Educational attainment in childhood cancer survivors: a meta-analysis

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ABSTRACT

Objective To assess differences across educational outcomes in survivors of childhood cancer (CCS) compared with peers.

Design Systematic review and meta-analysis of observational studies.

Data sources and study selection Medline, EMBASE, ERIC, CINAHL and PsycInfo from inception to 1st August 2018. Any peer reviewed, comparative study with a population of any survivor of childhood cancer, from high-economy countries, reporting outcomes on educational attainment, were selected.

Results 26 studies representing 28 434 CCS, 17 814 matched controls, 6582 siblings and six population studies from 11 high-income countries, which have similar access to education and years of mandatory schooling as reported by the Organisation for Economic Cooperation and Development, were included. CCS were more likely to remain at compulsory level (OR 1.36, 95% CI 1.26 to 1.43) and less likely to complete secondary (OR 0.93, 95% CI 0.87 to 1.0) and tertiary level education (OR 0.87, 95% CI 0.78 to 0.98). They were more likely to require special educational needs (OR 2.47, 95% CI 1.91 to 3.20). Subgroup analyses revealed that survivors, irrespective of central nervous system (CNS) involvement, were less likely to progress onto secondary level compared with cancer-free peers (OR 1.77. 95% CI 1.46 to 2.15; OR 1.19, 95% CI 1.00 to 1.42, respectively). This, however, changed at tertiary level where those with CNS involvement continued to perform worse (OR 0.61, 95% CI 0.55 to 0.68) but those without appeared to perform similarly to their peers (OR 1.12, 95% CI 1.0 to 1.25).

Conclusions Compared with controls, we have elucidated significant differences in educational attainment in survivors. This is sustained across different countries, making it an international issue. CNS involvement plays a key role in educational achievement. Clinicians, teachers and policymakers should be made aware of differences and consider advocating for early educational support for survivors.

What is already known on this topic?

- There has been remarkable progress in childhood cancer survival worldwide. As more children survive into adulthood, long-term complications are becoming more apparent.
- The impact of childhood cancer on education has been a subject of interest due to its association with emotional well-being and economic growth.
- Many, but not all, large population-based studies suggest poorer educational achievement in survivors.

What this study adds?

- This is the first and most comprehensive meta-analysis exploring the impact of childhood cancer on educational achievement.
- Survivors underperform at all educational levels, with central nervous system involvement resulting in worst outcomes.
- Clinicians need to consider educational support early.

INTRODUCTION

The global incidence of childhood cancer is increasing, with approximately 300 000 children being diagnosed with cancer yearly.[1] Fortunately, as treatment regimens continue to improve, more individuals with childhood cancer are surviving into adulthood, with up to 90% 5-year survival rates for acute lymphoblastic leukaemia and up to 80% for central nervous system (CNS) tumours recorded in high-income countries.[2]

Now, more attention is directed to understanding the late complications of childhood cancer.[3 4] The potentially detrimental consequences of childhood cancer on educational attainment are of particular global interest because it impacts emotional well-being, social fulfilment and economic growth.[5–7]

Educational attainment is the highest level of formal education completed by an individual within a country's education system.[8] It is most frequently assessed through questionnaires and registry-based studies. Educational attainment provides a direct measurable outcome of education. Its widespread use makes it amenable for comparisons. To allow for international comparisons, the International Standard Classification of Education (ISCED) was established in 1997 (updated 2011) to provide a global framework.[9]

Studies have demonstrated a variety of educational attainment across survivors of childhood cancer. Results include the following: (1) similar outcomes for both survivors and controls[10–16]; (2) findings showing significantly poorer educational outcomes for survivors[17–20] and (3) findings demonstrating significantly better educational attainment, particularly at university level, for survivors.[21 22]

One possible explanation for these differences is that early single-centre studies were most likely

