Published in final edited form as:

Pediatr Blood Cancer. 2015 May ; 62(5): 875–882. doi:10.1002/pbc.25396.

Concentration, Working Speed and Memory: Cognitive Problems in Young Childhood Cancer Survivors and Their Siblings

L. Wengenroth, MSc¹, C. S. Rueegg, PhD^{1,2}, G. Michel, PhD^{1,2}, M. E. Gianinazzi, PhD^{1,2}, S. Essig, MD^{1,3,4}, N. X. von der Weid, MD⁵, M. Grotzer, MD⁶, and Claudia E. Kuehni, MD, MSc^{1,*},^a for the Swiss Paediatric Oncology Group SPOG

¹Swiss Childhood Cancer Registry, Institute of Social and Preventive Medicine, University of Bern, Switzerland ²Department of Health Sciences and Health Policy, University of Lucerne, Switzerland ³Institute of Primary and Community Care, Lucerne, Switzerland ⁴Swiss Paraplegic Research, Nottwil, Switzerland ⁵Pediatric Hematology/Oncology Unit, University Children's Hospital Basel (UKBB), University of Basel, Switzerland ⁶Department of Oncology, University Children's Hospital Zurich, Switzerland

Abstract

Background—Cognitive problems can have a negative effect on a person's education, but little is known about cognitive problems in young childhood cancer survivors (survivors). This study compared cognitive problems between survivors and their siblings, determined if cognitive problems decreased during recent treatment periods and identified characteristics associated with the presence of a cognitive problem in survivors.

Methods—As part of the Swiss Childhood Cancer Survivor Study, a questionnaire was sent to all survivors, aged 8–20 years, registered in the Swiss Childhood Cancer Registry, diagnosed at age <16 years, who had survived ≥5 years. Parent-reported (aged 8–15 years) and self-reported (aged 16–20 years) cognitive problems (concentration, working speed, memory) were compared between survivors and siblings. Multivariable logistic regression was used to identify characteristics associated with cognitive problems in survivors.

Results—Data from 840 survivors and 247 siblings were analyzed. More often than their siblings, survivors reported problems with concentration (12% vs. 6%; $P=0.020$), slow working speed (20% vs. 8%; $P=0.001$) or memory (33% vs. 15%; $P<0.001$). Survivors from all treatment periods were more likely to report a cognitive problem than were siblings. Survivors of CNS tumors (OR = 2.82 compared to leukemia survivors, $P<0.001$) and those who had received cranial irradiation (OR = 2.10, $P=0.010$) were most severely affected.

*Correspondence to: Claudia E. Kuehni, Institute of Social and Preventive Medicine, University of Bern, Finkenhubelweg 11, 3012 Bern, Switzerland. kuehni@ispm.unibe.ch.

^aSwiss Paediatric Oncology Group (SPOG) Scientific Committee: Dr. med. R. Angst, Aarau; PD Dr. med. M. Ansari, Geneva; PD Dr. med. M. Beck Popovic, Lausanne; Dr. med. P. Brazzola, Bellinzona; Dr. med. J. Greiner, St. Gallen; Prof. Dr. med. M. Grotzer, Zurich; Prof. Dr. med. K. Leibundgut, Bern; Prof. Dr. med. F. Niggli, Zurich; PD Dr. med. J. Rischewski, Lucerne; Prof. Dr. med. N. von der Weid, Basel.

Conflict of interest: Nothing to declare.

Conclusion—Childhood cancer survivors, even those treated recently (2001–2005), remain at risk to develop cognitive problems, suggesting a need to improve therapies. Survivors with cognitive problems should be given the opportunity to enter special education programs.

Keywords

childhood cancer; cognitive outcomes; cohort study; questionnaire survey; siblings; survivors

Introduction

Childhood cancer and its treatment may lead to various cognitive problems [1–4]. In developed countries, continuous improvements in therapy have increased five-year survival of childhood cancer to over 80% [5,6] leading to a growing population of long-term survivors. Because cancer and its treatment can cause adverse effects after the illness has been cured [7], it is increasingly important to assess long-term somatic outcomes, including cognitive problems. Cognitive problems with concentration, working speed or memory can be associated with learning difficulties and diminished educational achievements [8–10]. Previous studies from our group found that survivors of acute lymphoblastic leukemia (ALL) and central nervous system (CNS) tumors were particularly prone to develop problems with concentration, working speed and memory [11–14].

Studies that assessed cognitive problems in survivors were conducted on small non-population based samples [12–16] and included only specific diagnostic groups, like those with ALL [1,11,17,18], tumors of the central nervous system (CNS) [2,19,20] or neuroblastoma [21]. Studies that assessed cognitive problems in a large sample of survivors from different diagnostic groups focused on adult survivors, treated decades ago with treatment protocols that are no longer in use [3,4]. Young survivors are still attending school or vocational training, where they need to learn new things every day. Cognitive problems can severely interfere with a child's learning process and influence their later educational achievements [9,10]. There is no population-based study on cognitive problems in young childhood cancer survivors of all diagnostic groups treated recently.

For our study, we used a representative nationwide cohort approach to (i) compare cognitive problems (concentration, working speed, memory) in young childhood cancer survivors including all diagnostic groups and their siblings; (ii) determine if cognitive problems have decreased in recent treatment periods; and to (iii) identify characteristics associated with cognitive problems in survivors.

Materials and Methods

The Swiss Childhood Cancer Survivor Study (SCCSS)

The Swiss Childhood Cancer Survivor Study (SCCSS) is a population-based long-term follow-up study of all patients registered in the Swiss Childhood Cancer Registry (SCCR), diagnosed 1976–2005 at 16 years, who survived 5 years after diagnosis [22]. The SCCR includes all children and adolescents in Switzerland diagnosed with leukemia, lymphoma,

CNS tumors, malignant solid tumors or Langerhans cell histiocytosis (LCH) before age 16 years [23].

