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**Long term issues and supportive care needs of adolescent
 and young adult childhood brain tumour survivors and their
 caregivers: A systematic review**

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Complete List of Authors:	Nicklin, Emma; Leeds Institute of Medical Research at St James's Velikova, Galina; Leeds Institute of Medical Research at St James's Hulme, Claire; University of Exeter Medical School; University of Leeds Leeds Institute of Health Sciences Rodriguez Lopez, Rocio; University of Leeds Leeds Institute of Health Sciences Glaser, Adam; Leeds Teaching Hospitals NHS Trust, Leeds Cancer Centre; Leeds Institute of Medical Research at St James's Kwok-Williams, Michelle; Leeds Teaching Hospitals NHS Trust Boele, F; Leeds Institute of Medical Research at St James's; University of Leeds Leeds Institute of Health Sciences
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3 **Long term issues and supportive care needs of adolescent and young adult childhood brain**
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5 **tumour survivors and their caregivers: A systematic review**
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23 Emma Nicklin, Galina Velikova, Claire Hulme, Rocio Rodriguez Lopez, Adam Glaser, Michelle
24
25 Kwok-Williams and Florian Boele
26
27

28 *Leeds Institute of Medical Research at St James's, St James's University Hospital, Leeds, LS9 7TF,*
29
30 *United Kingdom (EN, GV, AG, FB); Institute of Health Research, University of Exeter Medical*
31
32 *School, South Cloister, St Luke's Campus, Exeter EX1 2LU, United Kingdom (CH); Leeds Institute*
33
34 *of Health Sciences, Worsley Building, 6 Clarendon Way, Leeds, LS2 9NL, United Kingdom (RRL, FB,*
35
36 *CH) ; Leeds Cancer Centre, Leeds Teaching Hospitals NHS Trust, Leeds, LS9 7TF, United Kingdom*
37
38 *(AG, MKW)*
39
40

41 **Corresponding author:** Emma Nicklin (ss12ef@leeds.ac.uk / 0113 206 8330). Leeds Institute of
42
43 Medical Research at St James's, Level 06, Bexley Wing, St James' Institute of Oncology, Beckett
44
45 Street, Leeds, LS9 7TF
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Abstract

Objective: Long term issues following diagnosis and treatment of a childhood brain tumour often become apparent as the survivor enters adolescence and young adulthood. Their caregivers may additionally face long term impacts on their emotional and psychological functioning. This review synthesised evidence on the issues and supportive care needs of adolescent and young adult (AYA) survivors of a brain tumour diagnosed in childhood and their caregivers.

Methods: Electronic databases were searched up until September 2017. All studies reporting on issues or needs of childhood brain tumour survivors (aged 14-39) and their caregivers were included. Narrative synthesis methods were used to summarise, integrate and interpret findings.

Results: 56 articles (49 studies) met the inclusion criteria. Social issues (i.e. isolation, impaired daily functioning) were most commonly reported by survivors, followed by cognitive (i.e. impaired memory and attention) and physical issues (i.e. endocrine dysfunctions and fatigue). Survivors experienced poorer social functioning, sexual functioning, and were less likely to be employed or have children, when compared to other AYA cancer survivors. Caregivers experienced reduced support as the survivor moved into young adulthood. Caregivers reported uncertainty, increased responsibilities and problems maintaining their own self well-being and family relationships. Few studies reported on supportive care needs. Survivors expressed a need for better educational support and age-specific psychosocial services.

Conclusions: Surviving a childhood brain tumour can be particularly challenging for AYA survivors and their caregivers. Robust structured research is needed to identify specific support needs of both survivors and their caregivers and how these can be optimally addressed.

Keywords: cancer, oncology, adolescent; brain tumours; caregivers; supportive care; survivors; systematic review; young adult

Introduction

In children and young adults under 19 years of age, primary brain and central nervous system tumours are the most common solid tumour, with an annual age-adjusted incidence rate of 5.57 per 100,000.¹ With improved duration of survival,^{2,3} more attention is required to address the potential late effects on quality of survival.

Adolescence and early adulthood is a unique and complex developmental phase characterised not only by significant physical and cognitive changes but also critical psychosocial challenges, relating to self-identity, relationships, individualisation, developing autonomy, and intimacy/sexuality.⁴ Disruptions associated with brain cancers treatment can delay or complicate the achievement of age-appropriate 'life events'. Adolescent and young adult (AYA) survivors may therefore be particularly vulnerable to experiencing late effects or other issues.

A brain tumour affects not only the survivor but also those around them. Responsibility for caring and supporting childhood survivors in the longer term is often met by their immediate family. Neurocognitive symptoms and personality changes of the survivor importantly mark the caregivers' experience. Many caregivers feel inadequately prepared and suffer from symptoms of depression, anxiety and distress.^{5,6}

The 2006 National Institute for Health and Clinical Excellence (NICE) guidelines promote that continuous aftercare should meet the needs of brain tumour survivors allowing for age, gender and cultural differences. The guidelines state:

“Younger patients with continuing care needs should also be carefully considered... procedures should be in place to ensure the continuing care needs of younger patients with CNS tumours are appropriately met”⁷

However, there is little information in the guidelines on how follow-up care should address and meet young survivors and caregivers supportive care needs.

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3 Previous systematic reviews have focused on the experiences of AYA survivors or caregivers with
4 mixed cancer diagnoses.^{8,9} Other reviews have concentrated on the experiences of children,^{10,11} adults,¹²
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6 or caregivers of adult brain tumour survivors.¹³ To date, no systematic review has collated evidence on
7
8 the experiences of AYA childhood brain tumour survivors and/or their caregivers. Given the complex
9
10 developmental stages and increased occurrence of life events during adolescence and young
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12 adulthood, it is expected that the experience and impact of a childhood brain tumour on AYA
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14 survivors will be different from those still in childhood or older brain tumour survivors.
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18 We aimed to systematically identify and narratively synthesise evidence on the issues that AYA
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20 childhood brain tumour survivors and their caregivers face and their supportive care needs. We hope
21
22 that the results will help identify gaps in service provision, help clinical staff understand their role
23
24 throughout the survivorship period and guide policy and service development.
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31 **Methods**

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33 PRISMA guidelines¹⁴ for systematic reviews were utilized as a template for the methodology. The
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35 following electronic databased were searched: Medline (Ovid), Embase (Ovid), PsycInfo (Ovid),
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37 Pubmed, CINAHL (Ebsco), and the Cochrane library (Wiley). The grey literature were searched using
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39 Web of Science and the NHS Evidence. The end date of the searches was September 2017. The searches
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41 were developed for the concepts: brain tumours, children and survivorship. Guided by an Information
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43 Specialist (RRL), the searches were developed combining subject headings and free text terms for each
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45 concept. See Supporting Information 1 for the full search strategy.
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50 *Selection criteria*

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52 Original, peer-reviewed articles were included according to the following criteria:

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54 1. Human participants with a primary diagnosis of a brain tumour and/or a primary caregiver of a
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56 survivor. If the study had a mixed cancer participant group, brain tumour data had to be reported
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58 separately.
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2. Survivors of a paediatric brain tumour, currently aged 14-39 (, or caregivers of survivors within this age range. The study sample could extend beyond these age parameters provided the results for the target age range were clearly reported.
 3. Articles reporting data that focused on any issues, needs or unmet needs of brain tumour survivors and/or their caregivers.

There are contradictions across the oncology literature regarding how the AYA age group should be defined.^{15, 16} Definitions differ greatly amongst organizations, countries and AYA literature. For this review, we set the AYA age range as 14-39.

Exclusion criteria were: articles not in English, reviews, reports on incidence of brain tumours or treatment trials / intervention programmes not covering AYA patient or caregiver issues and needs.

There was no restriction on publication date or study type. The lead investigator (EN) determined whether the articles were eligible for inclusion, with a random sample (20%) independently screened by a second reviewer (FB).

Data extraction and Quality Assessment

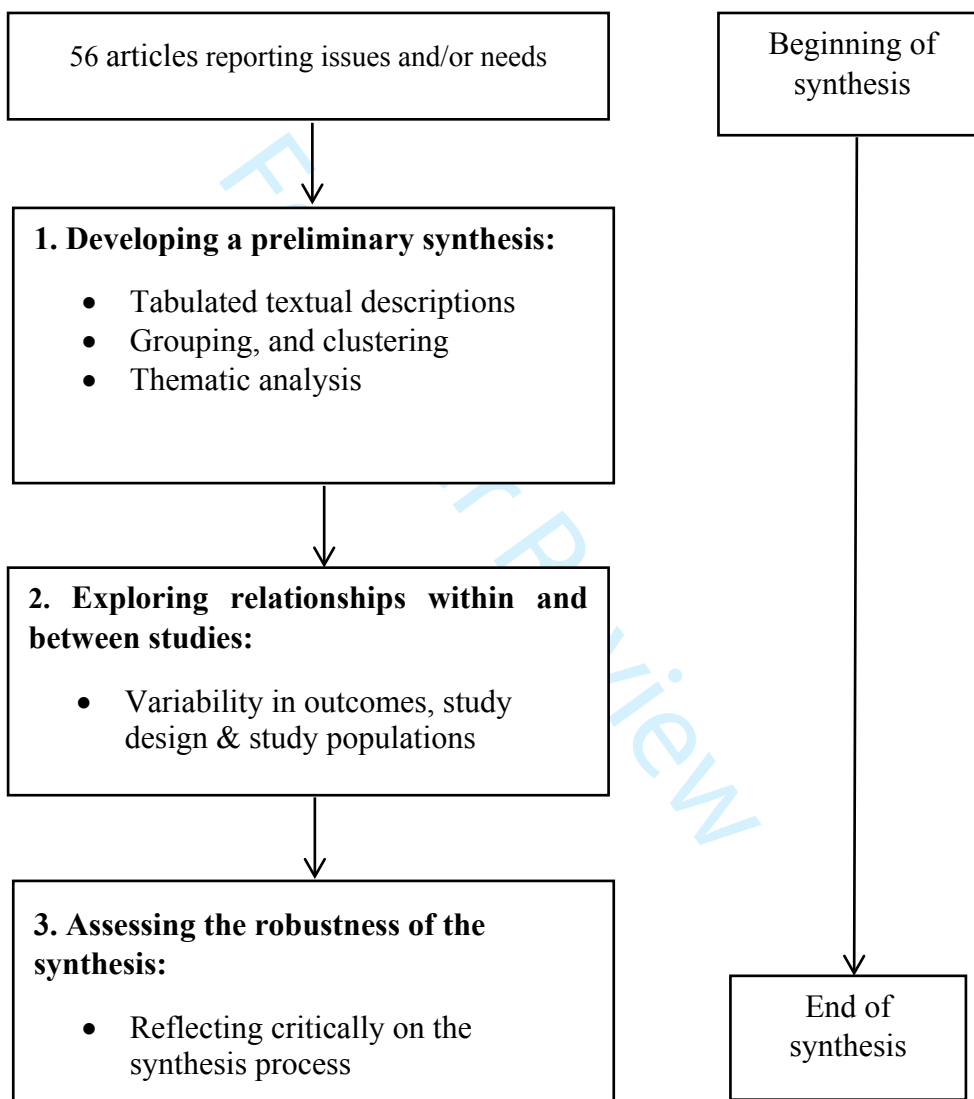
Data extraction was performed using a standardized template. Data were extracted for the study objective, design, sample-size, clinical characteristics of the survivors, measures and outcomes. All included studies were assessed using the Mixed Methods Appraisal Tool (MMAT),¹⁷ which has been validated for the critical appraisal of studies with diverse designs. See Supporting Information 2 for MMAT scores. No studies were removed because of their appraisal score but lower quality study findings should be interpreted with greater caution and in consideration of their limitations.

