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The Association of Length of Hospital Stays and Number of ED Visits with Executive Functioning Among Childhood Cancer Survivors.

The Association of Neighborhood Poverty Status and Executive Functioning Among Childhood Cancer Survivors.

By

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Thesis

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Table of Contents

List of Tables

List of Figures

The Association of Length of Hospital Stays and Number of ED Visits with Executive Functioning Among Childhood Cancer Survivors.

Abstract:

Background: Childhood cancer survivors are at increased risk of executive dysfunction. Stimulating environment; whether at school, day care, or home results in cognitive growth. Children with complicated health issues visit Emergency Departments (ED) multiple times in a school year and spend a very high number of days in the hospital, which can interfere with normal development.

Objective: The current study aims to understand the association of total of hospital days and number of ED visits with executive functioning of children with cancer.

Methods: We used a cohort of 77 childhood cancer survivors for this study. Parents were asked to complete several surveys and additional information was collected from the medical record and administrative data sets. Total hospital days and number of ED visits and were derived from the medical record and administrative dataset and executive functioning was assessed by a parent-rated instrument, the Behavior Rating Inventory of Executive Functions (BRIEF). Multiple linear regressions were used to determine the relationship between total hospital days and BRIEF scores and number of ED visits and BRIEF scores.

Results: There is a positive correlation between number of ED visits and executive functioning, as measured by the BRIEF parent report scale. Moreover, there is a positive correlation between total hospital days and global score of executive dysfunction on the BRIEF. In multiple linear regressions, children with higher number of ED visits had more problems reported in multiple aspects of executive functioning; moreover, children with higher number of total hospital days

had more problems with Global Executive Composite (GEC) component of executive functioning after adjusting for co-variables.

Conclusion: An association was found between ED visits and length of hospitalization on parent-reported executive functioning. ED visits and hospitalization are often related to medical complications, and may reflect severity of illness, but may also influence children's ability to participate in school and other aspects of normal development. Follow-up prospective studies with a longer duration are needed to explore potential confounds and understand the course of this relationship.

Background:

The incidence of pediatric cancer has been increasing steadily in the USA since 1975[1], and 10,380 new cases were projected to occur among children 0 to 14 years of age in 2016 in the United States(1). At the same time, advancements in cancer therapy and supportive care management have improved the survival of childhood cancer considerably. The 5-year relative survival rate increased from 58% in the mid 1970's to 83% in the most recent time period (1). The increase in the incidence of childhood cancer and the improved survival rate has led to a growing population of cancer survivors. Although the majority of cancer survivors are healthy, 40% have at least one chronic medical condition and 20% have serious medical conditions following treatment (2, 3).

"Late effects" are complications, disabilities or adverse outcomes as a result of a disease process, the treatment or both (4). Common late effects of childhood cancer include neurocognitive, psychological, cardio-pulmonary, endocrine effecting growth and fertility,

[1] #Population based registry started in USA in 1975

musculoskeletal, and secondary malignancies (4). In particular, the most frequently reported late effect among childhood cancer survivors is neurocognitive impairment (3). Many survivors of acute lymphoblastic leukemia (ALL) and CNS tumor require special education services (5). Neurocognitive functions has multiple domains, including attention, concentration, information processing speed, executive functioning, memory, language, spatial ability, and psychomotor ability (6). Survivors can have impairments in any area of neurocognitive functioning, but executive functioning is particularly vulnerable (7-10). Executive functioning is a combination of interrelated cognitive processes necessary for goal-directed behavior like emotional regulation, working memory, planning, and task flexibility (11) and are strongly associated with life milestones, such as living independently, marrying, achieving higher education, and becoming employed (8, 12-16).

In his 2014 publication, *Developing Interventions for Cancer-Related Cognitive Dysfunction in Childhood Cancer Survivors*, Castlellino proposed that cancer therapy, tumor factors, and host factors contribute to cancer-related cognitive dysfunction (including executive dysfunction) in childhood cancer survivors (17). Castellino has operationalized tumor factors as CNS involvement of leukemia, primary brain tumor location, brain tumor size and brain metastasis; therapy factors as use of chemotherapy, cranial radiation field, cranial radiation dose, use of intracranial surgery; and host factors as age, pre-existing neurodevelopmental status, socioeconomic status (SES), learning environment, gender and genetics (17). There is extensive literature about the effects of cancer therapy and tumors factors on neurocognitive and developmental outcomes of children with cancer, but there is limited information in the published literature regarding the effect of number of emergency department (ED) visits and number of days spent in hospital on the cognitive outcome of the childhood cancer survivor.