In 2007–2010, we traced addresses of all survivors who were eligible for the SCCSS, according to the criteria mentioned above, and sent them a questionnaire [23]. Non-responders were mailed a second copy of the questionnaire and, if they again failed to respond, were contacted by phone. In 2010–2011, we again contacted survivors to obtain consent to contact their siblings. We sent the same questionnaire without cancer related questions to siblings; those who did not respond were sent a second copy 4–6 weeks after the first, but were not contacted by phone. Parents of study participants aged 15 years completed the questionnaires for their children. Study participants aged 16 years completed their own questionnaires. Questionnaires were similar to those used in US and UK childhood cancer survivor studies [24,25]. We added questions about health behaviors and socio-demographic measures from the Swiss Health Survey 2007 [26] and the Swiss Census 2000 [27]. For this study, we included all survivors and siblings from the SCCSS, who were aged 8–20 years at survey.

Approval of the study was granted through the general cancer registry permission of the SCCR by the ethics committee of the canton of Bern.

Assessment of Socio-Demographic and Clinical Data

For the survivors, we extracted diagnosis, treatment modalities (surgery, chemotherapy, radiotherapy, bone marrow transplantation), year of treatment start, age at diagnosis, duration of treatment, time since diagnosis and relapse status from the SCCR. We coded diagnosis according to international ICC-3 code [28].

The following socio-demographic variables for survivors and siblings were assessed by questionnaire: gender; age at survey; migration background; language region of Switzerland; parents' educations; and, current educational situation. Participants who fulfilled one of the following criteria were coded as having a migration background: not born in Switzerland; no Swiss citizenship at birth; or, at least one parent with no Swiss citizenship. In Switzerland different languages are spoken. Language region was coded as German, French, or Italian. Parents' education was divided into three categories: primary education (compulsory schooling only; 9 years); secondary education (vocational training or upper secondary education); and, tertiary education (university or technical college education).

Assessment of Cognitive Problems

In previous studies, we had investigated cognitive problems in subgroups of Swiss childhood cancer survivors, using standardized instruments. These included the Wechsler test [29] in 150 ALL survivors [11]; and the child behavior checklist (CBCL) [30], the Paediatric quality of life inventory (PedsQL™) [31], and the Munster Heidelberg Abilites Scale [32] in CNS survivors [12,14,33]. We found that children were mainly affected in the areas of concentration, working speed and memory [11,12,14,33]. For the current large-scale epidemiological study, we thus asked participants the following three questions to assess cognitive problems: (i) How good is your concentration at school/work? ("Poor" or "not very good" were coded as reporting a *concentration problem*; "excellent," "very good" or

“good” were coded as no concentration problem); (ii) How fast do you work in comparison to classmates or colleagues? (“Very slow” or “slow” were coded as reporting *slow working speed*; “very fast,” “fast” or “average” were coded as no slow working speed); (iii) Do you have trouble remembering things? (“Often” was coded as reporting *a memory problem*; “never,” “rarely” or “sometimes” were coded as no memory problem).

For the purpose of multivariable logistic regressions, we built the outcome variable *cognitive problem*. Every participant who reported one or more of the three cognitive problems was coded as *reporting a cognitive problem*, while participants who did not report any of the three cognitive problems were coded as *not reporting a cognitive problem*.

Statistical Analysis

For all analyses, we standardized the sibling population for gender, age at survey, migration background, language region, and parents’ education, based on the survivor population. To achieve this standardization we used a multivariable logistic regression, for which survivor status was used as an outcome to compute weights. These weights ensured that the weighted marginal distribution of the sibling population was identical for gender, age at survey, migration background, language region, and parents’ education to the survivor population. Details on the weighting procedure are described elsewhere [34].

First, we used *F*-tests to compare the socio-demographic data and cognitive problems of survivors and siblings. Second, we calculated multivariable logistic regressions to determine associations of period of treatment start, treatments and diagnostic groups in survivors with cognitive problems, while siblings served as the reference population. We used robust variance estimation for clustered data [35] to account for dependence of observations between survivors and their siblings. A non-parametric Wilcoxon–type test for trend was used to determine if cognitive problems have decreased in recent treatment years [36]. Third, in survivors only, we fitted socio-demographic variables in a multivariable logistic regression to determine their association with reporting a cognitive problem. Fourth, in survivors only we added clinical variables to the multivariable logistic regression to determine their associations with reporting a cognitive problem. Diagnostic groups with $n < 50$ were summarized in the category “other.” *P*-values < 0.05 were considered as statistically significant. All analyses were performed with Stata, version 12.1 (StataCorp LP, College Station, Texas).

Results

Characteristics of the Study Population

We contacted the families of 1,326 survivors and 525 siblings (Fig. 1). Questionnaires were returned for 882 survivors (67% of those contacted, 63% of those eligible) and 249 siblings (47% of those contacted, 27% of those eligible). An abridged version of the questionnaire was completed by 29 survivors; these were not included in this study. Thirteen more survivors and two siblings had not started school yet, and were excluded. We included in our analysis data on a total of 840 survivors (440 self-reported, 400 parent-reported) and 247 siblings (140 self-reported, 107 parent-reported).

The weighting procedure in siblings for gender ($P = 0.903$), age groups ($P = 0.983$), migration background ($P = 0.356$) language regions ($P = 0.861$) and parental education ($P = 0.822$) ensured similar distribution among survivors and siblings (Table I). Of the survivors, 21% attended primary school, 49% attended secondary school, and 30% had already finished school. These proportions were comparable for siblings ($P = 0.460$). Of those who finished school: 81% of survivors and 67% of siblings completed vocational training; 16% of survivors and 26% of siblings were currently working; and 3% of survivors and 9% of siblings went to university ($P = 0.024$). In survivors 5% attended special needs schools compared to 2% in siblings ($P = 0.067$).