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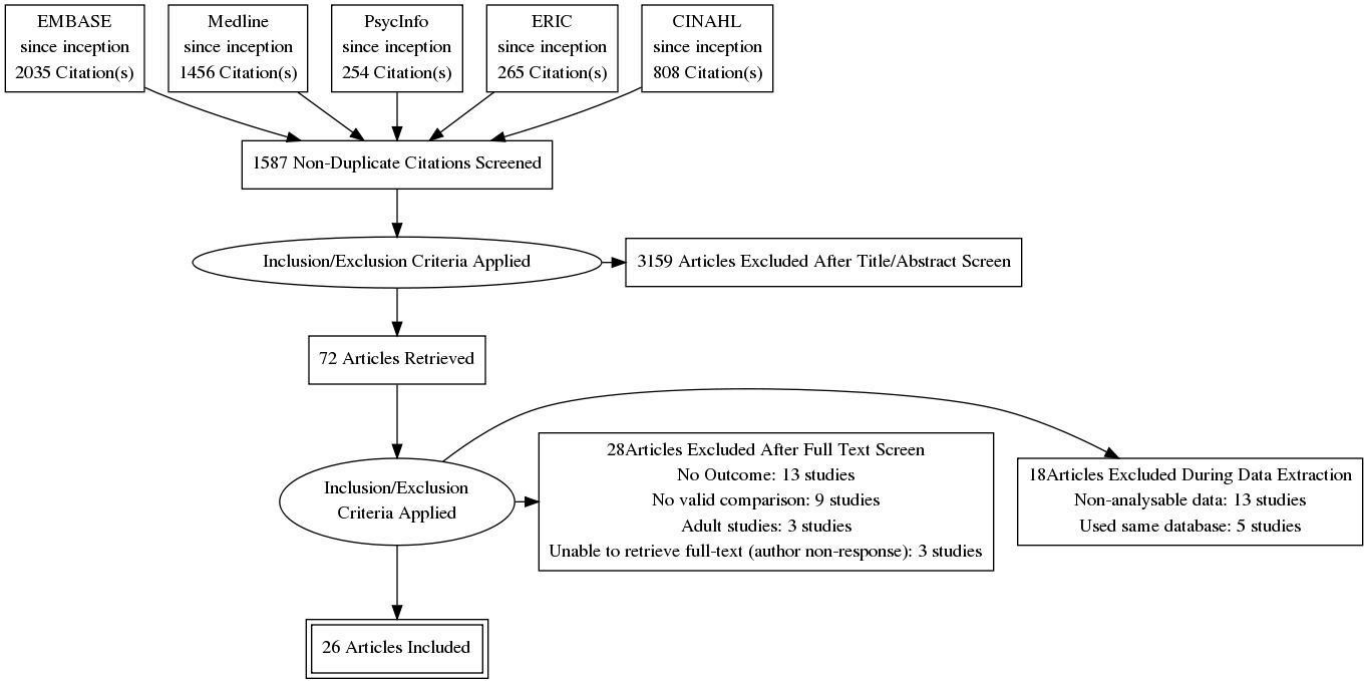

Figure 1 Study flow diagram.

statistically underpowered to detect a difference, given the rarity of childhood cancer. Thus, it would be expected that the more recent multi-centre, national cohorts of childhood cancer survivors[17 19 21 23–25] would provide more consistent findings. Indeed, overall results tend towards poorer outcomes in survivors. Nevertheless, findings appear to still be variable.[21 26 27] These differences are most likely secondary to the type of cancer and treatment received, as well as due to the differences in which educational outcomes are measured. Several studies suggest survivors who had CNS involvement tend to perform worse than their peers,[21 26 28] whereas other cancer types appeared to perform equally[16] or in some cancers, such as osteosarcoma, perform better than their peers.[22] At this stage, a meta-analysis of the current studies would be timely to deliver statistically more powerful, as well as conclusive results and may, in turn, provide clinicians, teachers and policymakers with a stronger understanding of the educational input survivors would benefit from.

METHODOLOGY

The Meta-analysis of Observational Studies in Epidemiology guidelines were followed.[29]

Search strategy

We systematically searched Medline, EMBASE, ERIC, CINAHL and PsycInfo, from inception to 1st August 2018, for search terms within the title or abstract of the publication, including 'child(ren)', 'p(a)ediatric', 'adolescent', 'survivor', 'cancer', 'education(al)', 'school', 'academic', 'achievement', 'qualification', 'degree', 'attainment', 'outcome'. Full search strategies are available from the online supplementary appendix. There were no language restrictions. Reference lists of publications were hand-searched.

Study selection

Studies had to fulfil the following criteria to be included: (1) a study population of 'survivors of any childhood cancer', where survival is defined as alive and in remission for at least 2 years after diagnosis; (2) a comparative study, (3) report an outcome of interest defined as 'level of educational attainment', where each level is defined as follows:

- Primary (Level 1): Completion of compulsory schooling only (*ie, the number of years of education a child must complete within that country*).
- Secondary (Level 2): Education which is not mandatory (educated beyond the minimum statutory level within that country, but not entering university level education). Includes vocational training.
- Tertiary (Level 3): Higher education (university degree level or postgraduate qualification).

Two reviewers (AT and DS) independently assessed the eligibility of each title and abstract. On agreement, for studies deemed eligible, full-text articles were retrieved for further assessment of inclusion. Studies that did not have a valid comparison group or had reported findings incompletely were excluded. Any disagreement was resolved by assessment of a third senior reviewer (AGS). Authors of studies that were only available as abstracts were contacted to retrieve the full text. Any studies available only as an abstract or which were unpublished were then excluded.