Narrative Synthesis

Narrative synthesis methods were used to summarise, integrate and interpret the findings articles included within the review. A narrative synthesis was appropriate given that there was little uniformity amongst the methods, findings, or outcomes measures used. Fig. 1. shows the processes undertaken in the narrative synthesis, guided by Popay et al.¹⁸ and the Cochrane Consumers and Communication

review group handbook.¹⁹ The City of Hope quality-of-life conceptual model²⁰ was adapted to map the survivors issues. The original model proposed a quality of life model for long term cancer survivors: physical wellbeing and symptoms, psychological well-being, social well-being and spiritual well-being. We added cognitive symptoms to better fit AYA brain tumour survivor issues.

Figure 1 – Narrative Synthesis Process

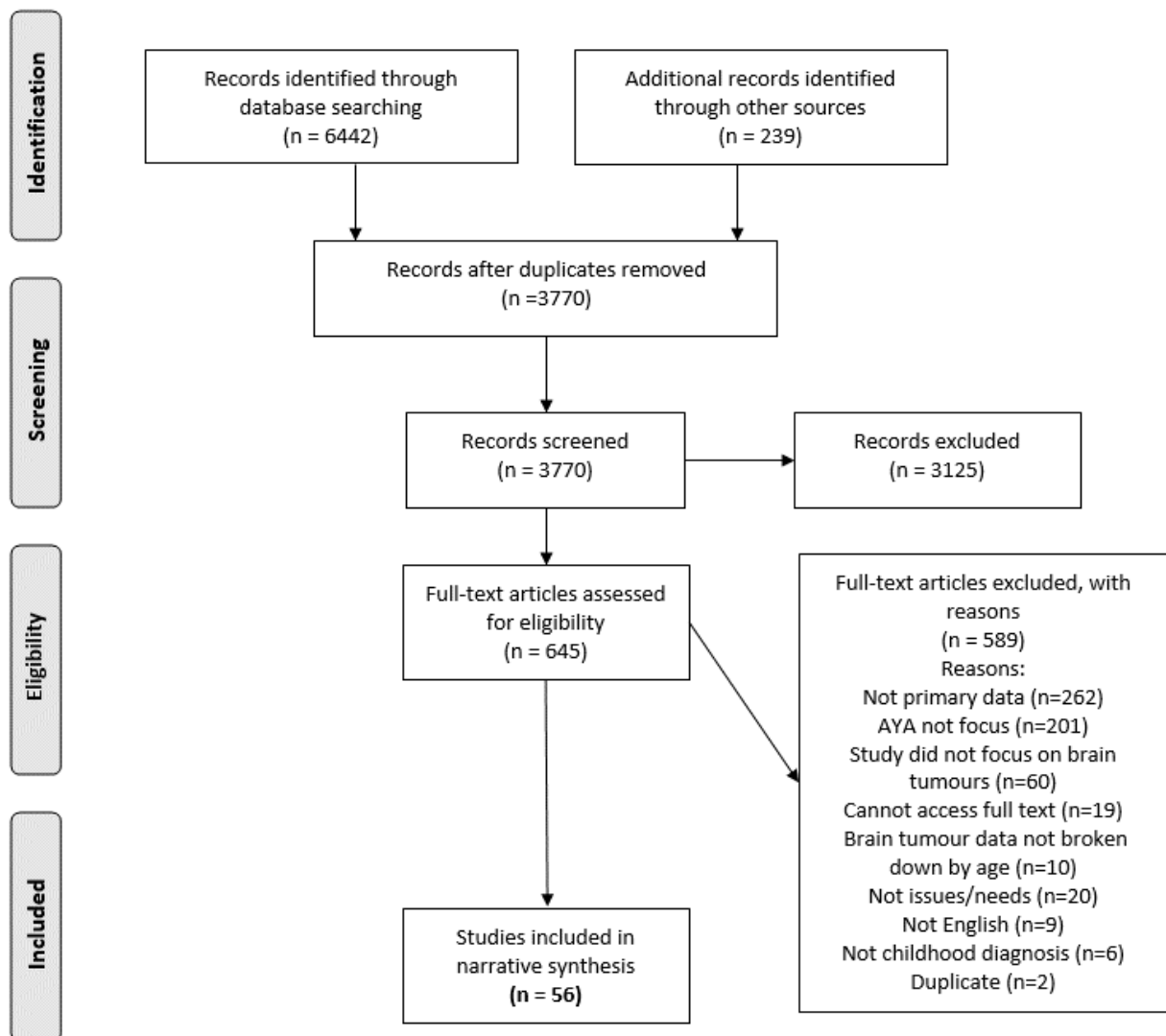


Results

Search Results

In total, 6642 article citations were found. 239 additional records were identified through hand searching journals and reference lists. Once duplicates were removed a total of 3770 articles remained. We excluded 3125 after reading the abstract because they did not meet the inclusion criteria. Of those remaining, 645 were retrieved in full-text, we excluded 589 because they did not meet the inclusion criteria. In total 56 articles (49 studies) remained for inclusion within the narrative synthesis. The process of searching and sifting is shown in Fig. 2.

Figure 2 – Flow chart showing selection of studies



Abbreviations: AYA = Adolescent and Young Adult

Study characteristics

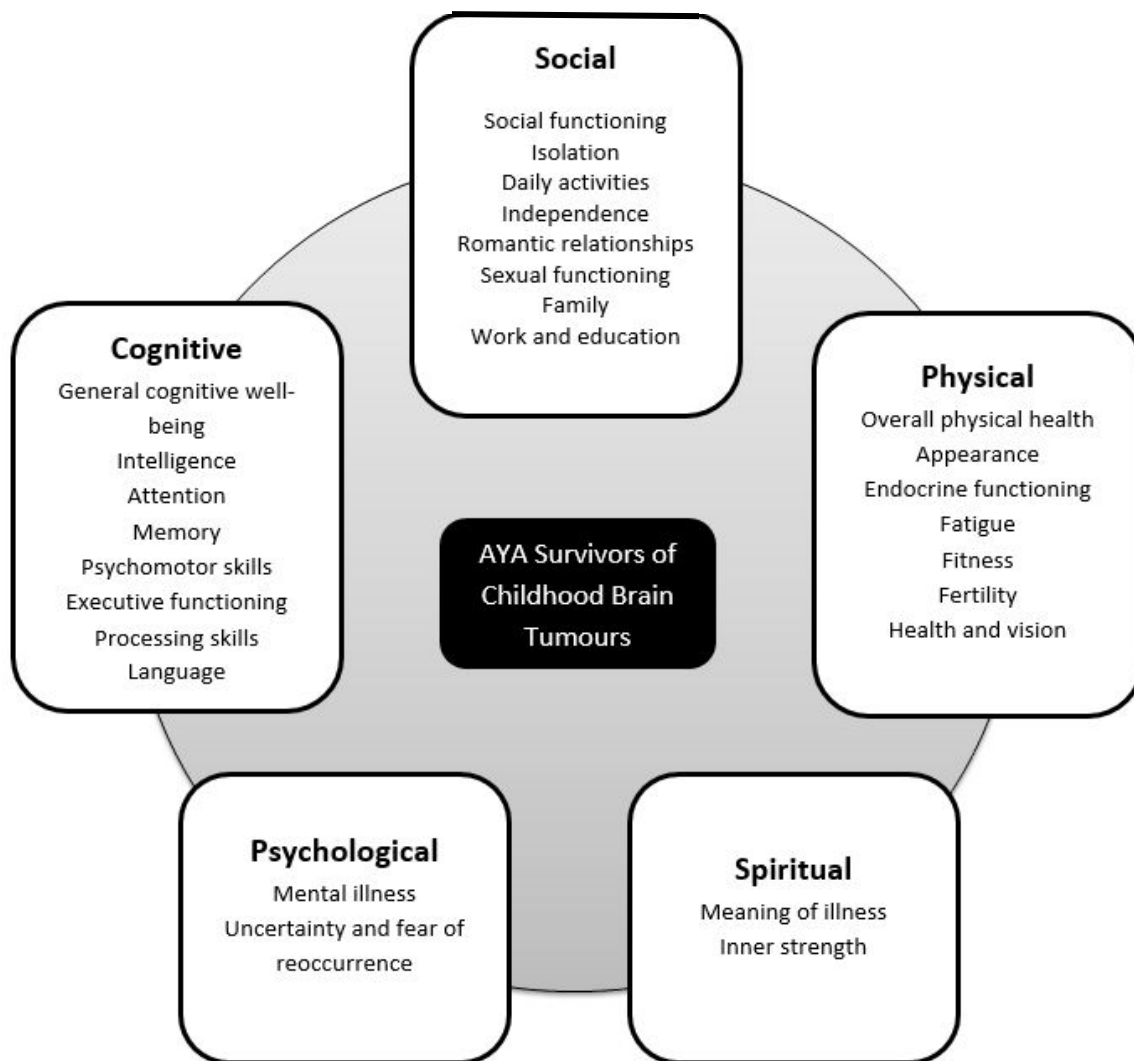
Over half of the studies had been published after 2013 (57%), and 53% of studies originated within the United States. The majority of studies (76%) reported quantitative data; five (10%) were qualitative; and seven (14%) utilised a mixed methods approach. The majority collected data from the survivors only (86%), in three studies (6%) data was solely from caregivers and in four (8%) there was data from both survivors and caregivers. In over a third of studies (35%) there was a comparison or control group.

