IMPORTANCE Despite advancements in cancer therapy and supportive care, childhood cancer survivors remain at risk for chronic morbidities associated with disease and treatment, such as hearing impairment (HI) and neurocognitive deficits. This study, to our knowledge, is the first to objectively measure hearing and neurocognitive function in a large cohort of long-term survivors of childhood cancer stratified by treatment exposures.

OBJECTIVE To assess the association of HI with neurocognitive function and the factors in HI that mediate neurocognitive outcomes in survivors of childhood cancer.

DESIGN, SETTING, AND PARTICIPANTS Data analyzed in this cross-sectional study were collected for the period April 25, 2007, to June 30, 2017, from participants in the St. Jude Lifetime Cohort Study (SJLIFE), an ongoing study that quantifies the long-term health outcomes of survivors of childhood cancer. Participants included those treated at St. Jude Children’s Research Hospital (Memphis, Tennessee) for childhood cancer who survived 5 or more years after their original diagnosis and who were eligible for audiologic and neurocognitive testing. Hearing outcomes were coded using the Chang Ototoxicity Grading Scale. Data analysis was performed from March 22, 2019, to March 5, 2020.

MAIN OUTCOMES AND MEASURES Hearing and neurocognitive function. Survivors were grouped by hearing sensitivity (normal hearing [Chang grade 0], mild HI [Chang grades 1a, 1b, and 2a], or severe HI [Chang grade 2b]) and stratified by treatment exposure (platinum-only exposure group [treated with cisplatin and/or carboplatin chemotherapy], cochlear radiotherapy [RT] exposure group [treated with cochlear RT with or without platinum-based chemotherapy], or no exposure group [no platinum-based chemotherapy or cochlear RT]). Multivariable log-binomial models were adjusted for age at diagnosis, time since diagnosis, sex, and relevant treatment exposures.

RESULTS A total of 1520 survivors of childhood cancer were analyzed, among whom 814 were male survivors (53.6%), the median (interquartile range [IQR]) age was 29.4 (7.4-64.7) years, and the median (IQR) time since diagnosis was 20.4 (6.1-53.8) years. Prevalence and risk of severe HI among survivors were higher in survivors in the platinum-only (n = 107 [34.9%]; relative risk [RR], 1.68 [95% CI, 1.20-2.37]) or cochlear RT (n = 181 [38.3%]; RR, 2.69 [95% CI, 2.02-3.57]) exposure group compared with those in the no exposure group (n = 65 [8.8%]). Severe HI was associated with deficits in verbal reasoning skills (no exposure group RR, 1.11 [95% CI, 0.50-2.43]; platinum-only exposure group RR, 1.93 [95% CI, 1.21-3.08]; cochlear RT exposure group RR, 2.00 [95% CI, 1.46-2.75]), verbal fluency (no exposure group RR, 1.86 [95% CI, 1.19-2.91]; platinum-only exposure group RR, 1.83 [95% CI, 1.24-2.71]; cochlear RT exposure group RR, 1.45 [95% CI, 1.09-1.94]), visuomotor speed (no exposure group RR, 1.87 [95% CI, 1.07-3.25]; platinum-only exposure group RR, 3.10 [95% CI, 1.92-4.99]; cochlear RT exposure group RR, 1.40 [95% CI, 1.11-1.78]), and mathematics skills (no exposure group RR, 1.90 [95% CI, 1.18-3.04]; platinum-only exposure group RR, 1.63 [95% CI, 1.05-2.53]; cochlear RT exposure group RR, 1.58 [95% CI, 1.15-2.18]), compared with survivors with normal hearing or with mild HI.

CONCLUSIONS AND RELEVANCE Results of this study suggest that severe HI in childhood cancer survivors is associated with neurocognitive deficits independent of the neurotoxic treatment received. Early screening and intervention for HI may facilitate the development and maintenance of neurocognitive function and identify individuals at risk for impairment.
Long-term survival from childhood cancers now exceeds 85% in the United States. Despite major advancements in cancer therapy and supportive care, childhood cancer survivors remain at risk for chronic morbidities associated with disease and treatment, such as hearing impairment (HI) and neurocognitive deficits. Among survivors, those who received cranial radiotherapy (RT) for central nervous system (CNS) malignant neoplasms experience the highest risk for neurocognitive dysfunction. Treatment-induced HI is associated with platinum-based chemotherapy or radiotherapy directed to the cochlea and is typically bilateral, permanent, and progressive.

