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A Meta-Analysis of the Neurocognitive Sequelae of Treatment for Childhood Acute Lymphocytic Leukemia

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Background. Impaired neurocognitive functioning is one increasingly recognized long-term consequence of childhood ALL treatment. However, research findings have been inconsistent regarding the domains affected and the degree to which they are compromised. ***Procedure.*** A comprehensive meta-analytic review of the long-term neurocognitive effects of childhood ALL was conducted. Studies were included if they were published in English, reported original quantitative data on the post-treatment neurocognitive functioning of childhood ALL patients in first remission and control groups, and used neurocognitive measures with adequate psychometric properties and published normative data. ***Results.*** Data from 28 empirical studies yielding 13 effect sizes across nine domains were extracted and analyzed. All effects were negative ($g = -0.34$ to -0.71), demonstrating that ALL survivors consistently experienced significant deficits in intellectual functioning, academic achievement, and specific neurocognitive abilities compared to control groups. The role of potential moderators, including treatment with cranial irradiation, age at time of diagnosis, and time since treatment ended, was examined. However, no effects emerged as clearly and consistently moderated by these variables. ***Conclusions.*** The results from this meta-analysis suggest that declines in both global and specific areas of areas of neurocognitive functioning occur as a result of contemporary ALL treatment. Such deficits have significant implications for survivors' academic achievement and overall quality of life. Neurocognitive assessment plays a critical role in determining what remedial or specialized instruction is needed in childhood ALL survivors and should be included as a standard part of long-term follow-up care. Pediatr Blood Cancer 2007;49:65–73.

Key words: acute lymphocytic leukemia; late effects of cancer treatment; pediatric oncology

INTRODUCTION

Impaired neurocognitive functioning is one increasingly recognized long-term consequence of ALL treatment. Declines in overall intellectual ability [1], academic performance [2], memory and learning [3], attention and concentration [4], information processing speed [5], visuospatial skill [6], psychomotor functioning [7], and executive functioning [8] are among the adverse neurocognitive outcomes reported in the literature. However, research findings have been inconsistent with regard to which domains of functioning are affected and to what degree these domains are compromised.

Several narrative literature reviews of neurocognitive outcomes in ALL have been published summarizing the growing body of research in this field; however, with the exception of one meta-analytic review of overall cognitive ability in children treated for ALL [9], none has attempted to quantitatively review all available studies in order to determine the size of treatment effects. The purpose of the current paper is to present the first known comprehensive meta-analytic review of the long-term general and specific neurocognitive effects of treatment, particularly CNS prophylaxis, for childhood ALL. This meta-analysis examines treatment effects in broad areas of cognitive functioning and academic performance, as well as specific neurocognitive domains in children who were treated for ALL.

METHODS

Literature Search and Selection of Studies

Studies of the neurocognitive effects of childhood ALL treatment were identified through computerized literature searches of MEDLINE and PsycInfo using combinations of the following key words: *leukemia, chemotherapy, radiation, treatment, long-term effects, sequelae, survivor, cognitive, neurocognitive, neuropsychological, and child**. In addition, reference lists from identified articles and previous literature reviews were examined for additional studies. Studies were included based on the following inclusion criteria: Studies had to be published in English and report original quantitative data on the post-treatment neurocognitive functioning of childhood ALL patients, and neurocognitive measures administered to the study sample had to have adequate psychometric properties (i.e., established reliability and validity), as well as published normative data. Finally, study samples could not be composed of patients who underwent bone marrow or stem cell transplantation, who experienced a CNS relapse during or following ALL treatment, or who had known premorbid cognitive impairment or learning disorders (e.g., mental retardation; ADHD). The final sample included in the meta-analysis consisted of 28 studies that contained usable data from which effect sizes could be extrapolated (e.g., means and standard deviations; *P*-values).

Data Extraction

Sample and methodological characteristics from all studies meeting inclusion criteria were coded using a form adapted from Lipsey and Wilson [10]. Sample characteristics included sample size, subgroup information (e.g., ALL group vs. healthy sibling comparison group), specific treatment information (e.g., level of risk; years during which participants underwent ALL treatment), age at time of diagnosis and at the time of neurocognitive testing, time since treatment ended, gender composition, and ethnicity or SES information if reported. Methodological characteristics included study design (i.e., comparison to control group, comparison to normative data), neurocognitive domains assessed

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(e.g., IQ/general cognitive ability; verbal memory), and the specific measures used. Two raters independently abstracted data for the first 15 studies included in the meta-analysis, and any disagreements were resolved by discussion.

