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# Social Attainment in Survivors of Pediatric Central Nervous System Tumors: A Systematic Review and Meta-Analysis from the Children's Oncology Group

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## Abstract

**Purpose:** Improved therapies for pediatric central nervous system (CNS) tumors have increased survival rates, however, many survivors experience significant long-term functional limitations. Survivors of pediatric CNS tumors can experience deficits in social attainment. The aim of this review was to systematically amalgamate findings pertaining to social attainment (i.e., educational attainment, marriage, employment outcomes) in survivors of pediatric CNS tumors.

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Dr. Schulte declares that she has no conflict of interest.
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**Methods:** PubMed(Web-based), PsycINFO(EBSCO), EMBASE(Ovid), and Web of Science(Thomson Reuters) were used to identify articles published between January 2011 and September 2018. Eligible studies reported outcomes for survivors of pediatric CNS tumors diagnosed before age 21 years, and >5 years from diagnosis and/or >2 years off therapy. All data were independently abstracted by two reviewers. Random-effects meta-analyses were performed using Review Manager 5.0.

**Results:** The search yielded 7,021 unique publications. Forty-six were included in the current review. Meta-analyses revealed survivors of CNS tumors were significantly more likely to have completed compulsory education only (OR = 1.87, 95% CI = 1.66, 2.12, p < 0.00001), less likely to be married (OR = 4.70, 95% CI = 3.89, 5.68, p <0.00001), and more likely to be unemployed (OR = 2.84, 95% CI = 2.62, 3.08, p < 0.00001) compared to non-cancer controls. Cranial radiation therapy, neurocognitive deficits and younger age at diagnosis were associated with poorer outcomes. Hearing loss and bilateral blindness were also related to poorer outcomes. Sex did not impact social attainment outcomes.

**Conclusions:** Survivors of pediatric CNS tumors are at elevated risk for poor attainment of key adult social outcomes.

**Implications for Cancer Survivors:** There is a critical need to develop interventions to support survivors in becoming independent and productive adults.

## Introduction

Improved therapies for pediatric central nervous system (CNS) tumors have increased survival rates, with the majority of survivors living well into adulthood. Currently, there are more than 115,000 survivors of pediatric CNS tumors in North America.[1] However, many survivors experience significant long-term functional limitations. Specifically, survivors of pediatric CNS tumors can experience debilitating deficits in social attainment following their treatment.[2] These deficits often worsen with time, and impact survivors' quality of life.[2, 3] Compared to siblings, these survivors have been reported to be less likely to attend college, less likely to live independently, less likely to be married, and are at increased risk of unemployment.[4] Yet, no study to date has attempted to systematically amalgamate these findings in order to fully appreciate the prevalence and severity of the difficulties among this population.

Specific risk factors affecting the severity and burden of social late effects in survivors of pediatric CNS tumors are still unclear, but evidence suggests that patient characteristics such as female sex, younger age at diagnosis and lower family socioeconomic status, as well as diagnosis and treatment elements (e.g., tumor location, treatment modality, therapy dosage) may be influential.[5] Due to the nature of pediatric CNS tumors, treatment is often invasive, typically including two or more treatment modalities. Surgery, the most common treatment and typically the first line of therapy, may cause structural and functional changes to the developing brain. Chemotherapy and radiation therapy, typically used for higher-grade tumors, may adversely affect targeted and surrounding tissues and organ systems.[6] Cranial radiation therapy (CRT) has emerged as a significant risk factor for social late effects in this population.[7]

While there is increasing evidence to suggest social attainment difficulties for survivors of pediatric CNS tumors, to our knowledge, there has not been a systematic, meta-analytic examination of social attainment deficits and associated risk factors in this population. Our goal for this systematic review, therefore, was to evaluate the available evidence of social attainment outcomes of survivors of pediatric CNS tumors in the literature. Our specific objectives were to: 1) describe the social attainment outcomes of survivors of pediatric CNS tumors and study characteristics (e.g., study design, sample size, characteristics of pediatric CNS survivor group studied); 2) complete a meta-analysis comparing achievement of social outcomes (i.e., educational attainment, employment, marital status) in survivors of pediatric CNS tumors compared to controls; and 3) document risk factors related to adverse social outcomes in survivors of pediatric CNS tumors as described in the literature.

## Methods

### Data Sources and Searches

In March 2016 the Children's Oncology Group (COG) Guideline Task Force on Neurocognitive and Psychosocial late-effects performed an extensive review of the literature to identify updates for the COG Long-Term Follow-Up Guidelines (version 5.0).[6] This review was extended for the current manuscript. A trained health sciences librarian (author B.O.B.) with experience conducting and documenting searches for systematic reviews performed a thorough, extensive search of the literature to identify studies on social attainment in childhood cancer survivors published in the English language. Databases searched were: PubMed (Web-based), PsycINFO (EBSCO), EMBASE (Ovid), and Web of Science (Thomson Reuters). Relevant articles published from January 1, 2011 to September 30, 2018 were included. Narrative and systematic reviews and meta-analyses on this topic published within this date range were also evaluated to identify relevant manuscripts, but the reviews themselves were not included in the current analysis. Dissertations, books, book chapters, editorials, letters, and conference proceedings/abstracts were excluded.