Children develop their cognitive abilities through direct and indirect interaction within their social environment (18). A stimulating environment; whether at school, day care or at home, results in cognitive growth (19-23). School absenteeism has been associated with poor academic achievements, an increased risk of high school dropout, lack of graduation, and future maladaptive behavior and unemployment (24). Children with complicated health issues visit ED multiple times in a school year and spend a very high number of days in the hospital which can interfere with regular development. For example, Molnar- Varga et al showed that duration of hospitalization was a significant predictor of general intellectual functions in pediatric renal transplant recipients (25).

Statement of Purpose:

The current study focused on understanding the effect of number of ED visits and total number of hospital days on executive functioning of children with a history of cancer. We hypothesized that:

1: children with a higher number of ED visits will have more problems with executive functioning among childhood cancer survivors

2: children with a higher total number of days in the hospital will have more problems with executive functioning among childhood cancer survivors.

Methods:

Data: For the purpose of the study, we used a cohort of parents of 77 cancer survivors aged 6-18 years, from Hasbro Children Hospital clinic; some were recruited during a medical appointment and some were recruited during a neurocognitive appointment. After obtaining signed consent for participation in the study, parents were asked to complete several surveys. Additional information was collected from the medical record and administrative data sets including: demographic data, utilization data, diagnosis, and treatment.

Predictor Variable: There are two different predictor variables for this study. First is the total number of the ED visits, which is the cumulative sum of the number of ED visits at this institution since diagnosis until enrollment in this study. The second predictor variable is total hospital days, which is the cumulative sum of number of ED days (considering every ED visit as equal to one day in the hospital) and number of inpatient days since diagnosis until enrollment in the study. Both of these variables include visits or stays that were not exclusively related to the oncologic diagnosis.

Outcome variable: The outcome for this study is executive functioning of childhood cancer survivors. We assessed executive functioning of the child through a parent-rated instrument, the Behavior Rating Inventory of Executive Functions (BRIEF).

The BRIEF has good validity and reliability for screening of executive functioning of children aged 5 to 18 years with Cronbach alpha coefficient of 0.80-0.98 for clinical and normative samples and parent-teacher inter-rater agreement $r=0.32$ (range: 0.15-0.50; consistent with expectation because of different environmental settings) (26). There are multiple versions of BRIEF instruments available, but for the purpose of this study, we used a parent rating scale which has 86 questions with a three-point scale answers (Never, Sometimes, Often) (26). There are eight subdomains of executive functioning; three subdomains, i.e. Inhibit, Shift, and Emotional Control together result in a composite Behavioral Regulation Index (BRI). The five other subdomains Initiate, Working Memory, Plan/Organize, Organization of Materials, and Monitor form a composite Metacognition Index (MI). The combination of BRI and MI gives a Global Executive Composite (GEC) (26). The BRIEF has been shown to be a good screening tool to detect cognitive deficits, as well as problems with emotional and behavioral disorders, executive dysfunction, and poor health related quality of life in children treated for a brain tumor (27) and has been used previously to study late effects of brain cancer, leukemia and sarcomas in children (28-30). The BRIEF is normed with a mean T-score of 50 with a standard deviation of 10; and children with executive dysfunction score higher. By convention, the score of 65 or higher is considered to represent significant problems with executive functioning (26, 31).

Co-variables: All of the parents participating in the study were asked to complete several surveys and information was obtained for co-variables including age at the time of study participation, age at the time of diagnosis, gender, race, ethnicity, education level of the parent, if intrathecal chemotherapy was given, if any chemotherapy given, if central nervous system (CNS) radiation given, annual household income, and child's diagnosis from the parent-filled survey. These variables were selected based on previous similar studies (22-24, 32). For analyses, race was collapsed into three groups: Caucasian, African-American and others. Similarly, cancer diagnosis was categorized based on the parent-reported cancer types; (1) brain tumor, (2) leukemia and (3) others, including Wilm's Tumor, Osteosarcoma, hepatoblastoma, Hodgkin's lymphoma, rhabdomyosarcoma, nasopharyngeal carcinoma, neuroblastoma and fibrosarcoma. Moreover, reported annual household income was collapsed into tertiles: <$60,000, $60,000-$99,999 and ≥ $100,000. Time since diagnosis is a derived variable, calculated as the difference in age at the time of the study and the age at the time of the diagnosis.