Leukemia (35%) was the most common cancer among survivors, followed by CNS tumors (17%) and lymphoma (10%). Most survivors (81%) had received chemotherapy; 64% had surgery; 23% had radiotherapy (9% including cranial irradiation); and, 5% had bone marrow transplantations. Mean age at diagnosis was 4.5 years ($SD = 3.4$), mean duration of treatment was 465 days ($SD = 648$) and mean time since diagnosis was 11.4 years ($SD = 3.6$); period of treatment start was between 1989 and 2005; 11% had a relapse.

Cognitive Problems in Survivors and Siblings

Cognitive problems were more common in survivors than in siblings. Overall, 40% ($n = 333$) of survivors, and 22% ($n = 54$; $P < 0.001$) of siblings, reported a cognitive problem (Table II). In survivors, 12% and 6% of siblings reported a concentration problem ($P = 0.020$); 20% of survivors and 8% of siblings reported slow working speed ($P < 0.001$); and, 33% of survivors and 15% of siblings reported a memory problem ($P < 0.001$). When we stratified for age groups, we found that in children (aged 8–15 years), parent-reported concentration problems and slow working speed were more frequent in survivors than in siblings (concentration problem: 14% vs. 5%, $P = 0.007$; slow working speed: 24% vs. 10%, $P = 0.003$). In adolescents (aged 16–20 years), self-reported slow working speed and memory problems were more frequent in survivors than in siblings (slow working speed: 15% vs. 6%, $P = 0.008$; memory problem: 29% vs. 3%, $P < 0.001$). The results for each answer category of the three cognitive problems are displayed in the supplement (Supplemental Table I).

In general, survivors were more likely to report a cognitive problem than siblings ($OR = 2.48$, $P < 0.001$; Fig. 2), also when stratified by periods of treatment start (1989–1995: $OR = 3.08$, 1996–2000: $OR = 2.41$, 2001–2005: $OR = 2.32$; $P < 0.001$ each). There was a non-significant trend for less cognitive problems in more recent periods (non-parametric test for trend; $P = 0.062$). Regardless of the type of treatment, survivors were significantly more likely to report cognitive problems compared to siblings. Survivors of the following diagnostic groups were mainly affected: Leukemia ($OR = 2.33$, $P < 0.001$); lymphoma ($OR = 1.83$, $P = 0.041$); CNS tumors ($OR = 6.27$, $P < 0.001$); neuroblastoma ($OR = 2.17$, $P = 0.024$); and renal or hepatic tumors ($OR = 2.16$, $P = 0.009$).

Predictors for Cognitive Problems in Survivors

Among survivors, adolescents were less likely to report a cognitive problem than were children ($OR = 0.70$, $P = 0.015$; Table III). Gender, migration background, language region

and parents' education were not significantly associated with reporting cognitive problems. Compared to survivors of leukemia, survivors of CNS tumors were more likely to report a cognitive problem (OR = 2.82, $P < 0.001$). Compared to survivors without radiotherapy, survivors who had received cranial irradiation were more likely to report a cognitive problem (OR = 2.10, $P = 0.010$). Among survivors treatment with chemotherapy or bone marrow transplants, period of treatment start, age at diagnosis, duration of treatment, time since diagnosis and relapse status were not significantly associated with reporting cognitive problems.

Discussion

This survey of children and adolescents who had survived cancer found that survivors, even those treated recently with modern protocols, reported cognitive problems more often than siblings. Survivors of CNS tumors and those treated with cranial irradiation were most affected. Although other studies looked at cognitive problems in specific diagnostic groups of young survivors [1,11,17–21], we found no study that had surveyed concentration, working speed and memory problems in young survivors of all diagnostic groups and siblings.

It is known that adult survivors report more cognitive problems than siblings [3]. In addition, we found that in children, where cognitive problems were parent-reported, concentration problems and slow working speed were more frequent in survivors than in siblings, while in adolescents who self-reported cognitive problems, slow working speed and memory problems were more frequent in survivors than in siblings. This difference may be due to a different perception of cognitive problems. Teachers of children with low working memory described these children as having poor concentration (highly inattentive, poor attention span, high levels of distractibility) [37]. Further, those cognitive problems are closely related. A study showed that children with attention problems also had impaired working memory [38]. Among survivors, adolescents were less likely to report any cognitive problem than were parents who reported for younger children. Adolescents may evaluate their cognitive abilities differently than their parents. This has been shown for quality of life, where parents sometimes report poorer quality of life for their children than these report for themselves [39,40].

Survivors of CNS tumors had the highest risk for cognitive problems, which is well known [19]. In an earlier SCCSS study, we also found lower levels of education in adult survivors of CNS tumors than in healthy peers [41]. In this study, we additionally found that survivors of leukemia, neuroblastoma, and renal or hepatic tumors were more likely to report cognitive problems than siblings. For neuroblastoma survivors, especially those with hearing loss, an increased risk of learning problems has also been reported from the US [21]. Survivors of leukemia treated with cranial irradiation had significantly worse results for short-term verbal memory, arithmetics, concentration and speed of processing [11]. A study from the US found that memory problems were more frequent in survivors of non-CNS cancers (12.5%), including survivors of leukemia, lymphoma and neuroblastoma than in siblings (7.6%) [4]. In this study, we surveyed only a small number of survivors of renal ($n = 73$) and hepatic tumors ($n = 11$). Further research is necessary for these diagnostic groups. Survivors treated

with cranial irradiation were more likely to report cognitive problems than survivors who received no irradiation. These results accord with studies from other cohorts [16] and from previous studies from our group: In 150 ALL survivors, we found that irradiated survivors had worse scores on short-term verbal memory, arithmetics, concentration and speed of processing than survivors who were not irradiated [11]. Survivors of medulloblastoma who had been treated with cranial irradiation showed significant impairment in at least one neurocognitive function (attention and processing speed, learning and memory, language, visual perception, and executive functions) [12].