Data extraction

Data were extracted by two reviewers (AT and DS) using a standardised form (online supplementary appendix) and included information on publication details, study design, participant characteristics, exposure descriptions and results.

Quality assessment

Both reviewers (AT and DS) used the Newcastle-Ottawa Scale to assess risk of bias.[30] Any disagreement was resolved by a third senior reviewer (AGS).

Data analysis

Our primary outcome was 'educational attainment' and our secondary outcome was 'requirement of special educational

needs (SEN)'. For each study, we extracted the total number of participants and the number of study participants who reached each attainment level or required educational support. We used this to generate the summary statistic of the study, that is, OR and SE, if not already provided by the study. Any disagreement was resolved through further assessment by a third senior reviewer (AGS). Any missing data were addressed by contacting authors. For publications that had overlapping data, we included the most recent publication and did not include the same cohort within the same analysis.

Statistical analysis

Random-effects meta-analyses, using the generic inverse variance method and Mantel-Haenszel methods, were carried out to calculate summary estimates. Heterogeneity was measured using I^2. This measure assesses the percentage of the total observed variance, which can be accounted for by between-study variation. We assessed publication bias using funnel plots, as well as the Trim-and-Fill method.

To explore the potential causes of heterogeneity, we carried out subgroup and meta-regression analyses. Pre-determined covariates including different control groups, type of childhood cancer, type of cancer treatment, age and time-period of cancer diagnosis were used.

We present our findings in forest plots. All analyses were carried out using Review Manager, V.5.3 and Comprehensive Meta-Analysis, V.3.0.

RESULTS

A total of 3231 publications were screened to assess their eligibility for inclusion. There were 72 articles eligible for full-text review. In all, 26 publications met the inclusion criteria (figure 1).[31] Excluded studies are detailed in the online supplementary appendix.

The study and population characteristics are presented in table 1. All studies were retrospective cohort studies where eight studies used matched controls, 12 studies used sibling controls and six had population controls. The study included only high-economy countries, with similar access to education and years of mandatory schooling as reported by the Organisation for Economic Cooperation and Development (OECD).[32] Studies with cancer diagnosis age of up to 21 years were included. From the 26 studies, 13 included a small proportion of adolescent and young adult population (ages 16–21 years) but overall had a cohort mean diagnosis age of less than 16 years, as seen in table 1. The other 13 studies restricted their study population to under 16 years. A sensitivity analysis excluding the 13 studies that included the adolescent population did not alter overall results (online supplementary appendix). Year of diagnosis ranged from 1940 to 2011. To ensure that there was a complete follow-up period, age at diagnosis and age at survey were reviewed. For studies investigating educational attainment, the median age at study participation ranged from 20 to 36 years, while studies investigating the secondary outcome (SEN status) had lower median ages ranging from 11 to 20. All studies required participants at the time of the questionnaire response to be in remission, although the period of remission varied from above 2 to

Table 1 Population and study characteristics of included studies within the meta-analysis*

Study uthor	Control group	Methodology	Country	Type of cancer	Age at diagnosis	Time period of diagnosis	Age at survey
Dongen-Melman *et al*[40]	Matched	Survey	Netherlands	Leukaemia	4.92	1983	10.2
Maule *et al*[26]	Matched	Linkage	Italy	Mixed	6.81	1971–2000	N/A
Lorenzi *et al*[25]	Matched	Survey/linkage	Canada	Mixed	4.6	1975–1995	N/A
Ahomaki *et al*[17]	Matched	Linkage	Finland	Mixed	8.8	1960–2009	27
Stam *et al*[15]	Matched	Survey	Netherlands	Mixed	7.3	1971–1984	24
Langeveld *et al*[20]	Matched	Survey	Netherlands	Mixed	8	1972–1995	24
Barerra *et al*[41]	Matched	Survey	Canada	Mixed	4	1981–1990	11
Gerdhart *et al*[42]	Matched	Survey	USA	Mixed	11.5	–	18
Kuehni *et al*[28]	Population	Survey	Switzerland	Mixed	8.1	1976–2003	27
Freycon *et al*[43]	Population	Survey/linkage	France	Leukaemia	8.3	1988–2011	23
Lancashire *et al*[19]	Population	Survey	UK	Mixed	6.5	1940–1991	22
Dumas *et al*[21]	Population	Survey	France	Mixed	6	1948–2000	36
Ghaderi *et al*[44]	Population	Survey/linkage	Norway	Mixed	10	1965–1985	N/A
Boman *et al*[45]	Population	Survey/linkage	Sweden	Mixed	–	1963–1976	31.6
Essig *et al*[46]	Sibling	Survey	USA/Canada	Leukaemia	3.5	1970–1986	27.8
Taylor *et al*[47]	Sibling	Survey	USA	Leukaemia	–	–	–
Allen *et al*[10]	Sibling	Survey	UK	Mixed	9	1975–1980	20.5
Moe *et al*[13]	Sibling	Survey	Norway	Leukaemia	5.3	1975–1980	–
Ishida *et al*[12]	Sibling	Survey	Japan	Mixed	8.4	–	21
Ness *et al*[48]	Sibling	Survey	USA	Mixed with HSCT[1]	9.7	1974–1998	26
Hudson *et al*[24]	Sibling	Survey	USA	Mixed	10	1970–1986	26.8
Kingma *et al*[49]	Sibling	Survey	Netherlands	Leukaemia	3	1988–1992	14
Kingma *et al*[18]	Sibling	Survey	Netherlands	Leukaemia	4	1979–1984	20
Molgard-Hansen *et al*[50]	Sibling	Survey	Nordic Countries	Leukaemia	5.5	1984–2003	16.2
Haupt *et al*[11]	Sibling	Survey	USA/Canada	Leukaemia	10.2	1970–1987	–
Kelaghan *et al*[33]	Sibling	Survey	USA	Mixed	13.25	1945–1974	30.9