Neurocognitive Domains and Measures

Various domains of neurocognitive functioning were assessed by a number of different measures across studies. The following neurocognitive domains were compiled based on measures used in the research literature: overall cognitive functioning (i.e., intelligence) measured by the Wechsler scales of intelligence (i.e., WPPSI, WISC, WAIS), Stanford-Binet, McCarthy Scales of Children's Abilities, Kaufman Brief Intelligence Test (K-BIT), Kaufman Assessment Battery for Children (K-ABC); Academic Achievement (Reading, Arithmetic, and Spelling) measured by the Wide Range Achievement Test (WRAT), the Woodcock-Johnson Tests of Achievement, KeyMath; Attention, measured by the Wechsler Digit Span subtest, Trail Making Test A; Executive Functioning, measured by Wisconsin Card Sorting Test (WCST) perseverative errors, Verbal Fluency, Trail Making Test B, Stroop Color-Word Interference; Information Processing Speed, measured by WISC Coding or WAIS Digit-Symbol subtests; Psychomotor Skill, measured by Finger Tapping (preferred/dominant hand), Grooved Pegboard (preferred/dominant hand), Purdue Pegboard (preferred/dominant hand); Verbal Memory, measured by the Wide Range Assessment of Memory and Learning (WRAML) verbal subtest, California Verbal Learning Test (CVLT-C), Rey Auditory Verbal Learning Test (RAVLT) immediate or delayed recall, Buschke Selective Reminding Task; Visuospatial Skill measured by the Beery-Buktenica Developmental Test of Visual-Motor Integration (VMI), Rey-Osterrieth Complex Figure Test—Copy, Wechsler Block Design subtest, Judgment of Line Orientation (JLO); Visuospatial Memory measured by the WRAML visual subtest, Rey-Osterrieth Complex Figure Test delayed recall, Benton Visual Retention.

Effect Size Calculations

Hedges g was calculated for each study finding based on a random effects model. This weighted effect size statistic represents the number of standard deviations by which an ALL treatment group mean on a given neurocognitive test differed from the mean of a normative sample or comparison group and controls for the bias small sample sizes present. The comprehensive meta-analysis computer program [11] was used to determine statistical significance and produce 95% confidence intervals for each mean effect size. Positive effect sizes indicate that the ALL sample performed better than the normative sample or comparison group. Conversely, negative values indicate that the ALL sample performed more poorly. According to Cohen [12] effect sizes less than 0.2 indicate a negligible effect, those between 0.2 and 0.5 indicate a small effect, those between 0.5 and 0.8 indicate a medium effect, and those greater than 0.8 are considered large effects. When means and standard deviations were not provided, inferential statistics or P-values were used to calculate effect sizes. If no data were provided but authors stated that no significant between group differences were found, effect sizes were calculated based on a P-value of 0.1 for the purpose of making a conservative estimate. Similarly, if the authors indicated a statistically significant group difference, effect sizes were calculated based on a conservative estimated P-value of 0.05. Each effect size was weighted by the inverse of the variance.

If multiple measures were used to assess the same neurocognitive domain in a study, the effect sizes were averaged to form a single effect size for the analysis. Homogeneity analyses were conducted with the Q-statistic in order to determine whether the individual effect sizes included in the averaged means for each domain adequately represented a common population mean.