Survivors treated with radiotherapy, but also those treated with surgery or chemotherapy alone were more likely to report cognitive problems than siblings. This has also been shown for ALL survivors treated with chemotherapy alone: They had neurocognitive impairments [42], smaller volumes of neocortical and subcortical grey matter, and lower hippocampal memory performance [43]. Treatments for childhood cancer patients improved over time: Modern protocols include less damaging irradiation, make use of stereotactic radiosurgery or fractionated stereotactic radiotherapy for CNS tumors [44] and reduce prophylactic CNS irradiation in patients of ALL [1]. Despite these improvements, we found cognitive problems even in survivors treated recently. However, the OR decreased slightly from 3.08 (1989–1995) to 2.41 (1996–2000) and 2.32 (2001–2005), with a borderline significant test for trend ($P = 0.062$). Continuous research is needed to determine whether these new treatments have really caused less cognitive impairments.

Patients should be asked about cognitive problems during follow-up, since they can lead to health-related unemployment and less-skilled work in adult survivors [45]. Assessing cognitive problems in detail could assist hospital schools or special education services in tailoring individual support. Intervention studies from the US showed that targeted interventions can reduce cognitive problems in survivors [46–48]. Home-based computerized working memory training increased visual memory and reduced parent-reported learning problems in survivors of CNS tumors and ALL [46]. Cognitive remediation programs increased survivors' academic achievements [47], and changed brain activity in survivors of CNS tumors [48]. Intervention programs and remediation programs are feasible: 60% to 75% of survivors completed all training sessions [46,47]. Home-based computerized training is also feasible [46] and allows survivors who live in remote areas access to materials on their own schedule. Programs could be offered while patients are treated in hospital schools, or as special education programs in mainstream schools soon after the patient is finished with therapy.

Our study has some limitations. First, response in siblings was lower than in survivors, so our sample might not accurately represent the whole sibling population. We tried to overcome this limitation by weighing the sibling population for socio-demographic factors. Second, because questions on cognitive problems were self-reported for adolescents, and parent-reported for children, we cannot be sure if the lower risk of cognitive problems in adolescents is due to the fact they were older at the time of survey, or due to bias introduced by comparing self- to parent-reported cognitive problems. To differentiate the effect of age and self-vs-parent-reports, we would need longitudinal data, with repeated parental and self-assessments for the same individuals. Further, our questions on cognitive problems are not

validated, because we lacked the space to include lengthy standardized instruments in the current multipurpose questionnaire. Thus we developed short questions covering the areas which had been most affected in our previous studies, where we had used standardized instruments, that is, concentration, working speed and memory [11–14]. Last, we could not retrieve the exact dose of chemotherapy survivors had received, and so could not determine if dosage affected cognitive impairment.

A strength of our study is its large representative population-based sample of 5-year survivors covering all diagnostic groups. Further, we were able to include survivors who had been treated in different time periods, including recent periods with modern treatment protocols. Finally, we assessed different cognitive problems (concentration, working speed, memory) separately and then combined them, in order to capture all types of cognitive problems, irrespective of how they were perceived and described by the study participant.

Conclusion

Young survivors, between 8 and 20 years old, of several diagnostic groups were more likely to report cognitive problems than were their siblings. In addition to survivors of CNS tumors, survivors of leukemia, neuroblastoma and renal or hepatic tumors were also affected. Cranial irradiation was confirmed as the most important treatment-related risk factor for cognitive problems. Although our study population has been treated fairly recently (between 1989 and 2005), cognitive problems were still common, suggesting a remaining need to improve therapies. Survivors who report cognitive problems should be identified early and be given the opportunity to enter special education programs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank all childhood cancer survivors and families for participating in our survey. We thank the study team of the SCCSS (Erika Brantschen-Berclaz, Julia Koch, Fabienne Liechti), the data managers of the SPOG (Claudia Anderegg, Nadine Beusch, Rosa-Emma Garcia, Franziska Hochreutener, Friedgard Julmy, Nadine Lanz, Heike Markiewicz, Genevieve Perrenoud, Annette Reinberger, Renate Siegenthaler and Verena Stahel) and the team of the SCCR (Vera Mitter, Elisabeth Kiraly, Marlen Spring, Christina Krenger, Priska Wölfli). We thank Ben Spycher and Marcel Zwahlen for their statistical advice, and Kali Tal for her editorial assistance. This study was supported by Cancer League Aargau, the Bernese Cancer League and Swiss Cancer Research (grant 02631-08-2010). GM and SE were funded by the Swiss National Science Foundation (GM: Ambizione-Fellowship-grant PZ00P3_121682, PZ00P3-141722, SE: MD-PhD-grant 323630-133897; www.snf.ch) and Swiss Cancer Research (SE: MD-PhD-grant 02606-06-2010; www.krebsforschung.ch; MG: grant 02631-08-2010). The work of the SCCR is supported by the Swiss Paediatric Oncology Group, GDK, Swiss Cancer Research, Kinderkrebshilfe Schweiz, Ernst-Göhner Stiftung, Stiftung Domarena, CSL Behring and National Institute of Cancer Epidemiology and Registration.