Data Analysis: We used Stata statistical software, version 11.2 SE (Statacorp, College Station, TX) for our statistical analysis. In addition to descriptive statistics, mean group differences were examined by t-tests or ANOVA's. Correlations between variables were also assessed. The primary question was evaluated with a linear regression model. We used a forward stepwise method for building the model. We added variable one at a time to the model and retained any confounders that were significant at p=0.2 level.

Results:

Table 1.1 shows the descriptive demographic, socioeconomic, diagnostic and therapeutic characteristics of all the children included in the study. The average age of children at the time of the study was 11 years, while the mean patient age at the time of the diagnosis was 5.7 years and mean time from the diagnosis was 5.6 years. The study participants were evenly distributed by gender, (50.7% female vs 49.4% male), predominantly Caucasians (92.1%) and non-Hispanic (92.2%). A variety of oncologic diagnoses were represented, with most having had leukemia, followed by brain tumors. The mean GEC, MI, and BRI scores for the study participants were 53.7, 53.2 and 53.5 respectively. Although mean scores were generally within the normal range, 23.4%, 22.1% and 18.2% of the children in the study had GEC, MI and BRI in the abnormal range (above 65) respectively, as compared to 6.68% expected for a normally distributed sample.

Table 1.2 shows the mean GEC, MI and BRI scores and correlation coefficients for the study cohort according to the socioeconomic and treatment variables. There is a statistically significant, albeit weak, correlation between total number of ED visits and GEC, MI and BRI score (r^2= 0.32**, 0.25* and 0.35**[2] respectively). Similarly, there is a statistically significant, but weak, correlation between total number of hospital days and GEC (r^2=0.24*), and between the time since diagnosis and MI score (r^2= 0.25*). It was also noted that children from low income households had problems with MI scores ($f(2,74)$=3.21; p=0.04*). Otherwise, there were no statistically significant correlations or statistically significant differences in the mean GEC, MI or GEC scores by any other examined demographic, socioeconomic or treatment characteristics

[2] * = p<0.05, **=p<0.01

(e.g., gender, grade school age, race, ethnicity, parents' education level, cancer type, CNS radiation, any chemotherapy or intrathecal chemotherapy).

Total ED visits, time interval since diagnosis, and the other demographic, socioeconomic, or treatment characteristics (e.g., gender, grade school age group, race, ethnicity, parent education, annual household income, cancer type, intracranial radiation, any chemotherapy and intrathecal chemotherapy) were included in three forward stepwise models to examine relative relationships with BRIEF scores. Any variable that was significant at a predetermined level ($p=0.2$) was included in the final model (table 1.3). Among the childhood cancer survivors, higher number of ED visits was associated with more global executive dysfunction (GEC score) after adjusting for the interval since diagnosis, parent education status, and race. Survivors who were further away from diagnosis had more Global executive dysfunction, while survivors with more educated care givers had better global executive functioning. Race was not associated with global executive dysfunction. Similarly, higher number of ED visits was associated with more problems the cognitive components of executive functioning (MI score) after adjusting for the time interval since diagnosis, and annual household income among childhood cancer survivors. Cognitive dysfunction was also worse for survivors who are further away from the diagnosis, while household income ≥$100,000 was associated with better cognitive functioning. Moreover, among childhood cancer survivors, higher number of ED visits was associated with more problems with behavioral and emotional regulation (BRI score) after adjusting for parent education status, intrathecal chemotherapy, intra-cranial radiation and cancer type. Intrathecal chemotherapy was associated with worse behavior and emotional regulation, and compared to brain tumor survivors; leukemia survivors had better behavior and emotional regulation. Parent education and intracranial radiation was not associated with behavior and emotional regulation.

Three similar regressions were calculated using total hospital days, instead of ED visits. Among the childhood cancer survivors, a higher number of total hospital days were associated with more global executive problems (GEC) after adjusting for the interval since diagnosis and the annual household income level. Survivors with more time interval since diagnosis were again shown to have worse global executive functioning while household income did not have any association with global executive functioning. The total number of hospital days, however, was not associated with cognitive (MI) or behavioral-emotional factors (BRI) of executive functioning. Rather, cognitive features of executive dysfunction were primarily related to interval since diagnosis and annual house hold income. Cognitive dysfunction was worse for survivors who were further away from the diagnosis, and household income ≥$100,000 was associated with better cognitive functioning. Similarly, use of intrathecal chemotherapy was related to poor behavioral-emotional regulation.

