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Educational attainment in childhood cancer survivors: a systematic review and meta-analysis

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1. Title Page

Educational attainment in childhood cancer survivors: a meta-analysis

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2. Abstract/Summary

Objective: To assess differences across educational outcomes in survivors of childhood cancer (CCS) compared to 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: Twenty-six studies representing 28,434 CCS, 17,814 matched-controls, 6,582 siblings and 6 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 (OECD), were included. CCS were less likely to progress onto secondary level (OR 1.36 (95%CI 1.26-1.43)) and to complete secondary (OR 0.93 (95%CI 0.87-1.0)) and tertiary level education (OR 0.87 (95%CI 0.78-0.98)). They were more likely to require special educational needs (OR 2.47 (95%CI 1.91-3.20)). Subgroup analyses revealed that survivors, irrespective of central nervous system involvement, were less likely to progress onto secondary level compared to cancer-free peers (OR 1.77 95%CI 1.46-2.15, OR 1.19 95%CI 1.00-1.42, respectively). This however changed at tertiary level where those with central nervous system involvement continued to perform worse (OR 0.61 95%CI 0.55-0.68) but those without appeared to do equally well or better than their peers (OR 1.12 95%CI 1.0-1.25).

Conclusions: Compared to controls, we have elucidated significant differences in educational attainment in survivors. This is sustained across different countries, making it an international issue. Central nervous system 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.

3. 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 is 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 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 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), (33)], whilst 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.

4. Methodology

The Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines were followed[30].

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 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 two 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 *(i.e. 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. Upon 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 was extracted by two reviewers (AT and DS) using a standardised form (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[28]. 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, i.e. odds ratios (OR) and standard errors (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 sub-group and meta-regression analyses. Pre-determined co-variates 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, version 5.3 and Comprehensive Meta-Analysis, Version 3.0.

5. Results

A total of 3231 publications were screened to assess their eligibility for inclusion. There were 72 articles eligible for full-text review. Twenty-six publications met the inclusion criteria (Figure 1)[29]. Excluded studies are detailed in the Supplementary Appendix.

Figure 1 goes here

The study and population characteristics are presented in Table 1. All studies were retrospective cohort studies where 8 studies used matched-controls, 12 studies used sibling-controls and 6 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)[31]. Studies with cancer diagnosis age of up to 21 years were included. From the twenty-six studies, thirteen included a small proportion of adolescent and young adult population (ages 16-21) but overall, had a cohort mean diagnosis age of less than 16 years, as seen in Table 1. The other thirteen studies restricted their study population to under 16 years. A sensitivity analysis excluding the thirteen studies that included the adolescent population did not alter overall results (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, whilst 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 above 5 years. There was sparse data on gender and therefore it was not included post-hoc as a covariate in the analysis.

Study Author	Control Group	Methodology	Country	Type of cancer	Age at diagnosis	Time period of diagnosis	Age at survey
Dongen-Melman (1997)(38)	Matched	Survey	Netherlands	Leukaemia	4.92	1983	10.2
Maule (2017)(26)	Matched	Linkage	Italy	Mixed	6.81	1971-2000	N/A
Lorenzi (2009)(25)	Matched	Survey/Linkage	Canada	Mixed	4.6	1975-1995	N/A
Ahomaki (2016)(17)	Matched	Linkage	Finland	Mixed	8.8	1960-2009	27
Stam (2004)(15)	Matched	Survey	Netherlands	Mixed	7.3	1971-1984	24
Langeveld (2003)(20)	Matched	Survey	Netherlands	Mixed	8	1972-1995	24
Barerra (2005)(39)	Matched	Survey	Canada	Mixed	4	1981-1990	11
Gerdhart (2007)(40)	Matched	Survey	United States	Mixed	11.5	-	18
Kuehni (2012)(33)	Population	Survey	Switzerland	Mixed	8.1	1976-2003	27

Freycon (2014)(41)	Population	Survey/Linkage	France	Leukaemia	8.3	1988-2011	23
Lancashire (2010) (19)	Population	Survey	United Kingdom	Mixed	6.5	1940-1991	22
Dumas (2016) (21)	Population	Survey	France	Mixed	6	1948-2000	36
Ghaderi (2016) (42)	Population	Survey/Linkage	Norway	Mixed	10	1965-1985	N/A
Boman, 2010(43)	Population	Survey/Linkage	Sweden	Mixed	-	1963-1976	31.6
Essig (2014) (44)	Sibling	Survey	United States/Canada	Leukaemia	3.5	1970-1986	27.8
Taylor (1987) (45)	Sibling	Survey	United States	Leukaemia	-	-	-
Allen (1990) (10)	Sibling	Survey	United Kingdom	Mixed	9	1975-1980	20.5
Moe (1997) (13)	Sibling	Survey	Norway	Leukaemia	5.3	1975-1980	-
Ishida (2011) (12)	Sibling	Survey	Japan	Mixed	8.4	-	21
Ness (2005) (46)	Sibling	Survey	United States	Mixed with HSCT[1]	9.7	1974-1998	26

Hudson (2003) (24)	Sibling	Survey	United States	Mixed	10	1970-1986	26.8
Kingma (2002) (47)	Sibling	Survey	Netherlands	Leukaemia	3	1988-1992	14
Kingma (2000) (18)	Sibling	Survey	Netherlands	Leukaemia	4	1979-1984	20
Molgard-Hansen (2011)(32)	Sibling	Survey	Nordic Countries	Leukaemia	5.5	1984-2003	16.2
Haupt (1994) (11)	Sibling	Survey	United States/Canada	Leukaemia	10.2	1970-1987	-
Kelaghan (1988)(34)	Sibling	Survey	United States	Mixed	13.25	1945-1974	30.9

Table 1. Population and study characteristics of included studies within the meta-analysis. (Please note, where data unavailable, it has been annotated with (-))[1] Haematopoeitc Stem Cell Transplant

The quality assessment scores were calculated using the Newcastle-Ottawa Scale (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

Twelve studies reported data on level 1 educational attainment. These included 3 matched-controls, 6 sibling-controls and 3 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 1.26, 1.43, p<0.00001)) (Figure 2). There was minimal heterogeneity across studies (I^2=7%).

Figure 2 goes here

- Level 2

Fourteen studies reported data on secondary level educational attainment. These included 2 matched-controls, 6 sibling-controls and 6 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, 1.0, p<0.04)) (Figure 3).

Figure 3 goes here.

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 co-variates revealed any significant association (Supplementary Appendix).

- Level 3

Thirteen studies reported data on tertiary level educational attainment. These included 3 matched-controls, 6 sibling-controls and 4 population-controls as comparison. Overall, a significantly lower proportion of

survivors were found to have completed tertiary level education (pooled OR 0.87 (95% CI 0.78, 0.98, p=0.02)) (Figure 4).

Figure 4 goes here

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 5 matched-controls and 4 sibling-controls as comparison. Overall, more survivors of childhood cancer required SEN (pooled OR 2.47 (95% CI 1.91, 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 co-variates revealed any significant association (Supplementary Appendix).

Figure 5 goes here.

Educational attainment with CNS involvement

As previous studies suggest; poorer outcomes may solely be 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 (e.g. CNS tumour and leukaemia) and finally survivors who had no CNS involvement (Supplementary Appendix). Results demonstrated survivors of CNS-tumours had statistically significant poorer outcomes at moving beyond level 1 education (*pooled OR 1.77 95%CI 1.46, 2.15, p<0.00001, I^2=51%)* and at completing tertiary level education *(pooled OR 0.61 95%CI 0.55, 0.68, p<0.00001, I^2=11%*). Educational outcomes at level 2 remained similar to previous findings (*pooled OR 0.81 95%CI 0.67,1.00, 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, 1.48, p<0.00001, I^2=0%;* **level 2:** *pooled OR 0.97 95%CI 0.92,1.02, p=0.17, I^2=25%,* **level 3:** *pooled OR 0.73 95%CI 0.66,0.81, 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, 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, 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%).*

6. 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 to children without cancer (17 814 matched-controls and six population studies) and to 6 572 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 to 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 to controls but this appeared to resolve at tertiary level. This finding is of significance, as it provides novel insight into previous literature[17, 19, 33, 34]. 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 to the general population, which in turn, has been shown to negatively affect educational success[48].

Despite the important insight this meta-analysis provides, there are several limitations that need to be considered when interpreting the conclusions. Firstly, as with any meta-analysis consisting of entirely observational studies, there was a possibility of selection bias and confounding[30], although most studies had moderate response rates (mean was 70%, 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 homogenous outcomes, suggesting comparability across the individual studies and generalizability 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 whilst comparing education across countries is the differing definition of educational attainment[49]. 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), in order

to make within-country attainment comparable. Further, 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[31].

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 co-variate. 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. Level 1 and 3 educational attainment, on the other hand, follow similar routes in all eleven 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 eleven countries included are reported to have similar access to healthcare and have robust healthcare systems, providing up-to-date treatments[50].

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, 35]. 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[36]. 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[36, 37]. 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.

Additional Information

- **Ethics approval and consent to participate**

  N/A

- **Consent for publication**

  N/A

- **Data availability**

  Data available through emailing corresponding author.

- **Conflict of interest**

  Authors declare no conflicts of interest.

- **Funding**

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- **Authors' contributions**

  DS and AGS conceptualized and designed the study, analyzed 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.

- **"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.

References

1. Steliarova-Foucher E, Colombet M, Ries LAG, Moreno F, Dolya A, Bray F, et al. International incidence of childhood cancer, 2001-10: a population-based registry study. Lancet Oncol. 2017;18(6):719-31.

2. Allemani C, Matsuda T, Di Carlo V, Harewood R, Matz M, Niksic M, et al.,. Global surveillance of trends in cancer survival 2000–14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. The Lancet. 2018;391(10125):1023-75.

3. Oeffinger KC, Mertens AC, Sklar CA, Kawashima T, Hudson MM, Meadows AT, et al. Chronic health conditions in adult survivors of childhood cancer. N Engl J Med. 2006;355(15):1572-82.

4. Stein KD, Syrjala KL, Andrykowski MA. Physical and psychological long-term and late effects of cancer. Cancer. 2008;112(11 Suppl):2577-92.

5. Oswald AJ. Happiness and economic performance: University of Warwick, Department of Economics; 1997. 28 ; 30.

6. Bradley BJ GA. Do health and education agencies in the United States share responsibility for academic achievement and health? A review of 25 years of evidence about the relationship of adolescents' academic achievement and health behaviors. Journal of Adolescent Health. 2013;52(5):523-32.

7. Bradshaw J, Hoelscher, Petra and Richardson, Dominic. An Index of Child Well-being in the European Union. Social Indicators Research. 2007:133-77.

8. United Nations. Principles and Recommendations for Population and Housing Censuses, Revision 1. 1998,:para. 2.153.

9. UNESCO. Institute for Statitics: International Standard Classification of Education. 2012.

10. Allen A, Malpas JS, Kingston JE. Educational achievements of survivors of childhood cancer. Pediatric Hematology and Oncology. 1990;7(4):339-45.

11. Haupt R, Fears TR, Robison LL, Mills JL, Nicholson HS, Zeltzer LK, et al. Educational attainment in long-term survivors of childhood acute lymphoblastic leukemia. Journal of the American Medical Association. 1994;272(18):1427-32.

12. Ishida Y, Kamibeppu K, Honda M, Ozono S, Okamura J, Maeda N, et al. Social outcomes and quality of life (QOL) of childhood cancer survivors in Japan: Marriage, education, employment and health related QOL (SF-36). Pediatric Blood and Cancer. 2010;55 (5):817.

13. Moe PJ, Holen A, Glomstein A, Madsen B, Hellebostad M, Stokland T, et al. Long-term survival and quality of life in patients treated with a national all protocol 15-20 years earlier: IDM/HDM and late effects? Pediatric Hematology and Oncology. 1997;14(6):513-24.

14. Pillon M, Tridello G, Boaro MP, Messina C, Putti MC, Varotto S, et al. Psychosocial life achievements in adults even if they received prophylactic cranial irradiation for acute lymphoblastic leukemia during childhood. Leukemia and Lymphoma. 2013;54(2):315-20.