Grant sponsor: Cancer League Aargau; Grant sponsor: Bernese Cancer League; Grant sponsor: Swiss National Science Foundation; Grant numbers: PZ00P3_121682; PZ00P3-141722; 323630-133897; Grant sponsor: Swiss Cancer Research; Grant numbers: 02606-06-2010

Abbreviations

ALL Acute lymphoblastic leukemia

CBCL	Child behavior checklist
CNS	Central nervous system
ICCC-3	International Classification of Childhood Cancer, Third edition
LCH	Langerhans cell histiocytosis
PedsQL	Paediatric quality of life inventory
SCCR	Swiss Childhood Cancer Registry
SCCSS	Swiss Childhood Cancer Survivor Study
UK	United Kingdom
US	United States

References

1. von der Weid N, Mosimann I, Hirt A, Wacker P, Nenadov Beck M, Imbach P, Caflisch U, Niggli F, Feldges A, Wagner HP. Intellectual outcome in children and adolescents with acute lymphoblastic leukaemia treated with chemotherapy alone: Age- and sex-related differences. *Eur J Cancer*. 2003; 39:359–365. [PubMed: 12565989]
2. Conklin HM, Ashford JM, Di Pinto M, Vaughan CG, Gioia GA, Merchant TE, Ogg RJ, Santana V, Wu S. Computerized assessment of cognitive late effects among adolescent brain tumor survivors. *J Neuro-oncol*. 2013; 113:333–340.
3. Clanton NR, Klosky JL, Li C, Jain N, Srivastava DK, Mulrooney D, Zeltzer L, Stovall M, Robison LL, Krull KR. Fatigue, vitality, sleep, and neurocognitive functioning in adult survivors of childhood cancer: A report from the Childhood Cancer Survivor Study. *Cancer*. 2011; 117:2559–2568. [PubMed: 21484777]
4. Kadan-Lottick NS, Zeltzer LK, Liu Q, Yasui Y, Ellenberg L, Gioia G, Robison LL, Krull KR. Neurocognitive functioning in adult survivors of childhood non-central nervous system cancers. *J Natl Cancer Inst*. 2010; 102:881–893. [PubMed: 20458059]
5. Gatta G, Zigon G, Capocaccia R, Coebergh JW, Desandes E, Kaatsch P, Pastore G, Peris-Bonet R, Stiller CA. Survival of European children and young adults with cancer diagnosed 1995–2002. *Eur J Cancer*. 2009; 45:992–1005. [PubMed: 19231160]
6. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. *CA: A cancer journal for clinicians*. 2013; 63:11–30. [PubMed: 23335087]
7. Oeffinger KC, Mertens AC, Sklar CA, Kawashima T, Hudson MM, Meadows AT, Friedman DL, Marina N, Hobbie W, Kadan-Lottick NS, Schwartz CL, et al. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med*. 2006; 355:1572–1582. [PubMed: 17035650]
8. Alloway TP. Working Memory, but Not IQ, Predicts Subsequent Learning in Children with Learning Difficulties. *EJPA*. 2009; 25:92–98.
9. Nevo E, Breznitz Z. Assessment of working memory components at 6 years of age as predictors of reading achievements a year later. *J Exp Child Psychol*. 2011; 109:73–90. [PubMed: 21115182]
10. McClelland MM, Acock AC, Piccinin A, Rhea SA, Stallings MC. Relations between Preschool Attention Span-Persistence and Age 25 Educational Outcomes. *Early Childhood Res Q*. 2013; 28:314–324. [PubMed: 23543916]
11. von der Weid N. Late effects in long-term survivors of ALL in childhood: Experiences from the SPOG late effects study. *Swiss Med Wkly*. 2001; 131:180–187. [PubMed: 11345808]
12. Ribí K, Rely C, Landolt MA, Alber FD, Boltshauser E, Grotzer MA. Outcome of medulloblastoma in children: Long-term complications and quality of life. *Neuropediatrics*. 2005; 36:357–365. [PubMed: 16429375]