RESULTS

Data from 28 empirical studies published between 1980 and 2004 were located and included in the analyses [3,8,13–38]. The demographic and medical data from these studies are summarized in Table I. The estimated mean age at time of diagnosis or start of treatment of children treated for ALL was, on average, 5 years of (range = 3–8), and the average time that had elapsed since ALL treatment ended was approximately 8 years (range 1–≥10). Mean age at the time of assessment was approximately 12 years (range = 6–18) for ALL survivors and 13 years (range = 5–18) for control participants. The mean percentage of females across studies was 52% for both ALL survivors and control participants. Only nine studies reported the ethnic or racial composition of their samples. Approximately 75% of the participants from these studies were White, 7% were Black or African-American, 17% were Latino or Hispanic, and 1% identified as Asian or Pacific Islander. With regard to ALL treatment characteristics, 32 ALL cohorts received both CRT and intrathecal chemotherapy as part of their treatment regimen, while 18 cohorts received only intrathecal chemotherapy. The remaining four ALL cohorts were heterogeneous with regard to treatment.

A total of 13 effect sizes (Hedges g) were weighted and combined [39] across the nine neurocognitive domains, all of which were in the negative direction ($g = -0.34$ to -0.71) suggesting relative declines in functioning for children treated for ALL when compared to all control groups combined (Table II). The findings indicate consistent deficits for groups of children treated for ALL across all neurocognitive domains. Forest plots illustrating the distribution of effect sizes and confidence intervals for overall verbal ability (VIQ) and attention are depicted in Figures 1 and 2. Separate analyses were conducted to determine whether the direction or magnitude of effects differed significantly for comparisons of ALL treated groups with healthy peers and siblings and those with groups of children treated for solid tumors or other chronic illnesses. All effects remained significant and negative regardless of method of comparison, and no significant differences in effect sizes were found across the various neurocognitive domains.

The role of potential moderators of variance not accounted for by expected sampling error was examined by conducting an analog to the analysis of variance (ANOVA), a technique used in meta-analytic reviews to test the homogeneity among effect sizes within and between groups for categorical variables by partitioning the heterogeneity indicated from the Q statistic [10]. Group differences are indicated by significant between-group variance, while significant within-group variance indicates that there is still variance left unaccounted for by the moderator variable being tested. Sensitivity analyses were conducted for the following variables: treatment type (CRT + Intrathecal Chemotherapy vs. Intrathecal Chemotherapy only), age at the time of diagnosis (<5 years of age

TABLE I. Empirical Studies Reporting Neurocognitive Data for ALL Survivors and Control Groups

Source	Type of treatment	Mean age at diagnosis	Mean time since treatment	Mean age at evaluation	% Female
Kaemingk et al., 2004 [13]					
ALL (n = 15)	IT	5	4	12	40
Control (n = 15)				13	40
Rodgers et al., 2003 [14]					
ALL (n = 17)	IT	4	5	10	35
Control (n = 17)				12	35
von der Weid et al., 2003 [15]					
ALL (n = 132)	IT	NR	≥2	15	50
Control (n = 100)				NR	50
Kingma et al., 2002 [16]					
ALL (n = 37)	IT	NR	4	10	42
Control (n = 225)				NR	NR
Precourt et al., 2002 [17]					
ALL (n = 19)	CRT + IT/IT	4	3	9	100
Control (n = 19)				9	100
Raymond-Speden, 2000 [18]					
ALL (n = 41)	CRT + IT/IT	4	NR	11	37
Control (n = 42)				11	40
Schatz et al., 2000 [19]					
ALL (n = 27)	CRT + IT/IT	6.5	≥7	17	64
Control (n = 27)				17	64
Brown et al., 1999 [20]					
ALL (n = 16)	IT	6	1	NR	NR
Control (n = 10)				NR	NR
Rodgers et al., 1999 [21]					
ALL (n = 19)	CRT + IT	4	NR	11	53
Control (n = 19)				11	63
Lesnik et al., 1998 [22]					
ALL (n = 10)	IT	NR	NR	NR	60
Control (n = 10)				NR	60
Regan and Reeb, 1998 [23]					
ALL (n = 11)	CRT + IT/IT	4	≥7	14	37
Control (n = 11)				15	45
Anderson et al., 1997 [8]					
ALL (n = 100)	CRT + IT/IT	4	5	12	55
Control (n = 100)				12	52
Hill et al., 1997 [3]					
ALL (n = 10)	IT	NR	NR	10	NR
Control (n = 10)				10	NR
Butler et al., 1994 [24]					
ALL (n = 60)	CRT + IT/IT	6	7.5	13	NR
Control (n = 26)				12	NR
Ciesielski et al., 1994 [25]					
ALL (n = 13)	CRT + IT	3	5	12	54
Control (n = 10)				11	60
Kingma et al., 1993 [26]					
ALL (n = 35)	CRT + IT	3.5	NR	11	46
Control (n = 225)				NR	NR
Brown et al., 1992 [27]					
ALL (n = 11)	IT	NR	≥3	8	64
Control (n = 12)				9	50
Giralt et al., 1992 [28]					
ALL (n = 54)	CRT + IT/IT	5	≥3	11	40
Control (n = 46)				11	37