15. Stam H, Grootenhuis M, Last B. The Course of Life of Survivors of Childhood Cancer. Psycho-Oncology. 2005;14(3):227-38.

16. Wong KF, Reulen RC, Winter DL, Guha J, Fidler MM, Kelly J, et al. Risk of Adverse Health and Social Outcomes Up to 50 Years After Wilms Tumor: The British Childhood Cancer Survivor Study. Journal of Clinical Oncology. 2016;34(15):1772-9.

17. Ahomaki R, Harila-Saari A, Matomaki J, Lahteenmaki PM. Non-graduation after comprehensive school, and early retirement but not unemployment are prominent in childhood cancer survivors-a Finnish registry-based study. Journal of Cancer Survivorship. 2016;06:06.

18. Kingma A, Rammeloo LA, van Der Does-van den Berg A, Rekers-Mombarg L, Postma A. Academic career after treatment for acute lymphoblastic leukaemia. Archives of Disease in Childhood. 2000;82(5):353-7.

19. Lancashire ER, Frobisher C, Reulen RC, Winter DL, Glaser A, Hawkins MM. Educational attainment among adult survivors of childhood cancer in Great Britain: a population-based cohort study. JNCI: Journal of the National Cancer Institute. 2010;102(4):254-70.

20. Langeveld N, Ubbink M, Last B, Grootenhuis M, Voute P, De Haan R. Educational achievement, employment and living situation in long-term young adult survivors of childhood cancer in the Netherlands. Psycho-Oncology. 2003;12(3):213-25.

21. Dumas A, Berger C, Auquier P, Michel G, Fresneau B, Setcheou Allodji R, et al. Educational and occupational outcomes of childhood cancer survivors 30 years after diagnosis: A French cohort study. British Journal of Cancer. 2016;114(9):1060-8.

22. Fidler MM, Frobisher C, Guha J, Wong K, Kelly J, Winter DL, et al. Long-term adverse outcomes in survivors of childhood bone sarcoma: the British Childhood Cancer Survivor Study. British Journal of Cancer. 2015;112(12):1857-65.

23. Boman KK, Bodegard G. Life after cancer in childhood: Social adjustment and educational and vocational status of young-adult survivors. Journal of Pediatric Hematology/Oncology. 2004;26(6):354-62.

24. Hudson MM, Mertens AC, Yasui Y, Hobbie W, Chen H, Gurney JG, et al. Health Status of Adult Long-term Survivors of Childhood Cancer: A Report from the Childhood Cancer Survivor Study. Journal of the American Medical Association. 2003;290(12):1583-92.

25. Lorenzi M, McMillan AJ, Siegel LS, Zumbo BD, Glickman V, Spinelli JJ, et al. Educational outcomes among survivors of childhood cancer in British Columbia, Canada: report of the Childhood/Adolescent/Young Adult Cancer Survivors (CAYACS) Program. Cancer. 2009;115(10):2234-45.

26. Maule M, Zugna D, Migliore E, Alessi D, Merletti F, Onorati R, et al. Surviving a childhood cancer: impact on education and employment. European Journal of Cancer Prevention. 2016;29.

27. Zynda A, Reinmuth S, Pfitzer C, Hohmann C, Keil T, Borgmann-Staudt A. Childhood leukemia and its impact on graduation and having children: Results from a national survey. Leukemia and Lymphoma. 2012;53(12):2419-22.

28. Wells GA BS, D O'Connell, J Peterson, V Welch, M Losos, P Tugwell. [Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp,].

29. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339.

30. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, t al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000;283(15):2008-12.

31. OECD. 2018 [Available from: https://data.oecd.org/?_ga=2.207370839.519595752.1546424528-1457311760.1546424528].

32. Molgaard-Hansen L, Glosli H, Jahnukainen K, Jarfelt M, Jonmundsson GK, Malmros-Svennilson J, et al. Quality of health in survivors of childhood acute myeloid leukemia treated with chemotherapy only: A NOPHO-AML study. Pediatric Blood and Cancer. 2011;57(7):1222-9.

33. Kuehni CE, Strippoli MP, Rueegg CS, Rebholz CE, Bergstraesser E, Grotzer M, et al. Educational achievement in Swiss childhood cancer survivors compared with the general population. Cancer. 2012;118(5):1439-49.

34. Kelaghan J, Myers MH, Mulvihill JJ, Byrne J, Connelly RR, Austin DF, et al. Educational achievement of long-term survivors of childhood and adolescent cancer. Medical & Pediatric Oncology. 1988;16(5):320-6.

35. Jacola LM, Edelstein K, Liu W, Pui CH, Hayashi R, Kadan-Lottick NS, et al. Cognitive, behaviour, and academic functioning in adolescent and young adult survivors of childhood acute lymphoblastic leukaemia: a report from the Childhood Cancer Survivor Study. The Lancet Psychiatry. 2016;3(10):965-72.

36. Thompson AL, Christiansen HL, Elam M, Hoag J, Irwin MK, Pao M, et al. Academic Continuity and School Reentry Support as a Standard of Care in Pediatric Oncology. Pediatr Blood Cancer. 2015;62 Suppl 5:S805-17.

37. McLoone JK, Wakefield CE, Cohn RJ. Childhood cancer survivors' school (re)entry: Australian parents' perceptions. Eur J Cancer Care (Engl). 2013;22(4):484-92.

38. Dongen-Melman V. Cranial irradiation is the major cause of learning problems in children treated for leukemia and lymphoma: a comparative study. Leukemia. 1997;11(8):1197-200.

39. Barrera M, Shaw AK, Speechley KN, Maunsell E, Pogany L. Educational and social late effects of childhood cancer and related clinical, personal and familial characteristics. Cancer. 2005;104(8):1751-60.

40. Gerhardt CA, Dixon M, Miller K, Vannatta K, Valerius KS, Correll J, et al. Educational and occupational outcomes among survivors of childhood cancer during the transition to emerging adulthood. Journal of Developmental and Behavioral Pediatrics. 2007;28(6):448-55.

41. Freycon F, Trombert-Paviot B, Casagranda L, Frappaz D, Mialou V, Armari-Alla C, et al. Academic difficulties and occupational outcomes of adult survivors of childhood leukemia who have undergone allogeneic hematopoietic stem cell transplantation and fractionated total body irradiation conditioning. Pediatric Hematology and Oncology. 2014;31(3):225-36.

42. Ghaderi S, Engeland A, Gunnes M, Moster D, Ruud E, Syse A, et al. Educational attainment among long-term survivors of cancer in childhood and adolescence: a Norwegian population-based cohort study. Journal of Cancer Survivorship. 2016;10(1):87-95.

43. Boman KK, Lindblad F, Hjern A. Long-term outcomes of childhood cancer survivors in Sweden: A population-based study of education, employment, and income. Cancer. 2010;116(5):1385-91.

44. Essig S, Li Q, Chen Y, Hitzler J, Leisenring W, Greenberg M, et al. Risk of late effects of treatment in children newly diagnosed with standard-risk acute lymphoblastic leukaemia: a report from the Childhood Cancer Survivor Study cohort. Lancet Oncology. 2014;15(8):841-51.

45. Taylor H, Albo VC, Phebus CK, Sachs BR, Bierl PG. Postirradiation treatment outcomes for children with acute lymphocytic leukemia: Clarification of risks. Journal of Pediatric Psychology. 1987;12(3):395-411.

46. Ness KK, Bhatia S, Baker KS, Francisco L, Carter A, Forman SJ, et al. Performance limitations and participation restrictions among childhood cancer survivors treated with hematopoietic stem cell transplantation: The bone marrow transplant survivor study. Archives of Pediatrics and Adolescent Medicine. 2005;159(8):706-13.

47. Kingma A, Van Dommelen RI, Mooyaart EL, Wilmink JT, Deelman BG, Kamps WA. No major cognitive impairment in young children with acute lymphoblastic leukemia using chemotherapy only: a prospective longitudinal study. Journal of Pediatric Hematology/Oncology. 2002;24(2):106-14.

48. Marina N, Hudson MM, Jones KE, et al. Changes in health status among aging survivors of pediatric upper and lower extremity sarcoma: a report from the childhood cancer survivor study. *Arch Phys Med Rehabil*. 2013;94(6):1062–1073.

49. Barro R. LJ. A new data set of educational attainment in the world, 1950–2010. Journal of Development Economics; 2013.

50. Tandon M, Lauer, Evans. MEASURING OVERALL HEALTH SYSTEM PERFORMANCE FOR 191 COUNTRIES. World Health Organisation; 2000.

Figure Legends

Figure 1. Study Flow Diagram

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, 1.44]).

Figure 3. Forest Plot demonstrating educational attainment at Level 2 for childhood cancer survivors and controls (95% prediction interval [0.74, 1.17]).

Figure 4. Forest Plot demonstrating educational attainment at Level 3 for childhood cancer survivors and controls (95% prediction interval [0.78, 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

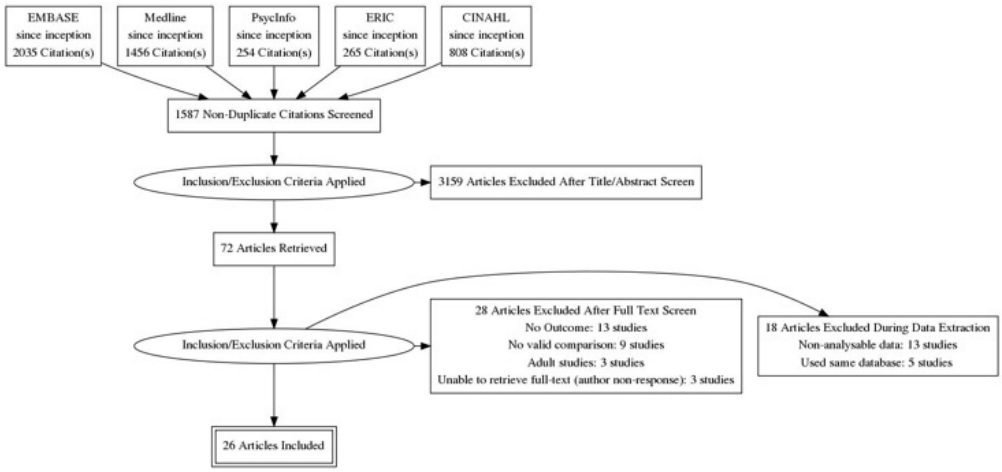

Figure 1. Study Flow Diagram

257x121mm (72 x 72 DPI)

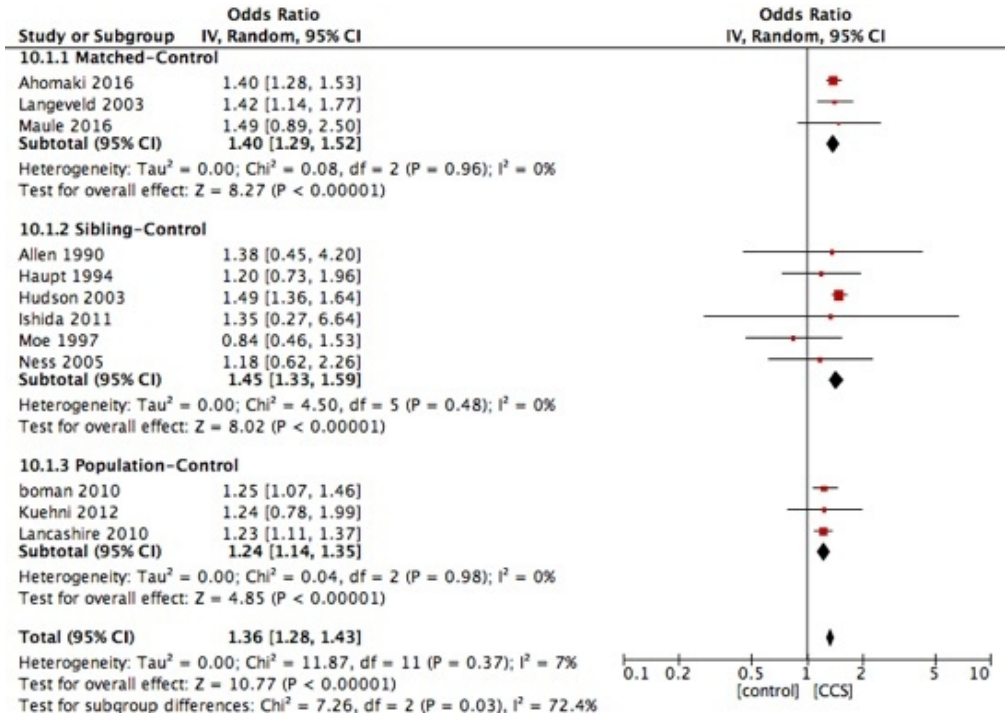

Figure 2. Forest Plot demonstrating having only Level 1 educational attainment as highest level of attainment for childhood cancer survivors and controls (95% prediction interval [1.28, 1.44]).