13. Gerber NU, Zehnder D, Zuzak T, Poretti A, Boltshauser E, Grotzer MA. Outcome of children with brain tumours diagnosed in the first year: Long-term complications and quality of life. *Arch Dis Child*. 2007
14. Zuzak TJ, Poretti A, Drexel B, Zehnder D, Boltshauser E, Grotzer MA. Outcome of children with low-grade cerebellar astrocytoma: long-term complications and quality of life. *Childs Nerv Syst*. 2008; 24:1447–1455. [PubMed: 18690461]
15. Roberts RM, Robins T, Gannoni AF, Tapp H. Survivors of childhood cancer in south Australia attending a late effects clinic: A descriptive report of psychological, cognitive, and academic late effects. *J Psychosoc Oncol*. 2013; 32:152–166.
16. Conklin HM, Ashford JM, Howarth RA, Merchant TE, Ogg RJ, Santana VM, Reddick WE, Wu S, Xiong X. Working memory performance among childhood brain tumor survivors. *J Int Neuropsychol Soc*. 2012; 18:996–1005. [PubMed: 22691544]
17. Conklin HM, Krull KR, Reddick WE, Pei D, Cheng C, Pui CH. Cognitive outcomes following contemporary treatment without cranial irradiation for childhood acute lymphoblastic leukemia. *J Natl Cancer Inst*. 2012; 104:1386–1395. [PubMed: 22927505]
18. Krull KR, Zhang N, Santucci A, Srivastava DK, Krasin MJ, Kun LE, Pui CH, Robison LL, Hudson MM, Armstrong GT. Long-term decline in intelligence among adult survivors of childhood acute lymphoblastic leukemia treated with cranial radiation. *Blood*. 2013; 122:550–553. [PubMed: 23744583]
19. Ach E, Gerhardt CA, Barrera M, Kupst MJ, Meyer EA, Patenaude AF, Vannatta K. Family predictors associated with academic achievement deficits in pediatric brain tumor survivors. *Psychooncology*. 2013; 22:1731–1737. [PubMed: 23059621]
20. Aarsen FK, Paquier PF, Arts WF, Van Veelen ML, Michiels E, Lequin M, Catsman-Berrepoets CE. Cognitive deficits and predictors 3 years after diagnosis of a pilocytic astrocytoma in childhood. *J Clin Oncol*. 2009; 27:3526–3532. [PubMed: 19433687]
21. Gurney JG, Tersak JM, Ness KK, Landier W, Matthay KK, Schmidt ML. Hearing loss, quality of life, and academic problems in long-term neuroblastoma survivors: A report from the Children's Oncology Group. *Pediatrics*. 2007; 120:e1229–e1236. [PubMed: 17974716]
22. Kuehni CE, Rueegg CS, Michel G, Rebholz CE, Strippoli M-PF, Niggli FK, Egger M, von der Weid NX, Group fitSPO. Cohort profile: The Swiss Childhood Cancer Survivor Study. *Int J Epidemiol*. 2012; 41:1553–1564. [PubMed: 22736394]
23. Michel G, von der Weid NX, Zwahlen M, Adam M, Rebholz CE, Kuehni CE. The Swiss Childhood Cancer Registry: Rationale, organisation and results for the years 2001–2005. *Swiss Med Wkly*. 2007; 137:502–509. [PubMed: 17990137]
24. Hawkins MM, Lancashire ER, Winter DL, Frobisher C, Reulen RC, Taylor AJ, Stevens MC, Jenney M. The British Childhood Cancer Survivor Study: Objectives, methods, population structure, response rates and initial descriptive information. *Pediatric Blood & Cancer*. 2008; 50:1018–1025. [PubMed: 17849473]
25. Robison LL, Armstrong GT, Boice JD, Chow EJ, Davies SM, Donaldson SS, Green DM, Hammond S, Meadows AT, Mertens AC, Mulvihill JJ, et al. The Childhood Cancer Survivor Study: a National Cancer Institute-supported resource for outcome and intervention research. *J Clin Oncol*. 2009; 27:2308–2318. [PubMed: 19364948]
26. Liebherr, R., Marquis, J., Storni, M., Wiedenmayer, G. Gesundheit und Gesundheitsverhalten in der Schweiz 2007 - Schweizerische Gesundheitsbefragung. Neuchâtel: Bundesamt für Statistik; 2010.
27. Germann, U. Abschlussbericht zur Volkszählung 2000. Neuchâtel: Bundesamt für Statistik; 2005.
28. Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P. International Classification of Childhood Cancer, third edition. *Cancer*. 2005; 103:1457–1467. [PubMed: 15712273]
29. Wechsler, D. Intelligence Scale for Children-revised. Helsinki: Psykologien Kustannus Oy; 1984.
30. Achenbach, TM. Manual for the Child Behavior Checklist 4–18 and 1991 profile. Burlington, VT: University of Vermont, Department of Psychiatry; 1991.
31. Felder-Puig R, Frey E, Proksch K, Varni JW, Gadner H, Topf R. Validation of the German version of the Pediatric Quality of Life Inventory (PedsQL) in childhood cancer patients off treatment and children with epilepsy. *Qual Life Res*. 2004; 13:223–234. [PubMed: 15058802]

