

REVIEW ARTICLE

A systematic review of self-reported pain in childhood cancer survivors

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Abstract

Aim: The aim of this systematic review was to examine the frequency and risk factors of pain among long-term childhood cancer survivors based on self-reported questionnaire studies. Participants aged 21 years or younger at the time of their cancer diagnosis were included.

Methods: The Medline (OVID), PubMed and PsycINFO databases were searched for manuscripts published between January 1, 1990, and August 31, 2018, following the PRISMA statement for reporting systematic reviews.

Results: In total, 25 studies, including five prospective cohort studies measuring pain up to 32 years post-diagnosis, were identified. Female sex, young age at diagnosis, older age at assessment, greater time since diagnosis, specific diagnoses (such as central nervous system [CNS] tumours, bone tumours and sarcoma), fatigue and persistent emotional distress were associated with cancer-related pain. The most common pain types were migraines, headaches and back pain.

Conclusion: A subset of childhood cancer survivors reported clinically significant self-reported pain. Identifying survivor subgroups at risk for pain could be essential for developing tailored intervention and prevention strategies. Prospective studies that use standardised and psychometrically sound tools to evaluate pain are needed.

KEYWORDS

childhood cancer survivors, demographics, medical and treatment, pain, psychological

1 | INTRODUCTION

Improvements in the survival rate of childhood cancer patients, which is currently up to 80% among most children,¹ have contributed to an increased focus on the late effects of cancer treatment during childhood. Two-thirds of childhood cancer survivors experience at least one physical late effect due to their treatment and disease status. These effects may affect their educational, psychological and social development.²

Late effects clinics treat childhood cancer survivors who frequently experience pain localised to the abdomen, head, neck, shoulders, back, knees and hips.^{3,4} The pain may be related to the survivor's cancer experience in childhood due to disease, treatment (such as surgery, chemotherapy and radiotherapy), procedures (such as lumbar puncture) or a combination of all three factors.^{2,4} However, despite its frequency in children and adolescents and evidence of pain persisting into adulthood, pain has remained understudied compared to other late effects.⁵

Abbreviations: ALL, acute lymphoblastic leukaemia; BPI, Brief Pain Inventory; CCSS, Childhood Cancer Survivor Study; CNS, central nervous system tumours; HRQOL, Health-Related Quality of Life; HUI, Health Utilities Index questionnaire; PCF, persistent chronic fatigue; PPST, Pediatric Pain Screening Tool; PRISMA, Systematic Reviews and Meta-Analyses; SF-36/RAND-36, Short Form Health Survey; SI, suicidal ideation.

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With the exception of a recent topical review of chronic pain in survivors of childhood cancer,⁵ to the best of our knowledge, no study has systematically reviewed the research literature on self-reported pain outcomes in long-term adult survivors of childhood cancer with a broader focus. The aim of this systematic review was to examine the frequency and risk factors of pain among long-term childhood cancer survivors based on self-reported questionnaire studies.

2 | PATIENTS AND METHODS

2.1 | Eligibility criteria and information sources

The inclusion criteria were as follows: (a) studies published in English in a peer-reviewed journal, (b) studies published between January 1, 1990, and August 31, 2018, (c) studies with at least one self-reported pain measure and/or Health-Related Quality of Life (HRQOL) self-report measure with a pain-specific domain and the assessment of pain as an outcome or predictor variable and (d) studies assessing pain in patients who transitioned into long-term survivorship, were aged 21 years or younger at the time of their cancer diagnosis and had a minimum follow-up time of 5 years after diagnosis. Literature reviews, case studies, qualitative methodologies, intervention studies examining pain treatment, methodological manuscripts and unpublished manuscripts were excluded.

The Medline (OVID), PubMed, and PsycINFO online databases were searched using the terms “*childhood cancer survivors*”, “*young adult survivors of childhood cancer*” and “*adult survivors of childhood cancer*”, each in combination with “*symptoms*” and “*pain*” and then further combined with “*quality of life*”, “*psychological*”, “*demographic*”, “*fatigue*” and “*medical and treatment*”. In addition, synonyms such as “*pediatric*”, “*paediatric*”, and “*oncology*” were used. Additional papers were identified in the reference lists of the eligible articles and via a search in Google Scholar. This review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for reporting systematic reviews.⁶

2.2 | Study selection and data collection process

The search was conducted at the following three levels. First, the titles were screened to exclude articles that were not relevant to the study's focus and to remove duplicates. Second, all relevant abstracts were reviewed. The first author (TR) screened the titles and abstracts of the eligible studies. Third, during the final stage, the full-text manuscripts were examined to ensure that the articles fulfilled the inclusion/exclusion criteria. Two reviewers (TR and LZ) independently screened the potentially eligible full-text articles for inclusion. After the full-text screening, the data were extracted from the included studies (TR and LZ), and any differences were resolved through discussion and reference to the original studies.

Key notes

- Pain does not appear to be more prevalent in survivors of childhood cancer than in the general population, except for specific subgroups of patients.
- Long-term survivors diagnosed at age <10 years report more pain in adult life than survivors diagnosed at an older age, indicating a need for better pain management during cancer treatment in childhood.
- Prospective studies investigating pain outcomes in childhood cancer survivors using psychometrically sound pain measurements are needed.

3 | RESULTS

3.1 | Literature search

Database searches identified 505 studies, and 5 additional articles were identified for inclusion using other sources, such as the reference lists of the eligible articles and a search in Google Scholar, for a total of 510 relevant studies. After the exclusion of 311 articles at the title stage and the removal of duplicates, 199 studies remained for screening. The abstracts were reviewed, resulting in the exclusion of 167 abstracts based on the inclusion/exclusion criteria (see Figure 1). Thirty-two full-text articles were further assessed for eligibility. Seven full-text manuscripts were excluded for various reasons (see Figure 1). A detailed summary of the 25 studies remaining for review is provided in Table 1.