(*Continued*)

TABLE I. (*Continued*)

Source	Type of treatment	Mean age at diagnosis	Mean time since treatment	Mean age at evaluation	% Female
Moore et al., 1992 [29]					
ALL (n = 24)	CRT + IT/IT	5	≥5	18	41
Control (n = 9)				18	41
Waber et al., 1990 [30]					
ALL (n = 51)	CRT + IT	5	8	13	53
Control (n = 15)				12	47
Said et al., 1989 [31]					
ALL (n = 106)	CRT + IT/IT	4	3	10	41
Control (n = 45)				9	44
Schlieper et al., 1989 [32]					
ALL (n = 30)	CRT + IT/IT	7	10	15	53
Control (n = 23)				15	70
Jannoun et al., 1987 [33]					
ALL (n = 19)	CRT + IT	NR	4	11	47
Control (n = 18)				11	47
Taylor et al., 1987 [34]					
ALL (n = 26)	CRT + IT	4	6	10	54
Control (n = 26)				10	50
Moore et al., 1986 [35]					
ALL (n = 19)	CRT + IT	5	≥5	13.5	55
Control (n = 12)				13	55
Copeland et al., 1985 [36]					
ALL (n = 49)	CRT + IT/IT	5.5	NR	12.5	53
Control (n = 25)				16	40
Stehbens and Kisker, 1984 [37]					
ALL (n = 13)	CRT + IT	NR	3	NR	31
Control (n = 11)				NR	45
Tamaroff et al., 1982 [38]					
ALL (n = 41)	IT	3, 8*	3.5	6, 12	NR
Control (n = 33)				5, 15	NR

*Two subgroups (<age 5 at diagnosis; >age 5 at diagnosis); CRT + IT, cranial irradiation and intrathecal chemotherapy; IT, intrathecal chemotherapy only; CRT + IT/IT, study included subgroups of children who received CRT and IT; NR, not reported.

vs. ≥5 years of age), and time elapsed since end of ALL treatment (<5 years vs. ≥5 years) for all effect sizes with significant heterogeneity. The dichotomization of the latter two variables reflects the way in which data from ALL groups were generally presented in the literature.

These analyses of the data were performed for the following reasons. First, data were not reported consistently in the literature. Some studies included medians rather than means or only gave ranges or estimates, while others reported no information on these variables (Table I). With regard to age at diagnosis, it is widely accepted that children less than 5 years of age at ALL diagnosis are more vulnerable to treatment sequelae, and several studies have actually compared subgroups created by dichotomizing age at diagnosis before and after age 5 [35]. While no developmentally indicated reason exists for using age five as the categorical age split per se, empirical evidence supports that younger children treated for ALL are more susceptible to neurocognitive impairment than are older children [40]. Similarly, time since end of treatment has also been widely dichotomized in the cancer literature in that patients surviving 5 years beyond end of treatment without relapse are often considered ''cured'' and labeled as ''survivors'' [41].

Results of our analyses were inconclusive with regard to these factors. No effects emerged as clearly and consistently moderated by these variables. With regard to the effects of CRT on neurocognitive function, ALL groups that received both CRT and intrathecal chemotherapy performed significantly more poorly for overall intellectual functioning than those who received intrathecal chemotherapy alone. However, the effects for the remaining CRT sensitivity analyses either indicated no significant difference between treatment groups or inconsistent results across methods of comparison. The remaining significant effects were not significantly heterogeneous indicating that no moderating variables accounted for these effects. Consequently it cannot be concluded from these analyses that children who received intrathecal chemotherapy without CRT are not at risk for long-term treatment-related neurocognitive effects.