191x135mm (72 x 72 DPI)

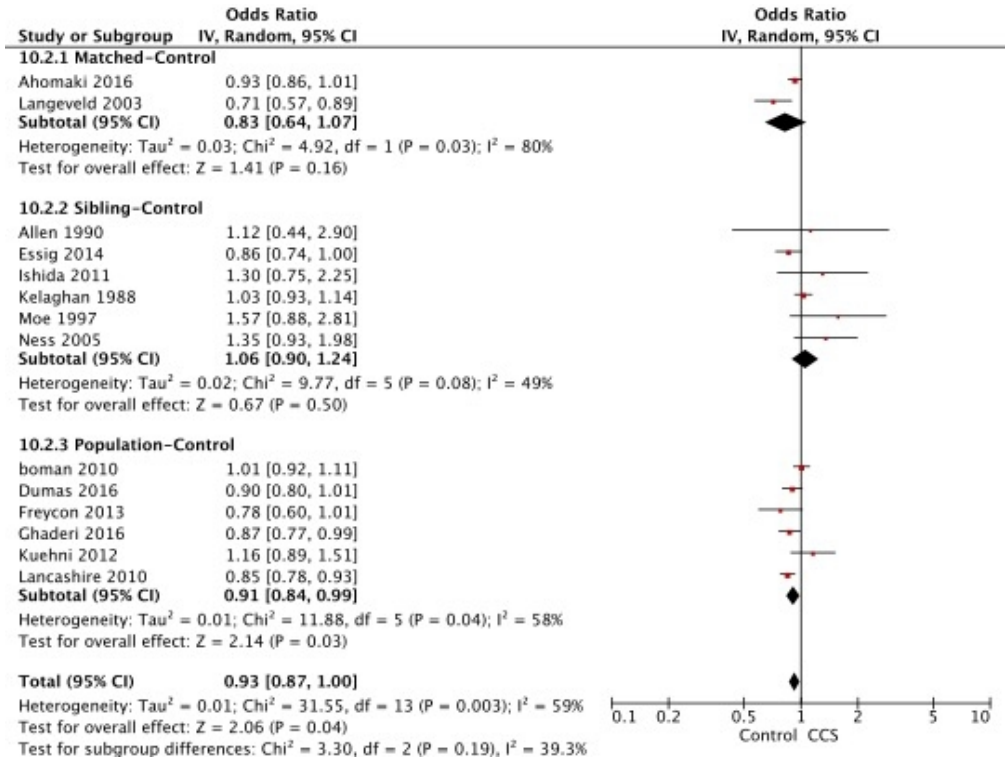

Figure 3. Forest Plot demonstrating educational attainment at Level 2 for childhood cancer survivors and controls (95% prediction interval [0.74, 1.17]).

189x142mm (72 x 72 DPI)

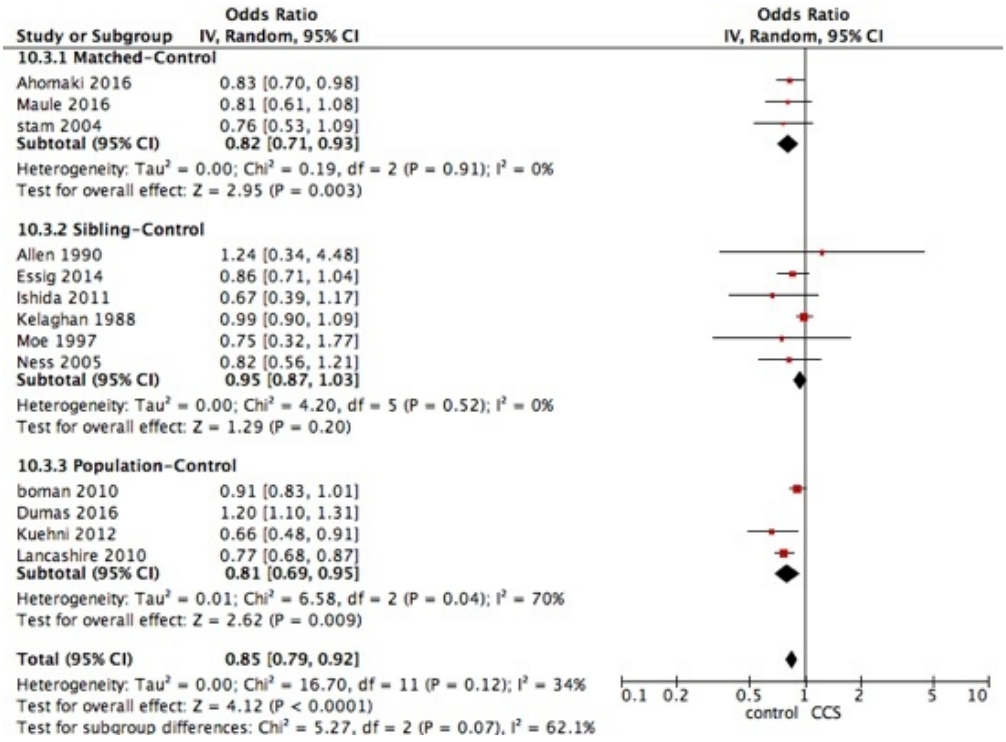

Figure 4. Forest Plot demonstrating educational attainment at Level 3 for childhood cancer survivors and controls (95% prediction interval [0.78, 0.93] with exclusion of Dumas et al., 2016).

192x141mm (72 x 72 DPI)

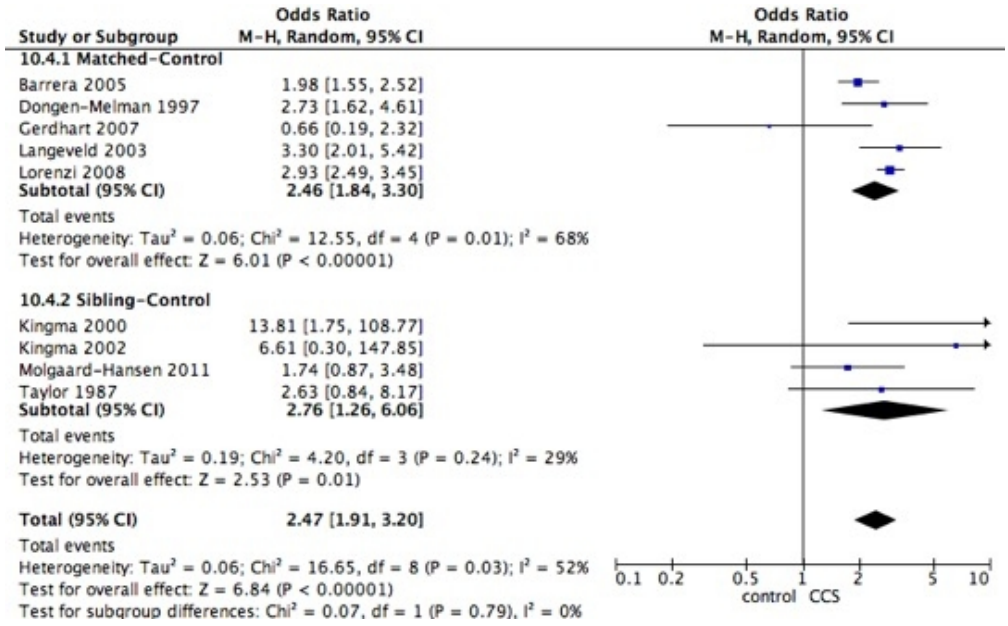

Figure 5. Forest Plot demonstrating registration of special educational need across childhood cancer survivors and controls.

190x117mm (72 x 72 DPI)

Supplementary Appendix (Online Material)

- Full Search Strategy (Supplementary Tables 1-5)
  - *Table 1- Full Search Strategy-Supplementary Table* ***EMBASE***

Child	1	(Neonat* OR Infant* OR Baby OR Babies OR Toddler* OR Child* OR Adolesc* OR Teen* or Young* OR Youth* OR Pe?diatric).mp	4,093,386
Cancer	2	exp neoplasm/ or childhood cancer/ or pediatric cancer/	3,942,103
	3	(Cancer* OR Malignan* OR Neoplas* OR Tumo?r * OR Leuk?emia* OR Sarcoma* OR Lymphoma* OR Blastoma*).mp	4,540,733
	4	2 OR 3	4,934,600
Survivor	5	Survivor/	50,216
	6	(survivo* or survive or survives or survived).mp	243,999
	7	(after* or follow* or subsequent* or remission* or ?live or living*) adj3 (3)	304,826
	8	5 OR 6 OR 7	535,852
	9	1 AND 4 AND 8	58,930
Educational Progression	10	((educat* or school* or universit* or college* or exam*) adj3 (attain* or outcome* or achiev* or progress* or attend* or perform* or level* or degree* or qualif* or status* or success* or test* or assess* or evaluat* or standard* or deficien* or fail* or skill* or learn* or diploma* or credential* or certificat*)).mp.	438,460
	11	exp academic achievement/ or educational status/	87,803
	12	10 OR 11	460,416
	13	9 AND 12	2,035

- *Table 2- Full Search Strategy-Supplementary Table* ***MEDLINE***

Child	1	(Neonat* OR Infant* OR Baby OR Babies OR Toddler* OR Child* OR Adolesc* OR Teen* or Young* OR Youth* OR Pe?diatric).mp	4,213,944
Cancer	2	exp neoplasm/ or childhood cancer/ or pediatric cancer/	2,920,655
	3	(Cancer* OR Malignan* OR Neoplas* OR Tumo?r* OR Leuk?emia* OR Sarcoma* OR Lymphoma* OR Blastoma*).mp	3,678,231
	4	2 OR 3	3,852,451
Survivor	5	Survivor/	19,895
	6	(survivo* or survive or survives or survived).mp.	191,067
	7	(after* or follow* or subsequent* or remission* or ?live or living*) adj3 (3)	285,470
	8	5 OR 6 OR 7	466,972
	9	1 AND 4 AND 8	54,425
Educational Progression	10	((educat* or school* or universit* or college* or exam*) adj3 (attain* or outcome* or achiev* or progress* or attend* or perform* or level* or degree* or qualif* or status* or success* or test* or assess* or evaluat* or standard* or deficien* or fail* or skill* or learn* or diploma* or credential* or certificat*)).mp	342,086
	11	exp educational status/	45,621
	12	10 OR 11	342,234
	13	9 AND 12	1,459

- *Table 3- Full Search Strategy-Supplementary Table* ***PsychInfo***

Child	1	(Neonat* OR Infant* OR Baby OR Babies OR Toddler* OR Child* OR Adolesc* OR Teen* or Young* OR Youth* OR Pe?diatric).mp	968,776
Cancer	2	exp neoplasm/ or childhood cancer/ or pediatric cancer/	43,656
	3	(Cancer* OR Malignan* OR Neoplas* OR Tumo?r* OR Leuk?emia* OR Sarcoma* OR Lymphoma* OR Blastoma*).mp.	70,512
	4	2 OR 3	70,802
Survivor	5	Survivor/	10,740
	6	(survivo* or survive or survives or survived).mp.	35,662
	7	(after* or follow* or subsequent* or remission* or ?live or living*) adj3 (3)	4,872
	8	5 OR 6 OR 7	39,367
	9	1 AND 4 AND 8	2,604
Educational Progression	10	((educat* or school* or universit* or college* or exam*) adj3 (attain* or outcome* or achiev* or progress* or attend* or perform* or level* or degree* or qualif* or status* or success* or test* or assess* or evaluat* or standard* or deficien* or fail* or skill* or learn* or diploma* or credential* or certificat*)).mp.	262,312
	11	exp academic achievement/ or educational status/	68,480
	12	10 OR 11	295,501
	13	9 AND 12	254