In PubMed, MeSH (medical subject headings) terms defined the concepts of cancer or neoplasms; children, childhood, adolescents, or pediatric; and social attainment. For optimal retrieval, all terms were supplemented with relevant title and text words. Full PubMed search parameters are available in the online appendix (See Supplementary Table 1). Search strategies for PsycINFO, EMBASE, and Web of Science were adjusted for the syntax appropriate for each database using a combination of thesauri and text words. Published reports in the peer-reviewed literature were identified and all abstracts were reviewed for eligibility. When additional information was needed, full-text articles were retrieved and reviewed. Original study authors were not contacted directly. Cochrane and PRISMA guidelines for completion of systematic reviews were followed.[8, 9]

### Study Selection

Inclusion and exclusion criteria were determined prior to study selection. Eligible studies: 1) were original research studies 2) were published in English; 3) included children diagnosed with a CNS tumor between 0–21 years of age; and 4) described survivors who were at least 5 years from diagnosis and/or 2 years from the completion of therapy. Studies that included

a wide range of ages and/or intervals from diagnosis and treatment were included only if the mean age and/or time interval met the aforementioned criteria. Studies for which CNS tumor patients were included as a subset of a larger sample were excluded if social attainment outcomes were not reported separately for survivors meeting these criteria.

Published articles were subjected to a two-step review process. In the first step, all available titles and abstracts were screened by two independent raters to identify potentially eligible studies for inclusion. Disagreements were resolved through consensus between these two raters. The identified studies based on the review of titles and abstracts were then retrieved in full and again, two independent reviewers reviewed the content of each full article for eligibility. Disagreements were again resolved through consensus between raters. Inter-rater reliability at each step was calculated using the Kappa statistic.[10]

## Data Abstraction and Quality Assessment

Data abstraction was completed according to the Late Effect Evidence Table (LEET) developed by the COG Late-Effects Guideline Task Force. The LEET includes sections on study design, median follow-up time, participation rate, and description of study objectives. In addition, risk of bias assessment for each study was considered and included evaluation of a number of domains adapted from the Cochrane Risk of Bias Tool[9] including: selection/subject bias, attrition bias, instrumentation and missing data and reporting outcomes. Each category was labeled ‘low risk of bias’, ‘high risk of bias’ or ‘unclear’ based on guidelines from the Cochrane Handbook for Systematic Reviews.[9] Data abstraction and bias assessments were completed by one independent rater for each published study.

## Statistical Methods

The pediatric CNS samples studied were summarized using percentages based on the following criteria: study design, sample size, and characteristics of CNS survivor group studied. Findings were then described qualitatively using a narrative synthesis.

Meta-analyses comparing achievement of social outcomes in survivors of pediatric CNS tumors compared to controls were performed using a fixed-effects model to estimate the odds ratio. Standardized mean differences and pooled effects were displayed on forest plots (including estimated overall effect and 95% Confidence Intervals [CI]). Synthesis was performed for studies that: a) reported social attainment outcomes (i.e., educational attainment, employment, marital status, independent living) for both survivors of pediatric CNS tumors and healthy controls; and b) provided dichotomous reports of these outcomes (i.e., yes/no). Only studies that reported frequencies could be included. Consistency of results across studies were evaluated by the $Chi^2$ and $I^2$ statistics for statistical heterogeneity. Significant pooled response means were considered as those with $p$-values $<0.05$. All meta-analyses were conducted using Review Manager (RevMan) (Windows) version 5.3.[11]

Factors associated with social attainment outcomes in survivors of pediatric CNS tumors reported in the literature were described using a narrative synthesis.

# Results

## Data abstraction

The review yielded 7,021 unique publications of which 560 abstracts were retrieved for full review. Interrater agreement at the first step of review for inclusion as determined by Cohen's kappa was good (k = 0.81). Of the 1,834 articles that were retrieved and reviewed 45 articles were included in the final review (Figure 1). Interrater reliability for selection of included articles after full review was also good (k = 0.78). Disagreements were resolved in all cases through discussions. Reasons for further exclusion are presented in Figure 1.

## Assessment of Bias

Of the 45 studies reviewed, 42% reported low-risk of bias with respect to selection/subject bias; 82% for instrumentation and missing outcomes and 69% for reporting outcomes. Few studies (9%) included data relevant for assessing attrition bias (see Figure 2).