Please note, where data unavailable, it has been annotated with (–).
*Haematopoeitc stem cell transplant.

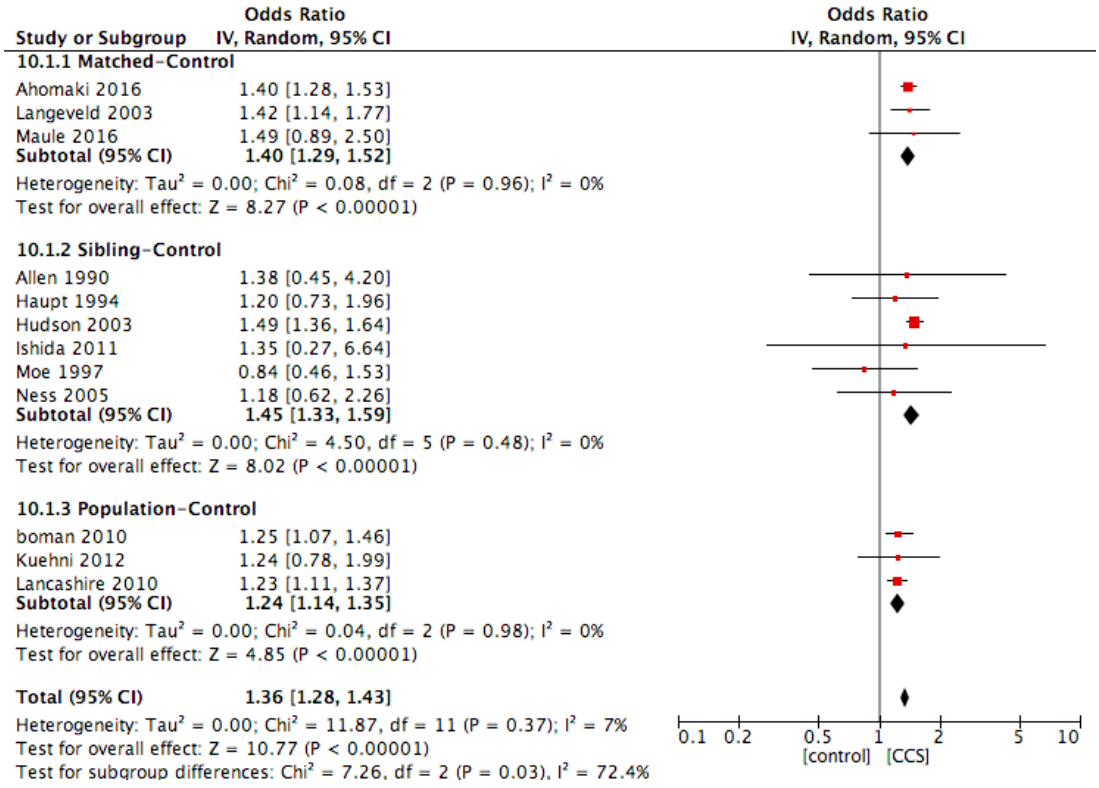

Figure 2 Forest plot demonstrating having only level 1 educational attainment as highest level of attainment for childhood cancer survivors and controls (95% prediction interval (1.28 to 1.44)).

above 5 years. There was sparse data on gender and therefore it was not included post-hoc as a covariate in the analysis.

The quality assessment scores were calculated using the Newcastle-Ottawa Scale (online supplementary appendix). The quality across studies were diverse, where some were deemed of high quality, low risk of bias (30%) and some were deemed as low quality, high risk of bias (17%).