- *Table 4- Full Search Strategy-Supplementary Table **ERIC***

Child	1	(Infant OR Baby OR Toddler OR Child OR Adolescent OR Teen OR Young OR Youth OR Pediatric OR Paediatric)	295,786
Cancer	2	(Cancer OR Malignant OR Malignancy OR Neoplasm OR Neoplastic OR Tumor OR Tumour OR Leukemia OR Leukaemia OR Sarcoma OR Lymphoma OR Blastoma)	2,462
	3	1 AND 2	634
Educational Progression	4	(Educate or education or school or schooling or university or universities or college or exam or exams or examinations)	1,309,487
	5	(Attain or attainment or outcome or achieve or achievement or progress or progression or attend or attendance or perform or performance or level or degree or qualify or qualification or success or test or assessment or evaulation or standard or deficiency or deficiencies or fail or failure or skill or learn or learning or diploma or credential or certificate or certification)	1,038,564
	6	3 AND 4	901,191
	7	3 AND 6	265

- *Table 5- Full Search Strategy-Supplementary Table* ***CINAHL Plus***

Child	S1	TX (Neonat* OR Infant* OR Baby OR Babies OR Toddler* OR Child* OR Adolesc* OR Teen* or Young* OR Youth* OR Pe?diatric)	1,071,551
Cancer	S2	MH neoplasms OR MH childhood neoplasms	59,180
	S3	TX (Cancer* OR Malignan* OR Neoplas* OR Tumo?r* OR Leuk?emia* OR Sarcoma* OR Lymphoma* OR Blastoma*)	476,288
	S4	S2 OR S3	476,288
Survivor	S5	MH Survivors	8,329
	S6	TX (survivo* or survive or survives or survived)	42,916
	S7	(after* or follow* or subsequent* or remission* or ?live or living*) N3 (3)	20,304
	S8	S5 OR S6 OR S7	59,897
	S9	S1 AND S4 AND S8	8,386
Educational Progression	S10	TX ((educat* or school* or universit* or college* or exam*) N3 (attain* or outcome* or achiev* or progress* or attend* or perform* or level* or degree* or qualif* or status* or success* or test* or assess* or evaluat* or standard* or deficien* or fail* or skill* or learn* or diploma* or credential* or certificat*))	188,454
	S11	MH educational status OR MH academic achievement	32,691
	S12	S10 OR S11	190,856
	S13	S9 AND S12	808

- *Table 6-* ***Data Extraction Form***

Hello! Who is entering information into the form?
Study ID (DOI)
Citation (Lead Author, YYYY)
Date of Publication
Contact Email of Study Author
Study Title
Study Design
Additional Information
Study Location (Country)
Diagnosis
Age Criteria: Lower Limit
Age Criteria: Upper Limit
Additional inclusion criteria?
Additional Inclusion Criteria (1)
Are there any specified exclusion criteria?
Exclusion Criteria (1)
Does the study report any significant baseline imbalances
Description of Imbalances (1)
Does the primary paper meet the inclusion criteria for entry to the systematic review?
Reason for Exclusion
Case Identification
Case Identification Details
Data Capture
Does the data capture method include a database?
Data capture: Database information (1)
Total Cases Identified
Additional Information about total number of cases (if required)
Number of Cases with Data Capture
Control Inclusion
How are controls matched to cases?
Other information about matching (if required)
Data Capture
Does the data capture method include a database?
Data capture: database information (1)

Total Controls Identified
Additional Information about total number of cases (if required)
Number of Controls with Data Capture
Does the study provide level 1 outcome data?
Description of Level 1
Number of Cases achieving Level 1
Number of Controls achieving Level 1
Statistical measure reported in paper
General Direction (Case vs Control)
Size of Effect
Significance Test
Does the study provide level 2 outcome data?
Description of Level 2
Number of Cases achieving Level 2
Number of Controls achieving Level 2
Statistical measure reported in paper
General Direction (Case vs Control)
Size of Effect
Significant Test
Does the study provide level 3 outcome data?
Description of Level 3
Number of Cases achieving Level 3
Number of Controls achieving Level 3
Statistical measure reported in paper
General Direction (Case vs Control)
Size of Effect
Significance Test
Does the paper include special educational needs as an outcome measure?
Description of SEN
Number of Cases with SEN
Number of Controls with SEN
Statistical measure reported in paper
General Direction (Case vs Control)
Size of Effect

Significance Test
Does the study include analyses of specific subgroups that are relevant to the systematic review?
Description of Sub-Group 1
Total number of cases in Sub-Group 1
Additional Information about total number of cases (if required)
Total number controls in subgroup 1
Number of Cases in Subgroup 1 achieving Level 1
Number of Controls in Subgroup 1 achieving Level 1
Statistical measure reported in paper
General Direction (Case vs Control)
Size of Effect
Significance Test
Number of Cases in subgroup 1 achieving Level 2
Number of Controls in subgroup 1 achieving Level 2
Statistical measure reported in paper
General Direction (Case vs Control)
Size of Effect
Significance Test
Number of Cases in subgroup 1achieving Level 3
Number of Controls in subgroup 1 achieving Level 3
Statistical measure reported in paper
Size of Effect
Significance Test
Are specific cancer subtypes included for sub-group analysis
Cancer Subgroup
Are specific treatments included as sub-group analysis?
Treatment Subgroup
Is age at cancer diagnosis included as sub-group analysis?
Is year of diagnosis included as sub-group analysis?
Is gender used for sub-group analysis?
Which years of diagnosis have been used in stratification?
Are specific treatment types included for subgroup analysis?
Funding
Source
Miscellaneous Information

- Quality Assessment for Cohort Studies (NEWCASTLE-OTTAWA SCALE) (Supplementary Table 7-8)

Table 7. Risk bias assessment using the Newcastle-Ottawa Scale (28)

Selection
Representativeness of the exposed cohort
Selection of non exposed cohort
Ascertainment of exposure
Outcome of Interest at start of study
Comparability
Outcome
Type of outcome assessment
Length of follow up
Completeness of follow up
Total Score

Table 8. Risk bias assessment for all 26 studies using the Newcastle-Ottawa Scale (28)

Selection	**Ahomaki (2016)[17]**	**Stam (2004)[15]**	**Barrera (2005)[55]**	**Gerhardt (2007)[43]**	**Maule (2016)[26]**	**Lorenzi (2008)[25]**	**Kuehni (2012)[33]**	**Langeveld (2003)[20]**	**Freycon (2013)[44]**	**Lancashire (2010)[29]**	**Dumas (2015)[21]**	**Kelaghan (1988)[34]**	**Dongen-Melman (1997)[41]**
Representativeness of the exposed cohort	*			*	*					*			
Selection of non exposed cohort	*		*	*	*	*	*			*		*	
Ascertainment of exposure	*	*	*	*	*	*	*	*	*	*	*	*	*
Outcome of Interest at start of study	*	*	*	*	*	*	*	*	*	*	*	*	*
Comparability													
	**		**	**	**	*	*	*		*	*	*	
Outcome													
Type of outcome assessment	*	*			*	*	*	*	*	*	*	*	*
Length of follow up	*	*	*	*	*		*	*	*	*	*	*	*
Completeness of follow up			*							*	*		
Total Score	**8**	**4**	**7**	**6**	**7**	**6**	**6**	**5**	**4**	**8**	**6**	**6**	**4**

Table 8. Risk bias assessment for all 26 studies using the Newcastle-Ottawa Scale (28)

Selection	Molgard-Hansen (2011)	Kingma (2000)	Kingma, (2002)	Hudson (2003)	Ness (2005)	Ishida (2011)	Moe (1997)	Allen (1990)	Essig (2014)	Ghaderi (2016)	Boman (2010)	Taylor (1987)	Haupt (1994)
Representativeness of the exposed cohort							*		*	*	*		*
Selection of non exposed cohort	*	*	*	*	*	*	*	*	*	*	*	*	*
Ascertainment of exposure	*	*	*	*	*	*	*	*	*	*	*		*
Outcome of Interest at start of study	*	*	*	*	*	*	*	*	*	*	*	*	*
Comparability													
	*			*	*	**	**	*	*	*	**	*	*
Outcome													
Type of outcome assessment	*	*	*	*	*	*	*	*		*	*	*	*
Length of follow up	*			*	*		*		*	*	*		*
Completeness of follow up									*	*	*		
Total Score	**6**	**4**	**4**	**6**	**6**	**6**	**8**	**5**	**7**	**8**	**9**	**4**	**7**

- Forest Plots of CNS tumour survivors at each educational attainment level (Supplementary Figure 1-3)

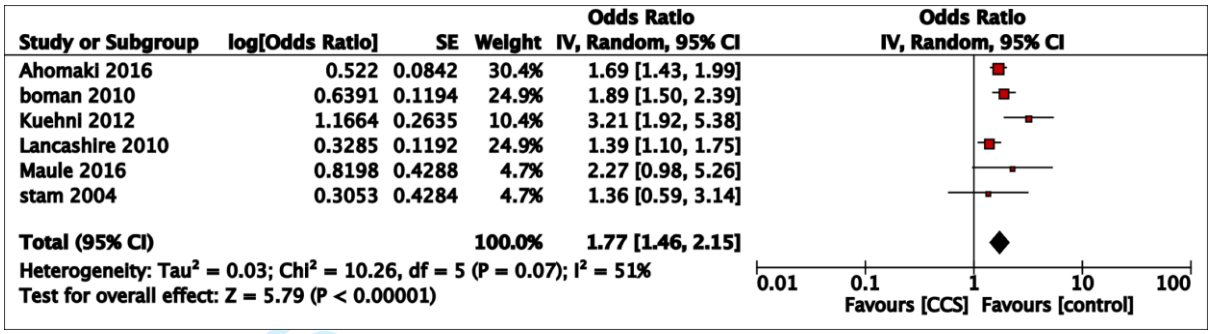

Figure 1. Forest Plot demonstrating educational attainment at Level 1 for CNS tumour childhood cancer survivors and controls (95% prediction interval [1.02, 3.08]).

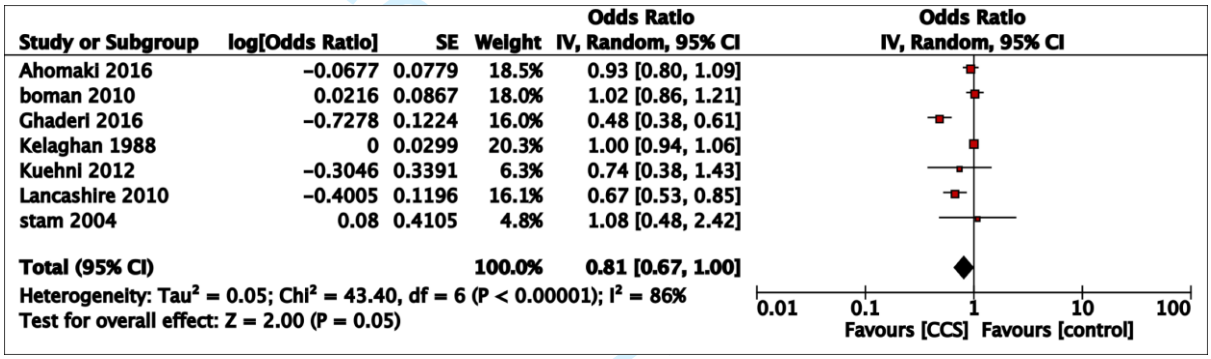

Figure 2. Forest Plot demonstrating educational attainment at Level 2 for CNS tumour childhood cancer survivors and controls (95% prediction interval [0.43, 1.53]).