Over half the studies (55%) reported data from mixed brain tumour samples. A further eight studies (16%) reported one specific brain tumour group. Fourteen studies (29%) had recruited patients with varied cancer types, but reported brain tumour data separately. See Supplementary material 2 for further description of studies.

Section 1: Survivor issues

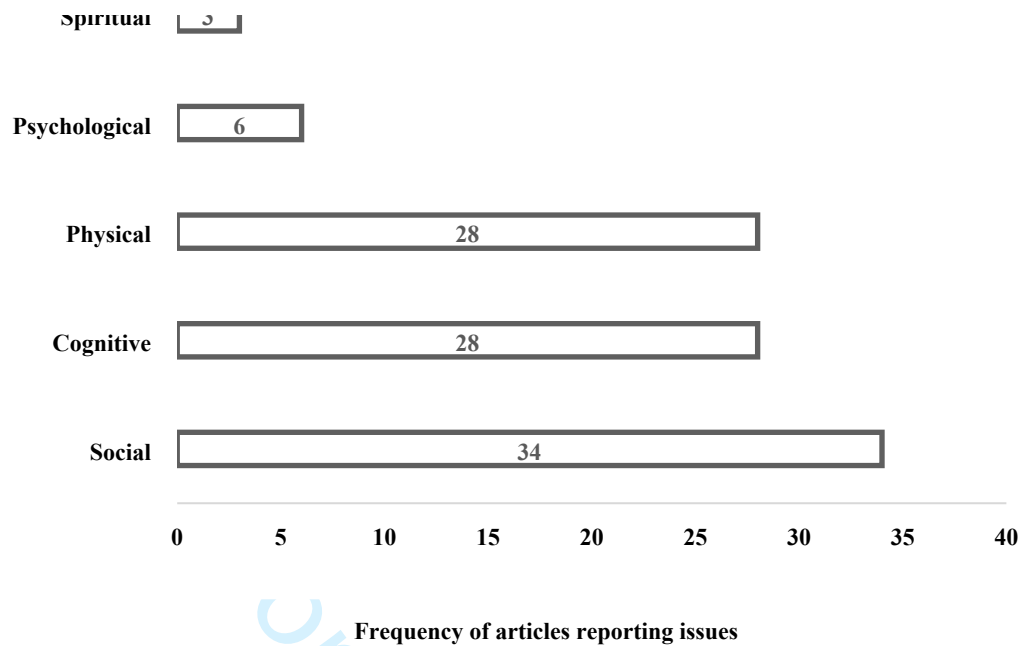
Survivor issues were derived from the main themes found in the articles and categories used in the City of Hope quality-of-life model.²⁰ The model depicts four domains: physical, psychological, social, and spiritual as priorities for assessment to ensure comprehensive quality care. The model has been adapted to illustrate the potential issues AYA brain tumour survivors may encounter which could impact on their quality of life (see Fig. 3.). The main adaptation is the addition of the cognitive wellbeing category.

Figure 3 – Adapted Quality of life Cancer survivorship model



Adapted from: Quality of Life Conceptual Model Applied to Cancer Survivors, City of Hope Beckman Research Institute 20

Figure 4 – Frequency of articles that reported survivor issues by theoretical framework theme



MMAT Scores by theme: Spiritual issues = All 75, Median = 75; Psychological = 75-100, Median = 75; Physical = 25-100, Median = 75; Cognitive = 25-100, Median = 75; Social = 25-100, Median = 75

Social well-being

Social well-being was the most commonly referred to theme (see Fig. 4): Thirty-four articles investigated the impact a childhood brain tumour may have on social domains of an adolescent or young adult.

Articles reported AYA survivors having impaired social functioning, expressed as e.g., avoiding social situations,²¹ or social isolation.²¹⁻²⁶ Poorer social functioning was reported among brain tumour survivors compared to other cancer groups.^{27, 28} Specifically, multiple studies reported a link between poorer social functioning and anti-cancer treatment and diagnosis.^{22, 24, 29, 30} During treatment, survivors spend a long time in social isolation after which some young people found it difficult to engage with others again.²⁴ Physical issues, e.g., headaches or impaired fitness, as well as cognitive deficits were linked to social functioning,^{21, 31, 32} and impacted on survivors' abilities to join in sports or hobbies.³²

Six articles reported impaired daily functioning and/or functional living skills,^{22, 31, 33-36} survivor restrictions ranged widely in severity,^{33, 34} with only a small minority reporting no limitation in daily activities.³⁶ Qualitative work linked these restrictions to impaired cognitive functioning through

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3 difficulties with reading or handling finances, or managing medications.²² AYA survivors rarely lived
4 independently,^{27, 35, 37, 38} which was linked to feelings of frustration.^{25, 31, 32} That said, survivors generally
5 report close relationships with their family.^{21, 22, 31} Poorer survivor cognitive functioning³⁹ and lower
6 income^{36, 39} was associated with worse family functioning.

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12 In romantic relationships, AYA survivors see themselves as less valuable mates to a prospective
13 partner.⁴⁰ Survivors were likely to be sexually inactive.^{27, 31, 35, 41-43} Reduced sexual activity was found when
14 compared to other cancer groups^{27, 41, 43} and the general population.³¹ Survivors of a childhood brain
15 tumour were also less likely to have children compared to general population controls⁴⁴ and other
16 cancer survivors.^{45, 46}

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24 Many AYA survivors need assistance to perform well in school.^{31, 38, 46} Education experiences were
25 often described as problematic: including missing school, cognitive difficulties - feeling misunderstood,
26 facing bullying and social isolation.^{24, 25, 32} Survivors were more likely to be unemployed later in life
27 when compared to age and gender matched controls⁴⁶⁻⁴⁸ and other cancer survivors,^{27, 49} with reported
28 unemployment rates varying from 8-70%.^{27, 33, 35-39, 46-51} Issues in attaining or keeping a job included
29 fatigue, poor concentration, physical issues (e.g., epilepsy), cognitive difficulties, and poor social
30 skills.^{22, 31, 32} Some survivors had sheltered work, a setting in which people with disabilities receive
31 services and training to develop work-related skills and behaviours.^{37, 38, 47} AYA survivors were found
32 to have significantly lower levels of vocational identity and career readiness (i.e. ability to perform
33 work tasks, social skills) when compared to AYA non-cancer survivors.⁵² Vocational identity is an
34 integral part of human development, especially for adolescents. This process includes the formation of
35 career: objectives, goals, aspirations and plans. Financial difficulties were also common in AYA brain
36 tumour survivors.^{39, 53, 54} AYA survivors were more likely than other cancer groups to be receiving
37 disability benefits.⁵⁴

38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 *Cognitive well-being*

56 Different aspects of cognitive deficits were reported in 28 articles. Overall, in these articles, cognitive
57 functioning was found to be impaired. AYA brain tumour survivors are often at higher risk of cognitive
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3 issues than other cancer survivors.^{27, 49, 53, 55} Impaired memory seemed to be the most common cognitive
4 issue.^{21-26, 35, 39, 47, 48, 56-59} Qualitative findings^{21-24, 31, 47, 56} established that impaired memory was a daily
5 issue. Memory issues were innate in how survivors' and their caregivers assessed their ability to self-
6 care and meet developmental milestones, such as living independently,²² making friendships,²³ and
7 educational achievements.³¹ For some memory loss was described as an invisible effect.²⁴ Unlike
8 physical effects, invisible effects may go undetected and mean the appropriate additional support may
9 not be offered.

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19 Attentional deficits were particularly challenging because of their consequent impact on the
20 development of other cognitive abilities, social functioning and academic achievement.^{21, 35, 48, 57, 59}
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23 Evidence suggested that AYA survivors scored lower in Intelligence Quotient (IQ) scores and had
24 limited mathematical skills.^{29, 33, 34, 47-49, 55, 58, 60} AYAs scored lower in IQ testing than population
25 controls.^{34, 60}

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Many survivors presented with poor processing speeds,^{21, 23, 37, 39, 48, 59, 61} leading to poorer physical
and/or mental health,³⁷ social functioning^{21, 23} and health-related quality of life.^{37, 39} Similarly language
and vocabulary issues were challenging.^{31, 35, 55, 60} Compared to matched healthy controls, brain tumour
survivors scored significantly lower in verbal assessments.^{31, 46, 60, 61}

Some survivors suffered from impaired motor skills.^{31, 34, 35, 37, 46, 48} Motor deficits contributed to social
isolation and vocational limitation by restricting the types of activities open to survivors (i.e. playing
sports or writing).^{31, 35}

Executive functions are a diverse set of cognitive processes broadly conceptualised according to four
primary domains: decision making, planning (e.g. organisation), purposive action (e.g. set shifting- the
ability to move back and forth between tasks), and effective performance (e.g., preservation, goal
maintenance). Survivors experienced poor executive functioning including: planning/organising,^{34, 48}
preservation,³⁴ set shifting,^{34, 35, 48} and flexibility.⁴⁸ Survivors self-reported less executive dysfunction
in comparison to when their mothers reported symptoms (by proxy). This may be problematic as
survivors who perceive fewer executive functioning difficulties may not pursue help or support, such

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3 as neuro-rehabilitation programmes, which may have a negative effect on other long term functional
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5 outcomes.⁶²
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8 *Physical well-being*