## Data Synthesis

Objective 1: Narrative Synthesis of Study Characteristics

Table 1 provides descriptive characteristics of the sample. Studies were largely observational, cohort study designs (40%, n = 18) with the remainder categorized as observational, cross sectional (33%, n = 15), observational, case control (11%, n = 5) and non-experimental (16%, n = 7). Sample size of studies ranged from 4 to 2,153 participants. Length of follow-up ranged from 6.98 to 20.00 years. Studies included sample populations of childhood cancer survivors with outcomes for CNS tumor survivors reported separately (33%, n = 15), heterogeneous populations of survivors of pediatric CNS tumor (31%, n = 14) or samples restricted to specific CNS tumor types (36%, n = 16). Social attainment outcomes evaluated included: educational attainment (64%, n = 29), employment (51%, n = 23), marital status (29%, n = 13) and independent living (16%, n = 7). Two studies (5%) reported outcomes classified as 'other' but were considered to be related to social attainment. Specifically, one study reported on the income of pediatric cancer survivors[12] and the other reported on legal difficulties experienced by this population.[13]

Of all the studies reviewed, 47% (n = 21) included a control group: Healthy or population controls (n=15), siblings (n=6), or another chronic illness (i.e., type 1 diabetes mellitus) (n=1). The remaining 53% did not include a control sample.

Objective 2: Meta-Analysis of Social Outcomes

Of those studies that included a control group, 9 did not report necessary statistics for either the control group or for in survivors of pediatric CNS tumors to be included in meta-analyses. In total, 12 studies were considered eligible for the meta-analysis.

Meta-analyses were completed for three primary outcomes: educational attainment, employment and marital status.

**Educational Attainment.—**Of 26 studies that described educational attainment, specifically, not graduating or completing compulsory education only, 12 included a control group and 4 met criteria for meta-analysis.[14-17] Data were available for 1,697 survivors of CNS tumors and 1,222,785 healthy controls. Based on the results of the pooled analysis, survivors of CNS cancer were significantly more likely to have not graduated or completed compulsory education only compared to healthy controls (OR = 1.87, 95% CI = 1.66, 2.12, $p < 0.00001$). There was evidence of moderate heterogeneity in this pooled analysis ($Chi^2 = 6.86$, df = 3, p = 0.08; $I^2 = 56\%$), suggesting that results across the studies reviewed may not be consistent, so results should be interpreted with caution.

**Employment.—**Twenty studies described employment outcomes. Of these, 8 included a control group and 5 included a dichotomous outcome (i.e., currently employed vs. not).[14, 17-20] In total, 5 studies were included in a meta-analysis comparing survivors of CNS tumor to healthy controls, including siblings. Data were available for 4,400 survivors and 18,805 healthy controls. In the pooled analysis, CNS tumor survivorship was associated with significantly higher risk of unemployment (OR = 2.84, 95% CI = 2.62, 3.08, $p < 0.00001$). There was evidence of heterogeneity in this comparison ($Chi^2 = 84.19$, df = 4, $p < 0.000$; $I^2$=95%), suggesting that results across the studies reviewed may not be consistent so results should be interpreted with caution (see Figure 3).

**Marital Status.—**Eleven of the included studies described marital status, specifically, married/unmarried. Of these, 6 included a control group and an additional 1 study included data from non-CNS cancer survivors. In total, 3 studies contained data suitable for meta-analysis. Data were available on 724 survivors of CNS tumor and 4,678 healthy controls. There was a significant risk of CNS tumor survivors to not be currently married (OR = 4.70, 95% CI = 3.89, 5.68, $p <0.00001$) and no evidence of heterogeneity in these analyses ($Chi^2 = 0.03$, df = 2, p = 0.98; $I^2$=0%) suggesting that results were consistent across studies.

Objective 3: Factors Related to Social Outcomes

Of the 45 studies included in the current review, 18 examined demographic and treatment factors that might be related to social attainment outcomes. With respect to sociodemographic outcomes, the majority of studies reported that sex did not significantly impact social attainment outcomes,[14, 21] with the exception of one study that reported that males were more likely to be unemployed compared to females.[14]

Examination of clinical variables revealed that, where assessed, CRT,[12-14, 18, 19, 22, 23] and perhaps specifically CRT greater than 35Gy,[20] was consistently associated with poorer outcomes. Neurocognitive impairment[24, 25] was also consistently related to poorer social attainment outcomes. Younger age at the time of diagnosis or treatment was associated with poorer educational and employment outcomes,[14, 15, 26, 27] although one study found an association between older age at diagnosis and completion of compulsory schooling only (i.e., high school or secondary school).[16] Finally, late effects of treatment such as hearing loss and bilateral blindness were also associated with increased risk of not graduating college, not living independently, unemployment and being unmarried.[24, 28]

Treatment era was explored in some of these studies which found that generally, treatment before 1999 was associated with a lesser likelihood of college graduation[15, 27] and a greater likelihood of being unemployed.[14] With respect to marital status, however, it appeared that fewer survivors have married over time.[29]

## Discussion

The current review aimed to summarize the literature pertaining to social attainment outcomes of survivors of pediatric CNS tumors for the purpose of updating the COG Psychosocial Long-Term Follow-Up Guidelines (version 5.0)[6]. Specifically, we sought to review the most recent literature with respect to social attainment outcomes, and for the purposes of this manuscript, to focus on outcomes pertinent to survivors of pediatric CNS tumors. Although there has been previous literature describing the social attainment outcomes of survivors of pediatric cancer[4], this is the first review to focus exclusively on survivors of pediatric CNS tumors and to attempt to amalgamate the findings across a range of studies. Our findings clearly demonstrate a significantly increased risk for a number of poor social attainment outcomes in this group of survivors including: likelihood to graduate college, be employed, and be married.