The association between HI and neurocognitive deficits in healthy children has been reported in the literature but has only recently been examined in childhood cancer survivors. Gurney et al observed that child survivors of neuroblastoma with parent-reported HI were twice as likely to have difficulties with reading, mathematics, and/or attention; required more special educational services; and experienced worse quality of life than those with normal hearing. Specific areas of inferior cognition associated with these poor outcomes were not identified. In a retrospective study of 5937 adult survivors of non-CNS cancers, HI was associated with diminished task efficiency, organization, memory, and emotional regulation; however, neurocognitive functioning and HI were self-reported rather than clinically assessed. Previous studies of the implication of HI for pediatric CNS tumor survivors treated with platinum-based chemotherapy and cranial RT demonstrated an independent association between HI and low-level neurocognitive performance.

The association of HI with neurocognitive function in childhood cancer survivors who were not treated with cranial RT has not been reported. The goals of the current study were to describe the prevalence, severity, and risk of objectively assessed HI in a large cohort of childhood cancer survivors; to assess the association of HI with neurocognitive function; and to examine the HI factors that mediate neurocognitive outcomes among survivors treated with cranial RT.

**Methods**

This cross-sectional study was approved by St. Jude Children’s Research Hospital Institutional Review Board. All participants provided written informed consent. Data were collected for the period April 25, 2007, to June 30, 2017. Data analysis was performed from March 22, 2019, to March 5, 2020.

**Participants**

The present study analyzed data of eligible survivors who participate in the St. Jude Lifetime Cohort Study (SJLIFE), which has been previously described. Briefly, SJLIFE is an ongoing institutional follow-up study designed to quantify the long-term health outcomes of survivors of childhood cancer. These participants included individuals treated at St. Jude Children’s Research Hospital (Memphis, Tennessee) for childhood cancer who survived 5 or more years after their original diagnosis and who were eligible for audiologic and neurocognitive testing. Of the 1678 eligible survivors we identified, 137 did not participate in the present study, 17 had preexisting or non–treatment-induced HI, and 4 did not have evaluable audiologic data. A total of 1520 participants were evaluable for this cross-sectional study (Figure 1).

**Neurocognitive and Audiologic Assessments**

Survivors completed a standard battery of developmentally and age-appropriate neurocognitive assessments, which were administered by certified examiners under the general supervision of a board-certified neuropsychologist (K.R.K.). Assessment measures were categorized under the main domains: intelligence, attention, memory, executive function, processing speed, and academic function. Survivors were permitted to wear hearing aids during testing; measures for which the examiner observed that HI interfered with the validity of the test were not included in analyses. Age-adjusted z scores were calculated, and deficits were defined as z scores of -1.28 or lower, which were equivalent to the 10th percentile of the normative distribution. All subtests for each neurocognitive domain are listed in eTable 1 in the Supplement.

Survivors completed otoscopy, tympanometry, pure-tone audiometry, and speech audiometry. Pure-tone air conduction thresholds were measured at 0.25, 0.5, 1, 2, 3, 4, 6, and 8 kHz, and bone conduction thresholds were assessed at 0.25, 0.5, 1, 2, 3, and 4 kHz to establish the type of HI (ie, conductive, sensorineural, or mixed). Each audiogram was assigned a grade using the Chang Ototoxicity Grading Scale (grades range from 0-4, with the highest grade indicating the most severe HI) (eTable 2 in the Supplement).