3.2 | Study characteristics

Based on the eligibility criteria, 25 articles were identified, including five prospective cohort studies measuring pain that ranged from five to 32 years after diagnosis with a reported mean time since diagnosis of 17.4 years.^{1,7-10} Twenty cross-sectional studies were identified (Table 1). Seventeen studies were multicentre studies^{1,2,7-21} and fifteen of those studies were based on data from the Childhood Cancer Survivor Study (CCSS). The CCSS is a large multi-institutional cohort study of childhood cancer survivors in the United States and Canada.²² All studies compared the outcomes with one of the following: age-matched population norms,^{1,3,13,18,20,23-25} both age-matched norms and cancer groups,^{14,23} siblings,^{2,7,10-12,15-17,21} both siblings and age- and gender-specific population norms,² and other cancer/treatment groups.²⁶⁻²⁸ Three studies compared the samples over two⁸ or three time points,⁹ and one study compared the samples over three decades.¹⁷ The sample sizes ranged from 388 to 16 079 in the longitudinal studies^{1,10} and from 27 to 14 566 in the cross-sectional studies.^{17,27} Age at the time of evaluation was generally ≥ 18 years. The mean ages at assessment ranged from 15.7 to

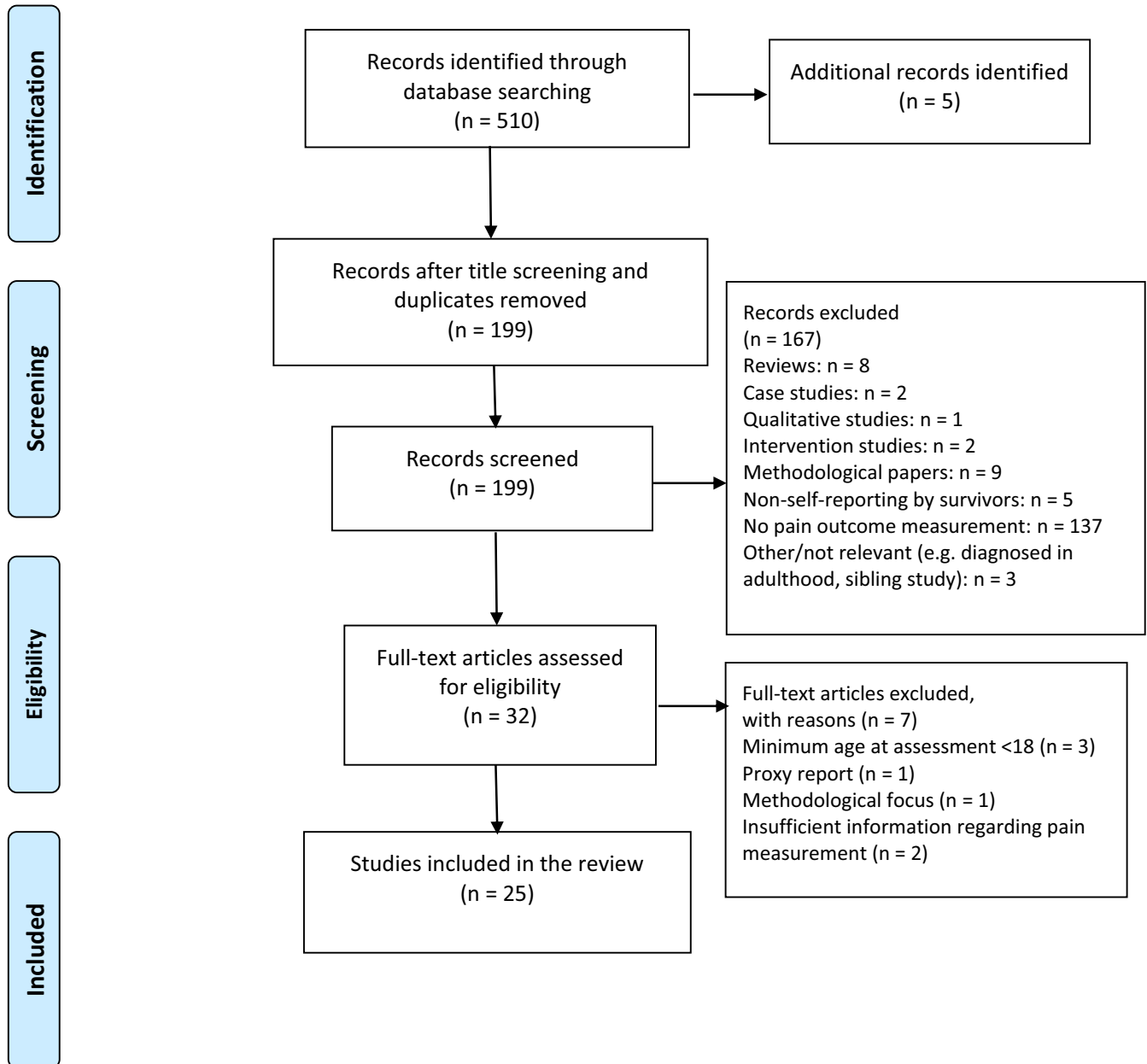


FIGURE 1 Flow diagram of search results

63.3 years in the cross-sectional studies and 27.4 to 33 years in the longitudinal prospective studies (Table 1).

Regarding diagnostic groups, 17 studies included patients with heterogeneous diagnoses.^{1-3,7-12,14,16,17,19,21,23,25,26} Furthermore, nine studies focused on specific homogenous subgroups of patients with diagnoses such as acute lymphoblastic leukaemia (ALL), leukaemia, lymphoma,^{24,27-29} Hodgkin's lymphoma,¹³ rhabdomyosarcoma,¹⁵ osteosarcoma, soft tissue sarcoma, Ewing's sarcoma, other bone tumours⁸ and CNS tumours.^{18,20}

The bodily scale from the 36-item Short Form Health Survey (SF-36) was used in eight studies,^{2,7,13,14,19,25,29,30} the RAND-36, which is similar to the SF-36, was used in one study,²³ and the other studies used the Brief Pain Inventory (BPI) method.^{27,28} The Health Utilities Index questionnaire (HUI2 and HUI3) was used by Alessi

et al²⁶ and two Swedish studies.^{18,20} Nine studies^{1,8,9,12,13,15,17,21,24} used health status domains, including pain questions from the CCSS baseline survey, and 3 studies^{7,10,11} used pain questionnaires (CCSS baseline survey) (Table 1). All studies were based on survivor self-reporting. Three studies used both the generic SF-36 measure and a pain measure from the CCSS survey.^{3,7,13}

The main results and the specific pain types associated with the various factors mentioned in the results section are shown in Table 1.