There is an extensive literature that has documented the neurocognitive and social difficulties among this population.[2, 30] The current work demonstrates how these deficits translate into functional impairments for survivors of CNS tumors across the lifespan. While the latest version of the COG Long-Term Follow-Up Guidelines[6] recommend yearly psychosocial assessment with attention to educational and/or vocational progress and social withdrawal, the type of assessment that should be completed and how long these survivors should be followed is not specified. The results of the current study highlight that assessment and tailored interventions are critical for this vulnerable population of survivors and are likely required throughout the lifespan. To date, interventions designed for this population have targeted school-age survivors and have focused on improving social skills[31-33] or peer-mediated interventions.[34] While these interventions have been found to be feasible and acceptable, the effect on social outcomes is typically small.

In keeping with the intention of the COG Long-Term Follow-Up Guidelines to document exposure-based risk factors and late effects and provide recommendations for screening,[6] we attempted to identify risk factors related to social attainment outcomes in this population. Consistent with the existing guidelines, CNS directed therapy (namely CRT) and neurocognitive impairment were highlighted as risks for poor social attainment outcomes. We additionally highlighted the finding that late effects of treatment such as hearing loss and bilateral blindness were also associated with increased risk of not graduating college, not living independently, unemployment and being unmarried.[24, 28]

Limitations of the current review include the considerable heterogeneity across studies with respect to the age of participants and, whether studies described a childhood cancer survivor population in general, a heterogeneous population of CNS survivors or a specific CNS diagnosis. Moreover, studies varied largely with respect to the types of control samples employed from no control sample to siblings, healthy controls or population norms. It

should also be acknowledged that consistent with the goal of the Children's Oncology Group (COG) Late Effects Task Force, which is to provide updates to the guidelines based on the last five years of data, the current review only included research conducted between 2011–2018 and therefore may have missed some additional, important work published outside of this timeframe.

Finally, although associations identified in this study were strong, results suggested that pooled analyses were heterogeneous and should be interpreted with caution. In other words, findings across studies were not always consistent. Moreover, the completed quantitative analyses only represent a minority of studies included in the full review (12 of 45). These 12 studies may not adequately represent all studies that have evaluated the social attainment in this population. Finally, findings from this review should be interpreted in the context of the bias assessments.

Future investigations in this field should aim to consider a lifespan approach to measuring social outcomes among this population. Specifically, how does social functioning in childhood relate to social function in adulthood? Moreover, over the past several years, multiple papers have addressed theoretical models of social competence that might be applied to survivors of childhood CNS tumors.[35, 36] These models have been proposed in an effort to advance the field and deepen our understanding of the difficulties experienced by this population. In addition, ongoing investigations into the impact of treatment and treatment-related toxicities on social attainment are warranted. For example, it remains unknown whether newer therapies aimed to reduce neurotoxicity (e.g., proton radiotherapy) are associated with better social outcomes compared to conventional techniques. Clarity on the mechanisms responsible for social attainment difficulties is required before focus can be placed on developing interventions. Finally, pediatric brain tumors are not a homogenous group and therefore future research in this field must consider the uniqueness of brain tumor diagnosis, treatment, and related comorbidities.

