definition varied across studies) was associated with increased psychological distress (level C). Although survivors had a higher risk of anxiety, psychological distress, and stress-related mental health disorders with increased age (all level C; appendix p 271), findings from child and adolescent survivors aged 8–18 years suggest that young survivors are also at risk for mental health disorders and symptoms.^{12,23–27,30,31}

Recommendation four: mental health surveillance is recommended for all survivors of childhood, adolescent, and young adult cancers at every follow-up visit (or at general medical health checks; strong recommendation; level C evidence)

Our strong recommendation for ongoing surveillance was based on the reported prevalence of mental health problems, observed changes in mental health over time (tables 1 and 2), low risk for harm, stakeholder support, and high potential for benefit to survivors. If a survivor has mental health problems, these should be recognised and treated as early as possible to prevent unnecessary suffering or worsening of the survivors' health.

Evidence suggests that symptoms of anxiety or depression worsen over time for 10% to 12% of survivors of childhood, adolescent, and young adult cancer, and symptoms improve over time for 15% to 16% of survivors.³⁶ Additionally, persistent or increasing symptoms of depression or anxiety were more prevalent in survivors versus siblings (level C; clinical question 2, table 1).³⁷

Recommendation five: focusing the medical history on survivors' mental health is recommended (strong recommendation; expert opinion)

Augmenting survivors' medical history, case history, or anamnesis to screen for mental health problems is recommended to help identify potential mental health late-effects of treatment.

Recommendation six: for survivors of childhood, adolescent, and young adult cancers reporting mental health problems during their medical history, further testing with a validated parent-report or self-report measure by a mental health professional is recommended (strong recommendation; level A–C evidence; expert opinion)

After reviewing the evidence on the validity and reliability of mental health measures and discussing the feasibility of implementing these identified measures as part of international, long-term follow-up care, the panel was not able to recommend specific surveillance methods. Although there is evidence that the Brief Symptom

Panel 2: Gaps in knowledge and future directions for research

- Observational studies with multiple comparator groups (ie, siblings, general population, and measurement norms) and analytic approaches to evaluate differences in mental disorder symptoms and proportions of participants experiencing mental health impairment
- Research investigating sex (biological) and gender (psychosocial influencing factors) differences in risk for mental disorders after childhood, adolescent, and young adult cancer
- Development and evaluation of brief screening tools for use in long-term follow-up to assess survivors of childhood, adolescent, and young adult cancer for depression, anxiety, distress, stress-related disorders, behavioural problems, and suicidality at point of care
- Evaluation of interventions to address the mental health needs of survivors of childhood, adolescent, and young adult cancer
- Evidence from geographical areas other than North America or central and northern Europe and establishment of novel cohorts of survivors of childhood, adolescent, and young adult cancer
- Longitudinal research evaluating long-term effects of modern decreases in cancer treatment toxicity, immunotherapies, the SARS-CoV-2 pandemic, and the transition to older adulthood on survivors' mental health