Discussion:

Childhood cancer survivors have problems with executive functioning later on in life (7-10), which may be related to the impact of cancer therapy. Our study has shown that childhood cancer survivors with more frequent ED visits have more problems in executive functioning. This association between number of ED visits and executive functioning among cancer survivors has not been reported previously in the literature.

Moreover, childhood cancer survivors with higher number of total days in hospital have more problems with executive functioning. Surprisingly, total number of the days spent in hospital has a statistically significant relation with a global measure of executive functioning, but not with the two main subcomponents: metacognitive and emotional-behavioral factors. Our results are consistent with previous studies involving children who underwent kidney transplant and adults with hematopoietic cell transplant, where the length of hospital stay was found to be associated with the poor neurocognitive outcome including executive functioning (25, 33).

This study shows that there is a complex relationship between executive functioning and treatment, demographic, and socioeconomic variables. Depending on the specific aspect of executive functioning, there may be different risk factors. ED visits and number of hospital days may reflect an indication of the severity of the illness. Time since diagnosis was also a significant contributor to understanding executive functioning. Previous studies have shown that neurocognitive functioning, including executive functioning of childhood cancer survivors' declines over time, at least partly secondary to inadequate development of normal-appearing white matter (34). In addition, some measures of socioeconomic status were also related to reported executive functioning. Socioeconomic status is also known to be associated with executive functioning in childhood cancer survivors, with children from lower socioeconomic settings showing poor clinician measured executive functioning compared to children from higher socioeconomic settings (35).

The information pertaining to the number of the ED visits and total hospital days was derived directly from medical records and administrative data sets, not from the parents' recall. So, the exposure variable is not subject to recall bias. Hasbro Children's Hospital is the only children's hospital in the area; however, it is possible that this may not account for all ED visits and hospitalizations. Moreover, visits were not evaluated related to the primary admitting diagnosis, and may include non-oncologic visits.

Pediatric oncologists understand that children actively receiving cancer treatment are at higher risk of getting infections and they need to be evaluated promptly in the ED for fevers and may require frequent hospital admissions. That being said, the pediatric oncology centers should function as a patient centered medical home for children with cancer and every effort should be made to limit ED visits. This can be done by proper patient education and the availability of the after-hours phone consults.

Limitation: There are several limitations to this study. Our team had approached the families of children aged 6-18 who had completed treatment for cancer, but participation in the study was voluntary and data is not available on families who declined to participate. It is possible that parental concern about executive functioning effected decision about participation in the study.

The study showed that the mean scores of GEC, MI and BRI were not statistically significantly different between the children with brain tumors, leukemia and other cancers. Previous studies have shown that children with brain tumors and leukemia have relatively poor executive functioning outcomes as compared to children with sarcomas (36). The inability to see this difference may be attributed to the small sample size. It is possible that the sample is powered to show the association between number of ED visits and executive functioning and total hospital days and executive functioning, but not the association between the cancer type and executive functioning.

The multiple variable regression analysis has shown that there is a statistically significant association between poor executive functioning outcome, i.e. GEC, BRI and MI scores, and increased number of ED visits. There is an additional relationship between the GEC score and increased number of total hospital days, but the coefficients of regression are very small, and we do not know if this statistically significant result converts to clinical significance.

Conclusions:

Future bigger studies with a longer duration of follow up are needed to analyze if the statistically significant effect of number of the ED visits and days in the hospital with executive functioning translates into a clinically significant effect.

Table1.1: Socioeconomic and treatment characteristics of all patients (n=77).

	All patients
Mean age, years (mean, 95% CI)	11.0 (3.6-18.4)
Mean age at time of diagnosis, years (mean, 95% CI)	5.7 (0-13.3)
Mean years from dx to consent (mean, 95% CI)	5.6 (0-11.6)
Gender, %(n)	
Female	50.7% (39)
Male	49.4% (38)
Race, %(n)^	
Caucasian	92.1%(70)
African American	4.0% (3)
Other	4.0% (3)
Ethnicity, %(n)	
Hispanic	7.8% (6)
Non-Hispanic	92.2 (71)
Diagnosis, %(n)	
Leukemia (ALL, AML)	48.1% (37)
Brain Tumor	14.3% (11)
Others (all others)[@]	37.7% (29)
Education of primary caregiver, %(n)	
High School or less	15.6% (12)
More than high school	84.4% (65)
Family income, %(n)	
<$60,000	29.9% (23)
$60,000 to $99,999	35.1% (27)
≥$100,000	35.2% (27)
CNS Radiation, %(n)	
Yes	22.0% (17)
No	78.0% (60)
Intra-thecal chemotherapy, %(n)^	
Yes	54.0% (41)
No	46.0% (35)
Any Chemotherapy, %(n) ^	
Yes	93.4% (71)
No	6.6% (5)
BRIEF scores (mean, 95% CI)	
GEC	53.7 (29.1-78.3)
MI	53.2 (28.8-77.6)
BRI	53.5 (29.7-77.3)
Patients with Elevated BRIEF scores, %(n)	
GEC	23.4% (18)
MI	22.1 %(17)
BRI	18.2 %(14)
Hospital Services Utilization (mean, 95% CI)	
ED visits	6.8 (0-19.4)
Total hospital days (inpatient days and ED visits)	58.4 (0-139.2)