For the present study, we assigned a Chang grade to permanent or mixed HI on the basis of air conduction thresholds rather than bone conduction measurements to accurately reflect the severity of HI. We graded sensorineural and temporary conductive or mixed hearing losses on the basis of bone conduction thresholds or air conduction thresholds with a normal tympanogram result. Chang grades were categorized as follows: 0 for normal hearing; 1a, 1b, and 2a for mild HI; and 2b or higher for severe HI. The grade for the better-hearing ear was used for survivors with asymmetrical HI, and the result of the audiologic evaluation conducted closest to the neurocognitive assessment date was used for survivors with
multiple examinations. The audiologist (J.K.B.) was unaware of the survivor’s neurocognitive function at the time of testing and at the time of assigning a Chang grade. Adherence to the use of a hearing intervention (ie, hearing aid or cochlear implant) was self-reported by survivors.

**Statistical Analysis**

We used summary statistics to describe demographic (including investigator-identified categories of race/ethnicity) and treatment characteristics of survivors. Survivors were grouped by HI severity (Chang grade <2b vs ≥2b) and treatment exposure (platinum-only exposure group [cisplatin and/or carboplatin chemotherapy], cochlear radiotherapy [RT] exposure group [cochlear RT with or without platinum-based chemotherapy], and no exposure group [no platinum-based chemotherapy or cochlear RT]). Multivariable log-binomial models with a modified Poisson approach were used to examine the relative risk (RR) by treatment exposure for severe HI, adjusting for age at diagnosis, time since diagnosis, sex, and cisplatin or carboplatin chemotherapy treatment (yes or no). A standardized incidence ratio was calculated by comparing the proportion of severe HI in survivors (grouped by age) who were not exposed to ototoxic treatment with the high-frequency HI data in the general adult population of the 2011 to 2012 National Health and Nutrition Examination Survey, to assess whether the rate of HI differed from that of the survivor reference group. Within each treatment exposure group, multivariable log-binomial models were used to examine the associations between severe HI (vs normal hearing and mild HI) and neurocognitive deficits, adjusting for age at diagnosis, time since diagnosis, sex, and neurotoxic treatment variables if existing within the group (ie, cranial RT dose, intrathecal methotrexate sodium, high-dose intravenous methotrexate, and high-dose intravenous cytarabine chemotherapy). A summary of outcomes, factors, and covariates are presented in the Box.
We performed a mediation (path) analysis to examine the association between cranial RT and neurocognitive deficits mediated by severe HI. To prepare for path analysis, we conducted multivariable log-binomial models to examine the associations between neurocognitive deficits and potential risk factors, including severe HI (vs normal hearing and mild HI), age at diagnosis, time since diagnosis, sex, and neurotoxic treatment variables if existing within the group (ie, cranial RT dose, intrathecal methotrexate [yes or no], high-dose intravenous methotrexate [yes or no], and high-dose intravenous cytarabine chemotherapy [yes or no]). Any risk factor that was statistically significantly associated with neurocognitive deficits was considered a potential risk factor. The distribution of HI for survivors by treatment exposure group is presented in the Table. The frequency of mild HI was 7.3% (n = 54) among the survivors in the no exposure group, 20.2% (n = 62) in the platinum-only exposure group, and 22.2% (n = 105) in the cochlear RT exposure group. Risk for developing severe HI was higher among survivors in the platinum-only exposure group (107 [34.9%]; RR, 1.34 [95% CI, 1.05-1.72]) and cochlear RT exposure group (181 [38.3%]; RR, 2.69 [95% CI, 2.02-3.57]) compared with those in the no exposure group (65 [8.8%]) (Table eTable 4 in the Supplement). Of note, among the 138 survivors with normal hearing in the platinum-only exposure group, 96 (69.6%) were treated with carboplatin chemotherapy only. Most survivors with mild HI (41 of 62 [66.1%]) or severe HI (78 of 107 [72.9%]) in the platinum-only exposure group received cisplatin chemotherapy only. Severe HI in the no exposure group was more prevalent in survivors aged 7 to 39 years compared with the general US population (age 7-29 years standardized incidence ratio, 2.34 [95% CI, 1.45-3.57]; age 30-39 years standardized incidence ratio, 2.59 [95% CI, 1.45-4.27]) (eTable 5 in the Supplement).