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10 Survivors had impaired general physical health.^{21, 27, 28, 30, 31, 46, 53} More specifically symptoms included:
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12 poor mobility,^{21, 31, 38, 46} poor physical functioning,^{22, 30} reduced bone mineral density,^{63, 64} hearing
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14 and/or vision issues,^{21, 23, 25, 31, 38, 46, 65} and poor fitness levels.^{31, 55}
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18 At a time when physical appearance becomes increasingly more salient, AYA survivors reported having
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20 issues with their appearance.^{22, 24, 27, 31, 32, 38} Visible effects after the tumour and treatment included –
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22 small stature, hair loss, weight issues and scars.^{22, 24, 31, 32} Parents of survivors described that issues with
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24 body image contributed to starting/maintaining peer relationships because survivors worried they
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26 looked different from their peers.^{32, 38}
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30 AYA survivors' commonly had endocrine dysfunctions.^{21, 23, 31, 37, 38, 49, 58, 66-69} More specifically, growth
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32 hormone deficiency was reported in 22-97% of survivors.^{33, 38, 49, 66, 67, 69} Other frequently reported
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34 endocrine disorders included hypothyroidism,^{33, 67, 69} hypogonadism^{31, 33, 69} and cortisol deficiency.³⁰
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36 Issues with endocrine functioning during adolescence could impact on growth and development, weight
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38 gain, reproductive processes, and mood.
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41 Many survivors experienced increased levels of fatigue as adolescents and young adults.^{21, 23, 26, 27, 31, 32,}
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43 ^{53, 67, 70, 71} In comparison to other cancer survivors, brain tumour survivors were more likely to report
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45 difficulty with tiredness and fatigue.^{26, 53} Whilst fatigue is reported as a physical issue following the
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47 cancer survivorship model, it is also a common symptom of many cognitive and psychological problems.
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49 Survivors expressed how fatigue had stopped them doing hobbies/sports and socialising.³⁸
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53 Regarding fertility, childhood brain tumour survivors fell pregnant significantly less often than healthy
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55 peers.⁴⁴ That said, brain tumour survivors' desire to have children was significantly lower than healthy
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57 peers of the same age.⁴⁴ For some fertility was not currently an issue, especially for adolescents, but it
58
59 was something they were anxious about facing in the future.³²
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Psychological well-being

Survivor mental health did not differ from general population controls.^{25,46} However, one article found that AYA brain tumour survivors reported significantly poorer mental health than other cancer survivors.²⁸ Another reported that AYA brain tumour survivor had poorer psychological functioning than other cancer survivors.²⁷ The most frequent psychological problems for survivors were internalising problems and withdrawal.²⁹ Psychotic symptoms (i.e. mood dysfunction, delusional thinking and hallucinations) were diagnosed in a small number of survivors, with antipsychotic medication having little effect.⁷²

Despite improvements in recurrence-free survival rates for children diagnosed with brain tumours, AYA survivors still worry about recurrence. In two qualitative studies participants expressed that the anxiety of whether the tumour was going to return, was one of the realities of living as a survivor.^{25,56} In some cases the uncertainty of recurrence negatively affected survivors' ability to plan for the future or feel engaged in life.^{25,56} Both studies highlight that the fear of recurrence may become an issue as survivors enter young adulthood; especially if they feel unable to plan a future, they may not reach the same developmental milestones.

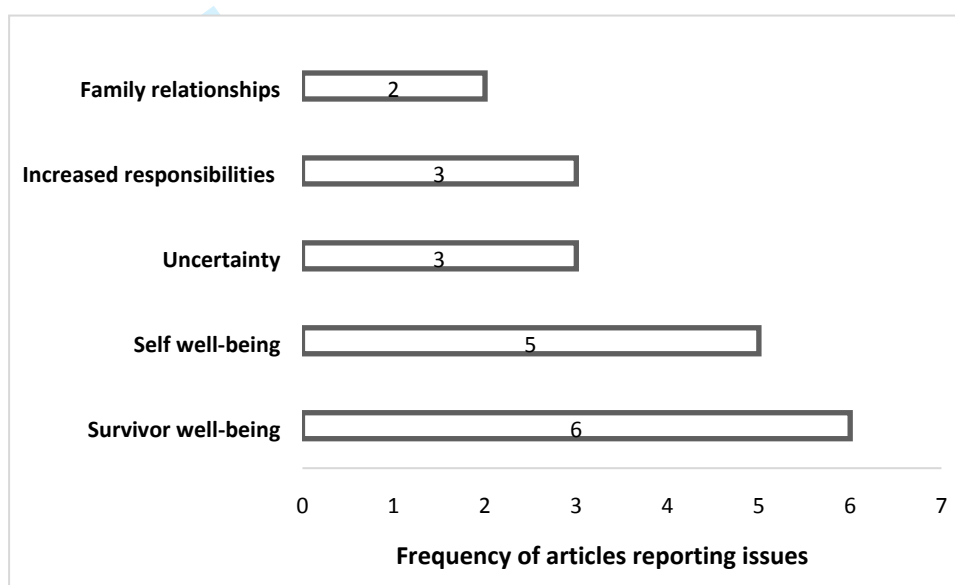
Spiritual well-being

Compared to other AYA cancer survivors, brain tumour survivors had significantly poorer optimism, self-esteem and vitality.²⁸ However, survivors were not less resilient.²⁷ The way survivors viewed the meaning of their illness differed vastly.^{22,25,31} Some focused on the negative effects of illness, seeing themselves as 'losers' for their deficits. Some survivors said they were treated differently because of their cancer history, and felt that others pitied them.³¹ Yet in the same study half of survivors described at least one positive consequence of surviving a brain tumour on their world view.³¹ Some survivors positively viewed their experience of surviving a brain tumour, feeling it had made them more mature and were trying to move beyond the illness.²⁵

Section 2: Caregiver Issues

Eight articles reported caregivers' issues,^{21, 23, 24, 30, 32, 36, 73, 74} four focused specifically on studying the role of the family caregiver.^{30, 36, 73, 74} Caregiver participants consisted of parents (mothers and fathers),^{21, 30, 75} mothers only^{23, 36, 73, 74} and mixed family members (including grandparents).²⁴ Caregiver issues had five themes (see Fig. 5): Survivor well-being; Uncertainty; Increased responsibilities; Self-well-being and Family relationships.

Figure 5 – Frequency of articles that reported caregiver issues by theme



MMAT Scores by theme: Family relationships = All 75, Median = 75; Increased responsibilities = All 75, Median = 75; Uncertainty = All 75, Median = 75; Self well-being = 75, Median = 75; Survivor well-being = 75, Median = 75

Survivor well-being

Parents were concerned about the survivor's well-being. Caregivers worried that survivors had limited social life and that they weren't accepted into social groups.^{24, 32, 36, 73} They acknowledged that survivors' lives were fundamentally different to others their age because of the brain tumour and worried if they would ever recover their previously existing social network.³² Parents were not only worried about survivors' current issues but about potential issues in the future.³⁰ In particular their ability to find a romantic partner^{21, 30} and have children.³² Others feared that their potentially forever-dependent children might outlive them.³⁰

Uncertainty

Uncertainty was a common theme, especially regarding the survivors' future health.^{30, 32} Like seen in survivor reports, the threat of relapse was a pressing issue. In some cases this threat stopped parents from planning future activities, and instead they lived very much in the present.^{30, 32} Another source of uncertainty came from whether their child would ever reach independence.^{32, 74} In one study the majority of parents believed their child would never be independent.⁷⁴ Some worried about leaving them alone in the house or their ability to be financially independent.³²

Increased responsibilities

Caregivers had increased responsibilities, tasks that usually healthy AYAs handle independently. Qualitative findings described parents assisting survivors in: everyday tasks (i.e. cooking meals, managing finances and promoting hygiene); managing medications, education; arranging social contacts; and support with hobbies and leisure activities.^{24, 32, 73} In some cases parents decided to home school the survivor because they felt they needed extra assistance and support.^{24, 32}

Self-Well-being

Five studies reported diminished caregiver well-being.^{23, 30, 32, 36, 73} Parents revealed that because of their caregiving demands, they had less time and energy to dedicate to maintaining self. Parents described feeling fatigued,^{32, 73} having problems maintaining their own social relationships,^{23, 30, 73}; and not being able to pursue their own careers.⁷³ Their social lives declined because caring became their main priority, meaning they had less time to engage in social and leisure activities, thereby limiting their social world.^{23, 30} Caregiver health plays a major role in family life, one study highlighted the direct association between caregiver well-being and better family functioning.³⁶

Family relationships

The pressure of keeping healthy family relationships, whilst caring for a young brain tumour survivor, could prove to be challenging for caregivers. Families of children who have survived a brain tumour may face issues that make family management more difficult. For some caregivers their marriage had suffered – causing separation.^{21, 30} Strain was noted because of the added pressure of caring for the

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3 survivor and also because of discrepancies between partners about how best to care for their child.³⁰ For
4 others the diagnosis, treatment, and late-effects had brought them closer together.²¹ Parents worried
5 about their relationships with survivors' siblings, anxious they felt alone or as if they "*got the short end*
6 *of the stick*".²¹
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11 12 13 **Section 3: Supportive care needs**

14 15 16 *Survivor Needs*

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18 Only three studies aimed to specifically identify survivor needs.^{23, 56, 76} AYA needs differed from those
19 of paediatric and older adult survivors, including the need for age-specific social resources. AYA brain
20 tumour survivors were more likely to value social activities and support groups, compared to other
21 cancer groups.⁷⁶ Social activities and support groups were favoured above informational mailing,
22 weekend retreats, informational workshops or individual counselling.⁷⁶ Social resource
23 recommendations included creating several arenas for peer support.⁵⁶ Parents highlighted that their child
24 needed more opportunities to merely "hang out" with peers.²¹ When an AYA social support programme
25 was evaluated survivors relayed positive experiences.²³ Participation in the programme provided
26 survivors with "*something to look forward to*", a regular social activity, important in addressing some
27 of the social isolation issues. Furthermore, including the use of social media as a part of the programme
28 was recognised as a manageable and satisfying way to decrease isolation within the survivors.
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42 Some survivors felt the current health care delivery did not meet all their needs. Many were unsure how
43 to discuss issues with physicians, and others felt the information they received was inadequate because
44 the medical staff communicated solely with their parents.^{47, 56} Providing survivors with age-specific
45 resources about late effects and psychosocial challenges at each follow-up appointment may be helpful.
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Several studies stressed the need for comprehensive follow-up services for childhood survivors.^{31, 37, 38,}
^{50, 69, 70} The importance of follow-up in a survivorship clinic to offer coordinated, multidisciplinary care
that can address the multiple issues/needs of survivors of brain tumours while addressing caregiver
needs and family functioning was highlighted. One study stressed that health professionals should be