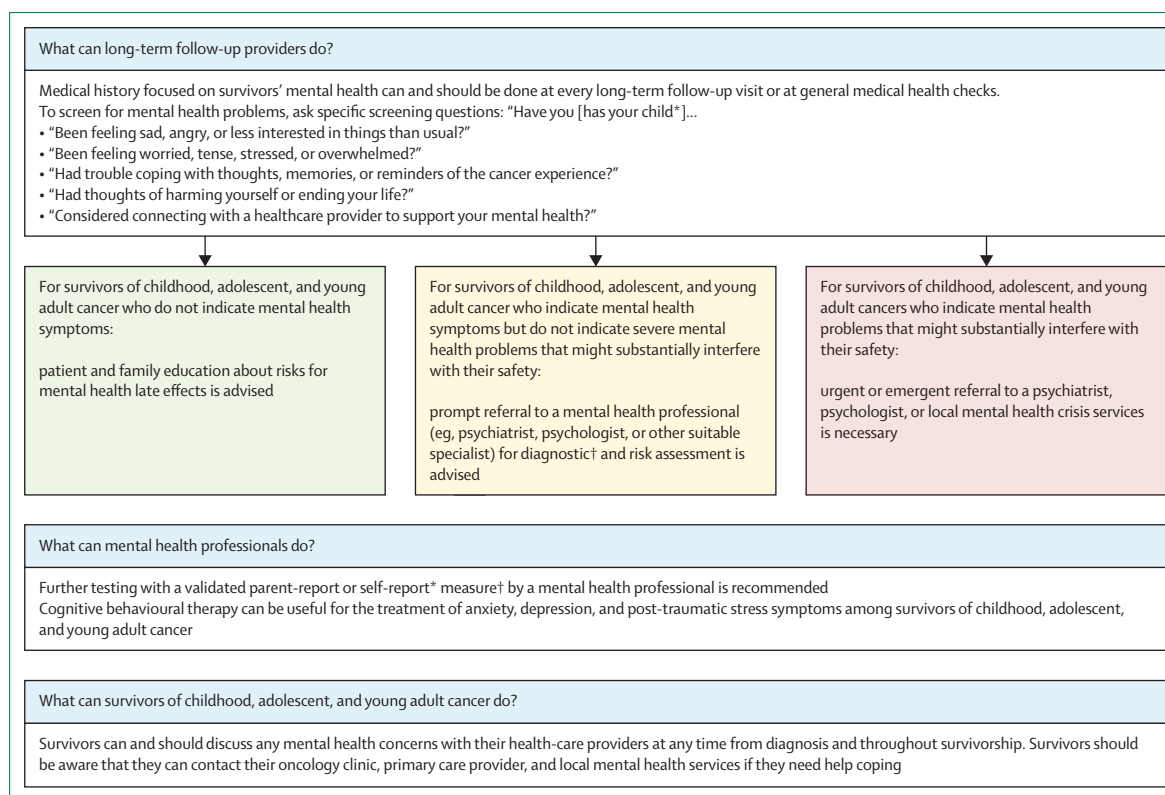


Figure 2: Considerations for implementing mental health surveillance recommendations

*If a parent report is indicated; self-report is generally preferred over parent report. †Recommended measures for children to assess mental disorders: Benefit and Burden Scale for Children, Beck Youth Inventories-II, Distress Screening Tool, and Strengths and Difficulties Questionnaire. Recommended measures for adults: Brief Symptom Inventory-18, Posttraumatic Stress Response Diagnostic Scale, Distress Thermometer, and General Health Questionnaire.

Inventory-18³⁷ is a reliable and valid measure of acute emotional distress in adult survivors of childhood, adolescent, and young adult cancer, it is a copyrighted measure available in few languages for clinical use and has financial costs associated with each administration. Given these constraints, we could not make a universal recommendation for its use as a surveillance measure in all adult survivors of childhood, adolescent, and young adult cancers. In terms of youth measures, the panel judged the utility, availability, and implementation feasibility of any specific measure as inadequate to warrant its recommendation for universal use as a screening instrument in long-term follow-up care. The development and evaluation of screening measures was identified as an important area in need of further research (panel 2). Instead, the panel formulated example screening questions to help health-care professionals quickly assess common mental health problems during the medical history (panel 1). In addition, the panel created a clinical algorithm to guide health-care professionals in the process of mental health surveillance (figure 2).

If there is an indication of mental health problems from medical history, survivors should be referred to a licensed mental health professional for further assessment, ideally with a psychometrically validated instrument (clinical

question 3, table 1; figure 2). This strong recommendation was based on the complexity of assessing different mental health problems, availability of psychometrically reliable and valid instruments, and feasibility of implementing recommendations. Mental health professionals are experienced in assessing, differentiating, and diagnosing different mental health problems and are therefore best suited to complete an in-depth assessment.

For adult survivors of childhood, adolescent, and young adult cancer, there is evidence that the Brief Symptom Inventory-18 is a reliable and valid measure of acute emotional distress (level A).^{29,38–40} Evidence also suggests that the Post-Traumatic Stress Response Diagnostic Scale³² and the Distress Thermometer^{25,41,42} are valid measures of distress in adult survivors of childhood, adolescent, and young adult cancer (both level C; clinical question 3, table 1).