3.3 | Prevalence, localisation and temporal changes in pain

Inconsistency in pain prevalence among survivors of childhood cancer was reported and ranged from 10%²¹ to 59%.³ Regarding

specific cancer diagnoses and the localisation of pain, the highest pain prevalence was reported in survivors of sarcoma (14.8%) and bone cancer (23%) in the study by Hudson et al,²¹ and back pain was a frequent symptom among adult ALL survivors.¹⁷ Furthermore, first primary rhabdomyosarcoma (RMS) survivors of the parameningeal region (23%), extremities (23%) or bladder/prostate (20%) were disproportionately affected by cancer pain compared with the overall proportion of survivors who reported this outcome (15%)¹⁵ Lu et al¹¹ found that pain conditions, including pain/abnormal sensations, migraines and other headaches, were reported by 12.3%, 15.5% and 20.5% of survivors, respectively. Furthermore, 21% of survivors attributed the pain to cancer and treatment. In a study conducted by Huang et al,³ survivors reported a high pain prevalence (>50%) involving sites other than the head, neck and back along with disfigurement; 49% of survivors reported back/neck pain, and 36% of survivors reported head pain. Phillips et al¹ found that the pain prevalence remained stable from the time since diagnosis.

One study on CNS survivors reported pain prevalence by severity, indicating that while most (35%) survivors reported mild or moderate pain, only 3% suffered from severe pain.¹⁸ Similarly, only 3.4% of survivors with mixed diagnoses reported severe levels of pain; however, moderate levels of current pain attributed to cancer or treatment were reported by 6.7% of the survivors.¹¹

Several studies found no difference in pain frequency and severity between survivors and the general population or siblings as controls,^{2,16,18,25} except for survivors of bone cancers and soft tissue sarcomas in the study by Zeltzer et al.² However, in the CCSS study, pain was more likely to occur among survivors in general compared to siblings as controls.^{7,10,11,26}

Furthermore, temporal changes in cancer therapy were investigated by Ness et al¹⁷ who found that cancer-related pain increased from 1970 to the 1990s among acute lymphocytic leukaemia and osteosarcoma survivors.

3.4 | Demographic factors associated with self-reported pain

In the survivor group, female sex was the most important covariable correlated with self-reported pain reports (HRQOL),^{2,21,26} current cancer-related pain⁸ and pain conditions (pain/abnormal sensation, migraines and other headaches), which were significantly more common in females than in males.¹¹

Other demographic variables associated with pain in long-term survivors of childhood cancer included sociodemographic variables, such as lower education,^{2,11,24} unemployment, single/unmarried status,^{2,11,15} annual household income <\$20 000²¹ and minority status^{11,15} (see Table 1). These risk factors correspond with known risk factors for pain in survivors of childhood cancer and in clinical and general adult populations (eg for gender,³¹ lower socioeconomic status,³² minority status³³ and unemployment³⁴). Furthermore, Oancea et al²⁴ found that cancer-related pain both directly and indirectly affected distress symptoms based on the socioeconomic status of the survivors.

3.5 | Diagnosis- and treatment-related factors associated with self-reported pain

The time since diagnosis was for some studies associated with worsening pain.^{3,8,9,23} Regarding treatment, patients with histories of abdominal radiation exhibited even more profound effects of current cancer-related pain,⁸ and surgery was associated with poor scores for bodily pain (SF-36).² Long-term survivors of CNS tumours,²⁶ retinoblastoma,²⁶ bone cancers^{2,11,17,21,26} and sarcoma^{2,21} reported more pain than survivors of other forms of cancer.

Morbidities generally increased with age, and older age at the time of the survey (survivors aged >30 years) was associated with bodily pain (SF-36)^{1,2} and current cancer-related pain.^{8,17,21} Younger age at diagnosis (ie ≤3 years in the study conducted by Lu et al¹¹ and <10 years in two other studies^{2,26}) was related to bodily pain as measured by HRQOL (SF-36) self-reports and cancer-related pain (eg headache and other bodily pain). In addition, pain was found to be associated with a poorer body image and lower sports- and physical activity-related confidence.²⁰

3.6 | Emotional distress associated with self-reported pain

Emotional distress was associated with self-reported pain in survivors of childhood cancer^{7,9,10,12,14,19,24,29,30} and was in a longitudinal study strongly associated with the increased use of pain medications⁷ and with persistent and increasing distress symptoms over time.⁹ Further, Recklitis et al¹² found that 8.8% of survivors reported suicidal ideation (SI) compared with 4.6% of the controls, and cancer-related pain¹² and severity¹⁴ was found to be associated with SI.

Comorbid distress was found to be associated with headaches, and bodily pain.¹⁰ In a study conducted by Rach et al,¹³ fatigue was associated with elevated bodily pain. In an investigation of long-term survivors of childhood ALL and lymphoma with persistent chronic fatigue (PCF), Zeller et al²⁷ found that a subgroup had more severe levels of pain. Furthermore, survivors with PCF reported significantly higher levels of pain severity and pain interfering with functioning,²⁸ and a higher proportion of survivors reported that the most intensive pain was located in their neck and shoulder regions.²⁷ Similar results were reported by Meeske et al²⁹; the presence of pain was associated with the presence of fatigue and depression.

4 | DISCUSSION

The frequency and risk factors of self-reported pain among long-term childhood cancer survivors were examined in this systematic review. Several studies indicated that bodily pain is not more prevalent in survivors of childhood cancer than in the general population.^{2,16,18,25} However, the studies reporting pain prevalence showed a great variation in scores,^{1,3,11,18} and the pain prevalence in the general population varied as well.³⁵ This may complicate the investigation of the prevalence of pain in childhood cancer survivors with regard

TABLE 1 Summary of studies included in this review of self-reported pain in long-term childhood cancer survivors