^:Information regarding race, intra thecal chemotherapy and Intravenous chemotherapy missing for 1 patient each.
@: Wilm's Tumor, Osteosarcoma, hepatoblastoma, lymphoma, rhabdomyosarcoma, nasopharyngeal carcinoma, neuroblastoma, fibrosarcoma

Table1.2: Un-adjusted mean (95%CI) and correlation coefficients for BRIEF GEC, MI and BRI scores according to treatment and socioeconomic characteristics (n=77)

	GEC		MI		BRI	
	Correlation coefficient	**p**	**Correlation coefficient**	**p**	**Correlation coefficient**	**p**
Total ED Visits	r^2=0.32	0.004**	r^2=0.25	0.026*	r^2=0.35	0.002**
Total hospital days	r^2=0.24	0.04*	r^2=0.19	0.100	r^2=0.20	0.09
Time since diagnosis	r^2=0.14	0.22	r^2=0.25	0.03*	r^2=-0.01	0.95
	Mean (95%CI)	**p**	**Mean (95% CI)**	**p**	**Mean (95% CI)**	**p**
Gender		0.56		0.64		0.42
Male	54.53 (50.61-58.44)		53.9 (50.11-57.72)		54.66 (50.55-58.76)	
Female	52.89 (48.77-57.01)		52.61 (48.53-46.79)		52.43(48.74-56.13)	
Grade school		0.96		0.97		0.84
Elementary	53.71(49.79-57.63)		52.91 (48.96-56.87)		54.14(50.26-58.03)	
Middle	54.17(48.56-59.78)		53.39 (48.40-58.38)		53.74 (47.75-59.73)	
High School	53.11(46.58-59.62)		53.74 (46.67-60.79)		52.16 (46.88-57.44)	
Race		0.62		0.67		0.63
Caucasians	54.11 (51.22-57.00)		53.66 (50.75-56.56)		53.88 (51.08-56.69)	
African American	47.33 (19.86-74.81)		48.33(19.54-77.12)		47(21.06-72.93)	
Others[@]	51.67(0-104.15)		49.67 (3.5-95.83)		54(2.37-105.63)	
Hispanic		0.49		0.55		0.94
No	53.42 (50.49-56.34)		53.01 (50.06-55.97)		53.56 (50.77-56.35)	
Yes	57.0 (44.72-69.27)		56.17 (47.63-64.70)		53.17 (38.17-68.16)	
Parents' Education		0.11		0.11		0.12
High school or less	58.92(51.31-66.52)		58.41 (50.99-65.83)		58.42 (50.07-66.76)	
More than high school	52.74 (49.72-55.75)		52.31 (49.29-55.32)		52.63 (49.77-55.49)	
Family income		0.06		0.04*		0.23
Less than 60,000	56.35 (50.06-62.63)		54.96(49.49-60.42)		56.09 (49.35-62.83)	
60-99,999	55.89 (50.89-60.88)		56.41 (51.14-61.68)		54.41 (49.90-58.91)	
≥100,000	49.26 (45.95-52.57)		48.67 (44.96-52.37)		50.48 (47.33-53.63)	
Cancer types		0.55		0.44		0.59
Brain Tumors	56.18 (48.49-63.87)		57.27 (49.31-65.24)		53.18 (46.05-60.31)	
ALL	54.4 (49.85-58.96)		53.27(48.97-57.57)		54.92 (50.39-59.45)	
OTHERS	51.86 (47.77-55.95)		51.72 (47.37-56.08)		51.89 (48.04-55.75)	
CNS Radiation		0.70		0.61		0.58
Yes	54.70 (48.22-61.19)		54.70(48.08-61.33)		52.23 (46.58-57.89)	
No	53.42 (50.25-56.58)		52.85 (49.73-55.97)		53.90 (50.74-57.06)	
Intrathecal Chemotherapy		0.31		0.71		0.08
No	52.4 (48.79-56.01)		52.91 (48.86-56.97)		51.17 (48.16-54.18)	
Yes	55.27 (51.04-59.49)		53.97 (50.03-57.92)		55.95 (51.64-60.26)	
Any Chemotherapy		0.58		0.87		0.28
No	51.00 (42.22-59.78)		52.60 (44.29-60.91)		48.20 (38.06-58.34)	
Yes	54.15 (51.21-57.09)		53.55 (50.60-56.49)		54.14 (51.30-56.98)	