For child and adolescent survivors, there is evidence to suggest that the Benefit and Burden Scale for Children,⁴³ Beck Youth Inventories-2,^{38,44} and Distress Screening Tool⁴⁵ are reliable and valid measures (all level C; clinical question 3, table 1). Evidence suggests that the Distress Rating Scale and the Distress Thermometer are not ideal for identifying psychological distress in paediatric and adolescent survivors of cancer (level B).^{25,44}

Recommendation seven: prompt referral to a mental health specialist for diagnostic and risk assessment is advised for survivors experiencing mental health symptoms. Immediate referral to a mental health specialist is necessary for survivors with severe mental health problems that could substantially interfere with their safety (strong recommendation; expert opinion). Cognitive behavioural therapy can be useful for the treatment of mental health problems in survivors (strong recommendation; level B)

This strong recommendation was based on existing clinical practice guidelines, the high risk of harm conferred by delayed access to mental health support, and survivor-stakeholder opinions about the potential harm to survivors who are not promptly supported after overcoming the barrier of disclosing mental health problems to a health-care provider. As recommended by existing clinical practice guidelines,^{16,18} survivors should be referred to a mental health specialist (eg, psychologist, psychiatrist, or other suitable specialist) in a timely manner when mental health symptoms are identified. Prompt access to support that facilitates diagnosis and treatment is essential for survivors who are experiencing mental health problems. For survivors reporting mental health problems that could substantially affect their safety (eg, psychosis, severe depression, suicidal ideation, or self-harming behaviours or impulses), immediate risk assessment and mental health care is critical. These childhood, adolescent, and young adult cancer survivors should be immediately referred to an appropriate mental health professional, hospital emergency room, or mental health crisis service (figure 2).

Our strong recommendation for cognitive behavioural therapy is based on the high potential benefit to survivors, low risk for harm, stakeholder support, and well established outcomes research that shows the effectiveness of cognitive behavioural therapy in the treatment of anxiety and depression among all ages in the general population.⁴⁶ The panel did not judge the other interventions to be well established enough to warrant their recommendation and identified intervention development and evaluation as a crucial gap in need of further research (panel 2).

The evidence suggests that cognitive behavioural therapy can be useful in the treatment of anxiety, depression, and post-traumatic stress symptoms among survivors of childhood, adolescent, and young adult cancer (level B, clinical question 4, table 1).^{47,48} Some evidence also indicated that family group intervention might be useful in the treatment of post-traumatic arousal symptoms,⁴⁹ and music therapy could be useful in the treatment of depression among survivors (level C, clinical question 4, table 1).⁵⁰

Discussion

In this Review, we present harmonised, international recommendations for the surveillance of mental health problems had by survivors of childhood,

adolescent, and young adult cancer. These recommendations address the discrepancies and gaps observed in existing clinical practice guidelines and relate to a spectrum of mental health symptoms and risk factors. By disseminating these recommendations to providers and other key stakeholders, our aim is to support the mental health surveillance of childhood, adolescent, and young adult survivors and facilitate their referral to appropriate psycho-oncology supports during and after cancer treatment. Consistent with the conclusions of the standards of psychosocial care for children with cancer and their families,^{51,52} our results highlight the necessity of ongoing surveillance for mental health symptoms across the lifespan. Considerations for implementing mental health surveillance recommendations in the clinical context are outlined in figure 2. Example screening questions to expedite provider assessment of common mental health problems are listed along with a clinical algorithm to guide next steps after surveillance. Survivors and their families can also use these recommendations as a tool to request support and raise awareness of mental health risks after having childhood, adolescent, and young adult cancer.

There were challenges in assessing the risk for multiple mental health problems across studies of survivors of childhood, adolescent, and young adult cancer. Results varied as a function of different comparator groups (ie, siblings, community controls, and instrument norms), and as a function of the outcomes assessed (ie, differences in prevalence of diagnosis *vs* magnitude of symptoms between groups). For example, level A evidence indicated that childhood, adolescent, and young adult cancer survivors were more likely to meet the threshold for clinically significant depression and anxiety compared with their siblings and the general population, but only level C evidence indicated that survivors had more symptoms of depression and anxiety than their siblings and the general population. Future research should attend to these distinctions by including multiple comparative groups and reporting both symptom counts and the proportion of individuals exceeding specific symptom thresholds (panel 2). Although there were nuanced differences based on comparators and outcomes, our recommendations for mental health surveillance were supported by a high quantity and quality of data that showed survivors' increased risk for various mental health problems.