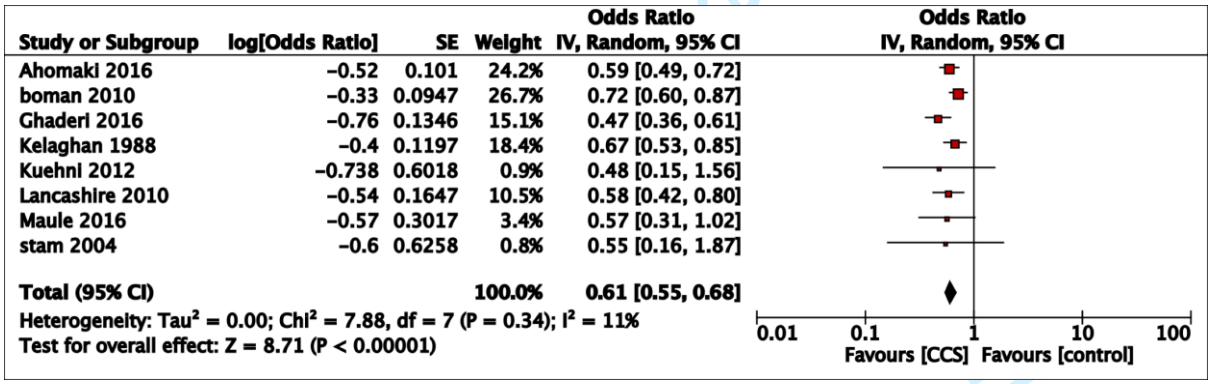

Figure 3. Forest Plot demonstrating educational attainment at Level 3 for CNS tumour childhood cancer survivors and controls (95% prediction interval [0.53, 0.70]).

- Forest Plots of CNS mediated therapy survivors at each educational attainment level (Supplementary Figure 4-6)

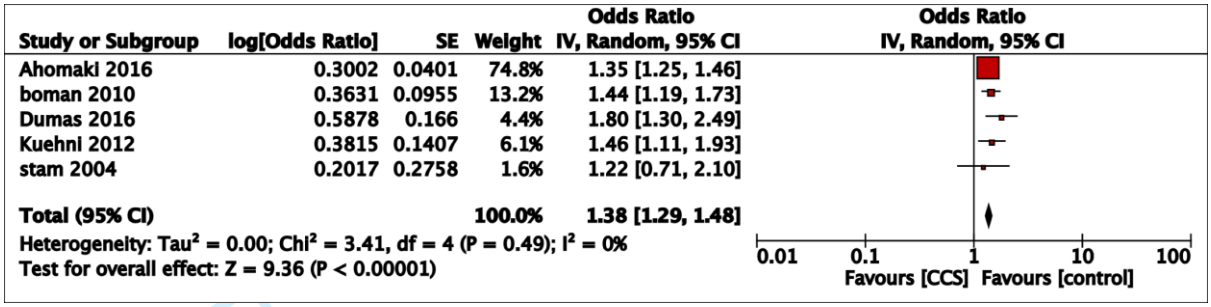

Figure 4. Forest Plot demonstrating educational attainment at Level 1 for childhood cancer survivors who received CNS -mediated therapy and controls (95% prediction interval [1.23, 1.54]).

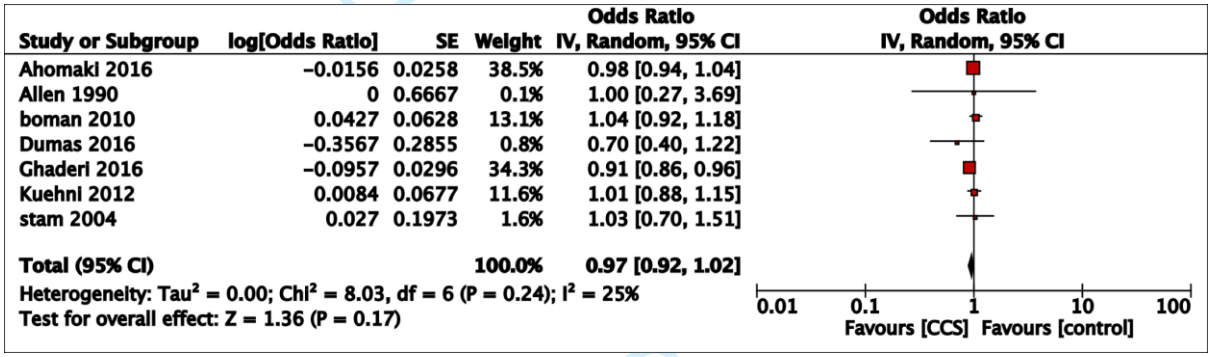

Figure 5. Forest Plot demonstrating educational attainment at Level 2 for childhood cancer survivors who received CNS -mediated therapy and controls (95% prediction interval [0.91, 1.04]).

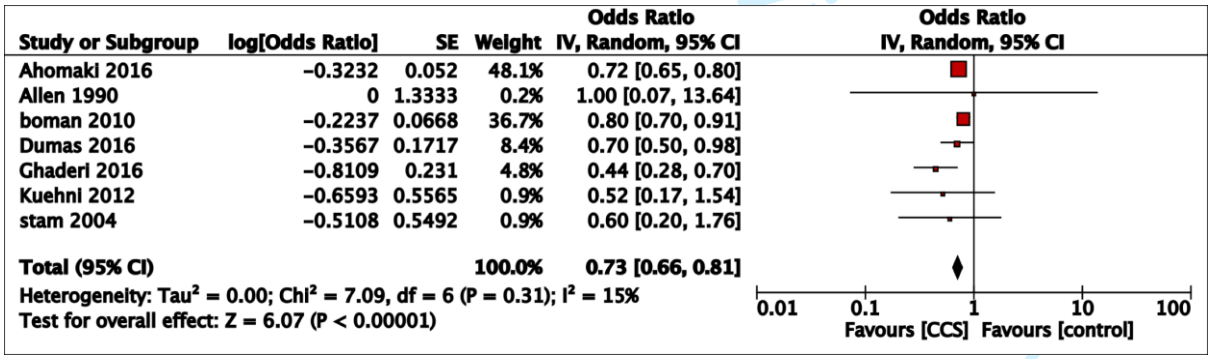

Figure 6. Forest Plot demonstrating educational attainment at Level 3 for childhood cancer survivors who received CNS -mediated therapy and controls (95% prediction interval [0.63, 0.84]).

- Forest Plots of CNS mediated therapy survivors at each educational attainment level, excluding Dumas et al., 2016 (Supplementary Figure 4a-6a)

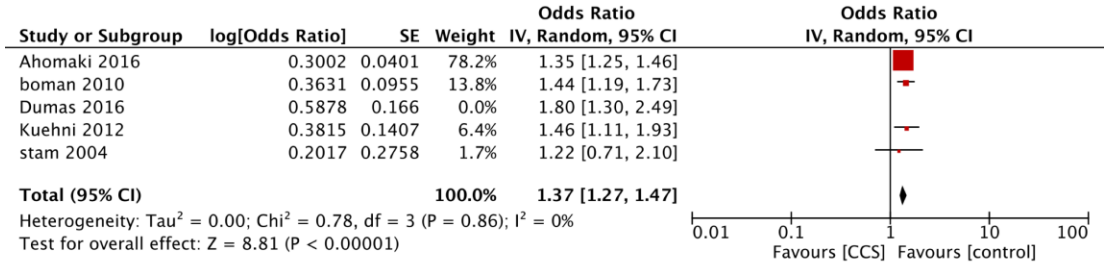

Figure 4a. Forest Plot demonstrating educational attainment at Level 1 for childhood cancer survivors who received CNS -mediated therapy and controls, excluding Dumas et al., 2016.

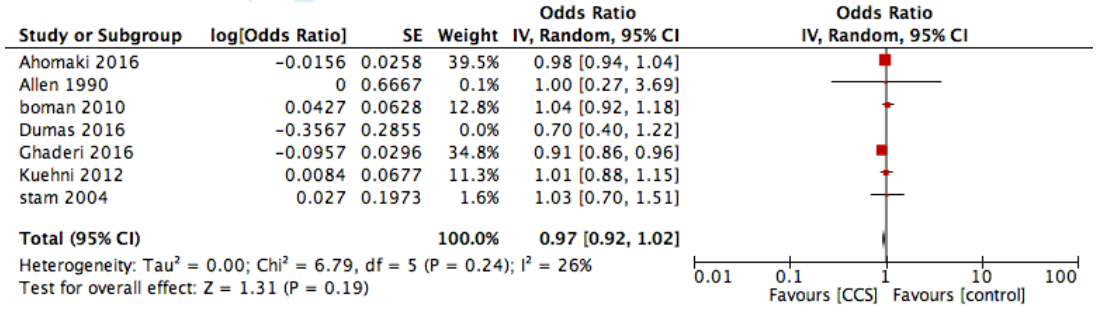

Figure 5a. Forest Plot demonstrating educational attainment at Level 2 for childhood cancer survivors who received CNS -mediated therapy and controls, excluding Dumas et al., 2016.

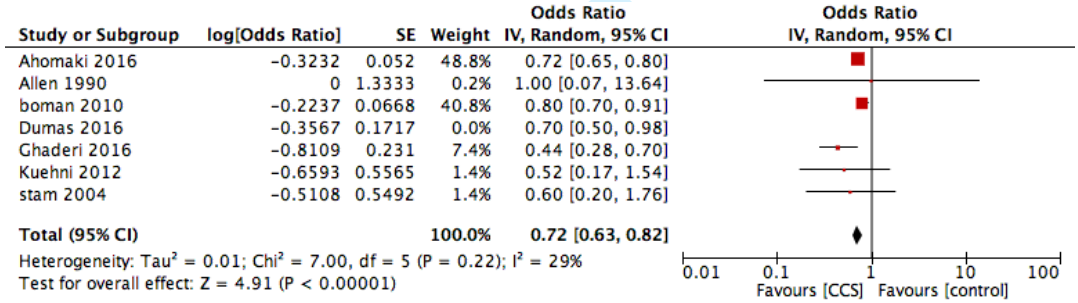

Figure 6a. Forest Plot demonstrating educational attainment at Level 3 for childhood cancer survivors who received CNS -mediated therapy and controls, excluding Dumas et al., 2016.

- Forest Plots of non-CNS survivors at each educational attainment level (Supplementary Figure 7-8)

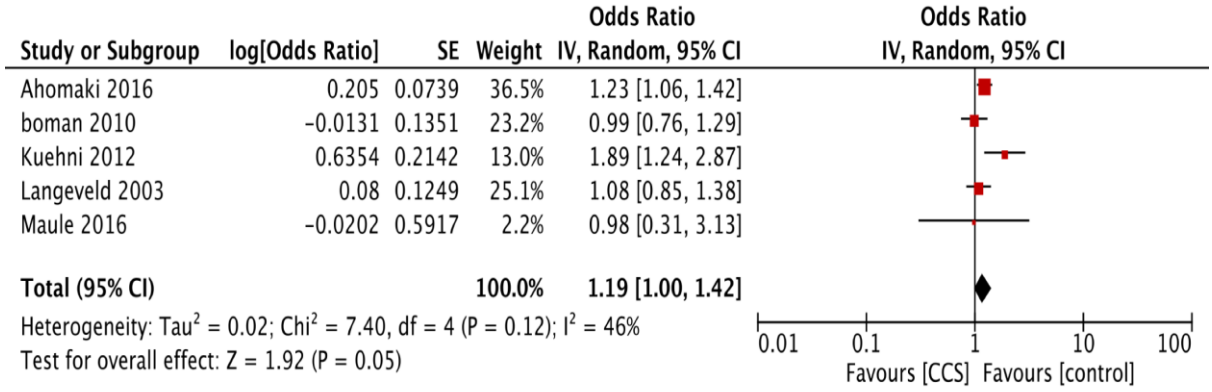

Figure 7. Forest Plot demonstrating educational attainment at Level 1 for non-CNS childhood cancer survivors and controls (95% prediction interval [0.7,2.03]).