32. Wolff JE, Daumling E, Dirksen A, Dabrock A, Hartmann M, Jurgens H. [Munster Heidelberg Abilities Scale—a measuring instrument for global comparison of illness sequelae]. *Klinische Padiatrie*. 1996; 208:294–298. [PubMed: 8992097]
33. Gerber NU, Zehnder D, Zuzak TJ, Poretti A, Boltshauser E, Grotzer MA. Outcome in children with brain tumours diagnosed in the first year of life: long-term complications and quality of life. *Arch Dis Child*. 2008; 93:582–589. [PubMed: 17634182]
34. Wengenroth L, Rueegg CS, Michel G, Essig S, Ammann RA, Bergstraesser E, Kuehni CE, Swiss Paediatric Oncology G. Life partnerships in childhood cancer survivors, their siblings, and the general population. *Pediatric Blood Cancer*. 2014; 61:538–545. [PubMed: 24136901]
35. Lin DY, Wei LJ. The Robust Inference for the Cox Proportional Hazards Model. *J Am Stat Assoc*. 1989; 84:1074–1078.
36. Cuzick J. A Wilcoxon-type test for trend. *Stat Med*. 1985; 4:87–90. [PubMed: 3992076]
37. Alloway TP, Gathercole SE, Kirkwood H, Elliott J. The cognitive and behavioral characteristics of children with low working memory. *Child Dev*. 2009; 80:606–621. [PubMed: 19467014]
38. Alloway TP, Rajendran G, Archibald LM. Working memory in children with developmental disorders. *J Learn Disabil*. 2009; 42:372–382. [PubMed: 19380495]
39. Engelen V, Koopman HM, Detmar SB, Raat H, van de Wetering MD, Brons P, Anninga JK, Abbink F, Grootenhuis MA. Health-related quality of life after completion of successful treatment for childhood cancer. *Pediatric Blood Cancer*. 2011; 56:646–653. [PubMed: 21298753]
40. van Dijk J, Huisman J, Moll AC, Schouten-van Meeteren AY, Bezemer PD, Ringens PJ, Cohen-Kettenis PT, Imhof SM. Health-related quality of life of child and adolescent retinoblastoma survivors in the Netherlands. *Health Qual Life Outcomes*. 2007; 5:65. [PubMed: 18053178]
41. Kuehni CE, Strippoli MP, Rueegg CS, Rebholz CE, Bergstraesser E, Grotzer MA, Von der Weid NX, Michel G. Educational Achievement in Swiss Childhood Cancer Survivors Compared With the General Population. *Cancer*. 2011; 118:1439–1449. [PubMed: 21823113]
42. Krull KR, Brinkman TM, Li C, Armstrong GT, Ness KK, Srivastava DK, Gurney JG, Kimberg C, Krasin MJ, Pui CH, Robison LL, et al. Neurocognitive outcomes decades after treatment for childhood acute lymphoblastic leukemia: a report from the St Jude lifetime cohort study. *J Clin Oncol*. 2013; 31:4407–4415. [PubMed: 24190124]
43. Genschaft M, Huebner T, Plessow F, Ikonomidou VN, Abolmaali N, Krone F, Hoffmann A, Holfeld E, Vorwerk P, Kramm C, Gruhn B, et al. Impact of chemotherapy for childhood leukemia on brain morphology and function. *PLoS ONE*. 2013; 8:e78599. [PubMed: 24265700]
44. Lo SS, Fakiris AJ, Abdulrahman R, Henderson MA, Chang EL, Suh JH, Timmerman RD. Role of stereotactic radiosurgery and fractionated stereotactic radiotherapy in pediatric brain tumors. *Exp Rev Neurotherapeutics*. 2008; 8:121–132.
45. Kirchhoff AC, Krull KR, Ness KK, Armstrong GT, Park ER, Stovall M, Robison LL, Leisenring W. Physical, mental, and neurocognitive status and employment outcomes in the childhood cancer survivor study cohort. *Cancer Epidemiol Biomarkers Prev*. 2011; 20:1838–1849. [PubMed: 21844244]
46. Hardy KK, Willard VW, Allen TM, Bonner MJ. Working memory training in survivors of pediatric cancer: a randomized pilot study. *Psycho-oncology*. 2013; 22:1856–1865. [PubMed: 23203754]
47. Butler RW, Copeland DR, Fairclough DL, Mulhern RK, Katz ER, Kazak AE, Noll RB, Patel SK, Sahler OJ. A multicenter, randomized clinical trial of a cognitive remediation program for childhood survivors of a pediatric malignancy. *J Consulting Clin Psychol*. 2008; 76:367–378.
48. Zou P, Li Y, Conklin HM, Mulhern RK, Butler RW, Ogg RJ. Evidence of change in brain activity among childhood cancer survivors participating in a cognitive remediation program. *Arch Clin Neuropsychol*. 2012; 27:915–929. [PubMed: 23079152]

* 127 siblings aged 8-15 were not contacted because another sibling from the same family in the same age category was already contacted.

Fig. 1.
Study participants.

Fig. 2.

Reporting of any cognitive problem in survivors compared to siblings, overall and stratified by period of diagnoses, treatment and diagnoses. Odds ratios are retrieved from four multivariable logistic regressions: 1. SURVIVORS: OR for being a survivor compared to being a sibling; 2. PERIOD OF TREATMENT: OR for having had the diagnoses in the period 2001–2005, 1996–2000 or 1989–1995 compared to being a sibling; 3. TREATMENT: OR for having had surgery only, chemotherapy (may include surgery), radiotherapy (may include surgery and/or chemotherapy or bone marrow transplantation (may include surgery,

and/or chemotherapy and/or radiotherapy) compared to siblings; 4. **DIAGNOSES:** OR for having a diagnosis of leukemia, lymphoma, CNS tumor, neuroblastoma, retinoblastoma, renal/hepatic tumor, bone tumor, soft tissue sarcoma, germ cell tumor, other tumor or Langerhans cell histiocytosis compared to being a sibling. All regressions were controlled for gender, age at survey, migration background, language region, parents' education. The siblings' population is standardized on age, gender, migration background, language region and parents' education according to the survivor population. Family clusters were used to adjust standard errors for the fact that siblings were not independent from survivors.

Table I
Characteristics of Survivors and Siblings

	<u>Survivors</u>		<u>Siblings^d</u>		<i>P</i> -value ^c
	<u>N=840</u>		<u>N=247</u>		
	n	(% ^b)	n	(% ^b)	
Socio-demographic characteristics used for standardization of sibling population					
Female gender	379	(45)	110	(45)	0.903
Age at survey (years)					
8–15	400	(48)	118	(48)	
16–20	440	(52)	129	(52)	0.983
Migration background	113	(13)	27	(11)	0.356
Language region					
German	578	(69)	173	(70)	
French	234	(28)	66	(27)	
Italian	26	(3)	8	(3)	0.861
Parental Education					
Primary education	66	(8)	17	(7)	
Secondary education	532	(66)	164	(67)	
Tertiary education	211	(26)	62	(26)	0.822
Educational characteristics					
Educational situation					
Primary school	170	(21)	49	(20)	
Secondary school	394	(49)	109	(46)	
Finished school	237	(30)	82	(34)	0.460
<i>Vocational training</i>	192	(81)	55	(67)	
<i>Work</i>	37	(16)	19	(26)	
<i>University</i>	8	(3)	8	(9)	0.024
Ever attended special needs school	42	(5)	4	(2)	0.067
Clinical characteristics					
Diagnosis (ICCC-3)					
I Leukemia	295	(35)			
II Lymphoma	88	(10)			
III CNS	145	(17)	n.a ^d	n.a ^d	n.a ^d
IV Neuroblastoma	59	(7)			
V Retinoblastoma	38	(5)			
VI Renal tumor	73	(9)			
VII Hepatic tumor	11	(1)			
VIII Bone tumor	20	(2)			
IX Soft tissue sarcoma	47	(6)			
X Germ cell tumor	22	(3)			
XI & XII Other tumors ^e	10	(1)			