The prevailing risk factors for mental health problems among survivors of childhood, adolescent, and young adult cancer identified by our systematic review included physical late effects or poor health status, unemployment, lower educational status, and female sex or gender. Our results showing female survivors of childhood, adolescent, and young adult cancer are at greater risk for anxiety, psychological distress, and post-traumatic stress than male survivors are consistent with the broader literature that shows increased risks of anxiety and mood disorders

among females in the general population.⁵³ Additional research is needed with survivors of childhood, adolescent, and young adult cancer to identify whether these risks are associated with sex differences (eg, biological factors such as sex hormone or hypothalamic–pituitary–adrenal axis responses) or gender differences (eg, psychosocial influencing factors such as differential rates of low self-esteem, violence and abuse, or gender discrimination experienced by women).⁵⁴ Similarly, previous literature has shown bidirectional biological links between many chronic medical conditions and anxiety and mood disorders.^{55,56} Associations between poor physical and mental health among survivors of childhood, adolescent, and young adult cancer could be further compounded by shared biological effects of cancer treatment including neurotoxicity, oxidative stress, or inflammation. In addition to biological factors, psychological stress associated with cancer treatment or having late effects could serve as a causal or exacerbating factor for mental health problems. Lastly, survivors are at a higher risk for poor social outcomes than the general population are, including unemployment and lower educational status,⁵⁷ which are associated with an increased risk for poor mental health outcomes. These social factors might impact mental health through financial stress or reduced economic access to mental health services. Taken together, our findings underscore the need for multidisciplinary, biopsychosocial approaches to long-term follow-up care to optimise survivors' health and quality of life after childhood, adolescent, and young adult cancer.

The strengths of this clinical practice guideline include the systematic approach to summarise current evidence and develop recommendations, a large international, multidisciplinary panel of experts involved in the process, and partnership with survivors of childhood, adolescent, and young adult cancer who informed recommendation development. There were limitations to the available evidence, which represent knowledge gaps and important areas for future research (panel 2). Although 62 studies characterised survivors' risk for poor mental health outcomes, only 16 studies assessed psychometrics of mental health surveillance measures and only five evaluated effects of mental health interventions. Additional research is needed to develop and evaluate brief screening tools to assess survivors' mental health at various points of care and follow-up. More research is needed to establish the efficacy and effectiveness of mental health interventions in populations of childhood, adolescent, and young adult cancer survivors to provide them with evidence-based options for treatment when mental health problems are identified. Only two of the studies identified assessed changes in survivors' mental health status over time. More longitudinal research is needed to help evaluate the long-term effects of various factors (eg, modern decreases in treatment toxicity, immunotherapies, SARS-CoV-2 pandemic, and transition to adulthood) on survivors' mental health.

Search strategy and selection criteria

We searched the literature in PubMed for articles published from Jan 1, 1990, to Sept 17, 2020. The search terms “childhood cancer” and “survivors” with synonyms and variations were used in both searches; we added the term “mental health problems” to the first search (detailed search strategy provided in the appendix [p 12]) and the term “diagnostic tools for mental health problems” to the second search (appendix p 13). Additionally, reference lists of included articles were manually searched (by SC and DK [Divine Kalenda; intern]). Only papers published in English were included.

Furthermore, most studies included survivors from North America or were the repeated study of the same cohorts of survivor participants (eg, the Childhood Cancer Survivor Study). Additional research is needed to better understand the mental health needs of survivors outside of North America and central and northern Europe to increase the generalisability of these recommendations to other parts of the world. Evaluation of novel cohorts of survivors of childhood, adolescent, and young adult cancer would add to our understanding of the mental health needs of younger survivors, including childhood and adolescent survivor populations. Future studies might seek to expand search criteria beyond traditional mental health terms to include survivors' self-identified needs for emotional support. Finally, this clinical practice guideline was aimed at survivors diagnosed before age 25 years; therefore, the evidence might not be generalisable to those diagnosed with cancer between 25 and 39 years. The goal is to update these recommendations within 5 years.