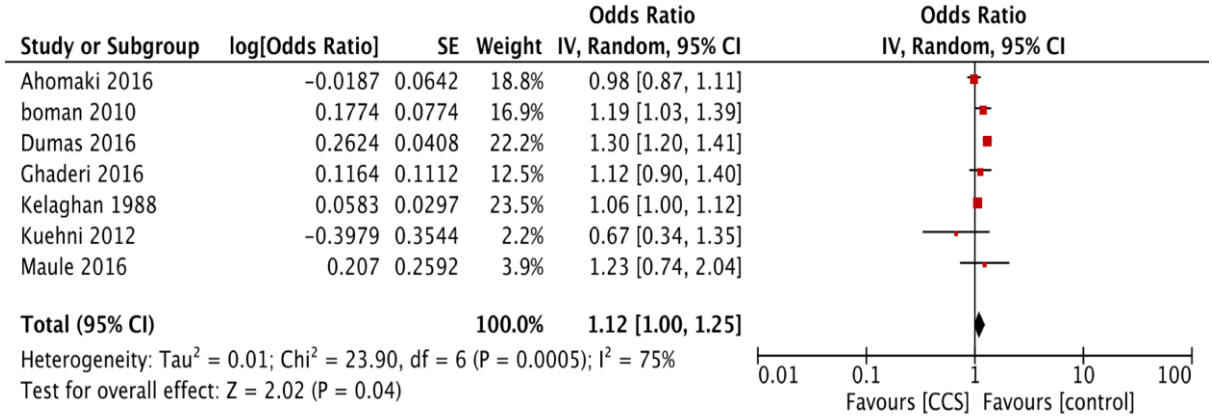

Figure 8. Forest Plot demonstrating educational attainment at Level 3 for non-CNS childhood cancer survivors and controls. (95% prediction interval [0.83, 1.5]).

- Forest Plots of survivors < 16 years of age at each educational attainment level

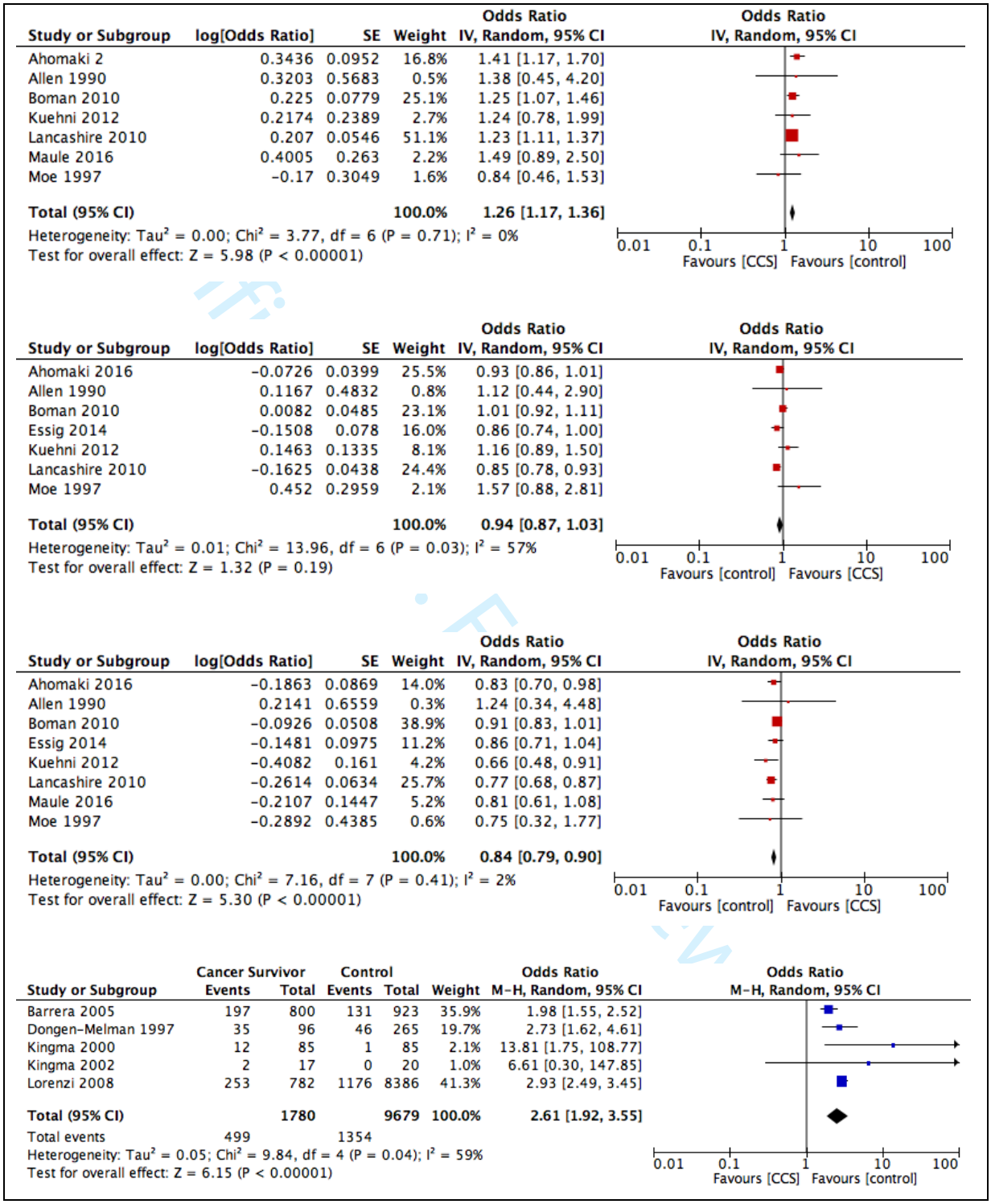

Figure 9. Forest Plots of primary and secondary outcomes in cohorts with children diagnosed with cancer under 16 years of age.

- Articles Excluded from the Meta-Analysis (Supplementary Table 9)

Table 9. Excluded citations with justifications

Study Author	Reason for Exclusion
Ait Khelifa-Gallois, (2014) [53]	No outcome of interest.
Armstrong, G (2009) [54]	Data cannot be analysed. No raw data or ORs.
Barrera, M (2008) [55]	No outcome of interest.
Boman, K (2004) [23]	Data cannot be analysed. No raw data or ORs.
Brinkman, (2016) [56]	No control group.
Brown, T (1998)[57]	No control group.
Buizer A, (2006) [58]	Database is same as other studies.
Chaume (2006)[59]	No outcome of interest.
Danoff, (1984) [60]	No control group.
Eilertsen (2011) [61]	Adult study.
Evans S, (1995) [62]	Data cannot be analysed. No raw data or ORs.
Fernandez-Pineda, I (2016)[63]	Cannot find full text. Main author died in 2016
Fidler, M (2015) [22]	No outcome of interest.
Glaser, (1997) [64]	No outcome of interest
Gray, (1992) [65]	Data cannot be analysed. No raw data or ORs.
Hays (1997) [66]	No outcome of interest.
Hays, D (1992) [67]	No outcome of interest.
Hoffman, R (2002)[68]	No outcome of interest.
Jacola, L (2016)[38]	Data cannot be analysed. No raw data or ORs.
King, A (2016)[69]	No control group.
Koch, (2004)[70]	Data cannot be analysed. No raw data or ORs.
Krull, K (2013)[71]	No control group.
Lahteenmaki P, (2002)[72]	Data cannot be analysed. No raw data or ORs.
Marino (2013)[73]	Data cannot be analysed. No raw data or ORs.
Massimo (2006)[74]	Cannot find full-text review
Meadows, (1989)[75]	Data cannot be analysed. No raw data or ORs.
Mitby (2003) [76]	Database is same as other studies.
Nagarajan, (2003)[77]	Database is same as other studies.
Ness (2010)[78]	No outcome of interest.
Ng, A (2007)[79]	Adult study.
Novakovic, B (1997)[80]	Adult study.
Pfitzer (2013)[81]	No control group.
Phipps (1995)[82]	No control group.
Pillon (2013)[14]	Data cannot be analysed. No raw data or ORs.

Pompilli (2002)[83]	No outcome of interest.
Schuler, (1990)[84]	Data cannot be analysed. No raw data or ORs.
Shah, A (2008)[85]	No control group.
Shaw (2004) [86]	No outcome of interest
Spiegler, B (2006)[87]	No outcome of interest.
Sutton, (1999)[88]	No outcome of interest.
Tebbi (1987)[89]	No control group.
Wasserman, (1987)[90]	Excluded - age range
Wong, (2016)[16]	Database is same as other studies.
Yagci-Kupeli (2013)[91]	Data cannot be analysed. No raw data or ORs.
Yonemoto (2007)[92]	Database is same as other studies.
Yssing (1990)[93]	Adult study.
Zynda, (2012)[27]	Data cannot be analysed. No raw data or ORs.

- Qualitative Synthesis (Supplementary Table 10)

Table 10. Summary of qualitative synthesis of all studies included within the systematic review

Study ID	Number Cases	Number Controls	Response Rate (%)	Outcome
Dongen-Melman (1997)[41]	96	265	Case: 86 Control: 100	More childhood leukaemia survivors are in special educational needs school than controls in a single centre in the Netherlands,
Maule (2017)[26]	520	N/A	Case:100 Control:N/A	No statistical significance between cases and controls for compulsory education and higher level (university) education in a linkage study using national databases in Italy.
Lorenzi (2009)[25]	782	8386	Case:72 Control:100	Special educational services required statistically more in childhood cancer survivors than controls in a regional data linkage study from Vancouver, Canada.
Kuehni (2012)[33]	961	N/A	Case:57 Control:N/A	Childhood cancer survivors more likely to remain at compulsory level education and less likely to complete university education in a population study from Switzerland.
Ahomaki (2016)[17]	3242	16214	Case:100 Control:100	Childhood cancer survivors more likely to remain at compulsory level education, although data available, no conclusion reported by authors for other levels of education from a national linkage study from Finland.
Stam (2004)[15]	355	508	Case:71 Control:62	No statistical differences noted across attaining compulsory education, upper secondary education & vocational training and university level and higher vocational training from a single-centre study from the Netherlands.
Langeveld (2003)[20]	500	1092	Case:92 Control:62	Childhood cancer survivors do better at completing compulsory education but do worse at completing upper secondary education from a single-centre study from the Netherlands. More childhood cancer survivors enrol in special educational needs programmes.
Barerra (2005)[42]	800	923	Case:69 Control:57	Childhood cancer survivors require more special educational needs programmes from a multi-centre study from Canada.
Gordhart (2007)[43]	56	60	Case:89	No difference between childhood cancer survivors and controls for requiring

			Control:86	special needs classes within a single centre (Ohio) in the US.
Freycon (2014)[44]	59	N/A	Case:100 Control: N/A	There is no statistical difference between leukaemia patients who received allogeneic hematopoietic stem cell transplant and population control regarding completion of French baccalaureate in France.
Lancashire (2010)[!9]	10488	N/A	Case:71 Control: N/A	Childhood cancer survivors more likely to only have compulsory education (O-level), less likely to have A-levels or university education compared to population controls in the UK.
Dumas (2015) [21]	2066	N/A	Case:59 Control: N/A	Childhood cancer survivors do better in completing university education compared to controls. No statistical significance noted at compulsory level education or high school/vocational school in France.
Ghaderi (2016) [45]	2213	N/A	Case:100 Control:N/A	Childhood cancer survivors do worse in both completing intermediate (secondary level) and undergraduate/graduate education compared to population control in Norway.
Boman, 2010[46]	1716	1456089	Case:100 Control:100	Childhood cancer survivors: 10% complete only compulsory education, 55% complete secondary education and 35% complete compulsory education in Sweden.
Essig (2014) [47]	556	2232	Case:100 Control:100	There is no difference between childhood cancer survivors and sibling controls for completing all levels of education under college level. 38% of childhood cancer survivors and 41% of sibling controls complete graduate school in the Childhood Cancer Cohort Study (CCSS).
Taylor (1987) [48]	26	26	Case:67 Control: 100	There is no significant difference between need of special assistance between childhood cancer and sibling controls in the US.
Allen (1990) [10]	37	37	Case:37 Control:100	There is no statistical significance at any level of educational outcome between childhood leukaemia survivors and their sibling controls in a single centre in the UK.
Moe (1997) [13]	98	90	Case:100 Control: 92	For all the leukaemia diagnoses between 1975-1980 (identified through national registry) in Norway, there is no significant difference at any level of education compared to sibling controls.
Ishida (2011) [12]	189	72	Case:72 Control:100	There was no significant difference in compulsory level education between childhood cancer survivors and sibling controls in a multi-centre study in Japan.