In conclusion, this is the first study, to our knowledge, to systematically assess social attainment outcomes of survivors of pediatric CNS tumors across published studies. Our findings highlight that survivors remain at significant risk of failing to graduate, remaining unemployed, and never marrying. Risk of poor outcomes is increased by a number of treatment related factors including cranial radiation therapy. Although COG Long-Term Follow-Guidelines currently stipulate ongoing assessment for educational and vocational needs as well as social withdrawal, the type of assessment that is completed and the length of time survivors should be followed is currently not specified. Results of the present study suggest that monitoring of outcomes may be required throughout the lifespan. Ultimately, interventions are needed so that more of these at-risk survivors may lead productive and fulfilling lives.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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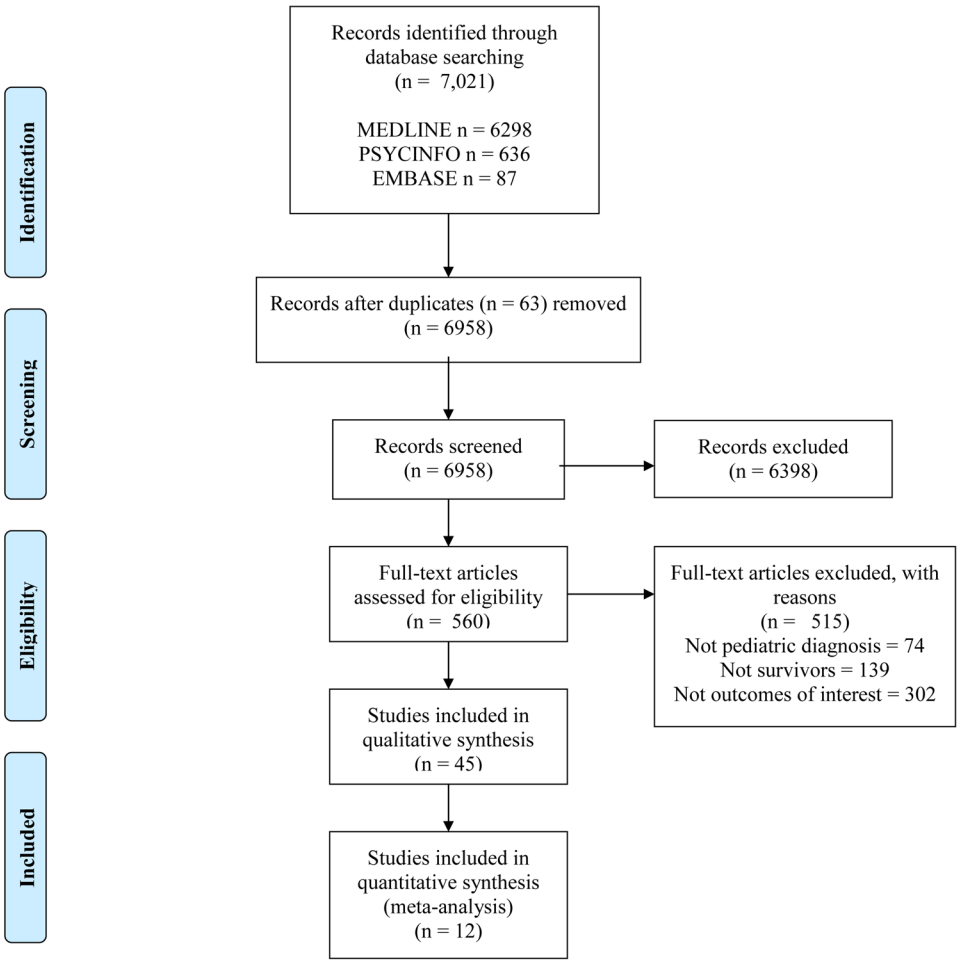



**Figure 1:**
PRISMA flowchart of review search

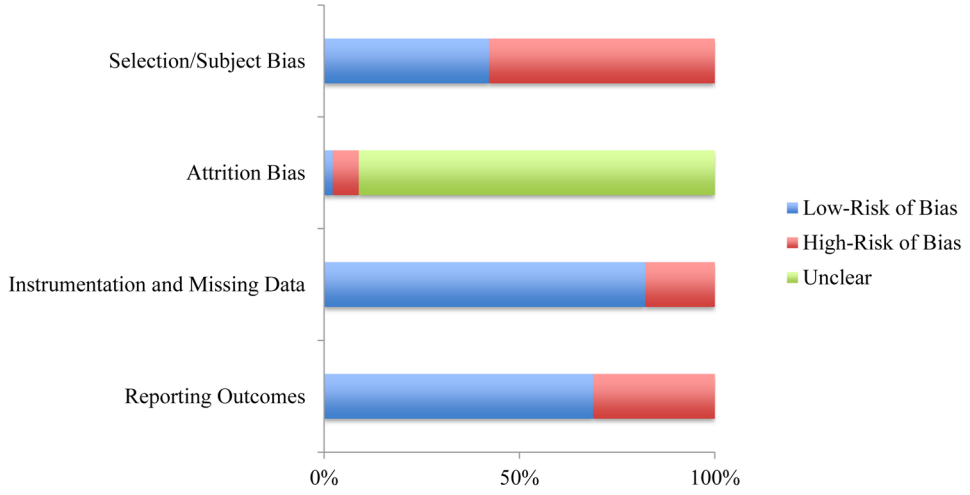
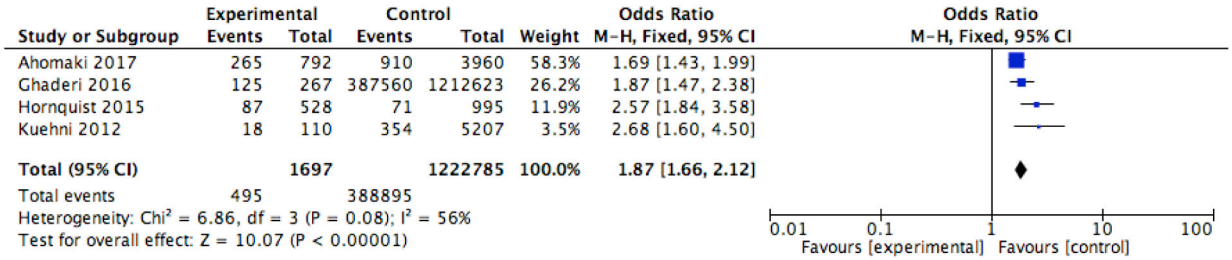
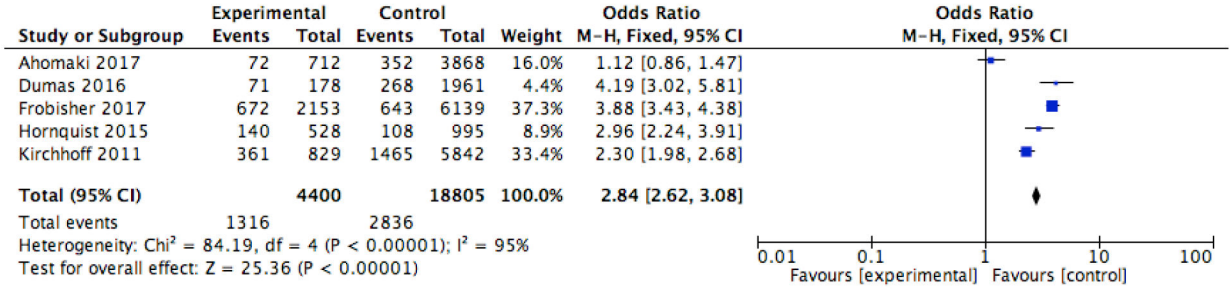