In conclusion, these recommendations promote the adoption of a detect-and-intervene approach for mental health problems aligned with traditional surveillance for physical late effects in long-term follow-up care.^{57–68} Furthermore, these recommendations highlight the importance of including mental health as a key component of survivor-focused health care to mitigate the negative effects of childhood, adolescent, and young adult cancer and support survivors' quality of life.

Contributors

JGM, SC, RLM, LCMK, MMH, RS, LSC, JV, JLL, and GM contributed to the conception and design of the study. JGM, SC, KB, JMCB, TMB, IE, EH, NSK-L, JWTK, JL, CJR, CEW, LW, RLM, LCMK, JLL, JV, and GM contributed to the search strategy, data extraction, interpretation of the data, and formulation of the recommendations. All authors, members of the International Guideline Harmonization Group Psychological Late Effects Guidelines Group, and survivor stakeholders critically revised the recommendations. JGM and SC drafted, and RLM, LCMK, MMH, RS, LSC, JV, JLL, and GM critically revised the Review. All authors approved the final version.

Declaration of interests

We declare no competing interests.

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References

- Ward ZJ, Yeh JM, Bhakta N, Frazier AL, Girardi F, Atun R. Global childhood cancer survival estimates and priority-setting: a simulation-based analysis. *Lancet Oncol* 2019; **20**: 972–83.
- Australian Childhood Cancer Registry, Cancer Council Queensland. Australian Childhood Cancer Statistics Online. CCQ: Brisbane A. Based on data from the ACCR (1983–2017). Brisbane, QLD: Cancer Council Queensland. 2021.
- Close AG, Dreyzin A, Miller KD, Seynnaeve BKN, Rapkin LB. Adolescent and young adult oncology—past, present, and future. *CA Cancer J Clin* 2019; **69**: 485–96.
- Miller KD, Fidler-Benaoudia M, Keegan TH, Hipp HS, Jemal A, Siegel RL. Cancer statistics for adolescents and young adults, 2020. *CA Cancer J Clin* 2020; **70**: 443–59.
- Brinkman TM, Recklitis CJ, Michel G, Grootenhuys MA, Klosky JL. Psychological symptoms, social outcomes, socioeconomic attainment, and health behaviors among survivors of childhood cancer: current state of the literature. *J Clin Oncol* 2018; **36**: 2190–97.
- Landier W, Skinner R, Wallace WH, et al. Surveillance for late effects in childhood cancer survivors. *J Clin Oncol* 2018; **36**: 2216–22.
- Zeltzer LK, Recklitis C, Buchbinder D, et al. Psychological status in childhood cancer survivors: a report from the childhood cancer survivor study. *J Clin Oncol* 2009; **27**: 2396–404.
- Burghardt J, Klein E, Brähler E, et al. Prevalence of mental distress among adult survivors of childhood cancer in Germany—compared to the general population. *Cancer Med* 2019; **8**: 1865–74.
- Michel G, Rebholz CE, von der Weid NX, Bergstraesser E, Kuehni CE. Psychological distress in adult survivors of childhood cancer: the Swiss childhood cancer survivor study. *J Clin Oncol* 2010; **28**: 1740–48.
- Fidler MM, Ziff OJ, Wang S, et al. Aspects of mental health dysfunction among survivors of childhood cancer. *Br J Cancer* 2015; **113**: 1121–32.
- Hudson MM, Oeffinger KC, Jones K, et al. Age-dependent changes in health status in the childhood cancer survivor cohort. *J Clin Oncol* 2015; **33**: 479–91.
- Gianinazzi ME, Rueegg CS, Wengenroth L, et al. Adolescent survivors of childhood cancer: are they vulnerable for psychological distress? *Psychooncology* 2013; **22**: 2051–58.
- Brinkman TM, Li C, Vannatta K, et al. Behavioral, social, and emotional symptom comorbidities and profiles in adolescent survivors of childhood cancer: a report from the childhood cancer survivor study. *J Clin Oncol* 2016; **34**: 3417–25.
- Zebrack BJ, Gurney JG, Oeffinger K, et al. Psychological outcomes in long-term survivors of childhood brain cancer: a report from the childhood cancer survivor study. *J Clin Oncol* 2004; **22**: 999–1006.
- Lown EA, Hijiya N, Zhang N, et al. Patterns and predictors of clustered risky health behaviors among adult survivors of childhood cancer: a report from the childhood cancer survivor study. *Cancer* 2016; **122**: 2747–56.
- Dutch Childhood Oncology Group. Guidelines for follow-up in survivors of childhood cancer 5 years after diagnosis. The Hague and Amsterdam: SKION, 2010.