The rate of severe HI among survivors in the no exposure group was likely elevated because survivors with HI that was considered permanently conductive, noise-induced, or aminoglycoside-related were included in the analyses. Moreover, the Chang Ototoxicity Grading Scale is more sensitive in detecting HI than the criterion used in the 2011 to 2012 National Health and Nutrition Examination Survey.42 Thus, more cases of HI were identified in the present cohort. Among the 330 survivors with severe HI for whom a hearing aid was recommended, 75 (22.7%) reported using a hearing aid or cochlear implant.

### Results

A total of 1520 participants in SJLIFE were included in this cross-sectional study. Of these survivors, the median (interquartile range [IQR]) age was 29.4 (7.4-64.7) years and the median (IQR) time since diagnosis was 20.4 (6.1-53.8) years. This cohort comprised 706 female survivors (46.5%) and 814 male survivors (53.6%).

Demographic and treatment characteristics of survivors in each treatment exposure group are provided in eTable 3 in the Supplement. Survivors who were not exposed to platinum-based chemotherapy or cochlear RT (n = 740) did not differ from survivors treated with platinum-based chemotherapy only (n = 307) in sex (female: 359 [48.5%] vs 154 [50.2%]; male: 381 [51.5%] vs 153 [49.8%]), race/ethnicity (eg, white: 597 [80.7%] vs 233 [75.9%]), median (IQR) age at diagnosis (6.2 [2.9-12.6] years vs 5.4 [1.3-12.3] years), median (IQR) age at follow-up (27.6 [20.1-36.6] years vs 27.2 [20.0-34.7] years), and median (IQR) age since diagnosis (18.6 [12.0-28.7] years vs 19.7 [13.3-25.5] years). Survivors treated with cochlear RT (>1 Gy) (n = 473) were slightly older at diagnosis (median [IQR] age, 7.9 [4.1-12.5] years) and had longer follow-up time (median [IQR] age at follow-up, 32.6 [27.0-39.6] years) compared with survivors in the no exposure and platinum-only exposure groups.

### Tables

**Table. Hearing Impairment Severity for All Survivors of Childhood Cancer by Treatment Exposure**

<table>
<thead>
<tr>
<th>Hearing sensitivity</th>
<th>No. (%)</th>
<th>Treatment exposure group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total survivors (n = 1520)</td>
<td>No exposure (n = 740)</td>
</tr>
<tr>
<td>Normal hearing (Chang grade 0)</td>
<td>946 (62.2)</td>
<td>621 (84.0)</td>
</tr>
<tr>
<td>Mild hearing impairment (Chang grades 1a, 1b, 2a)</td>
<td>221 (14.5)</td>
<td>54 (7.3)</td>
</tr>
<tr>
<td>Severe hearing impairment (Chang grades 2b, 3, 4)</td>
<td>353 (23.2)</td>
<td>65 (8.8)</td>
</tr>
</tbody>
</table>

Abbreviation: RT, radiotherapy.

a No exposure group (n = 740) comprised survivors who were not treated with platinum-based chemotherapy or cochlear RT.

b Platinum-only exposure group (n = 307) comprised survivors who were treated with cisplatin and/or carboplatin chemotherapy.

c Cochlear RT exposure group (n = 473) comprised survivors who were treated with cochlear RT with or without platinum-based chemotherapy.