Study Age at diagnosis (years)	Sample (N) Comparison group (N)	Age at evaluation (Years)	Time between diagnosis and evaluation of pain (years)	Pain measurements and type of pain	Pain-related findings Specific pain types (if reported in the reviewed papers)
Longitudinal					
Brinkman et al (2013), ⁷ Multicentre (26), the United States, Canada Median (range): 7 (0-20)	Mixed diagnoses, 10387 (baseline) Siblings, 3206	≥18 y Mean (s.d., range): 27.4 (6.0, 18-48)	≥5 y 5-10 (9.9%) 11-20 (64.3%) ≥21 (25.8%)	SF-36 (bodily pain subscale), past 4 wk Pain frequency and extent to which pain interferes with normal activities. Pain questionnaire (CCSS survey) Survivors were asked if they had 'ever been told by a doctor/other health care professional that they have or have had any of the following pain conditions': 'prolonged pain or abnormal sensation in the arms, legs, or back', 'migraine' or 'other frequent headaches'. Participants were given response op- tions of 'yes', 'no' or 'not sure'	1. Survivors were significantly more likely to report pain than their siblings. 2. Pain symptoms were associated with the use of medica- tions for psychiatric conditions (eg depression and anxiety). 3. Headache (vs. none) and bodily pain (vs. none) predicted psychoactive medication use at baseline and new onset psychoactive medication use in survivors. 4. Reduced functioning on the HRQOL Pain Subscale was associated with psychoactive medication (non-opioids, opioids, antidepressants and muscle relaxants).
Brinkman et al (2013), ⁹ Multicentre (26), the United States, Canada Mean (s.d., range): 10.0 (5.6, 0-20)	Mixed diagnoses, 4569 (baseline)	≥18 y Mean (s.d., range): 27.4 (6.0, 18-48) (1)	Mean (s.d.), (range): 17.4 (4.6), (6-32)	Health status domains (CCSS survey) Current cancer-related pain rated as 'none/small amount', 'medium amount/ or 'a lot/very bad'	1. Survivors' perception of increased pain severity was significantly associated with persistent and increasing distress symptoms over time.
Marina et al (2013), ⁸ Multicentre (26), the United States, Canada Median age (range): 13 (0-20)	Childhood extremity (upper and lower) sarcoma survivors, 1044 (baseline)	≥18 y Mean (range): 33 (10-53)	≥5 y 5-14 (42.1%) 15-19 (33.7%) 20-29 (24.2%)	Health status domains (CCSS survey) Current cancer-related pain, rated as 'none/small amount', 'medium amount' or 'a lot/very bad'	1. Cancer-related pain worsened over time as the survivors aged. 2. Pain was associated with older age at the time of the questionnaire. 3. Female sex and a history of abdominal radiation were associated with cancer-related pain.
Phillips et al (2015), ¹ Multicentre (9), the United States 0-19 y	Mixed diagnoses, 388501 CCSS samples com- pared to the SEER population ^a	≥20 y	≥ 5 y post-diagnosis (83%) ≥ 20 y (45%)	Pain refers to prevalence Health status domains (CCSS survey) Current cancer-related pain, rated as 'none/small amount', 'medium amount' or 'a lot/very bad'	1. Proportion of prevalent cases of impaired pain increased by age, ranging from 10% (20-29) to 42% (30-39) and 15% (40-49). 2. Estimated prevalence of pain morbidity (12%). 3. Time since diagnosis, for example survivors ≥5 y post- diagnosis. Pain remained stable by time since diagnosis, 11% (5-14), 11% (15-24), 13% (25-36).

(Continues)

TABLE 1 (Continued)

Study	Sample (N)	Age at evaluation (Years)	Time between diagnosis and evaluation of pain (years)	Pain measurements and type of pain	Pain-related findings
Age at diagnosis (years)	Comparison group (N)	Age at evaluation (Years)	Time between diagnosis and evaluation of pain (years)	Pain measurements and type of pain	Pain-related findings
D'Agostino et al (2016). ¹⁰ Multicentre (31), the United States, Canada Median age (range): 10 (0-20)	Mixed diagnoses, 16079 (baseline) Siblings, 3085	Median (range): 26 (18-48)	Median (range): 17.7 (6.4-31.1)	Pain questionnaire (CCSS survey) Survivors were asked if they had 'ever been told by a doctor/other healthcare professional that they have or have had any of the following pain conditions: 'prolonged pain or abnormal sensation in the arms, legs, or back', 'migraine' or 'other frequent headaches'. Participants were given response options of 'yes', 'no' or 'not sure'	Specific pain types (if reported in the reviewed papers) 1. Survivors reported significantly more pain than siblings. 2. Headaches and bodily pain were associated with comorbid distress.
Cross-sectional					
Hudson et al (2003). ²¹ Multicentre (26), the United States, Canada Mean (s.d., range): 10.0 (5.6, 0.1-20.9)	Mixed diagnoses, 9535 Siblings, 2916	Mean (range): 26.8 (18-48)	Mean (range): 17.4, (6-29)	Health status domains (CCSS survey) Current cancer-related pain, rated as 'none/small amount', 'medium amount' or 'a lot/very bad'	1. Pain prevalence in survivors by age: 8.5% (18-24) to 9.7% (25-29) and 12.8% (30-34) and 12.8 (≥35). 2. Total survivors with pain: 10.2%. 3. Highest pain prevalence: Survivors of sarcoma (14.8%) and bone cancer (23%). 4. Pain prevalence increased by age at diagnosis: 8.5% (0-4), 8.6% (5-9), 11.1% (10-14) and 15.7% (15-21) 5. Female sex was associated with adverse outcomes in all domains except for cancer-related pain. 6. Among all disease groups, cancer-related pain was associated with older age at the time of the interview. 7. Older survivors (35 y and older) were more likely to report adverse outcomes of cancer-related pain as a result of cancer or its treatment than survivors aged 18-24. 8. Cancer-related pain was more frequently reported by survivors of paediatric bone tumours and sarcoma treated with chemotherapy and aggressive surgery or radiation than by leukaemia survivors.
Recklitis et al (2006). ¹⁴ Multicentre (26), the United States, Canada Mean (s.d.): 10.08 (5.47)	Mixed diagnoses, 226 Normative population norms Comparison of suicidal and non-suicidal adults	Mean age (s.d.): 28.38 (7.91)	Mean (s.d.): 18.30 (7.90)	SF-36 (bodily pain subscale), past 4 wk Pain frequency and the extent to which pain interferes with normal activities	1. Current bodily pain was significantly associated with suicidal symptoms even after adjusting for treatment and depression.