PRIMARY OUTCOME: EDUCATIONAL ATTAINMENT

Level 1

In all, 12 studies reported data on level 1 educational attainment. These included three matched controls, six sibling controls and three population controls as comparison. Overall, a significantly higher proportion of survivors of childhood cancer only completed compulsory education and did not carry their education to the next level (pooled OR 1.36, 95% CI 1.28 to 1.43, p<0.00001) (figure 2). There was minimal heterogeneity across studies (I^2=7%).

Level 2

In all, 14 studies reported data on secondary level educational attainment. These included two matched controls, six sibling controls and six population controls as comparison. Overall, a lower proportion of survivors were found to have completed secondary level education (pooled OR 0.93, 95% CI 0.87 to 1.0, p<0.04) (figure 3).

There was moderate heterogeneity at this level of educational attainment (I^2=59%). Neither sensitivity analysis nor subgroup analysis and meta-regression of the pre-determined covariates revealed any significant association (online supplementary appendix).

Level 3

In all, 13 studies reported data on tertiary level educational attainment. These included three matched controls, six sibling controls and four population controls as comparison. Overall, a significantly lower proportion of survivors were found to have completed tertiary level education (pooled OR 0.85, 95% CI 0.79 to 0.92, p<0.001) (figure 4).

There was substantial heterogeneity across studies reporting this level of educational attainment (I^2=78%). A sensitivity analysis revealed that the majority of the heterogeneity arose from one individual study.[21] When excluded, the overall heterogeneity was low (I^2=34%).

Secondary outcome: SEN

Nine studies reported data on SEN. These included five matched controls and four sibling controls as comparison. Overall, more survivors of childhood cancer required SEN (pooled OR 2.47, 95% CI 1.91 to 3.20, p<0.00001) (figure 5). Moderate heterogeneity was observed (I^2=52%, p=0.02). Neither sensitivity analysis nor subgroup analysis and meta-regression of the pre-determined covariates revealed any significant association (online supplementary appendix).

Educational attainment with CNS involvement

Previous studies suggest that poorer outcomes may solely arise due to the study cohorts consisting of survivors with CNS tumours or CNS-mediated therapy. Thus, three subgroup analyses were carried out: first investigating CNS tumour survivors only, then survivors who receive CNS therapy (eg, CNS tumour and leukaemia) and finally survivors who had no CNS involvement (online supplementary appendix). Results demonstrated survivors of CNS tumours had statistically significant poorer