d Chang Ototoxicity Grading Scale range: (0-4, with the highest grade indicating the most severe hearing impairment).
Neurocognitive Function
Mean z scores and number of survivors with impaired neurocognitive function for each of the 15 tests are listed by treatment exposure group in eTable 6 in the Supplement. After adjusting for chemotherapy, cranial RT dose, and other relevant covariates, statistically significant differences in neurocognitive performance were observed between survivors with and without severe HI across treatment exposure groups (Figure 2). Compared with those with normal hearing or with mild HI, survivors with severe HI were at higher risk for deficits on assessment measures that were heavily language dependent, such as verbal fluency (no exposure group: RR, 1.86 [95% CI, 1.19-2.91]; platinum-only exposure group: RR, 1.83 [95% CI, 1.24-2.71]; and cochlear RT exposure group: RR, 1.45 [95% CI, 1.09-1.94]), verbal reasoning skills (no exposure group: RR, 1.11 [95% CI, 0.50-2.43]; platinum-only exposure group: RR, 1.93 [95% CI, 1.21-3.08]; cochlear RT exposure group: RR, 2.00 [95% CI, 1.46-2.75]), word reading skills (no exposure group: RR, 1.76 [95% CI, 0.69-4.48]; platinum-only exposure group: RR, 3.47 [95% CI, 1.56-7.73]; and cochlear RT exposure group: RR, 2.31 [95% CI, 1.36-3.92]), and mathematical computation skills (no exposure group: RR, 1.90 [95% CI, 1.18-3.04]; platinum-only exposure group: RR, 1.63 [95% CI, 1.05-2.53]; and cochlear RT exposure group: RR, 1.58 [95% CI, 1.15-2.18]) (Figure 2).

Performance on measures that were less language dependent, such as attention, executive function, and processing speed, was also associated with severe HI. Compared with those with normal hearing or with mild HI, survivors with severe HI in the platinum-only and cochlear RT exposure groups were more likely to have impaired focused attention (RRs, 2.56 [95% CI, 1.45-4.52] and 1.57 [95% CI, 1.16-2.14]) and cognitive flexibility (RRs, 1.64 [95% CI, 1.15-2.34] and 1.34 [95% CI, 1.06-1.68]). The presence of severe HI in survivors in all 3 treatment exposure groups was significantly associated with slower visuomotor speed (no exposure group: RR, 1.87 [95% CI, 1.07-3.25]; platinum-only exposure group: RR, 3.10 [95% CI, 1.92-4.99]; and cochlear RT exposure group: RR, 1.40 [95% CI, 1.11-1.78]). Survivors with severe HI showed 55% higher risk (RR, 1.55; 95% CI, 1.14-2.10) in the platinum-only exposure group and 25% higher risk (RR, 1.25; 95% CI, 1.04-1.49) in the cochlear RT exposure group for inadequate fine motor speed (Figure 2) compared with survivors without severe HI. Even survivors with milder forms of HI showed a 110% to 247% increased risk for neurocognitive dysfunction in the domains of attention, executive function, processing speed, and intelligence compared with normal-hearing survivors (eFigure 1 in the Supplement).

Discussion
To our knowledge, the present study is the first to objectively measure hearing sensitivity and task-specific neurocognitive function in a large cohort of long-term survivors of childhood cancer stratified by treatment exposures. Consistent with our expectations, survivors with severe HI demonstrated impaired function on 1 or more neurocognitive tests. Adjusting for age at diagnosis, time since diagnosis, sex, and relevant treatment factors, neurocognitive deficits were greater for survivors with severe HI vs normal hearing or mild HI, specifically for measures assessing executive function, processing speed, academic function, and intelligence.

Considerable evidence has been published of children with congenital or prelingual HI or deafness consistently performing worse in language, reading, mathematics, and overall academic achievement. Compared with peers with normal hearing. However, studies evaluating these academic measures in children with acquired HI are limited. Previous research found that approximately half of children with prelingual severe to profound HI were unable to read beyond the fourth-grade level at the time of high school graduation, with reading abilities not exceeding sixth-grade level for college students with HI. Orgel et al observed an association between substantial treatment-induced HI and specific neurocognitive deficits among those who survived pediatric brain tumor. Expanding on this research, Oliver et al examined specific neurocognitive skills important to reading in children with embryonal brain tumors. The present study expanded the work by Orgel et al and Oliver et al by showing that survivors who developed severe HI after platinum-based chemotherapy without cochlear RT performed worse on language-based measures, such as verbal intelligence, verbal fluency, and single-word reading compared with survivors with normal hearing or with mild HI. Furthermore, the results show that the association of HI with neurocognitive function does not subside but rather continues well into adulthood.