**Figure 2:**
Assessment of bias across studies reviewed.

A.




B.




C.

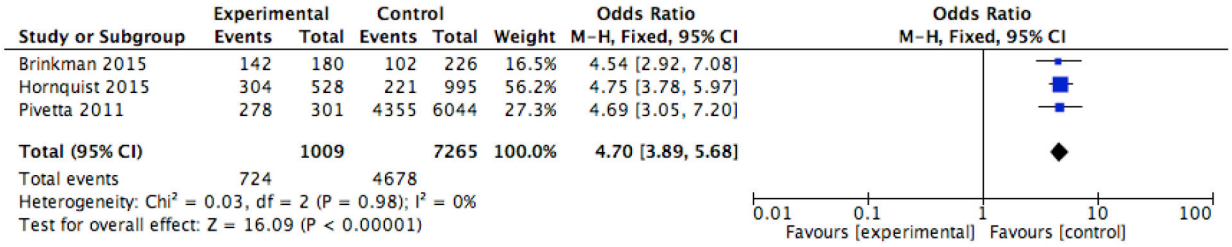



**Figure 3:**

Forrest plots comparing outcomes among pediatric CNS tumor survivors' social attainment and controls. (A) Educational attainment for survivors of CNS tumors compared to healthy controls. (B) Employment outcomes for survivors of CNS tumors compared to healthy controls. (C) Marital status of survivors of CNS tumors compared to healthy controls.

**Table 1.**

Summary of Included Studies

| Paper | Study Design | Study Population | CNS Sample Size | Age at Diagnosis (years) [Mean (SD)] | Age at Study (years) [Mean (SD)] | Time since Diagnosis (years) [Mean (SD)] | Non-CNS Tumor Survivor Comparison Group | Social Attainment Outcomes Assessed | Selection/ subject Bias | Attrition Bias | Instrumentation and Missing Data | Reporting Outcomes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ait Khelifa-Gallois et al. [37] | Observational – Case Control | CNS Survivors: cerebellar pilocytic astrocytoma | 18 | 6.8 (2.7) | 15.1 (1.8) | 7.8 (2.9) | Healthy controls | Education | − | N/A | − | − |
| Ahomaki et al. [14] | Observational – Case Control | Cancer survivors | 792 | Not reported | 27.1 * | 18.7 * | Population norms | Education, Employment | + | N/A | + | + |
| Barakat et al. [38] | Observational – Cross Sectional | CNS Survivors: Heterogeneous population | 186 | Not reported | 20.5 (5.3) | 12.7 (6.3) | None | Education, Employment | − | N/A | + | + |
| Bashore et al. [39] | Observational – Cross Sectional | Cancer survivors | 4 | Not reported | Not reported | Not reported | None | Education | − | − | − | − |
| Beek et al.[40] | Observational – Cross Sectional | CNS Survivors: Heterogeneous population | 45 | Not reported | 14.8 (1.9) | 7.4 (3.3) | None | Education | − | N/A | − | + |
| Brinkman et al. [41] | Observational – Cohort study | CNS Survivors: Heterogeneous population | 306 | 8.7 (4.6) | 26.3 (5.1) | 17.6 (5.0) | None | Employment, Marital Status, Independence | + | + | + | + |
| Brinkman et al. [24] | Observational – Cohort study | CNS and non-CNS Solid Tumor Survivors | 180 | 8.4 (4.6) | 26.6 (5.5) | 18.2 | None | Education, Employment, Marital Status, Independence | + | N/A | + | + |
| Brinkman et al. [42] | Observational – Cohort Study | CNS Survivors: Heterogeneous population | 224 | 8.7 * | 26.0 * | 17.7 * | None | Education, Employment, Independence | − | N/A | + | + |
| Chen et al.[43] | Observational – Case Control | CNS Survivors: Heterogeneous population | 60 | 9.13 (n/a) | 15.4 (1.56) | Not reported | Healthy controls | Education | − | N/A | − | + |
| Cheung et al. [44] | Observational – Case Control | Cancer survivors | 18 | Not reported | Not reported | Not reported | Siblings | Employment | − | N/A | − | − |
| de Blank et al. [28] | Observational – Cohort Study | CNS Survivors: Astroglial tumors | 587 | Not reported | 23.79 (7.30) | Not reported | None | Education, Employment, Marital | + | − | + | + |