- Scottish Intercollegiate Guidelines Network. Long term follow up of survivors of childhood cancer. A national clinical guideline. 2013. <http://www.sign.ac.uk/pdf/sign76.pdf> (accessed July 28, 2016).
- United Kingdom Children's Cancer Study Group Late Effects Group. Therapy based long term follow up—practice statement. April 2005. <https://www.cclg.org.uk/write/MediaUploads/Member%20area/Treatment%20guidelines/LTFU-full.pdf> (accessed Feb 18, 2022).
- American Psychological Association. APA Dictionary of Psychology. Washington, DC: American Psychological Association; 2015.
- Kremer LC, Mulder RL, Oeffinger KC, et al. A worldwide collaboration to harmonize guidelines for the long-term follow-up of childhood and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Pediatr Blood Cancer* 2013; **60**: 543–49.
- Gibbons RJ, Smith S, Antman E, American College of Cardiology, American Heart Association. American College of Cardiology/American Heart Association clinical practice guidelines: part I: where do they come from? *Circulation* 2003; **107**: 2979–86.
- Magid DJ, Aziz K, Cheng A, et al. Part 2: evidence evaluation and guidelines development: 2020 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2020; **142**: S358–65.
- Anestin AS, Lippe S, Robaey P, et al. Psychological risk in long-term survivors of childhood acute lymphoblastic leukemia and its association with functional health status: a PETALE cohort study. *Pediatr Blood Cancer* 2018; **65**: e27356.
- Krull KR, Huang S, Gurney JG, et al. Adolescent behavior and adult health status in childhood cancer survivors. *J Cancer Surviv* 2010; **4**: 210–17.
- Pépin AJ, Lippé S, Krajcinovic M, et al. How to interpret high levels of distress when using the Distress Thermometer in the long-term follow-up clinic? A study with acute lymphoblastic leukemia survivors. *Pediatr Hematol Oncol* 2017; **34**: 133–37.
- Schultz KA, Ness KK, Whitton J, et al. Behavioral and social outcomes in adolescent survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *J Clin Oncol* 2007; **25**: 3649–56.
- Zheng DJ, Krull KR, Chen Y, et al. Long-term psychological and educational outcomes for survivors of neuroblastoma: a report from the Childhood Cancer Survivor Study. *Cancer* 2018; **124**: 3220–30.
- Brinkman TM, Lown EA, Li C, et al. Alcohol consumption behaviors and neurocognitive dysfunction and emotional distress in adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Addiction* 2019; **114**: 226–35.
- Recklitis CJ, Parsons SK, Shih MC, Mertens A, Robison LL, Zeltzer L. Factor structure of the brief symptom inventory—18 in adult survivors of childhood cancer: results from the Childhood Cancer Survivor Study. *Psychol Assess* 2006; **18**: 22–32.
- Barakat LP, Kazak AE, Meadows AT, Casey R, Meeske K, Stuber ML. Families surviving childhood cancer: a comparison of posttraumatic stress symptoms with families of healthy children. *J Pediatr Psychol* 1997; **22**: 843–59.
- Schrag NM, McKeown RE, Jackson KL, Cuffe SP, Neuberger RW. Stress-related mental disorders in childhood cancer survivors. *Pediatr Blood Cancer* 2008; **50**: 98–103.
- Stuber ML, Meeske KA, Leisenring W, et al. Defining medical posttraumatic stress among young adult survivors in the Childhood Cancer Survivor Study. *Gen Hosp Psychiatry* 2011; **33**: 347–53.
- Kumin-Batson AS, Lu X, Balsamo L, et al. Prevalence and predictors of anxiety and depression after completion of chemotherapy for childhood acute lymphoblastic leukemia: a prospective longitudinal study. *Cancer* 2016; **122**: 1608–17.
- Lazor T, Pole JD, De Souza C, et al. Severity, change over time, and risk factors of anxiety in children with cancer depend on anxiety instrument used. *Psychooncology* 2019; **28**: 710–17.
- Myers RM, Balsamo L, Lu X, et al. A prospective study of anxiety, depression, and behavioral changes in the first year after a diagnosis of childhood acute lymphoblastic leukemia: a report from the Children's Oncology Group. *Cancer* 2014; **120**: 1417–25.
- Brinkman TM, Zhu L, Zeltzer LK, et al. Longitudinal patterns of psychological distress in adult survivors of childhood cancer. *Br J Cancer* 2013; **109**: 1373–81.