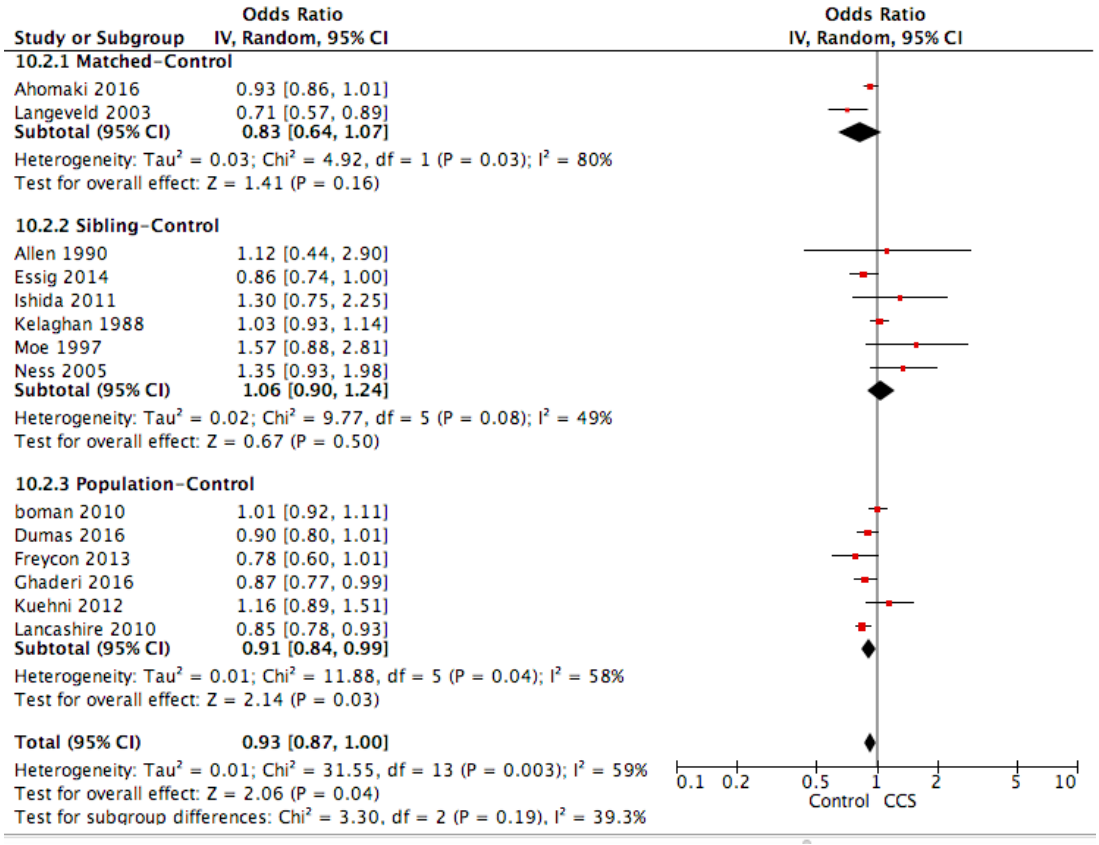

Figure 3 Forest plot demonstrating educational attainment at level 2 for childhood cancer survivors and controls (95% prediction interval (0.74 to 1.17)).

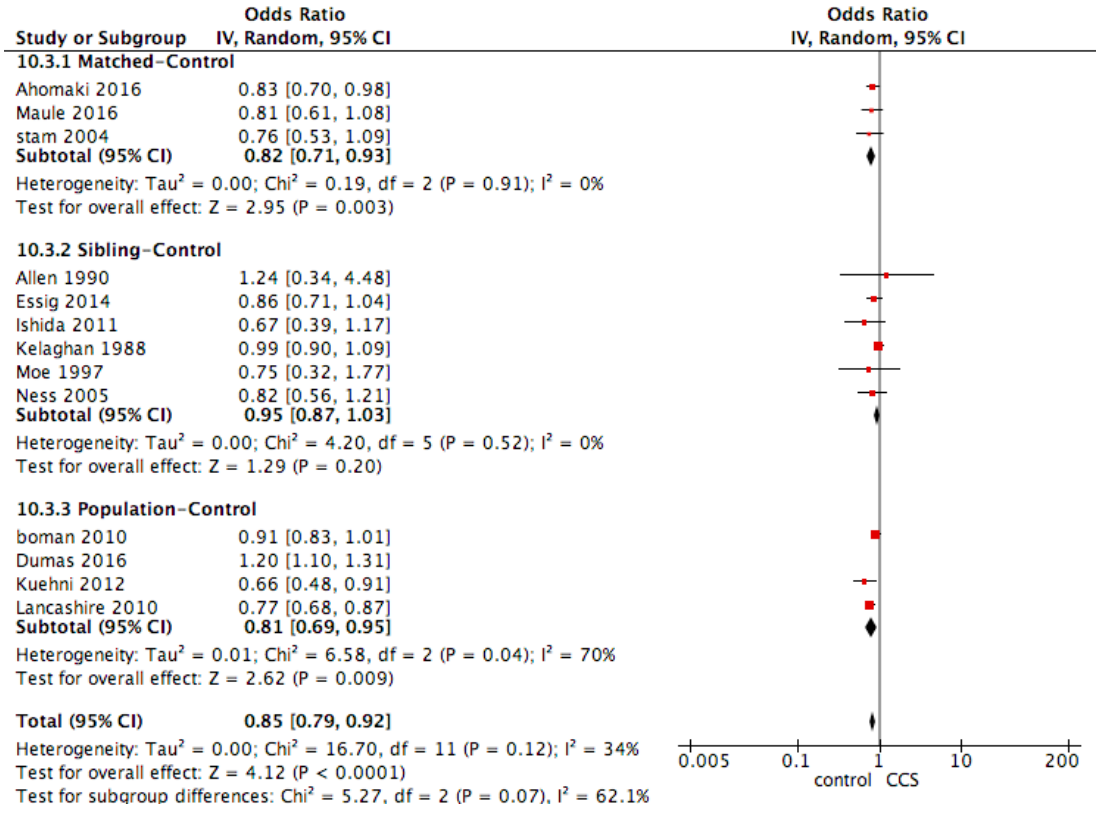

Figure 4 Forest plot demonstrating educational attainment at level 3 for childhood cancer survivors and controls (95% prediction interval (0.78 to 0.93) with exclusion of Dumas et al 2016).