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3 mindful that many survivors may define themselves as healthy and will not necessarily identify late-
4 effects caused by their illness/treatment.³¹ Findings specifically identified careful follow up of
5 endocrine function,⁶⁹ liver function,⁷⁰ and health related quality of life.^{37, 50}
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10 The stress of keeping up with their classmates in an environment that was not equipped to handle their
11 needs proved difficult for many young survivors.²⁴ Regarding educational support, survivors described
12 needing: extra time to complete assignments/exams, more one-on-one help, and extra encouragement.²⁴
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17 ³² Some survivors said that by appearing more “normal” meant that they were not always recognised as
18 needing additional support with their academic work.²⁴ Throughout survivor narratives, the paradox of
19 wanting special considerations within the classroom yet not wanting to be different or singled out among
20 their peers was strongly evident. Another study concluded that academic/vocational goals and
21 expectations must be observed over time, as learning needs may change.²²
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28 *Caregiver needs*

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30 Parents consistently reported that there was not enough support available for themselves or the survivor
31 during adolescence and young adulthood. Parents felt that when their child was undergoing treatment
32 they had support, but that support declined as they moved further away from the treatment. ^{30, 32}
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35 Regarding useful support services, parents expressed that parent support groups and survivorship
36 education classes would be most helpful. Other services mentioned were parental health and self-care
37 classes and practical support such as financial assistance.²¹
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44 Two articles highlighted that different caregivers and families deal with survivorship differently and
45 will have different needs.^{30, 74} One study found that clinicians find it challenging to tailor interventions
46 to family and caregiver needs, as tools to assess family functioning and caregiver coping are not
47 available.³⁰ Nuanced communication is needed, not only during treatment, but also into survivorship
48 with specific approaches to meet caregiver needs and provide coping skills to manage stressful
49 situations.^{30, 74}
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Discussion

This systematic review revealed that AYA brain tumour survivors can encounter various social, cognitive, physical, psychological and spiritual issues which have the potential to significantly impact upon their wellbeing. Social, cognitive and physical issues were the most frequently reported - with poor social functioning being the most pressing. A childhood diagnosis of a brain tumour appeared to inhibit or change how AYAs interact with family, friends and employers as well as how they cope with unexpected and unwanted changes in areas ranging from employment stability to romantic relationships. Survivors miss out or struggle with achieving key life-events including: independence, educational achievements and becoming parents.

Cognitive deficits meaningfully contribute to these poor social outcomes. Survivors experience neurocognitive late effects across multiple domains that often hinder their independence - and are associated with poorer social functioning. This is compounded by growing concerns about their physical issues as they move into adolescence and young adulthood.

Identified problems were frequently more prevalent, or more intense, than in other cancer groups, making it more likely that brain tumour survivors will have poorer overall well-being: Similar to the findings of the present review, a recent review reported poorer quality of life outcomes in paediatric brain tumour patients than those diagnosed with other cancers,⁷⁷ emphasising that brain tumour supportive care should be disease-specific and tailored to individual needs.

The majority of identified studies focused on only survivor's experiences rather than their caregivers'. Yet our findings highlight that caregivers may experience momentous stress related to the pressures associated with their caring responsibilities. These pressures can take their toll on well-being, especially when support is not available. Caregivers indicated that support had declined as they moved further away from the survivor's treatment into long term survivorship.

There was little data reported that specifically focused on the supportive care needs and/or unmet needs of AYA childhood brain tumour survivors. Equally none of the studies included in our review assessed the needs of the AYA survivor's caregiver. In a sample of mixed cancer survivors (not just those living

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3 beyond a diagnosis of a brain tumour),⁷⁸ over 50% of AYA survivors indicated that they had unmet
4 needs in relation to information and services. Based on the current review, it would be reasonable to
5 expect that this percentage would be higher for brain tumour survivors because of the higher prevalence
6 and complexity of late morbidities. However, it is still unclear what these specific needs are and whether
7 they are currently being met.
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13 *Limitations*

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15 There are several limitations to the research reported in this review. First, the quality of the evidence
16 varied per study, as reflected in the MMAT scores (see Supporting Information 2), and thus, findings
17 should be interpreted with caution. Second, the majority of the studies involve a cross-sectional design.
18 This is problematic as adolescence is a period of rapid development and change - behavioural patterns
19 are established, cognitive functions mature, physical changes occur, and complex social relationships
20 develop. Future research should focus on collecting longitudinal data that will allow us to examine if
21 and when survivors and caregivers issues/needs change as they progress into adulthood. Third, in the
22 majority of studies with caregiver participants, the views of the mothers dominated the sample, with
23 very little representation from fathers. Fourth, in three studies survivors had been treated up to four
24 decades ago, these results may not be relevant to survivors who have been treated more recently.^{26, 49, 66}
25 Older treatment periods may present varying treatment effects and therefore issues and needs, whilst
26 different levels of supportive care may have been available. Finally, this is a relatively new area of
27 study, and the majority of the studies included in this review have been conducted in the United States.
28 Therefore, additional studies are needed in other countries to identify specific issues and needs that
29 might be culturally tied or dependent upon differences across health and social care systems.
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49 There are limitations specific to our systematic review. First, due to the inclusion criteria, some studies
50 with important findings were excluded from this review. For example, the set age criteria (14-39) meant
51 that studies with participants outside this parameter were excluded, even if the majority of the
52 participants were aged 14-39.^{79, 80} Second, we appreciate that some potentially relevant articles may
53 have been missed for the following reasons: only 20% of the abstracts were reviewed by a second
54 reviewer, and we were not able to access all full-texts. We also appreciate that new evidence is
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3 constantly emerging and the review does not include any articles published after the last search date
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5 (September 2017). Third, in some studies brain tumour survivors were only a small percentage of the
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7 study population. Although some data were reported separately, allowing us to include the study within
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9 the review, this data was not always very detailed. Finally, only studies published in English were used
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11 due to resource limitations and time constraints.
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14 15 *Clinical implications*

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17 Currently, there is insufficient knowledge of what AYA brain tumour survivors specifically need from
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19 supportive care. Only a small number of studies in the review addressed unmet supportive care needs.
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21 Despite the numerous studies reporting survivor issues, it is known that the presence of issues is not
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23 always related to the need for, or uptake of supportive interventions.
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27 Our systematic review shows that AYA survivors often experience many unique long term issues as a
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29 consequence of the diagnosis and treatment of a childhood brain tumour. These issues are different to
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31 older survivors and those still in childhood. Their priorities and unique life events mean that the late
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33 effects of treatment impact their lives differently to other age groups. Adolescence is a period of trying
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35 to gain independence, but the review highlights that survivors can find this difficult – emotionally and
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37 practically. For example, impaired daily functioning and cognitive issues were integral to their ability
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39 to self-care and gain independence. Unlike children, AYAs have to make important decisions about
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41 their education and future careers. AYAs also start to plan for the future, with romantic relationships
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43 considered a critical developmental task marking one's entry into adulthood, alongside starting a family.
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45 Therefore, it is important that this group is provided with age-specific information, support and
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47 resources that guide them through adolescent life events, such as further education, learning to drive,
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49 paid work and relationships. Supportive services should be mindful that adolescence and young
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51 adulthood is a period of constant change and that the need for information and support may change
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53 rapidly, meaning regular reviews may be necessary. Information, support and resources should be brain-
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55 tumour specific, as experiences of brain tumour survivors differ significantly to those with other
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57 cancers.
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3 Furthermore, we recommend that caregivers' unique needs are considered by long-term follow up teams
4 and support services. They too face unique challenges and should have access to information, support
5 and resources for caring for an adolescent childhood brain tumour survivor.
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9 10 *Future research*

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12 Significant gaps exist in our understanding of the unique needs of adolescent and young adult brain
13 tumour survivors and their caregivers. The extent to which unmet needs are related to tumour and
14 treatment characteristics requires further research. With new research constantly emerging, regular
15 updates of this literature review will be necessary. From the systematic review, three areas of future
16 research are identified. First, studies are needed to describe the needs and more importantly unmet needs
17 of both AYA childhood brain tumour survivors and their caregivers. Increasing our understanding of
18 the unmet needs will help to develop more targeted and effective supportive care models. Second,
19 descriptive studies are needed to fully investigate survivor and caregiver expectations for supportive
20 care and how these expectations comply with the current use of long term follow-up care and supportive
21 services. Third, existing research seems to be omitting the perspectives of the healthcare professionals.
22 Their input would be valuable in regard to the development and evaluation of effective interventions
23 to support AYA survivors and their caregivers. Subsequent to the results from descriptive studies,
24 evidence based programmes and services need to be modified and/or developed to address both AYA
25 survivor and caregiver unmet and desired supportive care needs.
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47 **Conclusions**

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49 Surviving a childhood brain tumour can be particularly challenging for AYA survivors (aged 14-39)
50 and their caregivers. Many of their issues are unique when compared to other cancer diagnosis and age
51 groups. Survivors and caregivers continue to report long term issues and unmet needs throughout
52 follow-up. More research is needed on the specific unmet supportive care needs of both survivors and
53 their caregivers and how support services can best meet these needs. Understanding their unmet needs
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3 and recognising what services are required due to the late effects of treatment is critical to improving
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5 their quality of survival.
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Supporting Information 1: Search strategy

Database: MEDLINE (Ovid)

Search covers: 1946- present

- 1 exp brain neoplasm/
- 2 exp glioma/
- 3 ((brain* or cerebr* or cerebella* or infratentorial or supratentorial or "choroid plexus" or intracranial) adj4 (tumo?r* or neoplas* or cancer* or oncol* or metasta* or malignan*)).ab,ti.
- 4 (glioma* or astrocytoma* or glioblastoma* or ependymoma* or medulloblastoma* or neurocytoma* or pinealoma* or schwannoma* or craniopharyngioma* or PNET or DNET).ab,ti.
- 5 1 or 2 or 3 or 4
- 6 exp infant/
- 7 exp child/
- 8 (newborn* or "new born*" or baby or babies or infact* or infanc* or child* or p?ediat*).ab,ti.
- 9 6 or 7 or 8
- 10 5 and 9
- 11 exp Survivors/
- 12 exp "Adult Survivors of Child Adverse Events"/
- 13 "surviv*".ti.
- 14 11 or 12 or 13
- 15 10 and 14