Ness (2005) [49]	157	471	Case:30 Control:100	There is no statistical significance at any level of educational outcome between childhood cancer survivors who underwent hematopoietic stem cell transplant compared to other cohort's sibling controls in two centres in the US.
Hudson (2003) [24]	9535	2916	Case:47 Control:100	There was lower level of educational attainment in childhood cancer survivors compared to sibling controls from the Childhood Cancer Cohort Study (CCSS)
Kingma (2002)[50]	20	17	Case:65 Control:100	Special educational needs programme enrolment was higher for childhood leukaemia survivors compared to controls in the Netherlands.
Kingma (2000) [18]	85	85	Case:58 Control:63	Special educational needs programme enrolment was higher for childhood leukaemia survivors compared to controls in the Netherlands.
Molgard-Hansen (2011)[32]	102	86	Case:74 Control:91	No statistical significance between childhood acute myeloblastic leukaemia survivors and sibling controls with enrolment for learning disability programme in the Nordic countries (Denmark, Finland, Iceland, Norway, Sweden)
Haupt (1994) [11]	593	409	Case:81 Control:83	There is no statistical significance at any level of educational outcome between childhood leukaemia survivors and their sibling controls in the multi-centre cohort Childhood Cancer Group in the US.
Kelaghan (1988)[34]	2283	3261	Case:91 Control:90	Childhood CNS survivors do worse than sibling controls in 8 years of education and college completion but not 12 years of education. non-CNS tumour survivors do similarly at all levels of educational attainment in this multi-central cohort from the US.

- Bubble Plots demonstrating findings of meta-regression at Level 2 Educational Attainment using the following co-variates: 1) Age at Diagnosis *(p=0.37)* 2) % GDP spent on education *(p=0.13 R^2 0.75)* 3) % CNS within Cohort *(p=0.41)* 4) Time Period of Diagnosis *(p=0.37 R^2 0.48)* (Supplementary Figures 10-13)

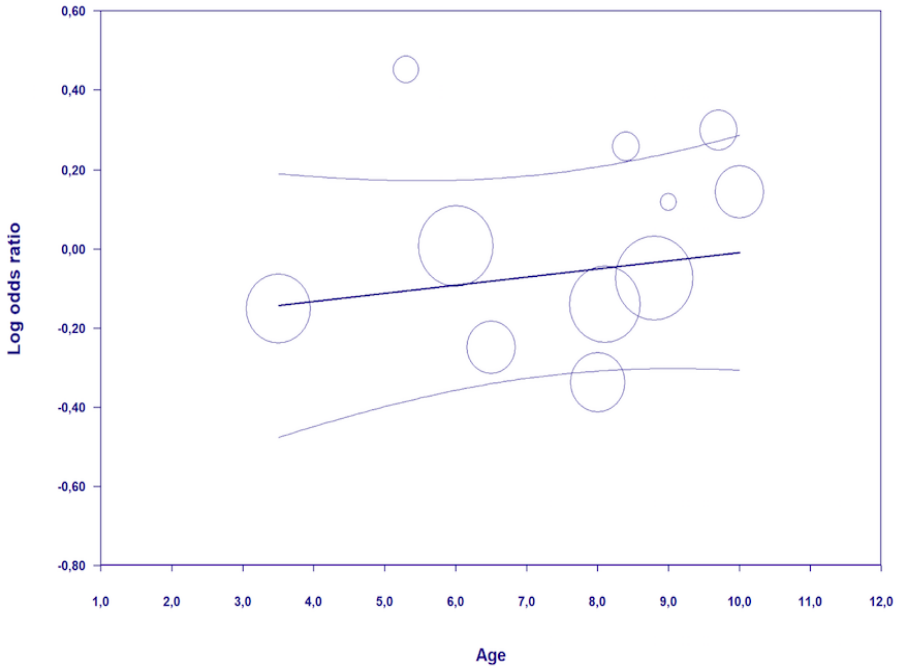

Figure 10. Age at diagnosis

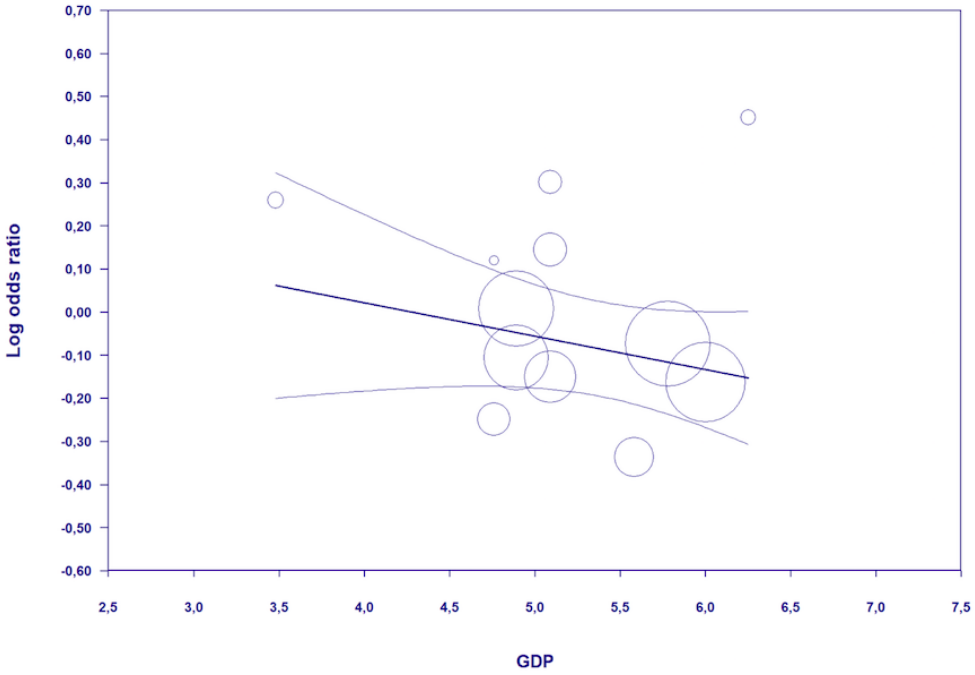

Figure 11. % GDP spent on education

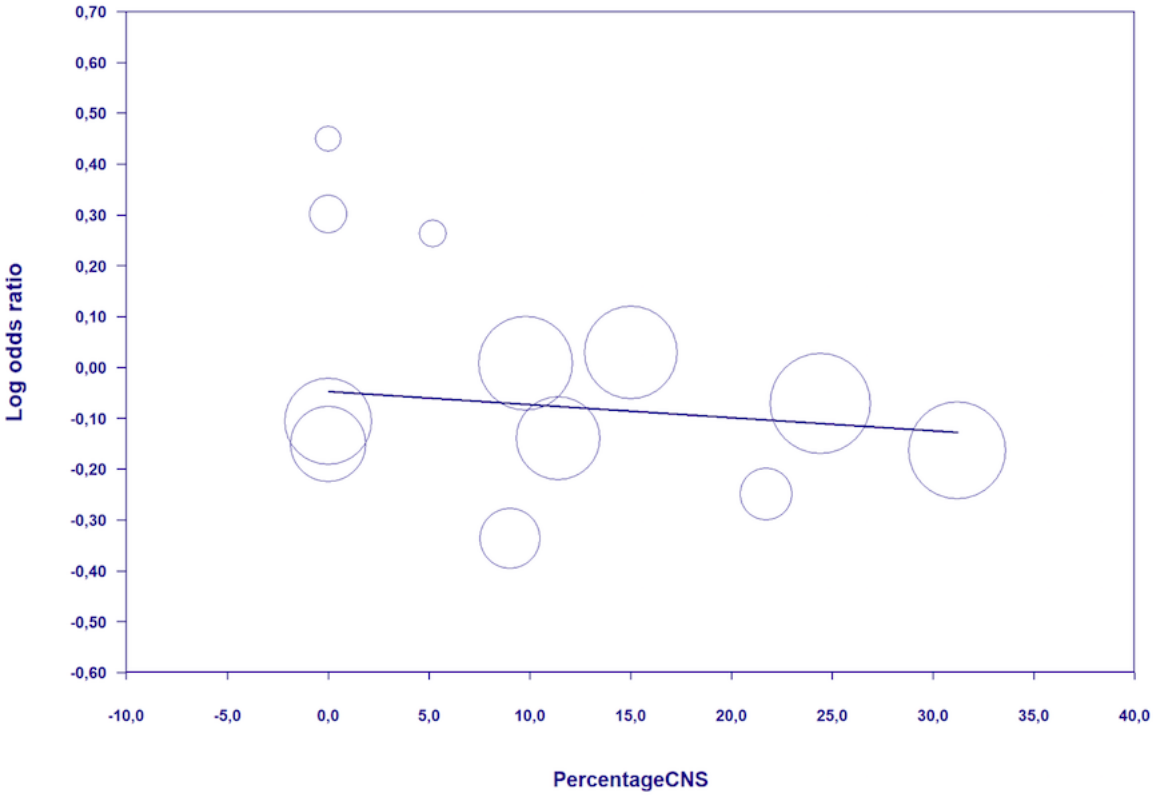

Figure 12. % CNS within Cohort

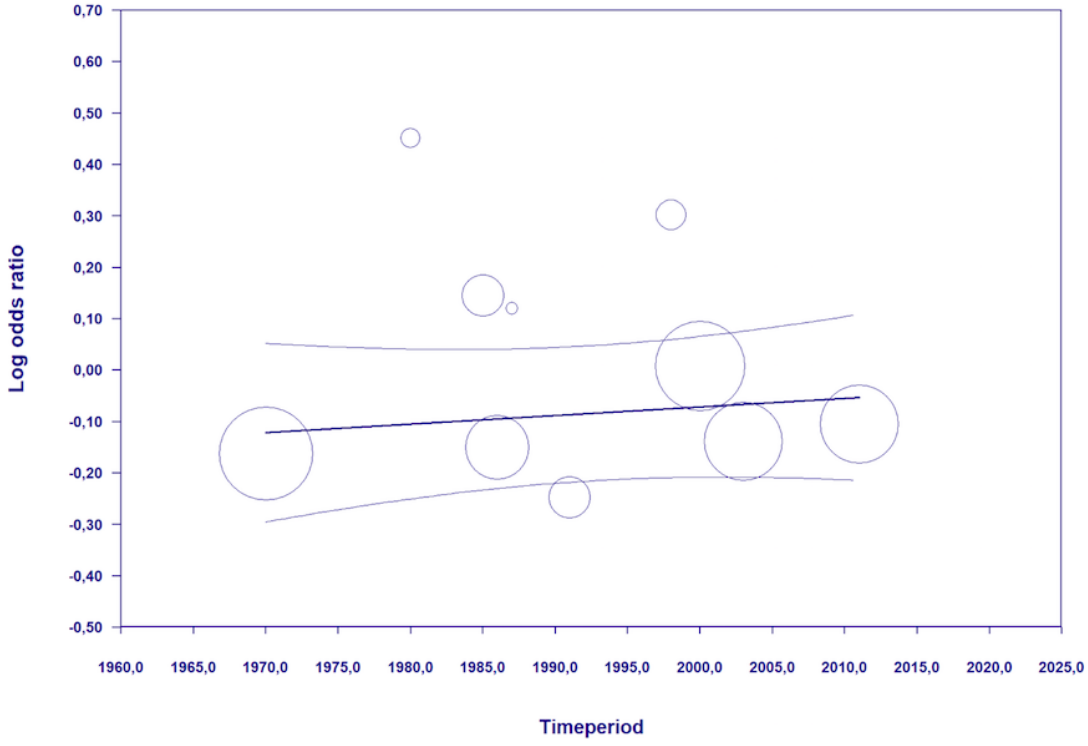

Figure 13. Time Period of Diagnosis

- Bubble Plots demonstrating findings of meta-regression SEN co-variates: 1) Age at Diagnosis *(p=0.32)* 2) % CNS within Cohort *(p=0.6)* (Supplementary Figures 14-15)