- 37 Derogatis LR, Fitzpatrick M. The SCL-90-R, the Brief Symptom Inventory (BSI), and the BSI-18. The use of psychological testing for treatment planning and outcomes assessment: instruments for adults. Volume 3, 3rd edn. Mahwah, NJ: Lawrence Erlbaum Associates Publishers, 2004: 1–41.
- 38 Liptak C, Manley P, Recklitis CJ. The feasibility of psychosocial screening for adolescent and young adult brain tumor survivors: the value of self-report. *J Cancer Surviv* 2012; **6**: 379–87.
- 39 Merport A, Recklitis CJ. Does the brief symptom inventory-18 case rule apply in adult survivors of childhood cancer? Comparison with the symptom checklist-90. *J Pediatr Psychol* 2012; **37**: 650–59.
- 40 Recklitis CJ, Rodriguez P. Screening childhood cancer survivors with the brief symptom inventory-18: classification agreement with the symptom checklist-90-revised. *Psychooncology* 2007; **16**: 429–36.
- 41 Recklitis CJ, Licht I, Ford J, Oeffinger K, Diller L. Screening adult survivors of childhood cancer with the distress thermometer: a comparison with the SCL-90-R. *Psychooncology* 2007; **16**: 1046–49.
- 42 van der Geest IMM, van Dorp W, Pluijm SMF, van den Heuvel-Eibrink MM. The distress thermometer provides a simple screening tool for selecting distressed childhood cancer survivors. *Acta Paediatr* 2018; **107**: 871–74.
- 43 Maurice-Stam H, Broek A, Kolk AM, et al. Measuring perceived benefit and disease-related burden in young cancer survivors: validation of the benefit and burden scale for children (BBSC) in The Netherlands. *Support Care Cancer* 2011; **19**: 1249–53.
- 44 Abate C, Lippe S, Bertout L, et al. Could we use parent report as a valid proxy of child report on anxiety, depression, and distress? A systematic investigation of father-mother-child triads in children successfully treated for leukemia. *Pediatr Blood Cancer* 2018; **65**: e26840.
- 45 Yoon SJ, Chung KM, Han JW, Hahn SM, Kim SH, Lyu CJ. Development and validation of self- and caregiver-report of a distress screening tool for pediatric cancer survivors. *Support Care Cancer* 2019; **27**: 4179–87.
- 46 Butler AC, Chapman JE, Forman EM, Beck AT. The empirical status of cognitive-behavioral therapy: a review of meta-analyses. *Clin Psychol Rev* 2006; **26**: 17–31.
- 47 Seitz DC, Knaevelsrud C, Duran G, Waadt S, Loos S, Goldbeck L. Efficacy of an internet-based cognitive-behavioral intervention for long-term survivors of pediatric cancer: a pilot study. *Support Care Cancer* 2014; **22**: 2075–83.
- 48 Poggi G, Liscio M, Pastore V, et al. Psychological intervention in young brain tumor survivors: the efficacy of the cognitive behavioural approach. *Disabil Rehabil* 2009; **31**: 1066–73.
- 49 Kazak AE, Alderfer MA, Streisand R, et al. Treatment of posttraumatic stress symptoms in adolescent survivors of childhood cancer and their families: a randomized clinical trial. *J Fam Psychol* 2004; **18**: 493–504.
- 50 Cheung AT, Li WHC, Ho KY, et al. Efficacy of musical training on psychological outcomes and quality of life in Chinese pediatric brain tumor survivors. *Psychooncology* 2019; **28**: 174–80.
- 51 Kazak AE, Abrams AN, Banks J, et al. Psychosocial assessment as a standard of care in pediatric cancer. *Pediatr Blood Cancer* 2015; **62** (suppl 5): S426–59.
- 52 Lown EA, Phillips F, Schwartz LA, Rosenberg AR, Jones B. Psychosocial follow-up in survivorship as a standard of care in pediatric oncology. *Pediatr Blood Cancer* 2015; **62** (suppl 5): S514–84.
- 53 Seedat S, Scott KM, Angermeyer MC, et al. Cross-national associations between gender and mental disorders in the World Health Organization world mental health surveys. *Arch Gen Psychiatry* 2009; **66**: 785–95.
- 54 Riecher-Rössler A. Sex and gender differences in mental disorders. *Lancet Psychiatry* 2017; **4**: 8–9.