(Continues)

TABLE 1 (Continued)

Study	Sample (N)	Age at evaluation (Years)	Time between diagnosis and evaluation of pain (years)	Pain measurements and type of pain	Pain-related findings
Blaauwbroek et al (2007). ²³	Mixed diagnoses, 313 (LF, 129); (VLF, 184)	Median (range): LF, 24 (19-45); VLF, 32 (21-60)	Median, (range): LF: 16 (7-20); VLF: 26 (21-38)	RAND-36 (SF-36) (bodily pain subscale), past 4 wk Pain frequency and the extent to which pain interferes with normal activities	Specific pain types (if reported in the reviewed papers) VLF: 1. Survivors diagnosed more than 20 y prior had significantly higher bodily pain than survivors with a follow-up of less than 20 y. LF: 2. LF patients had a significantly better score on the bodily pain subscale than the standard population. 3. Psychosocial late effects were negatively associated with bodily pain. 4. Orthopaedic and cosmetic late effects were negatively related to bodily pain.
Alessi et al (2007). ²⁶ Single centre, Italy 0-15 y	Mixed diagnoses, 691 Comparison of cancer types	15-25 25-34 ≥35	≥ 5 y	Health Utilities Index questionnaire Health status and HRQOL, including pain The attribute levels provide single-attribute utility scores estimated on a scale ranging from 0.00 (worst level) to 1.00 (best level or no impairment)	1. Female survivors reported more pain than male survivors. 2. Survivors with a younger age at diagnosis (<10 y) had more pain than survivors diagnosed between 10 to 14 y of age. 3. Long-term survivors of CNS tumours showed worse pain than survivors of other forms of cancer.
Punyko et al (2007). ¹⁵ Multicentre (26), the United States, Canada Age: <1-15+	First primary rhabdomyosarcoma (RMS), 417 Siblings = 2865	≥ 18 y 18-24 25-34 35-45	≥ 5 y	Health status domains (CCSS survey) Current cancer-related pain, rated as 'none/small amount', 'medium amount', or 'a lot/very bad'	1. Survivors reporting moderate to high levels of cancer-related pain had an increased likelihood of being married and a lower likelihood of completing high school. 2. RMS survivors of the parameningeal region (23%), extremities (23%), or bladder/prostate (20%) were disproportionately affected by cancer pain compared with the overall proportion of survivors who reported this outcome (15%).
Zeltzer et al (2008). ² Multicentre (26), the United States, Canada Median (range): 7 (0-20)	Mixed diagnoses, 7147, Siblings, 388 Age- and gender-specific population norms	≥18 y Median (range): 32 (18-58)	≥5 y Median (range): 23 (15-34)	SF-36 (bodily pain subscale), past 4 wk Pain frequency and the extent to which pain interferes with normal activities	1. No difference in bodily pain between survivors in general and siblings, except for increased bodily pain reported among soft tissue sarcoma and bone cancer survivors. 2. Increased risk of bodily pain was associated with older age, lower educational attainment and lack of employment. 3. Decreased risk of bodily pain was associated with a younger age at diagnosis, that is <10 y of age. 4. Survivors diagnosed >10 y of age or treated >30 y ago reported better HRQOL in bodily pain. 5. Female survivors reported more pain than male survivors.

(Continues)

TABLE 1 (Continued)

Study	Sample (N)	Age at evaluation (Years)	Time between diagnosis and evaluation of pain (years)	Pain measurements and type of pain	Pain-related findings
Boman et al (2013). ²⁰ Multicentre (6), Sweden Age: ≥8 y	CNS tumours, 708	≥18 y mean (s.d.) 26.3 (4.98)	Mean (s.d.) 15.7 (5.03)	Health Utilities Index questionnaire (HUI 2/3) Health status and HRQOL, including pain The attribute levels provide single-attribute utility scores estimated on a scale ranging from 0.00 (worst level) to 1.00 (best level or no impairment)	Specific pain types (if reported in the reviewed papers) 1. Pain associated with poorer body image and lower sports and physical activity-related confidence.
Boman et al (2009). ¹⁸ Multicentre (6), Sweden Age: ≥8 y	CNS tumours, 708 General population controls, 1000	≥18 y Mean (s.d.) 26.1 (5.0)	Mean (s.d.) 15.7 (5.1)	Health Utilities Index questionnaire (HUI 2/3) Health status and HRQOL, including pain The attribute levels provide single-attribute utility scores estimated on a scale ranging from 0.00 (worst level) to 1.00 (best level or no impairment)	1. No difference in pain frequency and severity between survivors and controls from the general population.
Zeller et al (2014). ²⁷ Single centre, Norway Median (range): 10.1 (1.6-18.4)	ALL with CF, 13 Lymphoma with CF, 14 Case-control: Survivors without CF, 35	Mean, (s.d.) 33.7 (6.6)	Median (range): 25.3 (11.3-39.9)	Brief Pain Inventory (BPI), Pain severity and interference, current and past 24 hours Algometer Commander, J-Tech Medical (measure of pain sensitivity)	1. Survivors with Persistent Chronic Fatigue (PCF) reported significantly more pain in both severity and interference with function, and a higher proportion had the most intensive pain in the neck and shoulder region. 2. No significant differences in pain pressure threshold between survivors with CF and controls.
Zeller et al (2014). ²⁸ Single centre, Norway Median (range): 10.1 (1.6-18.4)	ALL, Lymphoma, 79, Survivor controls without CF, 211	Mean 33.7 (6.6)	Median (range): 25.3 (11.3-39.9)	Self-report measure of headache, muscular pain, and joint pain rated on a scale from ('never/rarely present') to 5 ('present all time')	1. CF survivors reported increased frequency of headache, muscular pain and joint pain compared with controls.
Recklitis et al (2010). ¹² Multicentre (25), the United States Median (range): 7 (0-20)	Mixed diagnoses, 9126 Siblings, 2968	≥18 y, range: (18-48)	≥5 y, range: 6-29 y	Health status domains (CCSS survey) Current cancer-related pain, rated as 'none/small amount', 'medium amount' or 'a lot/very bad'	1. Prevalence and severity of cancer-related pain was associated with survivors reporting suicidal ideation (SI). 2. Higher prevalence of SI among CNS cancer survivors compared to leukaemia survivors. 3. SI was associated with the use of more pain medication in both survivors and siblings.

(Continues)

TABLE 1 (Continued)