| Paper | Study Design | Study Population | CNS Sample Size | Age at Diagnosis (years) [Mean (SD)] | Age at Study (years) [Mean (SD)] | Time since Diagnosis (years) [Mean (SD)] | Non-CNS Tumor Survivor Comparison Group | Social Attainment Outcomes Assessed | Selection/ subject Bias | Attrition Bias | Instrumentation and Missing Data | Reporting Outcomes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Status, Independence | | | | |
| Dumas et al. [18] | Observational – Cohort Study | Cancer survivors | 203 | Not reported | Not reported | Not reported | Population norms | Education, Employment | − | − | + | + |
| Ehrstedt et al. [45] | Non-experimental | CNS Survivors: Glioneuronal tumors | 20 | Not reported | 26.5 | Not reported | None | Education, Employment, Marital Status | + | N/A | + | + |
| Fjalldal et al. [46] | Observational – Cross Sectional | CNS Surviors: Craniopharyngioma | 42 | 12 * | 28 * for women, 29 * for men | 20 * | Population controls | Education, Employment | − | N/A | + | + |
| Font-Gonzalez et al.[22] | Observational – Cohort Study | Cancer survivors | 94 | Not reported | Not reported | Not reported | Population controls | Education, Employment, Independence | + | N/A | + | − |
| Fox et al.[47] | Observational – Cross Sectional | CNS survivors: Heterogeneous population | 76 | Not reported | 23.16 (4.12) | 15.68 (5.85) | None | Education | − | N/A | + | + |
| Frobisher et al. [19] | Observational – Cohort Study | Cancer survivors | 2153 | Not reported | Not reported | Not reported | Population controls | Employment | + | N/A | − | + |
| Gautier et al. [48] | Non-experimental | CNS survivors: Craniopharyngioma | 171 | 5.5/12.5 * | Not reported | 16.83/17.33 * | None | Education, Employment, Marital Status, Independence | + | N/A | − | + |
| Ghaderi et al. [15] | Observational – Cohort Study | Cancer survivors | 142 | n/a | 20 * | Not reported | None | Education, Employment | + | N/A | + | + |
| Gunn et al.[49] | Observational – Cross Sectional | CNS survivors: Heterogeneous population | 21 | 6.4 | 24 * | 17.0 * | None | Education, Employment | − | N/A | + | + |
| Hoag et al.[50] | Non-experimental | CNS survivors: Heterogeneous population | 10 | Not reported | 14.24 (1.66) | Not reported | None | Education | − | N/A | − | + |
| Hocking et al. [51] | Observational – Cross Sectional | CNS survivors: Heterogeneous population | 34 | 7.36 (4.64) | 23.53 (3.36) | Not reported | None | Employment | − | N/A | + | + |