- 55 Evans DL, Charney DS, Lewis L, et al. Mood disorders in the medically ill: scientific review and recommendations. *Biol Psychiatry* 2005; **58**: 175–89.
- 56 Roy-Byrne PP, Davidson KW, Kessler RC, et al. Anxiety disorders and comorbid medical illness. *Gen Hosp Psychiatry* 2008; **30**: 208–25.
- 57 Devine KA, Christen S, Mulder RL, et al. Recommendations for the surveillance of education and employment outcomes in survivors of childhood, adolescent and young adult cancer: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Cancer* (in press).
- 58 Armenian SH, Hudson MM, Mulder RL, et al. Recommendations for cardiomyopathy surveillance for survivors of childhood cancer: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Lancet Oncol* 2015; **16**: e123–36.
- 59 Christen S, Roser K, Mulder RL, et al. Recommendations for the surveillance of cancer-related fatigue in childhood, adolescent, and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *J Cancer Surviv* 2020; **14**: 923–38.
- 60 Clemens E, van den Heuvel-Eibrink MM, Mulder RL, et al. Recommendations for ototoxicity surveillance for childhood, adolescent, and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group in collaboration with the PanCare Consortium. *Lancet Oncol* 2019; **20**: e29–41.
- 61 Clement SC, Kremer LCM, Verburg FA, et al. Balancing the benefits and harms of thyroid cancer surveillance in survivors of Childhood, adolescent and young adult cancer: recommendations from the international Late Effects of Childhood Cancer Guideline Harmonization Group in collaboration with the PanCareSurFup Consortium. *Cancer Treat Rev* 2018; **63**: 28–39.
- 62 Mulder RL, Font-Gonzalez A, Green DM, et al. Fertility preservation for male patients with childhood, adolescent, and young adult cancer: recommendations from the PanCareLIFE Consortium and the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Lancet Oncol* 2021; **22**: e57–67.
- 63 Mulder RL, Font-Gonzalez A, Hudson MM, et al. Fertility preservation for female patients with childhood, adolescent, and young adult cancer: recommendations from the PanCareLIFE Consortium and the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Lancet Oncol* 2021; **22**: e45–56.
- 64 Mulder RL, Font-Gonzalez A, van Dulmen-den Broeder E, et al. Communication and ethical considerations for fertility preservation for patients with childhood, adolescent, and young adult cancer: recommendations from the PanCareLIFE Consortium and the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Lancet Oncol* 2021; **22**: e68–80.
- 65 Mulder RL, Hudson MM, Bhatia S, et al. Updated breast cancer surveillance recommendations for female survivors of childhood, adolescent, and young adult cancer from the International Guideline Harmonization Group. *J Clin Oncol* 2020; **38**: 4194–207.
- 66 Skinner R, Mulder RL, Kremer LC, et al. Recommendations for gonadotoxicity surveillance in male childhood, adolescent, and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group in collaboration with the PanCareSurFup Consortium. *Lancet Oncol* 2017; **18**: e75–90.
- 67 van der Kooi ALF, Mulder RL, Hudson MM, et al. Counseling and surveillance of obstetrical risks for female childhood, adolescent, and young adult cancer survivors: recommendations from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Am J Obstet Gynecol* 2021; **224**: 3–15.
- 68 van Dorp W, Mulder RL, Kremer LC, et al. Recommendations for premature ovarian insufficiency surveillance for female survivors of childhood, adolescent, and young adult cancer: a report from the International Late Effects of Childhood Cancer Guideline Harmonization group in collaboration with the PanCareSurFup Consortium. *J Clin Oncol* 2016; **34**: 3440–50.

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