Database: Embase (Ovid)**Search covers: 1996- present**

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1. exp brain tumour/
 2. exp glioma/
 3. ((brain* or cerebr* or cerebella* or infratentorial or supratentorial or "choroid plexus" or intracranial) adj4 (tumo?r* or neoplas* or cancer* or oncol* or metasta* or malignan*)).ab,ti.
 4. (glioma* or astrocytoma* or glioblastoma* or ependymoma* or medulloblastoma* or neurocytoma* or pinealoma* or schwannoma* or craniopharyngioma* or PNET or DNET).ab,ti.
 5. 1 or 2 or 3 or 4
 6. exp child/
 7. (newborn* or "new born*" or baby or babies or infact* or infanc* or child* or p?ediat*).ab,ti.
 8. 6 or 7
 9. 5 and 8
 10. exp survivor/
 11. "surviv*".ti.
 12. 10 or 11
 13. 9 and 12

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3 **Database: PsycINFO (Ovid)**

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5 **Search covers: 1806- present**

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12 1. exp brain neoplasms/
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16 3. ((brain* or cerebr* or cerebella* or infratentorial or supratentorial or "choroid plexus" or
17 intracranial) adj4 (tumo?r* or neoplas* or cancer* or oncol* or metasta* or malignan*)).ab,ti.
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19 4. (glioma* or astrocytoma* or glioblastoma* or ependymoma* or medulloblastoma* or
20 neurocytoma* or pinealoma* or schwannoma* or craniopharyngioma* or PNET or DNET).ab,ti.
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3 **Database: Web of Science**

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5 **Search covers: 1900- present**

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10 # 1 TOPIC: (((Brain* or cerebr* or cerebella* or infratentorial or supratentorial or "choroid plexus" or
11 intracranial) near/4 (tumo?r* or neoplas* or cancer* or oncol* or metasta* or malignan*)) OR
12 ((glioma* or astrocytoma* or glioblastoma* or ependymoma* or medulloblastoma* or neurocytoma*
13 or pinealoma* or schwannoma* or craniopharyngioma* or PNET or DNET))

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15 # 2 TOPIC: (newborn* or "new born*" or baby or babies or infant* or infanc* or child or p?ediatr*)

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17 # 3 TITLE: (surviv*)

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19 # 4 #1 AND #2 AND #3
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For Peer Review

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3 **Database: PUBMED**

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5 **Search covers: 1996- present**
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10 **#12 Search** (#9 AND #10 AND #11)

11 **#11 Search** (survivors[MeSH Terms]) OR surviv*[Title]

12 **#10 Search** (newborn*[Title/Abstract] OR “new born”[Title/Abstract] OR baby[Title/Abstract] OR
13 babies[Title/Abstract] OR infact*[Title/Abstract] OR infanc*[Title/Abstract] OR
14 child*[Title/Abstract] OR paediat*[Title/Abstract]

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17 **#9 Search** (((brain neoplasm[MeSH Terms]) OR glioma[MeSH Terms]) OR (((brain*[Title/Abstract]
18 OR cerebr*[Title/Abstract] OR cerebella*[Title/Abstract] OR infratentorial[Title/Abstract] OR
19 supratentorial[Title/Abstract] OR “choroid plexus”[Title/Abstract] OR intracranial)[Title/Abstract]
20 AND (tumo?r*[Title/Abstract] OR neoplas*[Title/Abstract] OR cancer*[Title/Abstract] OR
21 oncol*[Title/Abstract] OR metasta*[Title/Abstract] OR malignan*[Title/Abstract])) OR
22 glioma*[Title/Abstract] OR astrocytoma*[Title/Abstract] OR glioblastoma*[Title/Abstract] OR
23 ependymoma*[Title/Abstract] OR medulloblastoma*[Title/Abstract] OR
24 neurocytoma*[Title/Abstract] OR pinealoma*[Title/Abstract] OR schwannoma*[Title/Abstract] OR
25 craniopharyngioma*[Title/Abstract] OR PNET[Title/Abstract] OR DNET[Title/Abstract])
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Database: CINAHL (Ebsco)**Search covers: 1960- present**

#S13 S9 AND S12

#S12 S10 OR S11

#S11 TI surviv*

#S10 MH survivors OR MH cancer survivors

#S9 S5 AND S8

#S8 S6 OR S7

#S7 TI ((newborn* or “new born” or baby or babies or infact* or child* or p?ediatr*))
OR AB ((newborn* or “new born” or baby or babies or infact* or infanc* or child* or p?ediat*))

#S6 MH child*

#S5 S1 OR S2 OR S3 OR S4

#S4 TI ((glioma or astrocytoma* or glioblastoma* or ependymoma* or
medulloblastoma* or neurocytoma* or pinealoma* or schwannoma* or glioblastoma* or
ependymoma* or medulloblastoma* or neurocytoma* or pinealoma or schwannoma+ or
craniopharyngioma* or PNET or DNET))

#S3 TI (((brain* or cerebr* or cerebella* or infratentorial or supratentorial or “choroid
plexus” or intracranial) N4 (tumo?r* or neoplas* or cancer* or oncol* or metasta* or malignan*)))
OR AB (((brain* or cerbr* or cerebella* or infratentorial or supratentorial or “choroid plexus” or
intracranial) N4 (tumo?r* or neoplas* or cancer* or oncol* or metasta* or malignan*)))

#S2 MH glioma

#S1 MH brain neoplasms+

Database: Cochrane Library (Wiley)**Search covers: 2005- present**

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- #1 MeSH descriptor: [Brain Neoplasms] explode all trees
 - #2 MeSH descriptor: [Glioma] explode all trees
 - #3 (brain* or cerebr* or cerebella* or infratentorial or supratentorial or "choroid plexus" or intracranial) near/4 (tumo?r* or neoplas* or cancer* or oncol* or metasta* or malignan*):ti,ab,kw (Word variations have been searched)
 - #4 glioma* or astrocytoma* or glioblastoma* or ependymoma* or medulloblastoma* or neurocytoma* or pinealoma* or schwannoma* or craniopharyngioma* or PNET or DNET:ti,ab,kw (Word variations have been searched)
 - #5 #1 or #2 or #3 or #4
 - #6 MeSH descriptor: [Infant] explode all trees
 - #7 MeSH descriptor: [Child] explode all trees
 - #8 newborn* or "new born*" or baby or babies or infact* or infanc* or child* or p?ediat*:ti,ab,kw (Word variations have been searched)
 - #9 #6 or #7 or #8
 - #10 MeSH descriptor: [Survivors] explode all trees
 - #11 Surviv*:ti (Word variations have been searched)
 - #12 #10 or #11
 - #13 #9 and #12

Supporting Information 2: Study details

ADL=Activities of Daily Living, ALL= Acute Lymphoblastic Leukaemia, AYA = Adolescent and young adult, BT = Brain tumour, BMD = Bone Mineral Density, BTS = Brain tumour survivor, EF= Executive functioning, HRQOL= Health related quality of life, M= Mean, MD = Medulloblastoma, QOL= Quality of life.

Articles belonging to the same study are marked with either *, **, ***.

Author	Year	Country	Brain tumour participants	Caregivers	Controls	Methods	Aims/Measures	Summary of findings	MMAT Score (%)
Ahomäki et al.	2017	Finland	1300 cancer survivors (324 BTS) Age: 18 Diagnosed: 0-16		7209 population controls	Military service testing	Physical and cognitive performance	BTS were the second highest cancer group to be exempt from military service. AYA BTS in service scored poorly on fitness and cognitive testing, which was significantly worse than controls.	75
Ailion et al.	2016	USA	25 BTS Age: 18-35 (M=24) Diagnosed: 1-19 (M=9.3)		25 neuro-typical matched controls	Questionnaires; Brain magnetic resonance images	Measure cerebellar atrophy to determine its neurobehavioral correlates	80% of BTS had some degree of diffuse cerebellar damage; participants experienced on average 15% cerebellar atrophy. Young age at diagnosis and radiation was associated with cerebellar atrophy, which impacts both written and oral processing speeds.	75
Ait Khelifa-Gallois et al.	2015	France	64 astrocytoma survivors (48 aged: 18-30) Diagnosed: 0.4-13.4			Telephone semi-structured interviews	Long term outcomes	Around half of survivors reported long-term difficulties associated with cognitive and physical sequelae. Many had received support including - Remedial teaching, Speech therapy, occupational therapy, physiotherapy and psychomotor therapy.	100

Armuand et al.	2017	Sweden	1206 cancer survivors (225 BTS) Age: 18-39 Diagnosed: <21		2412 population controls	Observational-patient databases	Reproductive Patterns	Both males and females in the BT group were less likely to have had a first born child in young adulthood compared to other cancer diagnosis.	100
Barakat et al. *	2015	USA	126 BTS Age: 14-39 (M=20.5) Diagnosed: <9	186 mothers		Questionnaires	Predictors of physical and emotional HRQOL, by evaluating the mediating role of family functioning	AYA CBTS are at risk for poor HRQOL, many do not live fully independently, involvement of their family, and consequently their family's functioning, is likely critical to improving HRQOL.	75
Boman et al.	2009	Sweden	531 BTS Age: 18-36 Diagnosed: <19 (M=10.4)		996 population controls	Postal Questionnaires	Health-related and long term outcomes	AYA CBTS are at high risk for significant persistent functional, and health-related late effects, with female survivors being more vulnerable. Survivors were significantly more likely to have lower employment/educational status, use governmental subsidies and less likely to become parents.	100
Boydell et al.	2008	USA	14 BTS Age: 17-29	22 family members.		Focus groups; Semi-structured Interviews	Experiences and needs	AYA Survivors carry physical and emotional issues resulting from their tumour and treatment well into their years of emerging adulthood. Strategies to support these young people in ways that will cultivate and harness their strengths and determination need to be developed.	75
Brinkman et al.	2012	USA	20 MD Age: 21-36 (M=29) Diagnosed: 2-17			Pilot study; Neurocognitive and EF assessments.	Associations between cognitive processes and white matter	Reduced white matter integrity, was associated with poorer performance on tasks of executive function and observed neurocognitive dysfunction. Neurocognitive impairment was common across many specific domains of AYA	75