Limitations of meta-analytic reviews such as this include susceptibility to publication bias (i.e., the ''file drawer'' problem), as studies with significant effects are more likely to be published and thus included in the meta-analysis than those with null findings. The standard approach to addressing this problem is to calculate a ''fail-safe *N*,'' which estimates the number of unpublished or unretrieved studies with null findings needed to render the mean effects non-significant. Rosenthal [42] widely used formula was used to calculate fail-safe *N*: $[(\Sigma z)^2/2.706] - k$, where Σz is the sum of the combined z scores squared, 2.706 is the two-tailed critical

TABLE II. Neurocognitive Test Results for Comparisons With All Control Groups Combined

	FSIQ	VIQ	PIQ	Read	Arith	Spell	A	I	E	P	V	Mvb	Mvs
Number of samples	41	34	33	13	16	12	15	11	15	14	17	14	11
Wtd Hedges *g*	−0.71	−0.58	−0.66	−0.57	−0.60	−0.42	−0.57	−0.52	−0.46	−0.34	−0.57	−0.39	−0.62
95% CI—lower	−0.88	−0.76	−0.82	−0.74	−0.82	−0.63	−0.71	−0.75	−0.61	−0.50	−0.81	−0.63	−0.95
95% CI—upper	−0.54	−0.41	−0.49	−0.39	−0.39	−0.20	−0.42	−0.29	−0.30	−0.17	−0.32	−0.14	−0.28
P-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<001	<0.001
Fail-safe *N*	62	47	38	16	21	17	24	19	22	22	25	23	20

A, attention; I, information processing; E, executive function; P, psychomotor skill; V, visuospatial skill; Mvb, verbal memory; Mvs, visual memory.

value for statistical significance at $P = 0.05$, and k refers to the number of studies included. Rosenthal [42] recommends a tolerance level of $5k + 10$, which yields a highly unlikely number of unpublished studies that would be required to bring the meta-analysis results down to a nonsignificant level. The fail-safe *N*s calculated for the 13 significant effect sizes in the current meta-analysis ranged from 16 to 62 (Table II). According to Rosenthal [42] rule of thumb, these potential numbers of unpublished results with null findings do not exceed the cut-off, and therefore publication bias cannot be completely ruled out for the current sample of studies. However, the literature on the neurocognitive effects of childhood cancer includes several treatment studies yielding null findings [16], and it is possible that studies demonstrating that cancer treatment does not have adverse long-term effects in children would be considered important and would be published. Therefore, although the possibility of publication bias cannot be fully excluded for the results of this meta-analysis, it is unlikely that a large number of file drawer papers exist which show that ALL treatment has no significant effect on the neurocognitive abilities of children.

DISCUSSION

This paper is the first to quantitatively estimate the magnitude of both general and specific neurocognitive sequelae of treatment for childhood ALL. The meta-analysis included 28 empirical studies (54 samples) that reported sufficient data to calculate effect sizes for comparisons with control groups of healthy peers or siblings and groups of children treated for solid tumors or other chronic illnesses without CNS prophylaxis. All 13 mean effect sizes that extracted across the nine evaluated neurocognitive domains were in the negative direction ($g = -0.34$ to -0.71) demonstrating that children treated for ALL experienced consistent clinically significant deficits in overall cognitive or intellectual functioning, academic achievement, and specific neurocognitive abilities when compared to healthy or illness control groups.

Our results suggest that declines in multiple areas of neurocognitive functioning occur as a result of contemporary ALL treatment, a finding which has significant clinical implications. Sensible recommendations for assessment and intervention have been made elsewhere [43]; however, the consequences of neurocognitive declines upon the quality of life and productivity of childhood ALL survivors beyond the school setting have not been adequately addressed. For example, young adult survivors of childhood cancer are more likely to be underemployed and to have lower incomes [44]. It is likely that the failure to properly assess and address treatment-related learning problems in school leads to inadequate preparation for higher education or the workforce. Neurocognitive assessment plays a critical role in determining what remedial or specialized instruction is needed in childhood ALL survivors and should be included as a standard part of long-term follow-up care.