| Paper | Study Design | Study Population | CNS Sample Size | Age at Diagnosis (years) [Mean (SD)] | Age at Study (years) [Mean (SD)] | Time since Diagnosis (years) [Mean (SD)] | Non-CNS Tumor Survivor Comparison Group | Social Attainment Outcomes Assessed | Selection/ subject Bias | Attrition Bias | Instrumentation and Missing Data | Reporting Outcomes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Holland et al. [52] | Observational – Cross Sectional | CNS survivors: Medulloblastoma | 36 | 8.55 (4.34) | 14.07 (3.46) | Not reported | None | Education | − | N/A | + | − |
| Hornquist et al. [17] | Observational – Cohort Study | CNS survivors: Heterogeneous population | 528 | Not reported | 26.30 (4.98) | Not reported | Population controls | Education, Employment, Marital Status | + | N/A | + | + |
| Howard et al. [53] | Observational – Cross Sectional | CNS survivors: Heterogeneous population | 46 | 8.5 (4.7) | 27.0 (7.4) | Not reported | None | Employment | + | N/A | − | + |
| Jervaeus et al. [54] | Observational – Cohort Study | Cancer survivors | 10 | Not reported | Not reported | Not reported | Population controls | Independence | − | N/A | + | − |
| Jinguji et al. [55] | Non-experimental | CNS survivors: germinomas | 25 | Not reported | Not reported | Not reported | None | Education, Employment, Marital Status | − | N/A | − | + |
| King et al.[56] | Observational – Cohort Study | CNS survivors: Medulloblastoma | 380 | Not reported | Not reported | Not reported | Siblings | Education, Employment, Marital Status, Independence | + | N/A | + | + |
| Kirchhoff et al. [20] | Observational – Cohort Study | Cancer survivors | 829 | Not reported | Not reported | Not reported | Siblings | Employment | + | N/A | + | + |
| Koch et al.[21] | Observational – Cohort Study | Cancer survivors | 476 | Not reported | Not reported | Not reported | Population controls | Marital Status | + | N/A | + | + |
| Korinthenberg et al.[57] | Observational – Cross Sectional | CNS Survivors: Low-Grade Glioma | 51 | Not reported | Not reported | Not reported | None | Education, Employment, Marital Status, Independence | − | N/A | + | + |
| Kuehni et al. [16] | Observational – Cohort Study | Cancer survivors | 110 | Not reported | Not reported | Not reported | Population controls | Education | − | N/A | + | + |
| Longuad-Vales et al.[58] | Observational – Cross Sectional | CNS Survivors: Frontal lobe tumors | 21 | 7.8 (5.3) | 14.3 (5.3) | Not reported | Healthy controls | Education | − | N/A | + | + |
| Lundar et al. [59] | Non-experimental | CNS Survivors: Ependymomas | 10 | Not reported | Not reported | Not reported | None | Education, Employment | − | N/A | + | − |

| Paper | Study Design | Study Population | CNS Sample Size | Age at Diagnosis (years) [Mean (SD)] | Age at Study (years) [Mean (SD)] | Time since Diagnosis (years) [Mean (SD)] | Non-CNS Tumor Survivor Comparison Group | Social Attainment Outcomes Assessed | Selection/ subject Bias | Attrition Bias | Instrumentation and Missing Data | Reporting Outcomes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Massimino et al.[60] | Non-experimental | CNS Survivors: Medulloblastoma | 73 | Not reported | 9.5* | Not reported | None | Education, Employment, Marital Status | − | N/A | − | + |
| Memmesheimer et al.[61] | Observational – Cross Sectional | CNS Survivors: Craniopharyngioma | 59 | 10.17 (3.67) | 25.17 (5.83) | 14.75 (5.75) | Type 1 diabetes mellitus | Education, Employment | − | N/A | + | + |
| Olson et al.[62] | Observational – Cross Sectional | Cancer survivors | 36 | Not reported | Not reported | Not reported | None | Independence | + | N/A | − | + |
| Pfitzer et al. [27] | Observational – Cohort Study | CNS Survivors: Heterogeneous population | 203 | 11* | 22* | 12* | None | Other | − | N/A | − | + |
| Pivetta et al. [27] | Observational – Cohort Study | Cancer survivors | 301 | Not reported | Not reported | Not reported | Population controls | Marital Status | + | N/A | + | + |
| Pletschko et al. [63] | Observational – Cross Sectional | CNS Survivors: Cerebellar pilocytic astrocytoma | 14 | 8.10 (2.77) | 21.42 (5.40) | 13.29 (4.97) | Healthy controls | Education | − | N/A | + | + |
| Ruiter et al.[64] | Observational – Cross Sectional | CNS Survivors: Heterogeneous population | 82 | 6.87 (3.77) | 13.85 (3.15) | 6.98 (3.57 | Siblings | Marital Status | − | N/A | + | + |
| Wengenroth et al.[23] | Observational – Cohort Study | Cancer survivors | 129 | Not reported | Not reported | Not reported | Siblings and Population controls | Education | + | N/A | + | + |
| Wengenroth et al.[12] | Observational – Cohort Study | Cancer survivors | 197 | Not reported | Not reported | Not reported | Siblings | Marital Status Other | + | N/A | + | + |
| Yano et a[65] | Non-experimental | CNS Survivors: Craniopharyngioma | 26 | 7.3 | 27.4 | 19.1 | None | Other | + | N/A | − | − |
| Yuen et al.[66] | Observational – Case control | CNS Survivors: Craniopharyngioma | 260 | Not reported | 27.1 | Not reported | None | Independence | − | N/A | + | + |

*Median instead of mean

*J Cancer Surviv*. Author manuscript; available in PMC 2020 December 01.