	<u>Survivors</u>		<u>Siblings^a</u>		<i>P</i> -value ^c
	<u>N=840</u>		<u>N=247</u>		
	n	(% ^b)	n	(% ^b)	
Langerhans cell histiocytosis	32	(4)			
Received chemotherapy	682	(81)	n.a ^d	n.a ^d	n.a ^d
Received surgery	539	(64)	n.a ^d	n.a ^d	n.a ^d
Received radiotherapy					
No	644	(77)	n.a ^d	n.a ^d	n.a ^d
Yes, excluding cranial	118	(14)			
Yes, including cranial	78	(9)			
Received bone marrow transplantation	38	(5)	n.a ^d	n.a ^d	n.a ^d
Period of treatment start (calendar year)					
1989–1995	176	(21)	n.a ^d	n.a ^d	n.a ^d
1996–2000	296	(35)			
2001–2005	368	(44)			
Age at diagnosis (years)					
0–5	595	(71)	n.a ^d	n.a ^d	n.a ^d
>5–10	187	(22)			
>10–15	58	(7)			
Duration of treatment (days)					
100	290	(35)	n.a ^d	n.a ^d	n.a ^d
>100–<500	267	(32)			
500	280	(33)			
Time since diagnosis (years)					
5–10 years	353	(42)	n.a ^d	n.a ^d	n.a ^d
11–15 years	321	(38)			
16–<20 years	166	(20)			
Had relapse	95	(11)	n.a ^d	n.a ^d	n.a ^d

CNS, Central Nervous System; ICC-3, International Classification of Childhood Cancer, Third Edition; n, number; n.a., not applicable/not available. Percentages are based upon available data for each variable.

^aSibling population is standardized on age, gender, migration background, language region and parents' education according to the survivor population

^bColumn percentages are given

^cP-value calculated from F-test statistics that compare survivors and siblings

^dInformation on former cancer disease does not apply

^eOther malignant epithelial neoplasms, malignant melanomas, and other or unspecified malignant neoplasms.

Table II

Cognitive Problems in Survivors and Siblings

	All (8–20 years) Parent- and self-reported			Children (8–15 years) Parent-reported			Adolescents (16–20 years) Self-reported		
	Survivors n (%) ^b	Siblings ^a n (%) ^b	p ^c	Survivors n (%) ^b	Siblings ^a n (%) ^b	p ^c	Survivors n (%) ^b	Siblings ^a n (%) ^b	p ^c
Concentration problem	98 (12)	16 (6)	0.020	59 (14)	6 (5)	0.007	39 (9)	10 (7)	0.589
Slow working speed	162 (20)	19 (8)	<0.001	96 (24)	11 (10)	0.003	66 (15)	8 (6)	0.008
Memory problem	269 (33)	37 (15)	<0.001	144 (37)	31 (29)	0.145	125 (29)	4 (3)	<0.001
Any cognitive problem ^d	333 (40)	54 (22)	<0.001	176 (45)	32 (31)	0.018	157 (36)	19 (14)	<0.001

^a Sibling population is standardized on age, gender, migration background, language region and parents' education according to the survivor population

^b Column percentages are given

^c P-value calculated from chi-square statistics comparing survivors and siblings

^d Any cognitive problem was coded as reporting at least one of the three problems (concentration problem, slow working speed, memory problem).

Table III
Predictors for reporting a Cognitive Problem in Survivors in Logistic Multivariable Analysis

	OR ^a	95%CI ^b	P-value
Socio-demographic predictors ^c			
Gender			
Male	1		
Female	0.83	0.62–1.11	0.201
Age at survey			
Children (8–15 years)	1		
Adolescents (16–21 years)	0.70	0.52–0.93	0.015
Migration background			
No	1		
Yes	0.76	0.47–1.22	0.253
Language region			
German	1		
French	0.99	0.72–1.37	0.972
Italian	1.15	0.52–2.55	0.724
Parents' education			
primary	0.76	0.43–1.35	0.352
secondary	1		
tertiary	0.76	0.55–1.06	0.111
Clinical predictors ^d			
Diagnosis			
Leukemia	1		
Lymphoma	0.69	0.37–1.29	0.243
CNS	2.82	1.58–5.04	<0.001
Neuroblastoma	0.90	0.44–1.82	0.762
Renal/hepatic tumors	0.73	0.39–1.38	0.336
Other	0.61	0.36–1.06	0.078
Chemotherapy			
No	1		
Yes	1.60	0.96–2.66	0.072
Radiotherapy			
No	1		
Yes, excluding cranial	1.22	0.77–1.93	0.405
Yes, including cranial	2.10	1.20–3.68	0.010
Bone marrow transplantation			
No	1		
Yes	1.08	0.52–2.23	0.838
Period of treatment			
start (calendar year)			

	OR ^a	95%CI ^b	P-value
1989–1995	1.05	0.43–2.56	0.906
1996–2000	0.75	0.41–1.38	0.350
2001–2005	1		
Age at diagnosis (years)			
0–5	1		
>5–10	1.00	0.61–1.62	0.990
>10–16	0.77	0.33–1.79	0.547
Duration of treatment (days)			
<100	1		
100–500	0.69	0.43–1.10	0.119
>500	0.73	0.39–1.38	0.336
Time since diagnosis (years)			
5–10	1		
11–15	1.42	0.78–2.59	0.251
16–<20	1.20	0.51–2.81	0.682
Relapse			
No	1		
Yes	1.15	0.69–1.93	0.592

^aOdds Ratio

^b95% confidence interval

^cORs retrieved from multivariable logistic regression

^dORs retrieved from multivariable logistic regression controlled for gender, age at survey, migration background, language region and parents' education.