This meta-analysis also revealed clinically significant deficits in specific neurocognitive abilities, such as attention and speed of information processing, and also in areas of executive functioning. Deficits in these fundamental domains have implications beyond school, to areas such as occupational functioning, social relationships, emotion regulation, coping skills, and general quality of life. Assessment and intervention resources should focus on these specific neurocognitive domains. For instance, use of the psychostimulant methylphenidate has been shown to reduce deficits in

Study Name	Hedges_g	95% Confidence Interval	*P*-Value
Anderson (1997)	-0.56	-0.84 to -0.28	0.00
Ciesielski (1994)	-1.55	-2.46 to -0.64	0.00
Giralt (1992)	+0.73	+0.18 to +1.28	0.01
Giralt (1992)[2]	-0.58	-1.14 to -0.01	0.05
Hill (1997)	-1.58	-2.55 to -0.61	0.00
Jannoun (1987)	-1.03	-1.70 to -0.35	0.00
Kingma (1993)	-1.00	-1.36 to -0.63	0.00
Kingma (2002)[1]	-0.20	-0.69 to +0.29	0.43
Kingma (2002)[2]	-0.60	-1.04 to -0.13	0.01
Precourt (2002)[1]	-0.83	-1.70 to +0.05	0.07
Precourt (2002)[2]	-0.77	-1.66 to +0.13	0.09
Raymond-Speden (2000)[1]	-1.08	-1.71 to -0.44	0.00
Raymond-Speden (2000)[2]	-1.62	-2.31 to -0.92	0.00
Said (1989)	-1.08	-1.50 to -0.66	0.00
Schlieper (1989)[1]	+0.72	-0.13 to +1.56	0.10
Schlieper (1989)[2]	-0.72	-1.56 to +0.13	0.10
Schlieper (1989)[3]	-0.84	-1.82 to +0.14	0.09
Schlieper (1989)[4]	-0.98	-2.11 to +0.15	0.09
Taylor (1987)	-0.68	-1.23 to -0.13	0.02
Total	**-0.72**	**-0.98 to -0.46**	**0.00**

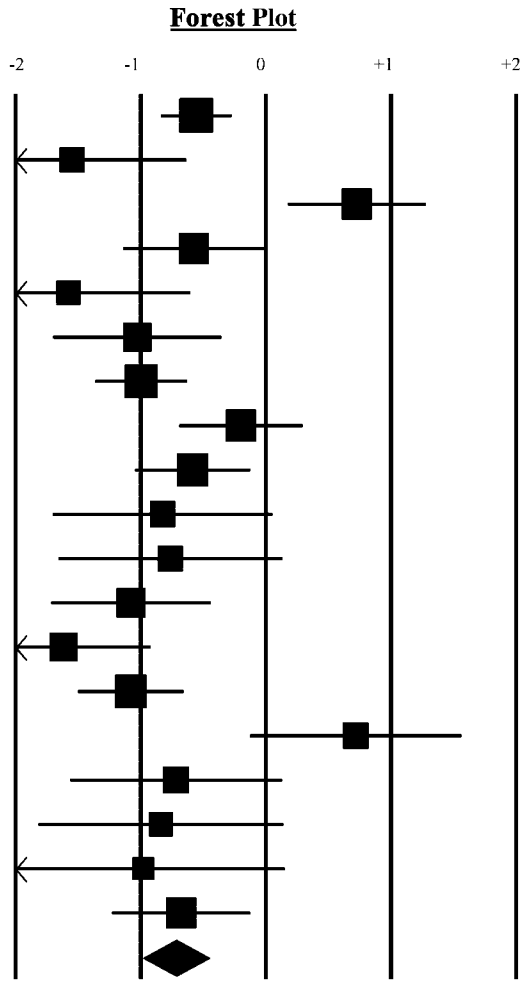

Fig. 1. Forest plot depicting results for VIQ for ALL survivor and healthy control group comparisons.