Poor reading skills have an association with pervasive, inferior overall academic achievement, hindering comprehension and the acquisition of higher-level reasoning ability. In a prospective study examining neurocognitive and academic outcomes in pediatric patients treated for medulloblastoma, Schreiber et al demonstrated that substantial HI was independently associated with a decline in intellectual and academic skills. Reading and linguistic difficulties in children with HI may expand to difficulties in other areas of academics, including mathematics. Although mathematics is a subject heavily dependent on visualization of figures and symbolic representation, children with HI have been found to consistently...
In a study by Kelly et al.,\textsuperscript{51} a significant association was observed between language proficiency and reading grade level and mathematical achievement among deaf college students. Consistent with the research, underperformance in mathematics is observed. The table and figure below illustrate the relative risk (RR) for neurocognitive deficits among survivors of childhood cancer with severe hearing impairment (HI) vs survivors with normal hearing or mild HI, stratified by treatment exposure. The analysis was adjusted for age at diagnosis, time since diagnosis, sex, and treatment variables (if any) within the group. These variables were cranial RT dose, methotrexate chemotherapy treatment (yes or no), intrathecal and high-dose methotrexate chemotherapy treatment (yes or no), and high-dose cytarabine chemotherapy treatment (yes or no).

**Table: Relative Risk (RR) for Neurocognitive Deficits**

<table>
<thead>
<tr>
<th>Assessment Measure</th>
<th>RR (95% CI)</th>
<th>Survivors with normal hearing or mild HI</th>
<th>Survivors with severe HI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Attention</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sustained</td>
<td>1.22 (0.59-2.50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-term</td>
<td>2.00 (0.99-4.06)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focused</td>
<td>1.44 (0.67-3.11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Memory</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-term</td>
<td>1.30 (0.73-2.32)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal learning</td>
<td>2.79 (1.52-5.10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual</td>
<td>1.63 (1.08-2.48)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Executive function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive flexibility</td>
<td>1.31 (0.82-2.10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal fluency</td>
<td>1.86 (1.19-2.91)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Working memory</td>
<td>2.28 (1.06-4.89)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Processing speed</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visuomotor</td>
<td>1.87 (1.07-3.25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual reasoning</td>
<td>4.26 (1.12-16.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fine motor</td>
<td>1.24 (0.83-1.85)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Intelligence</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal</td>
<td>1.11 (0.50-2.43)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Academic function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Word reading</td>
<td>1.76 (0.69-4.48)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mathematics</td>
<td>1.90 (1.18-3.04)</td>
<td></td>
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</tr>
</tbody>
</table>

**Figure 2. Relative Risk (RR) for Neurocognitive Deficits Among Survivors of Childhood Cancer With Severe Hearing Impairment (HI) vs Survivors With Normal Hearing or With Mild HI, Stratified by Treatment Exposure**

A, No exposure group (n = 740) comprised survivors who were not treated with platinum-based chemotherapy or cochlear radiotherapy (RT). B, Platinum-only exposure group (n = 307) comprised survivors who were treated with cisplatin and/or carboplatin chemotherapy. C, Cochlear RT exposure group (n = 473) comprised survivors who were treated with cochlear RT with or without platinum-based chemotherapy. Analysis was adjusted for age at diagnosis, time since diagnosis, sex, and treatment variables (if any) within the group. These variables were cranial RT dose, methotrexate chemotherapy treatment (yes or no), intrathecal and high-dose methotrexate chemotherapy treatment (yes or no), and high-dose cytarabine chemotherapy treatment (yes or no).
search by Kelly et al, the present study found that survivors with severe HI across all 3 treatment exposure groups were at an increased risk for lower mathematical proficiency. Research has suggested that deaf and hard-of-hearing students had great difficulty with mathematical vocabulary because many words used in testing were abstract, technical, had multiple meanings, or were represented by abbreviations or symbols. These data underscore the need for a more systematic method of teaching fundamental language concepts, such as morphological skills, to children with HI, with the intent of improving linguistic knowledge and generalization of language skills to enable the performance of higher-level neurocognitive tasks, such as mathematics.