Study Age at diagnosis (years)	Sample (N) Comparison group (N)	Age at evaluation (Years)	Time between diagnosis and evaluation of pain (years)	Pain measurements and type of pain	Pain-related findings Specific pain types (if reported in the reviewed papers)
Lu et al (2011). ¹¹ Multicentre (26), the US, Canada Median (range): 7 (0-20)	Mixed diagnoses, 10397 Siblings, 3034	≥18 y Age at study (years) 18-29 (n = 7165) 30-39 (n = 2901) >39 (n = 331)	≥5 y Mean (s.d., range): 16.5, (4.9, 5-31)	Pain questionnaire (CCSS survey) Survivors were asked if they had 'ever been told by a doctor/other healthcare professional that they have or have had any of the following pain conditions': 'prolonged pain or abnormal sensation in the arms, legs, or back', 'migraine' or 'other frequent headaches' Participants were given response options of 'yes', 'no' or 'not sure'	1. Frequency of pain conditions (pain/abnormal sensation, migraines, and other headaches) reported by 12.3%, 15.5% and 20.5% of survivors. 2. 21% attributed pain to cancer and treatment. 3. Risk of reporting pain conditions and using prescription analgesics was higher among survivors than siblings after adjusting for sociodemographic factors. 4. Increased risk of reporting pain conditions among sur- vivors with a younger age at diagnosis, a history of non- Hodgkin lymphoma, Wilms tumour or neuroblastoma (compared to leukaemia survivors). 5. Increased risk of reporting cancer-related pain and/ or migraines among survivors with bone cancer or soft tissue sarcoma compared to patients with leukaemia and non-brain scatter irradiation. 6. Prevalence of pain conditions and/or pain severity was higher among females and those with lower educational attainment, minority status, unemployment and single status.
Huang et al (2013). ³ Single centre, the United States	Mixed diagnoses, 1667 Population norms	≥18 y Mean, s.d (range) 33.7, 8.2 (18.9-63.3)	Mean (s.d., range): 25.5 (7.8, 11.0-48.0)	Twelve physical symptom classes (adapted from the CCSS health questionnaire) Including pain: pain in head (3 item), pain in back/neck (2 item), and pain involving sites other than the head, neck and back (7 items)	1. Pain prevalence: 58.7% in sites other than the head and neck, 35.9% in the head, and 48.5% in the back/neck. 2. Pain involving sites other than the head, neck, and back was significantly associated with impairment in HRQOL.
Meeske et al (2005). ²⁹ Single centre, the United States Median (range): 7.4 (0-18)	ALL, 161 (44%)	≥18 y	Mean 14 y	SF-36 (bodily pain subscale), past 4 wk Pain frequency and the extent to which pain interferes with normal activities	1. Presence of pain was associated with the presence of fatigue and depression. Pain increased the risk of fatigue and depression.
Ness et al (2008). ¹⁹ Multicentre (26), the United States 0-20 y	Mixed diagnoses, 7147 (76.8%)	Participated between 2002 - 2004	≥5 y	SF-36 (bodily pain subscale), past 4 wk Pain frequency and the extent to which pain interferes with normal activities	1. Lower physical performance, executive functioning and emotional health were each associated with higher likeli- hood of reporting bodily pain.
Sundberg et al (2010). ²⁵ Single centre, Sweden Mean age, 9 y	Mixed diagnoses, 246 (70%) 29% controls from the general population	≥18 y, mean age (24)	Median, 16 y post-diagnosis	SF-36 (bodily pain subscale), past 4 wk Pain frequency and the extent to which pain interferes with normal activities	1. No difference between survivors and general healthy population in severity of bodily pain.

(Continues)

TABLE 1 (Continued)

Study	Sample (N)	Age at evaluation (Years)	Time between diagnosis and evaluation of pain (years)	Pain measurements and type of pain	Pain-related findings
<p>Oancea et al (2014).²⁴ Single centre, the United States Median (range): 7 (0-20)</p>	<p>Mixed diagnoses, 1863, Leukaemia diagnoses 41% Compared to norms</p>	<p>Median age, (range) 32, (26-38)</p>	<p>≥10 y post-diagnosis</p>	<p>Health status domains (CCSS survey) Current cancer-related pain, rated as 'none/small amount of pain', 'medium amount' or 'a lot/very bad'</p>	<p>Specific pain types (if reported in the reviewed papers) 1. Increased cancer-related pain was associated with increased emotional distress. 2. Those who self-reported cancer-related pain were more likely to have elevated emotional distress than survivors reporting no cancer-related pain. 3. Increased pain was associated with increased risk of anxiety, depression and somatisation.</p>
<p>Rach et al (2017).¹³ Multicentre (26), the United States, Canada 0-20 y</p>	<p>Hodgkin's lymphoma, 751 Population norms ≥35 (majority)</p>	<p>18-24 25-29 30-34 ≥35 (majority)</p>	<p>>5 y</p>	<p>SF-36 (bodily pain subscale), past 4 wk Pain frequency and the extent to which pain interferes with normal activities Health status domains (CCSS survey) Current cancer-related pain, rated as 'none/small amount of pain', 'medium amount' or 'a lot/very bad'</p>	<p>1. Survivors with elevated bodily pain had an increased risk of fatigue and poorer sleep quality. 2. Bodily pain reported by survivors was related to excessive daytime sleepiness. 3. Elevated levels of cancer-related pain were associated with poorer sleep quality.</p>
<p>Huang et al (2017).¹⁶ Multicentre (26), the United States, Canada 0-20 y</p>	<p>Mixed diagnoses, 7103 Siblings, N = 390</p>	<p>31.8 (7.5)</p>	<p>>5 y 10-30+ 20-30 + (73%)</p>	<p>SF-36 (bodily pain subscale), past 4 wk Pain frequency and the extent to which pain interferes with normal activities</p>	<p>1. Bodily pain reported by survivors was comparable to sibling self-reports. 2. Participants with more symptoms of anxiety, depression and somatisation reported significantly worse pain (HRQOL) than those who reported less emotional distress (all $P < .001$). 3. Emotional distress was directly associated with bodily pain.</p>
<p>Ness et al (2017).¹⁷ Multicentre (26), the United States, Canada 0-20 y</p>	<p>Mixed diagnoses, 14566 Siblings, 3149</p>	<p>28.5 (6.4); 26.9 (6.0); 25.7 (5.8) (according to the treatment decades)</p>	<p>≥5 y</p>	<p>Health status domains (CCSS survey) Current cancer-related pain, rated as 'none/small amount of pain', 'medium amount' or 'a lot/very bad'</p>	<p>1. The percentage of survivors of ALL and osteosarcoma who reported cancer-related pain increased from the 1970s to the 1990s.</p>

^aSurveillance, Epidemiology and End Results (SEER) Program data from 1975 to 2011 (CCSS study data were used to obtain the morbidity burden indicator estimates).

to choosing the most appropriate comparison groups. Notably, the prevalence rates of pain among the young cohort (<39 years) of survivors in the study by Lu et al¹¹ were considered similar to rates in the general population of older adults.³⁵ These findings may confirm the known risk of complications related to health in survivors of childhood cancer.³⁶ The highest prevalence of pain was found in the study by Huang et al.³ However, survivors in this study were recruited from a single institution, which may limit the generalisation of their findings to other settings.