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							function; the worst scores being impaired visual memory and motor processing.	
Chen et al.	2008	Taiwan	7BTS (6 aged 17-22 Diagnosed: <18)	Semi structured interviews	Experiences from a sociocultural perspective.	Neurological, physical and psychosocial issues are a part of AYA survivorship. Numerous physical symptoms included—diabetes, sex hormone deficiency, and fatigue. Prominent psychosocial issues included isolation, relationship rejection.	75	
Chou et al.	2009	Taiwan	98 cancer survivors (49 BTS) Age: 18–21 (M=20.0) Diagnosed: <16	Pilot study; Questionnaires; Interviews; Focus groups.	QOL, long term outcomes (i.e. cognitive, social issues)	AYA BTS had poorer QOL amongst other issues (i.e. physical, psychological, social and cognitive) compared to ALL survivors. This is attributed to BTS survivors having less positive protective factors, more illness-related and individual risk factors and less positive resilience scores.	75	
Cohen et al.	2012	USA	36 BTS Age: 14-20 (M=16.9) Diagnosed: M=8.4	Observational; Medical assessments.	Bone mineral density (BMD)	AYA BTS had varied low-normal BMD. Lumbar spine BMD was significantly lower in those closer to diagnosis, suggesting that peri-treatment factors (illness, decreased activity) affect BMD and there may be some recovery over time.	75	
D’Agostino et al.	2013	Canada	22 cancer survivors (7 BTS) Age: 18-35 Diagnosed: <18	Focus groups	Challenges and resource needs	The impact of cancer seemed more complicated in AYA BTS. Survivors struggled with neurological sequelae which had psychosocial and practical implications (i.e. social relationships, and educational/vocational options). Individual programming to meet the unique challenges identified by BTS are required.	100	
de Blank et al.	2016	USA	587 BTS (255 aged 30-39) Diagnosed: <21	Questionnaires	Psychological and social outcomes of astroglial tumours with	The majority of BTS aged 30-39 group had no impairment’. Yet made up 41% of total bilaterally blind group. Survivors with bilateral blindness were significantly more likely to be unmarried, live dependently,	75	

							and without vision loss	and be unemployed in comparison with those without vision impairment.	
5	Deatrick et al.*	2014	USA	126 BTS Age: 14-39 (M=20.5)	186 mothers	Telephone questionnaires	Caregiver competence in association with caregiver/survivor health, and family functioning	Caregiver health directly predicted caregiving demands which related to family functioning and finally to caregiver competence. Caregiver health becomes important to how they evaluate the demands of caregiving, but may also limit their ability to access resources (their energy/motivation for the effort for caregiving).	75
15	Deatrick et al.	2009	USA	BTS Age: 14-30 (M=19.3)	22 parents (17 mothers, 5 fathers)	Interviews; Questionnaires	Family management in families of children with chronic conditions and those who survived a BT vs	Most BT parents reported that their child had medical effects, including cognitive, physical, and social issues. Parents voiced concern about reoccurrence and the ability to balance family life with survivor needs. Parents generally had the same interpretations of family management as parents of chronic conditions. Yet they described fears of loss and the future. Tools are not available to assess family functioning and clinicians find it challenging to tailor interventions to family needs.	75
29	Demers et al.	2016	Canada	36 BTS Age: 16-29 (M=21) Diagnosed: M=8.9	Compared with age norms	Questionnaires; ADL task performance	Activities of Daily Living (ADL) performance and its association with HRQOL.	ADL functioning in AYA BTS is significantly lower than norms but HRQOL is similar to the general population. The level of poor performance in ADL skills (motor and process skills) was significantly associated with poorer physical health and with mental health.	50
36	Frange et al.	2009	France	45 MD Age: 15-39 (M=25.2) Diagnosed:		Review of medical records; Questionnaires	Long term outcomes	Only a minority of AYA participants were free of sequelae. Most MD survivors suffer persistent deficits in several domains, with a significant impact on their psychosocial	100

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			1.4-17 (median=8.8).				functioning. The findings reinforce the importance of early intervention programmes to reduce the psychosocial impacts of their disease.	
Gray et al.	1992	Canada	62 cancer survivors (16 BTS) Age: 18-37 (M=26.3) Diagnosed: <18	51 healthy peers	Screening questionnaires; Semi-structured telephone interviews	Long term outcomes and experiences	BTS were more likely than other AYA cancer survivors to report difficulty with a variety of physical symptoms - significantly more memory problems, tiredness, coughing and ringing in the ears. However, there was no statistical significance between BTS survivors scoring worse than other cancer survivors in relation to other symptoms, such as pain, difficulties concentrating and shortness of breath.	25
Gunn et al.	2016	Finland	21 BTS Age: 14-35 (median=24) Diagnosed: <16	327 population controls	Semi-structured interviews; Questionnaires	QOL and Long term outcomes	BTS had significantly worse scores in the following dimensions: mobility, vision, hearing, eating, speech, usual activities, mental function, and sexual activity. Scores were lower among MD survivors, but not statistically significant. Still, the majority of the survivors described their QOL positively.	75
Heikens et al.	1998	Holland	20 MD Age: 19-33 (median 25) Diagnosed: 4-17 (M=8)		Endocrine evaluation	Long term endocrine sequelae of cranial irradiation	In 75% of AYAs endocrine abnormalities were observed. The main deficiency was GH impairment, with lack of energy as the major complaint. Young age at treatment was a significant determinant of GH deficiency. Post-treatment interval or chemotherapy were not determinants of endocrine impairment.	75
Hobbie et al.*	2016	USA	41 BTS Age: 15-36 (M=23) Diagnosed: 3-14		Semi-structured interviews	HRQOL and long term outcomes	Physical health issues and cognitive impairment were embedded in AYA accounts of their daily life. The majority said that their social functioning was most	75

							impacted by their BT and treatment. Loneliness was a prevailing theme for all of the survivors. Those with the most neurocognitive impairments had limited insight as to why they did not have friends or why they could not achieve their goals.	
Hocking et al. *	2015	USA	34 BTS Age: 18 to 30 (M=23.5) Diagnosed: M=7.4	34 mothers	Questionnaires; neurocognitive assessments	Association between survivor neurocognitive functioning, family functioning, and HRQOL.	Poorer survivor neurocognitive functioning was associated with worse family functioning and poorer survivor HRQOL.	75
Hoffman et al.	2015	Germany	19 Craniopharyngioma (CP) survivors Aged: 16-30 Diagnosed:2-20		Medical assessments	Nonalcoholic fatty liver disease (NAFLD)	NAFLD occurred in over 50% of AYA CP survivors. NAFLD should be planned for and managed as a major adverse late effect in follow-up care of CP patients.	100
Jayakar et al.	2015	USA	35 BTS Age: 17-36 (M=24) Diagnosed: 1-17 (M=8.17)	59 population controls	Questionnaires; Brain imaging data	Verbal memory and hippocampal volumes	AYA BTS exhibited smaller hippocampi compared with controls. Early declines in hippocampal volume are not fully compensated for in later life survivors grow to become young adults, as evidenced by volumes remaining lower than controls. Indices of verbal memory were significantly lower for survivors.	50
Jereb et al.	1994	Slovenia	42 cancer survivors (23 BTS) Age: 15-26 Diagnosed: <21 (M=8)	19 ALL	Physical, endocrine and psychological examinations; Interviews	Physical and psychosocial long term outcomes	Hormonal, emotional and physical deficiencies were more frequent in BTS than ALL. The degree of mental deterioration was lower for ALL survivors compared to BTS. The majority of BTS endocrinologically evaluated had	50

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							hormonal deficiencies (more frequent than ALL).	
Johannsdottir et al.	2012	Norway	398 cancer survivors (88 Astrocytoma) Age: 19-34 Diagnosed: 1-18	763 population controls	Postal questionnaire	Fatigue	Chronic fatigue was found in 13.6% of astrocytoma survivors, higher than general population controls (5.8%). There was no significant difference in fatigue levels when comparing the three diagnostic groups (Astrocytoma, Wilms Tumour and Acute Myeloid Leukaemia)	100
King et al.	2016	USA	68 BTS Age: 18-35 (M=24) Diagnosed: 0-17 (M=7.96)		Intellectual evaluations	Long-term intellectual and adaptive outcomes	AYA BTS on average performed similar to peers in intellectual and adaptive outcomes but a wide range of outcomes were evidenced. 17.6% were impaired on IQ scores and 29% of the sample were identified as impaired in adaptive functioning and day-to-day living skills.	50
King I et al.	2015	USA	17 BTS Age: 17-35 years (M=23.2) Diagnosed: 1-17 (Median=7)	17 demographically matched controls	Working memory, behavioural and neuropsychological measures	Working memory	AYA BTS evidenced lower working memory performance than controls. On all of measures survivors performed significantly lower than controls. High-grade embryonal tumour survivors performed the worst	75
King II et al.	2015	USA	31 BTS Age: 18-30 (M=22.5). Diagnosed: 1-19 (M=8.8)	33 demographically matched controls.	Questionnaires and assessments of EF.	Adaptive function and executive performance	Survivors had significantly lower planning and functional community living skills and greater perseveration. The range of scores was varied which suggests a wide range of functioning amongst BTS.	75
King III et al.	2015	USA	27 BTS Age: 18-32 (M=22.7) Diagnosis age: M=9	27 demographically matched controls.	Questionnaires; MRI and DTI (diffusion tensor imaging) data; IQ test	White matter integrity	Lower long-term intellectual outcomes of BTS are associated with lower white matter integrity. Radiation and adjunct chemotherapy treatment may play a role in greater white matter disruption. Those treated with radiotherapy were significantly different from non-radiotherapy and controls on all indices of intellectual	75

							abilities. The white matter disruption of the radiation with or without chemotherapy was positively correlated with IQ and cumulative neurological factors.	
Klosky et al.	2014	USA	307 cancer survivors (40 BTS) Age: 15-20 Diagnosed: <4		Postal questionnaire	Sexual functioning	AYAs with a history of BTS were significantly less likely to report a history of sexual intercourse.	100
Koustenis et al. ***	2013	Germany	203 BTS Age: 19-37 (median= 22) Diagnosed: <15		Questionnaire; Radiation exposure assessment.	Fertility	Irradiation of the pituitary gland >30 gray in AYA BTS was significantly associated with less pregnancies, increased infertility and absence of menstruation.	75
Lehmann I et al. **	2017	USA	144 cancer survivors (47 BTS) Age: 20-39 (M=28) Diagnosed: 5-18	144 population controls	Online survey	Psychosexual functioning	AYA BTS were less likely to be sexually experienced, partnered, and achieve milestones of psychosexual development compared with those treated with non-neurotoxic modalities. Survivors treated with high-dose neurotoxic modalities were least likely to be sexually experienced, in a relationship, or have children.	75
Lehmann II et al. **	2017	USA	149 cancer survivors 52 BTS Age: 20-39 Diagnosed: 5-18	149 population controls	Online survey	Romantic relationships - mate value	Comparisons between diagnostic groups indicated that AYA BTS reported significantly lower mate value than lymphoma as well as leukaemia survivors.	75
Liptak et al.	2016	USA	19 BTS Age: 14-26 (M= 19.8) Diagnosed: 0.6-19 (M= 7.7)	18 mothers	Semi-structured telephone interviews; Questionnaires	Social issues, psychosocial needs and evaluation of a developed social intervention.	Social isolation was prominent among survivors. The combination of lack of social opportunity and medical, neurocognitive, and psychological issues added to the social isolation. Survivors and caregivers described participation in the STEPS programme as a positive experience which reduced isolation and	75