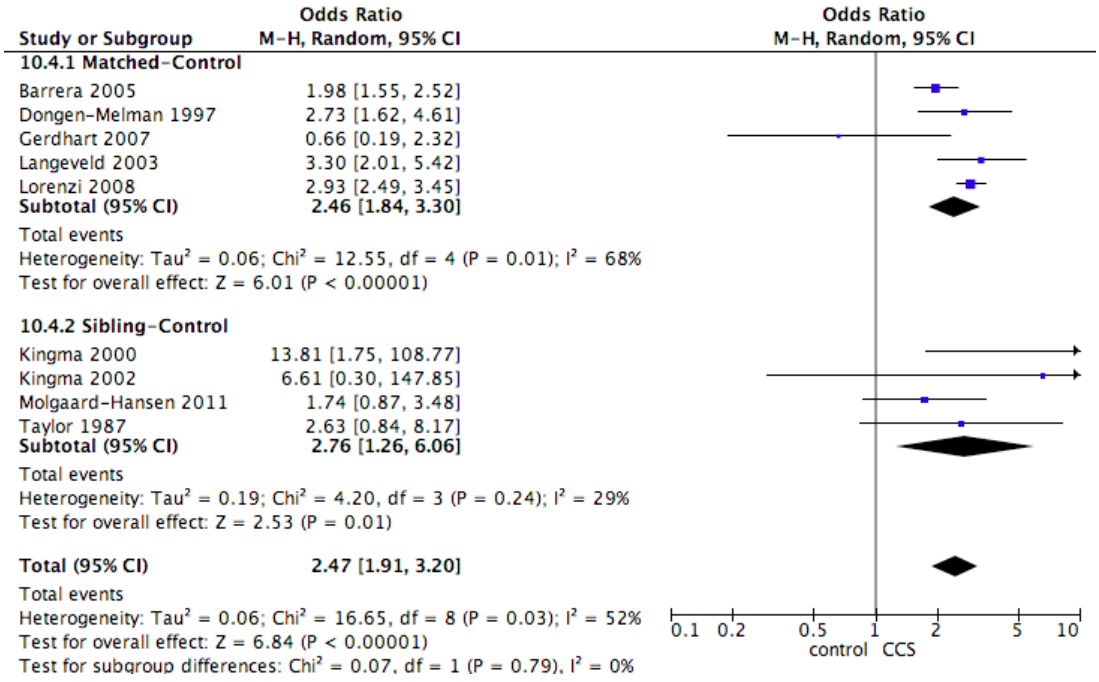

Figure 5 Forest plot demonstrating registration of special educational need across childhood cancer survivors and controls.

outcomes at moving beyond level 1 education (pooled OR 1.77 95% CI 1.46 to 2.15, p<0.00001, I^2=51%) and at completing tertiary level education (pooled OR 0.61, 95% CI 0.55 to 0.68, p<0.00001, I^2=11%). Educational outcomes at level 2 remained similar to previous findings (pooled OR 0.81, 95% CI 0.67 to 1.00, p=0.05, I^2=86%). This was similar in survivors with CNS-mediated therapy (*level 1*: pooled OR 1.38, 95% CI 1.29 to 1.48, p<0.00001, I^2=0%; level 2: pooled OR 0.97, 95% CI 0.92 to 1.02, p=0.17, I^2=25%, *level 3*: pooled OR 0.73, 95% CI 0.66 to 0.81, p<0.0001, I^2=15%). In survivors who had no CNS involvement, poorer outcomes moving beyond level 1 education still remained (pooled OR 1.19, 95% CI 1.00 to 1.42, p=0.05, I^2=46%). Completing tertiary level education, on the other hand, favoured survivors (pooled OR 1.12, 95% CI 1.0 to 1.25, p=0.04, I^2=75%). The majority of the heterogeneity observed at tertiary level arose from the same individual study as previous[21] and when excluded heterogeneity was low (I^2=17%).

DISCUSSION

This study is the first and most comprehensive meta-analysis investigating the impact of childhood cancer on educational achievement. It explored differences in educational attainment in 28 434 survivors of childhood cancer compared with children without cancer (17 814 matched controls and six population studies) and to 6572 siblings, from 11 high-economy countries.

Overall, this study demonstrates that survivors are significantly less likely to progress from primary level onto secondary level education or to complete tertiary level education, compared with controls. This study also highlights the possibility that survivors are less likely to complete secondary education and are more likely to require SEN. Importantly, these findings implicate the general need to provide additional educational support for survivors and there is a need to delineate which survivors are at higher risk.

We attempted to explore this risk by investigating outcomes in survivors who either had CNS or no CNS involvement. CNS involvement, as suggested in previous literature, was associated with poorer educational attainment overall. Interestingly for non-CNS involvement, moving beyond primary level also tended to be poorer compared with controls but this appeared to resolve at tertiary level. This finding is of significance, as it provides novel insight into previous literature.[17 19 28 33] Although this resolution suggests that non-CNS survivors may 'catch up', this should be interpreted with caution as our calculated prediction intervals suggest similar findings may not be replicated across a future population of survivors. Furthermore, survivors of non-CNS cancers have also been shown to suffer from poorer long-term health compared with the general population, which, in turn, has been shown to negatively affect educational success.[34]

Despite the important insight this meta-analysis provides, there are several limitations that need to be considered when interpreting the conclusions. First, as with any meta-analysis consisting of entirely observational studies, there was a possibility of selection bias and confounding,[29] although most studies had moderate response rates (mean was 70%, online supplementary appendix) and accounted for confounding factors, where able.