The reported findings indicate that pain is a significant clinical problem for specific subgroups of childhood cancer survivors, such as bone cancer, CNS tumours, sarcoma, RMS, retinoblastoma and ALL survivors, for whom back pain was reported to be a frequent symptom.¹⁷ Previous studies have shown that back pain and neuropathy are associated with the number of times intrathecal chemotherapy is administered.³⁷

Furthermore, the prevalence of pain may be influenced by the severity of pain, only 3% of survivors with CNS cancer¹⁸ and mixed diagnosis¹¹ suffered from severe levels of pain. There were a higher number of survivors with mild or moderate pain (35%) in the study by Boman et al¹⁸ compared to Lu et al's¹¹ study (6.7%). This could be explained by the diagnostic group investigated because CNS tumour survivors have been found to exhibit the worst pain.²⁶ Another explanation could be related to the type of pain scale. Lu et al¹¹ consider that the 'not sure' response to the pain condition question treated as a 'no' response, may have contributed to underestimate the pain rates among the survivors. Boman et al¹⁸ reported both mild and moderate pain categories together; as such, they may have found a higher number of respondents reporting pain severity.

The studies from the United States^{2,16} and Sweden^{18,25} that found no difference in pain reported between survivors and controls are encouraging. This finding may be related to positive adaptation due to the survivors' experience with a life-threatening situation such as cancer in childhood and its treatment, also known as positive growth.³⁸ However, the mean time was approximately 16 years post-diagnosis for both studies from Sweden. This time span might not be long enough to detect possible negative effects of cancer treatment on pain. For instance, in the study by Blaauwbroek et al,²³ survivors diagnosed more than 20 years prior had significantly higher bodily pain than survivors with a follow-up of <20 years.

In the two studies from the United States,^{2,16} the average follow-up time was at least 20 years for most survivors, but no significant differences for bodily pain were found between survivors and siblings or in comparison with the healthy population group. Regarding control groups, siblings may represent a better control group than population norms due to both genetic and family-of-origin similarities.³⁹ However, it is possible that siblings are at an elevated risk of pain outcomes due to their experience of having a sibling with cancer. These factors may underestimate the difference between survivors and non-sibling controls.

The SF-36, a generic HRQOL measurement, was used in three of the studies.^{2,16,25} To investigate pain among childhood cancer survivors, more specific pain measurements may be needed.

The studies that found differences in pain reports among survivors compared with siblings and healthy population norms were based on data from the CCSS study^{7,10,11} and indicate that clinically significant levels of pain may persist into adulthood. To measure pain, these studies used the Pain Questionnaire from the CCSS, focusing on specific pain conditions such as 'prolonged pain or abnormal sensation in the arms, legs, or back', 'migraine' or 'other frequent headaches'. These questions might be more specific and therefore more concrete for survivors to answer compared to the generic SF-36, which may explain the different result in studies comparing childhood cancer survivors with siblings as controls or healthy population norms.

4.1 | Demographic risk factors

Several demographic risk factors were associated with long-term self-reported pain in childhood cancer survivors. The risk factor with the greatest evidence was female sex, which was supported by five studies^{2,8,11,21,26} and confirmed previous studies that found female sex to be a risk factor for pain.⁴⁰ This finding is consistent with previous research^{41,42} showing that female survivors in general are more vulnerable to lower scores of HRQOL as well as psychological distress than controls in general. This may result from greater vulnerability to treatment-related toxicities among women,⁴³ or it may reflect similar trends in the general population.⁴³ In addition, some earlier studies considered the difference between males and females to be an effect of women's greater likelihood of discussing their problems more than men do,⁴⁴ as also found in healthy populations.⁴⁵ Female survivors may also have different coping mechanisms and expectations compared with male survivors.⁴⁶

Furthermore, some studies found lower education,^{2,11,24} unemployment,^{2,11,15} and lower income (annual household income <\$20 000)²¹ to be related to pain in survivors of childhood cancer. These findings are similar to previous research regarding lower socioeconomic status.⁴⁷ Single/unmarried status was supported by three studies,^{2,11,15} and minority status was supported by two studies,^{11,15} which corresponds with previous studies regarding minority status.⁴⁸

In general, all of the mentioned risk factors were associated with greater risks of using prescription pain medications and attributing pain to cancer.¹¹ These factors may be related to the availability of health insurance and health care⁴⁹ and are similar to known risk factors for poor health status in general⁵⁰ and poor psychological functioning in childhood cancer survivors.⁴¹

4.2 | Diagnosis- and treatment-related risk factors

In three studies, the time since diagnosis was associated with a higher percentage of self-reported bodily pain, in childhood cancer survivors,^{1,14,23} and treatment was also associated with self-reported pain.^{2,8,11,23} Many pain-related problems become visible as survivors age,^{2,8,21} and these problems increase as the time since diagnosis

increases. Importantly, a previous study showed that in the CCSS study, only 31% of survivors aged 18-19 years at the time of the interview had visited a health care provider at a childhood cancer centre during the previous 2 years and that this percentage decreased with age to 17% among those aged 35 years or older.⁵¹ In contrast, patients with follow-up times of less than 20 years had significantly better scores on the bodily pain subscale than those of the standard population.^{18,23,25} Individuals who survive a life-threatening disease often find their life to be more satisfying as a result of psychological adaptation, growth and resilience.³⁸

Regarding diagnosis, long-term survivors of CNS tumours, retinoblastoma, bone tumours and sarcoma had greater impairments in pain, than survivors of other forms of cancer. However, a comparison of types of cancer showed that CNS tumour survivors exhibited the worst pain.²⁶ A very recent study conducted by Ness et al¹⁷ found that the percentage of ALL and osteosarcoma survivors who reported cancer-related pain increased from the 1970s to the 1990s. Generally, the risks of health problems increased with age after treatment for childhood cancer¹⁷ and were associated with pain^{1,2,8,21} in several other studies. These results indicate that higher degrees of chronic disability may develop in childhood cancer survivors or that earlier treatments produce more comorbidity than contemporary therapies as survivors age.

Survivors diagnosed at a very young age, such as ≤ 3 years¹¹ and < 10 years,² had higher risks of reporting pain than those diagnosed at an older age (10-14 years).²⁶ Pain is especially problematic in younger children. It is necessary to consider the child's age, developmental level, cognitive and communication skills, previous pain experiences and associated beliefs when planning treatment.⁵² An explanation for the higher level of pain reported by survivors diagnosed at a younger age may be that undermanaged acute pain in young children could transition to chronic pain in survivorship.¹⁶ Other factors may include the specific diagnosis and treatment, such as brain tumours and cranial radiation treatment at a young age. Language has a major impact on the way children cope with and express their emotions. Language can help them cope with pain procedures and hospital treatments and may explain why survivors in the 10- to 14-year age group in Alessi et al's²⁶ study had better overall HRQOL scores and less pain morbidity than those diagnosed at a younger age.