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							reportedly contributed to the improvement in social confidence.	
Lucas et al. *	2016	USA	BTS Age: 15-36 (M=23.38)	45 mothers	Semi-structured interviews	Caregivers' expectations about survivors' functioning	Five main themes emerged as integral to mother expectations: realizing a difference in the survivor, noticing limitations to independence in the survivor, memories of learning about clinical prognoses as understood from consent meetings and education, managing these realizations, and acknowledging unresolved challenges. Pre-tumour expectations were a basis for post-tumour uncertainty and worry about the potential that the survivor is too different in important ways and that s/he may not become independent of her.	75
Maddrey et al.	2005	USA	16 MD Age: 14-28 Diagnosed: <16 years.	General population norms	Neuropsychological tests; Questionnaires	Cognitive performance, psychosocial functioning and QOL	Impairment existed in all cognitive domains (attention, memory, visuospatial ability, motor functioning, language and EF). Survivors 19+ years old were significantly impaired in all indicators of daily functioning (i.e. employment, education, driving) when compared to population norms. Despite impairment no significant differences were noted (compared to norms) in QOL.	50
Mandrell et al.	2012	USA	31 BTS (17 aged 14-25) Diagnosed: <14		Sleep evaluations.	Sleep disorders	The most common reason for sleep treatment in AYAs was excessive daytime sleepiness, snoring sleep apnea. BTs not only interferes with normal sleep patterns and increases daytime sleepiness, but also may further impair cognitive, physical and social functioning.	75

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3	Maunsell et al.	2006	Canada	1334 cancer survivors (238 BTS) Age: 15-37 Diagnosed: <20	1477 age- and sex-matched controls.	Postal questionnaires	QOL	AYA BTS were the only group to have consistently poorer physical and psychosocial functioning. Compared with controls BTS had significantly poorer QOL in several domains: general health, physical function, and role limitations.	100
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6	Maurice-Stam et al.	2013	The Netherlands	363 cancer survivors (38 BTS) Age: 18-31 Diagnosed: <16	508 population controls	Questionnaires	Disability benefits and psychosocial development	BTS made up 40.4% of cancer survivors with disability benefits. Cancer survivors with disability benefits had lower social and psychosexual scores than those without disability benefits.	75
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10	McClelland et al.	2013	USA	271 cancer survivors (51 BTS) Age: 18-38 Diagnosed: M=10.24		Questionnaires	Long term outcomes, experiences, and information needs	BTS in comparison to other AYA cancer survivors reported significantly worse cognitive late effects and financial difficulties. BTS did not experience significantly greater physical side effects, but they did report greater amounts of fatigue than other survivors. There is a need for development of educational materials appropriate for survivors and providers desiring more information.	50
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16	McCurdy et al.	2016	USA	34 BTS Age: 18 to 30 (M=23.5) Diagnosed: M=7	34 Mothers	Medical record review; Survivor performance-based assessments; Questionnaires	Survivor, mother, and performance-based estimates of executive functioning (EF)	Findings suggest that AYA BTS who received high intensity tumour-directed treatments may overestimate executive skills relative to mother reports and performance on objective measures. Both survivors and mothers reported greater executive dysfunction than the normative mean, though were both in the average range. Survivors with more Intensive treatment evidenced greater score discrepancies, reporting less executive dysfunction relative to mother-reported.	75
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Palma et al. *	2015	USA	BTS: Aged: 15-30 (M=23)	46 mothers	Semi-structured interviews	Caregiver demands/experiences	Four main categories of maternal daily caregiving demands were identified: managing the illness; identifying, accessing, and coordinating resources; assisting with everyday responsibilities; and fostering psychosocial health.	75
Petraroli et al.	2007	Italy	12 BTS (9 aged 14-25) Diagnosed: 5-15		Observational; Medical assessments and tests.	Bone mass/bone mineral density (BMD); Endocrine functioning	There was reduced BMD in all the AYA BTS. Most of the survivors had a BMD that was lower than normal in both the lumbar column and in the femoral neck. The main risk factor for bone mass loss in the sample was hypogonadism but also multiple hormonal deficiencies are associated with lower BMD values.	50
Pfizer et al. ***	2013	Germany	203 BTS Age: 19-37 (median=22) Diagnosed: 1-15 (M=11)		Questionnaires	Education	A third of CBTS obtained the highest school leaving certificate. Tumour irradiation, and young age at BT diagnosis may reduce chances for BTS better educational level. Patients without chemotherapy had highest education level.	75
Pietila et al.	2017	Finland	52 BTS (16 >18 group) Age: 18-28.7 Diagnosed: 0.1-15.5		Medical record review; Physical examination; Interviews.	Growth, pubertal development and gonadal function	Growth impairment, growth hormone deficiency and hypogonadism were common in childhood BTS. However, young adults aged 18-28 did not have statistically significant lower height standard deviation scores at follow up.	100
Poggi et al.	2005	Italy	76 BTS (21 aged 14-18) Diagnosed: <18		Cognitive and psychological evaluations	Cognitive and psychological behavioural disorders	All survivors were cognitively impaired, those aged 14-18 scored worse than younger groups. BTS were impaired in communication, daily living skills, social skills and motor skills. The most impaired domain was 'socialisation' and competence decreased as participants got older. Most frequent psychological and	100

							behavioural disorders were: internalising; withdrawn; social problems.		
5	Strauser et al.	2013	USA	43 BTS Age: 18-30 (M=22) Diagnosed: M=9.5	298 college students	Questionnaires	Career readiness and work personality	AYA BTS have significantly lower levels of work personality and career readiness when compared to controls. Individuals who are diagnosed age 6-12 may be at increased risk of developing lower levels of work personality which may lead to increased problems meeting the contextual demands of the work environment.	75
14	Taiwo et al.	2017	USA	61 BTS Age: 18-35 (M=24) Diagnosed: 0-17 (M=8)		Neuropsychological assessments; Medical record review	Neurocognitive outcomes	Findings suggest that survivors with more treatments and neurological sequelae experience greater working memory, processing speed, and attention deficits.	75
19	Turkel et al.	2007	USA	600 BTS (8 aged 14-20) Diagnosed: 6-13		Observational; Medical record review	Psychosis late effects	Psychotic symptoms were seen in BTS, but only in a small number. A delay of several years was seen between the time of diagnosis/treatment and onset of psychotic symptoms.	75
25	Uday et al.	2015	England	35 MD Age: 16-35 Diagnosed: 2-14 (M=8)		Longitudinal observational study	Endocrine functioning	Endocrine sequelae in AYA MD survivors was high. 97% of survivors developed either complete or partial GHD following treatment. Faltering height and tiredness were the most common presentation of GHD. Endocrine issues were more prevalent in those treated with concomitant chemotherapy and radiotherapy.	75
34	Vance et al.	2004	England	BTS Aged: 15-20 Diagnosed: 5-9	4 Parents (with survivors in age limit)	Semi-structured interviews	Long term outcomes, experiences	Survivors reported issues with education, cognitive functioning, physical effects, social functioning, relationships, isolation and independence. As AYAs get older parents were concerned about their child's future-especially their inability to self-care.	75

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							Parents need more support to help their child adjust to their late-effects.	
Wasilewski-Masker et al.	2016	USA	157 cancer survivors (22 BTS) Age: 15-30 Diagnosed: <20 years		Online questionnaires	Survivors' experiences of supportive services	BTS were more likely to value social activities or support groups compared with other survivors, and in comparison to informational mailing, weekend retreat, informational workshop or individual counselling. BTS considered social activities and support groups most important, this could may be indicative of poorer social outcomes observed among BTS.	75
Wilford et al.	2017	USA	BTS Age: M=44 BTS- Age: M= 15.7 Diagnosed: M= 4.5	20 parents	Semi-structured telephone interviews	Long term outcomes	Parents reported AYA survivors having social withdrawal and impaired peer/romantic relationships. Many parents reported impaired cognitive functioning and ongoing physical issues affecting social functioning. Parents worried about the future and reported chronic stress regarding the survivor's current and future health. Most commonly desired support services were parent support groups, parent survivorship education classes, and an age-matched, ability- matched social support group for BTS.	75
Zebrack et al.	2008	USA	176 cancer survivors (19 BTS) Age: 16-28 Diagnosed: <18		Medical record review; Questionnaire	QOL	BTS scored significantly lower on their overall QOL. BTS also scored lower in the social QOL dimension than all other survivors combined. BTS reported diminished well-being with regard to social activities, social relationships, and employment.	75
Zebrack et al.	2010	USA	599 cancer survivors (79 BTS)		Postal questionnaire	Sexual functioning	Findings suggest that BTS (especially males) are less likely than other paediatric malignancies to be sexually active.	75

Age: 18-39
 Diagnosed: <21

However, no statistically significant differences in sexual functioning were observed across cancer types.

For Peer Review

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