The review question of this meta-analysis was designed to capture all comparative studies to date. However, having a broad review question has its limitations mainly due to the between-study variations (i.e., heterogeneity) that arise. Nevertheless, this study has shown mainly homogeneous outcomes, suggesting comparability across the individual studies and generalisability of results. Heterogeneity was only observed in two outcomes, after sensitivity analysis. The causes of this heterogeneity are likely to be arising from (1) country-dependent factors and (2) disease-dependent factors.

Country-dependent factors

The main challenge while comparing education across countries is the differing definition of educational attainment.[35] To overcome this, we used a universally comparable way of measuring educational attainment, through categorising into pre-defined levels of education, using the ISCED framework.[9]

There however still remains the difficulty of comparing educational attainment across countries, when education is dependent on several country-specific factors such as percentage of educational spending within a country, equality of access to education and family background, including parental educational level, income and culture.[9] Although we cannot fully account for these potential confounding factors, we only included studies that had comprehensive control groups (sibling, matched or population controls), to make within-country attainment comparable. Furthermore, all countries were within OECD, reporting similar outcomes in their public spending, access to education and changes in family structure over the last 50 years.[32]

In this study, significant heterogeneity was observed in level 2 educational attainment and SEN outcome. Subgroup analysis or meta-regression did not isolate a significant covariate. We believe the underlying reason for heterogeneity at level 2 educational attainment is due to its definition being the most diverse across all countries, ranging from different routes of vocational training to more traditional pre-university training, making comparisons across countries challenging.[9] We believe this diversity is also significant when defining SEN. Levels 1 and 3 educational attainment, on the other hand, follow similar routes in all 11 countries.

Cancer-dependent factors

Childhood cancer prognosis varies across countries.[2] This variation, in turn, could influence childhood educational outcomes. Prognosis is thought to vary due to differences in access to healthcare, as well as differences in prevalence of subtypes of cancer and the available technologies used to treat them.[2] Nevertheless, the 11 countries included are reported to have similar access to healthcare and have robust healthcare systems, providing up-to-date treatments.[36]

Within studies in this meta-analysis, there was variation across cancer type, time period of diagnosis, age at diagnosis and treatment methodologies. Cautious of possible differences across study populations, we pre-specified that we would carry out a sensitivity analysis to explore if individual studies had extremely different study populations. Indeed, sensitivity analyses resulted in the identification of one study,[21] which individually accounted for the majority of heterogeneity in level 3 educational attainment. We believe this study was an outlier because participants were interviewed at a much older age, increasing the possibility of recall bias and had a low response rate of 59%, introducing the possibility of selection bias.

Future directions

Through this meta-analysis, we have demonstrated that survivors of childhood cancer do worse than their peers at each educational attainment level, independent of their country of residence, and require more educational support. An important question arising from this is why these differences occur. Although we cannot directly answer this through our findings from the meta-analysis, we hypothesise two potential mechanisms, disease-dependent factors and schooling factors, which could provide an explanation.

Studies have previously shown that type of cancer and treatment affect educational achievement, where CNS involvement has resulted in poorer outcomes.[19 21 37] This makes biological sense due to the direct effect on the brain and thus potentially on cognitive functioning. Our meta-analysis corroborates these findings. Although not as well investigated, studies have also highlighted the importance of taking measures to ensure successful school re-entry for survivors.[38] When there is lack of preparation for school re-entry, survivors have been noted to experience more hardship at school and consequently have poorer attainment.[38 39] This may explain the poorer outcomes at early levels of education we observe in survivors with no CNS involvement. Clearly, more research needs to be invested in understanding why survivors of childhood cancer perform worse than their peers. Multi-centre, collaborative cohort studies with larger number of survivors are required to further explain the effects of treatment and type of cancer on educational outcomes.

Clinical implications

Overall, there is sufficient evidence through this study to suggest that educational differences exist across survivors of childhood cancer and their peers. Early counselling with families affected by childhood cancer in clinical settings is recommended and could allow for timely seeking of assistance. Healthcare policymakers are encouraged to lobby for the creation of early re-integration pathways in schools and raising awareness of these educational differences among teachers could allow for more accessible day-to-day support.

Contributors DS and AGS conceptualised and designed the study, analysed data, and drafted as well as revised the manuscript. AT and BB were involved in the design of the study and revision of the manuscript.

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