4.3 | Comorbidities of depression, emotional distress and fatigue

The studies in the present review reveal that survivors reporting emotional distress symptoms also report significantly more pain,^{24,30} increased pain⁹ and comorbid stress associated with bodily pain.¹⁰ These findings confirm previous findings showing that patients with pain symptoms are more likely to experience depression than those without pain.⁵³ Screening for psychological comorbidities, such as depression, may therefore be necessary in patients presenting with pain symptoms.⁹

In the study by Recklitis et al,¹² cancer-related pain was significantly associated with SI in the survivors reporting the highest level

of pain (21.4%). This is consistent with a previous study showing that pain is a significant risk factor for suicide and SI.⁵⁴

Only a few studies investigated fatigue in long-term childhood cancer survivors and found pain to be similar to and associated with chronic fatigue.^{13,27-29} The impact of fatigue on pain has been examined less often in survivors. Based on their report from the CCSS, Mulrooney et al⁵⁵ emphasise that both chronic fatigue and pain should be further investigated as long-term outcomes. Pain may have a complex relationship with cancer-related fatigue. A previous study found a strong association between fatigue and pain in survivors of ALL⁵⁶; however as the authors consider, it is not certain whether there is a cause and effect relationship, or represent a co-existence of two neurologic symptoms in survivors of ALL.

4.4 | Methodological limitations of studies

Several limitations, including the possibility of bias, should be considered when interpreting the results of the present review. Unfortunately, only five longitudinal studies were included in the present review, limiting the formation of strong conclusions. The statistical power was usually not stated, and the effect sizes were often not reported when the results were significant. Furthermore, more ethnically diverse samples could enable greater generalisation of the findings. Because the CCSS study population includes cancer survivors treated between 1970 and 1986 and similar treatment periods were used in the other studies in this review, the health outcomes reported in these studies may not be relevant to patients treated more recently due to improvements in treatment outcomes. Recruitment bias must be considered in any long-term outcome study because survivors with more pain problems may be less likely to participate. Because the studies included in this review investigated childhood cancer survivors treated for different types of cancer with varying levels of disease, the heterogeneity among the samples further reduced the likelihood of consistent findings across the studies.

Encouragingly, 17 multicentre studies were included in this review, contributing to the generalisability of the results to other treatment sites. However, most studies were performed in the United States and Canada, except for six studies that were performed in Europe (Sweden,² Norway,² Italy and the Netherlands). More diverse study samples are needed. Standardised self-reporting measures were used in only 13 of the studies, including five different instruments measuring pain; however, nine of the studies used the same HRQOL measurement (SF-36), enabling comparisons among the studies. The use of the HRQOL self-report with the pain subscale (SF-36) can be considered a strength of the included studies because such measures provide other assessment options (eg proxy reports). The SF-36 is a generic HRQOL measurement that uses only two questions to measure pain. More specific pain measurements may be needed to sufficiently investigate the functionalities and disabilities related to pain among childhood cancer survivors. Nine studies used health status questionnaires from the CCSS baseline data, but these questionnaires were not validated. The use of self-reported

measures to investigate pain may provide an important contribution. Future studies could also use clinical interviews to evaluate pain outcomes to improve the precision of these estimates.

However, pain is a complex and subjective experience that raises many measurement challenges. Albert et al.⁵ emphasise in their review that multiple factors may contribute to pain, and limited pain assessments may therefore overlook other important factors that may influence the pain experiences among survivors.

The limitations of this systematic review should be noted. The inclusion of only English-language instruments limited the geographical scope of this review. Furthermore, we excluded intervention studies that could have provided additional information about pain in long-term survivors of childhood cancer. The quality of the instruments used in the included studies was assessed, including their validity and reliability, but we did not examine the quality of each study, which is an important issue that should be examined in future studies. It is further recommended that standardised risk of bias assessments be conducted in future reviews.

4.5 | Implications

A few studies included in the present review examined pain persisting over time (defined as pain that lasts or recurs for more than 3-6 months) or the prevalence of chronic pain among childhood cancer survivors. Therefore, we emphasise the need for prospective longer-term studies investigating pain and pain-related late effects following childhood cancer to investigate changes over time.

Validated and multidimensional assessments of pain are lacking. These limitations in assessments may contribute to an underestimation of pain prevalence and chronic pain among childhood cancer survivors. Survivors of cancer in childhood may experience pain from the primary disease process and its treatment, and the assessment and management of children with complex pain can be challenging. This highlights the need for better pain management during the treatment of young children. There may be a risk of persistent pain. Therefore, routine screening is recommended for all survivors of paediatric cancer and should be emphasised in future research. It is recommended that studies use brief tools, such as the Pediatric Pain Screening Tool (PPST), which captures pain-related risk,⁵⁷ or the PROMIS Pain Intensity and Pain Interference scales,⁵⁸ to identify survivors with frequent and severe pain, impairment and pain-related distress.

Childhood cancer survivors need comprehensive follow-up care to address their complex healthcare needs.⁵¹ Studies exploring the prevention of pain during treatment and interventions for survivors with pain and compromised HRQOL are needed. Individual interventions for survivors should be tailored based on their specific symptoms, such as cognitive behaviour therapy for pain.⁵⁹ Primary care clinicians should anticipate health deficits in survivors at risk (based on clinical and sociodemographic variables), such as health problems, including pain, when evaluating adults who are childhood cancer survivors. Among long-term survivors of CNS tumours, bone cancers, sarcoma, retinoblastoma, and ALL, diagnosis at a young

age, greater time since diagnosis, female sex, minority status, unemployment and single status, are all associated with a greater risk of reporting pain conditions. Therefore, these patients should be targeted with the most intensity.

5 | CONCLUSION

Although overall it appears that pain is not more prevalent in survivors of childhood cancer than in the general population, for specific subgroups of patients, pain is a significant clinical problem. Longitudinal studies are needed to study pain-related late effects after childhood cancer over a longer period because late effects may manifest many years later. Psychometrically sound pain measurements should be used. Tailoring individual interventions for survivors based on their specific symptoms related to self-reported pain and pain-related disability should be a priority. Attention should be paid to survivors diagnosed at a very young age, and appropriate pain management and care for young children diagnosed with cancer should be emphasised.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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