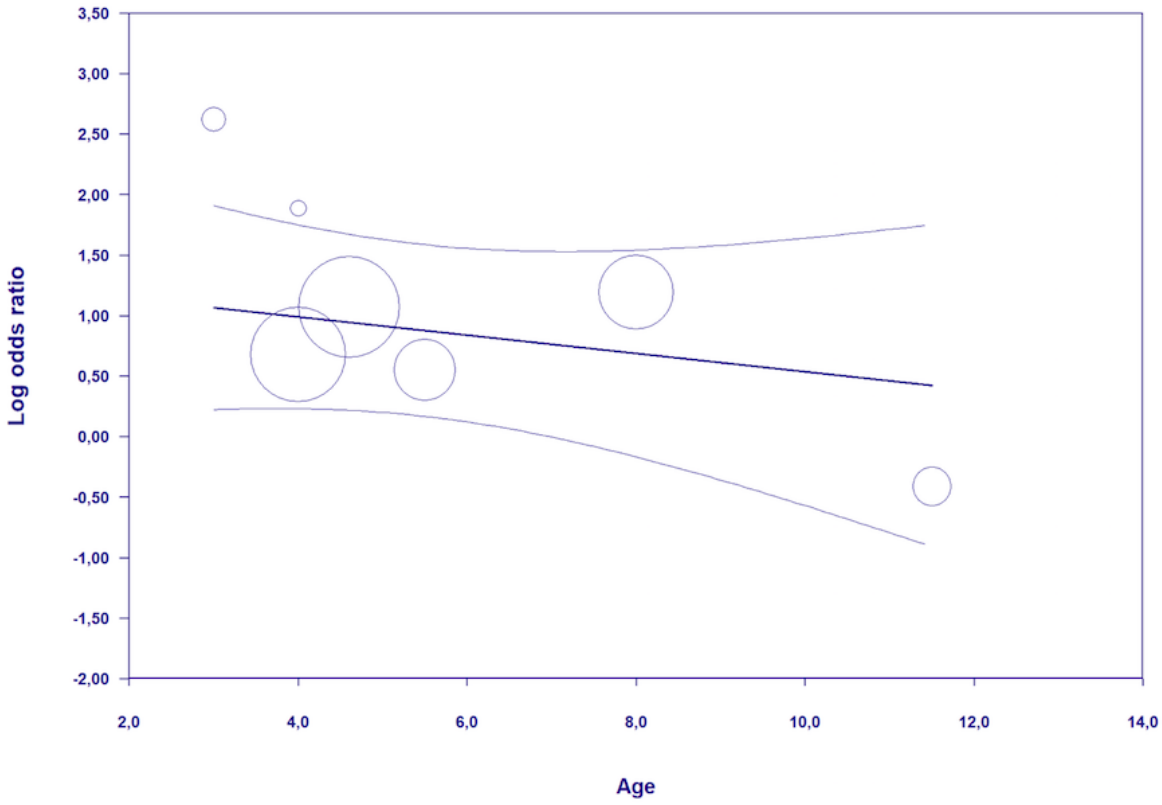

Figure 14. Findings of meta-regression SEN co-variates: Age at diagnosis

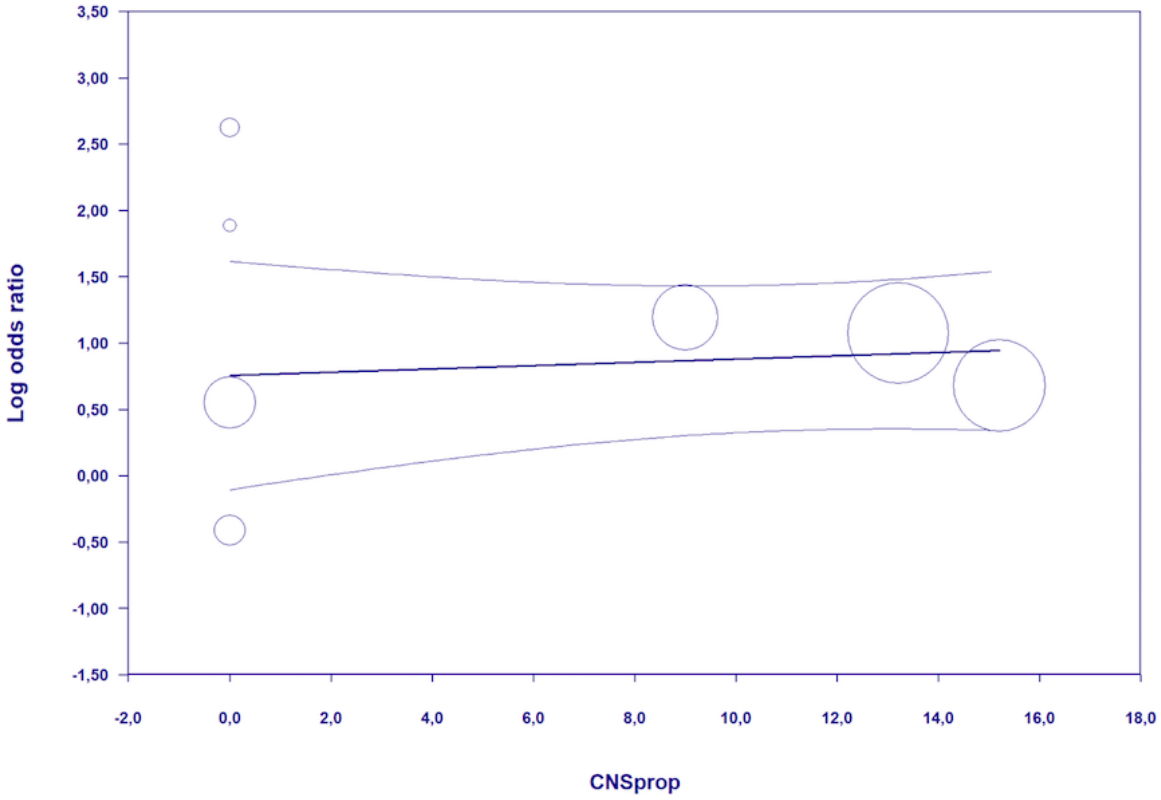

Figure 15. Findings of meta-regression SEN co-variates: % CNS within Cohort

- Educational Needs Outcome (Supplementary Figures 16-18)

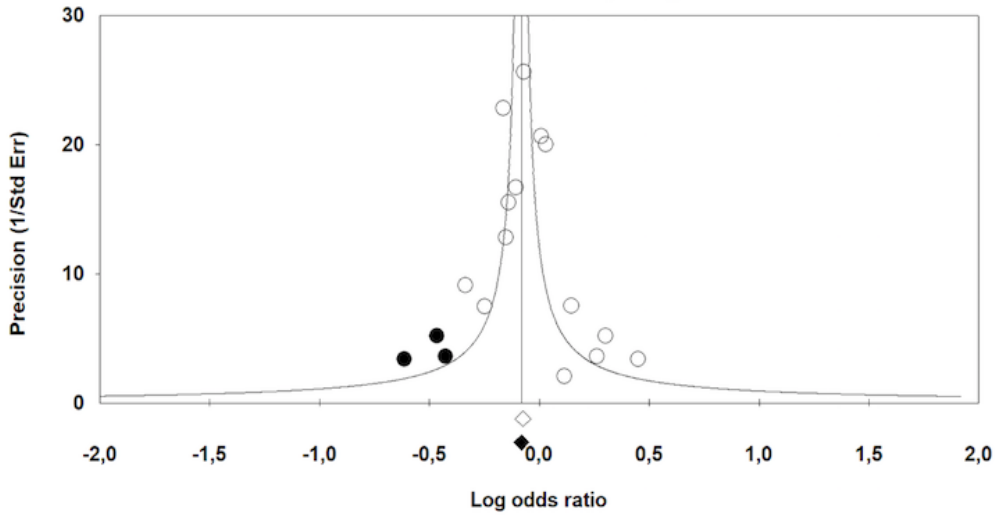

Figure 16. Funnel Plot for Level 2 Educational Attainment

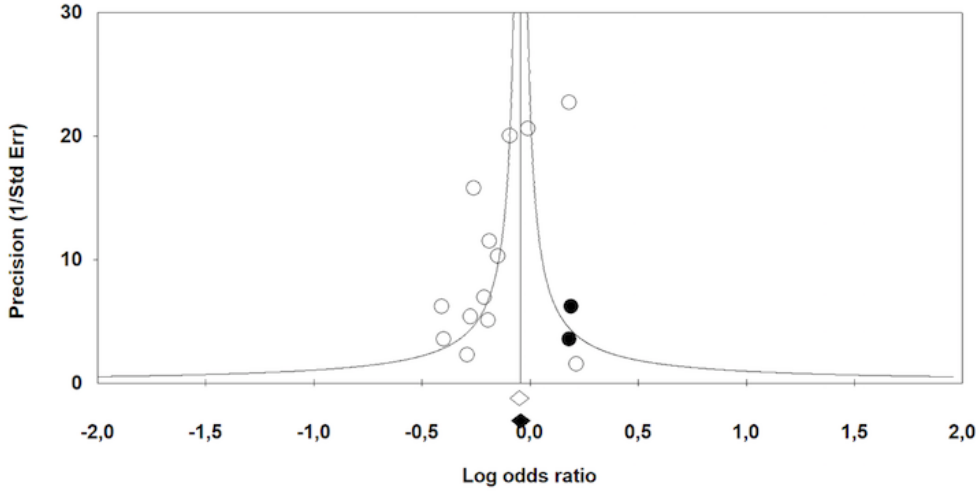

Figure 17. Funnel Plot for Level 3 Educational Attainment

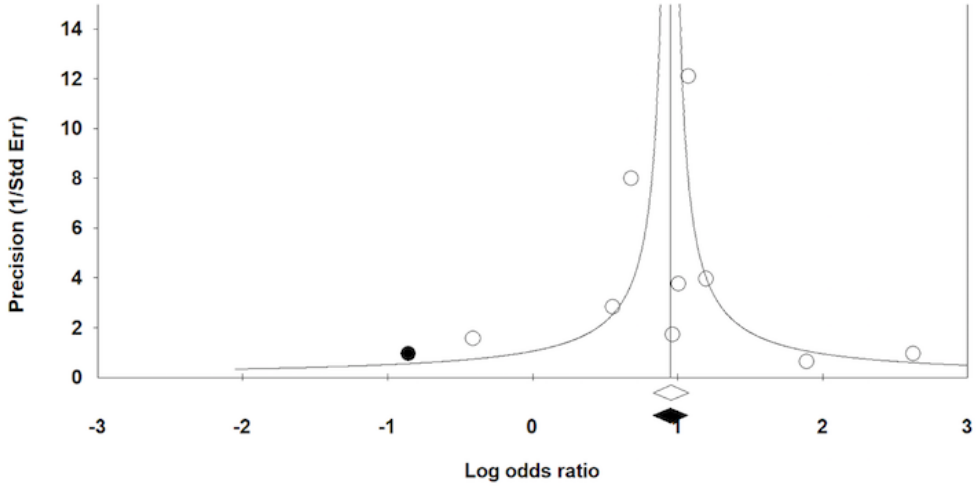

Figure 18. Funnel Plot for Special Educational Needs Outcome