Findings from this cross-sectional section indicated that survivors with severe HI were at an increased risk for deficits not only in verbal abilities but also in less verbally dependent skills such as focused attention, visual memory, executive functioning, and processing speed. Similar results have been reported in studies of children and adults with HI but without cancer. One theory addressing this finding concluded that auditory deprivation may lead to cortical reorganization between the temporal and frontal lobes of the brain and can alter the development of certain skills such as executive function and memory, particularly in young children with HI. A number of studies have suggested an association between language and executive function, and a recent study by Botting et al reinforced the idea of language being a key component in the development of optimal executive functioning skills in deaf children.

Survivors with mild HI in this study also demonstrated deficits in performing neurocognitive tasks compared with those with normal hearing, albeit to a lesser degree than survivors with severe HI. Studies in school-aged children with mild HI found an increased risk for diminished educational performance, attention, and communication skills, and Lin et al reported that older adults with mild HI experienced greater neurocognitive decline compared with individuals with normal hearing. A recent study also observed functional changes in the neural processing of auditory signals in children with mild to moderate HI, suggesting that even milder forms of HI can lead to structural and functional brain reorganization, further supporting the need for early intervention and management of HI.

As expected, the present study confirmed that cranial RT has a direct association with neurocognitive function; however, this study is the first, to our knowledge, to demonstrate that severe HI mediates a substantial portion of the association between cranial RT and neurocognitive deficits. This finding supports the need for long-term audiologic follow-up and early HI detection and intervention in a population already at risk for neurocognitive deficits. A neuropsychological consultation may help identify areas of low performance sooner and thus prevent or mitigate the association between HI and neurocognition.

**Strengths and Limitations**

This study has several strengths. It included a large sample size, a long-term follow-up, and high-quality and standardized audiological and neurocognitive assessments. It also had a high participation rate.

This study also has some limitations. First, the cross-sectional study design precluded the identification of the onset of neurocognitive difficulties and HI. However, it is probable that the significant associations involved HI preceding neurocognitive dysfunction given that current neurodevelopmental theories do not provide an explanation for how neurocognitive difficulties are associated with HI. Furthermore, we excluded from analyses those survivors with a preexisting neurodevelopmental or genetic condition or non-treatment-induced neurological injury associated with neurocognitive deficits. Prospective screening and intervention are needed nonetheless to fully understand the developmental sequence of these problems. Second, pretreatment neurocognitive assessment results were not available for survivors included in the study. Baseline neurocognitive testing is often not feasible and likely not a valid indication of typical premorbid functioning in survivors of solid tumors or CNS tumors attributed to young age and life-threatening illness at the time of diagnosis. Furthermore, many cognitive skills (eg, executive function) cannot be tested in a 2- to 3-year-old child.

Third, data for HI that was considered conductive, noise-induced, or aminoglycoside-related were not available and could not be included in the analyses. Fourth, only a small proportion of survivors for whom a hearing aid was recommended reported using a hearing aid, and data on key variables (eg, years of hearing aid use, hearing aid adherence, and appropriateness of hearing aid fitting) were not available. Thus, we had limited ability to adequately compare neurocognitive function between those who used a hearing aid and those who did not. Studies of the association of hearing aid use with neurocognitive function in children with HI are sparse; however, such studies in older adults with HI who use hearing aids have demonstrated better psychosocial and neurocognitive outcomes among those who used hearing aids compared with those who did not. These data suggest that earlier intervention with amplification may offset or attenuate the association of HI with neurocognitive performance, social isolation, and depression. Presumably, neurocognitive performance and psychosocial well-being would also be improved in children and young adults who consistently use amplification.

**Conclusions**

Hearing impairment is a serious medical condition, particularly if undetected or untreated, and, in this cross-sectional study, it appeared to be associated with an increased risk for neurocognitive deficits. More than one-third of childhood cancer survivors who received potentially ototoxic therapy were found to have severe HI. Early screening and intervention for HI, including adherence to hearing aids and cochlear implants, neuropsychological consultation, and educational accommodations, may facilitate the development and maintenance of neurocognitive function and may identify those who are at risk for future impairment. Prospective studies investigating the association between adherence to hearing aid use and neurocognitive outcomes in survivors of childhood cancer are needed.
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