Study Name	Hedges g	95% Confidence Interval	*P*-Value
Anderson (1997)	-0.34	-0.62 to -0.06	0.02
Giralt (1992)	-0.64	-1.18 to -0.09	0.02
Giralt (1992)[2]	-0.50	-0.29 to -0.08	0.08
Jannoun (1987)	-0.85	-1.51 to -0.19	0.01
Kaemingk (2004)	-0.77	-1.50 to -0.05	0.04
Kingma (1993)	-0.92	-1.28 to -0.56	0.00
Kingma (2002)[1]	-0.24	-0.73 to +0.25	0.34
Kingma (2002)[2]	-0.30	-0.76 to +0.15	0.19
Lesnik (1998)	0.00	-0.84 to +0.84	1.00
Precourt (2002)[1]	-0.90	-1.78 to -0.02	0.05
Precourt (2002)[2]	-0.76	-1.66 to +0.13	0.09
Rodgers (1999)	-0.98	-1.64 to -0.32	0.00
Rodgers (2003)	-0.47	-1.13 to +0.20	0.17
Total	**-0.55**	**-0.72 to -0.39**	**0.00**

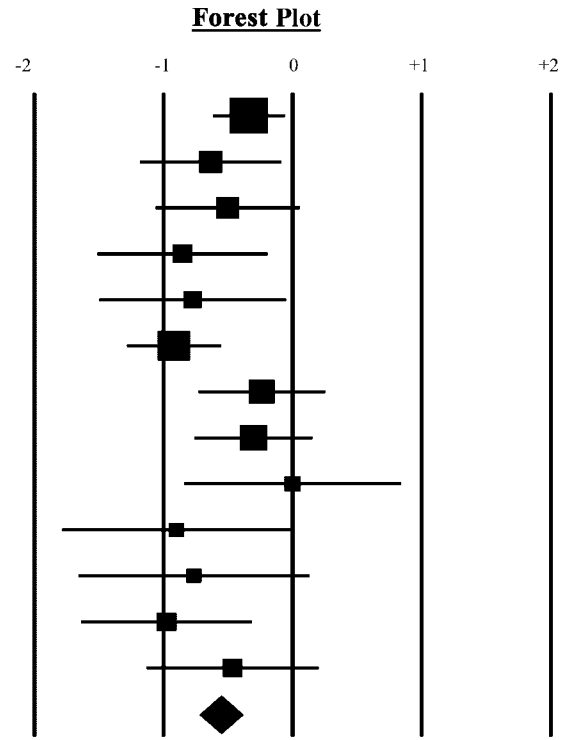

Fig. 2. Forest plot depicting results for attention for ALL survivor and healthy control group comparisons.

Pediatr Blood Cancer DOI 10.1002/pbc

attention and social skills problems in some survivors of childhood cancer [45].

The findings from this meta-analysis highlight needs in several areas for continued research on the neurocognitive effects of ALL treatment. First, more prospective longitudinal studies, which follow children from diagnosis beyond the completion of treatment are required to accurately assess the degree of decline experienced as a result of treatment in various neurocognitive domains and the underlying neuro-anatomical treatment processes. That is, this approach would allow for the within-individual comparisons over time from treatment, a design that has been used with adults [46] but rarely with children. Second, the data from this meta-analysis highlight the importance of including control groups in empirical studies as they appear to yield the most appropriate neurocognitive data for comparison. Further, such control groups, whether they are composed of healthy peers, siblings, cancer controls, or chronic illness controls, should be matched according to age, gender, and SES. Finally, multi-institutional clinical trials, such as those currently being conducted through the Children's Oncology Group, allow for larger sample sizes, comparisons between specific treatment groups to determine whether neurocognitive effects can be limited without sparing disease outcome (e.g., dexamethasone vs. prednisone), and use of standardized battery of neurocognitive tests across institutions.

In conclusion, children who are survivors of ALL appear to experience clinically significant declines in both global and specific areas of neurocognitive functioning as a consequence of the treatments used to cure their disease. However, these declines are obscured when ALL groups are compared with normative data; control groups drawn from the same local population as the ALL survivors provide more appropriate means of comparison. The potential risk factor variables examined in the meta-analysis, including the use of CRT for CNS prophylaxis, young age at diagnosis, and length of time since treatment, were not found to consistently moderate the significant effects and therefore the extent to which they influence the findings remains unclear. It is possible that other demographic or treatment variables that could not be examined, such as SES level or relapse risk, moderate the effects to some extent, which emphasizes the importance of measuring and reporting such information in future studies.

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