*p<0.05, **p<0.01,

@: Wilm's Tumor, Osteosarcoma, hepatoblastoma, lymphoma, rhabdomyosarcoma, nasopharyngeal carcinoma, neuroblastoma, fibrosarcoma

Table 1.3: Results of forward stepwise multiple regression on GEC, MI and BRI scores

Model	Predictor variable	α	β	95% CI	t	p	R^2	Adjust-ed R^2	Model probability
GEC	-	-	-	-	-	-	0.21	0.15	0.006**
	Constant	38.64	-	23.57 53.72	5.12	0.00**	-	-	-
	ED visits	-	0.62	0.19 1.04	2.90	0.005**	-	-	-
	Interval	-	1.04	0.13 1.95	2.27	0.02*	-	-	-
	Parent education	-	-8.34	-15.92 -0.77	-2.20	0.03*	-	-	-
	Race Caucasians Other	-	 13.04 12.94	 -6.39 32.48 -1.19 27.06	 1.34 1.83	 0.18 0.07	-	-	-
MI	-	-	-	-	-	-	0.22	0.17	0.002**
	Constant	45.40	-	37.88 52.93	12.04	0.00**	-	-	-
	Interval	-	1.37	0.44 2.29	2.95	0.004**	-	-	-
	ED visit		0.44	0.01 0.88	2.05	0.04*			
	Income <60k ≥100k	-	 -0.60 -7.14	 -7.39 6.18 -13.59 -0.69	 -0.18 -2.21	 0.86 0.03*	-	-	-
BRI	-	-	-	-	-	-	0.24	0.17	0.004**
	Constant	58.28	-	48.09 68.46	11.43	0.00**	-	-	-
	ED visits	-	0.61	0.19 1.03	2.88	0.005**	-	-	-
	Parent education	-	-5.95	-12.98 1.07	-1.69	0.09	-	-	-
	intra thecal chemotherapy	-	21.26	6.71 35.81	2.92	0.005*	-	-	-
	Intracranial radiation	-	-7.2	-15.64 1.23	-1.70	0.09	-	-	-
	Cancer type 2 ALL 3 OTHERS	-	 -23.02 -6.57	 -41.87 -4.17 -16.33 3.19	 -2.44 -1.34	 0.01* 0.18	-	-	-

α, intercept; β, Standardized regression coefficient; 95%CI, 95% confidence interval; t, obtained t value; p, probability; R^2, proportional variance explained. Adjusted R^2, Adjusted variance. *p<0.05, **p<0.01,

Table 1.4: Results of forward stepwise multiple regression on GEC, MI and BRI scores

Model	Predictor variable	α	B	95%CI	t	p	R^2	adjusted R^2	Model Probability
GEC	-	-	-	-	-	-	0.20	0.15	0.005**
	Constant	44.02	-	35.73 52.31	10.61	0.00**	-	-	-
	Total days	-	0.07	0.00 0.14	2.08	0.04*	-	-	-
	Interval	-	1.43	0.44 2.43	2.88	0.005**	-	-	-
	Income <60k ≥100k	-	 1.11 -5.95	 -5.69 7.93 -12.67 0.76	 0.33 -1.77	 0.74 0.08	-	-	-
MI	-	-	-	-	-	-	0.27	0.22	0.0004**
	Constant	42.42	-	34.53 50.30	10.75	0.00**	-	-	-
	Total days		0.06	-0.00 0.13	1.85	0.07	-	-	-
	Interval		1.86	0.92 2.81	3.94	0.00**	-	-	-
	Income <60k ≥100k		 0.23 -7.19	 -6.25 6.71 -13.59 -0.81	 0.07 -2.25	 0.94 0.02*	-	-	-
BRI	-	-	-	-	-	-	0.13	0.09	0.020*
	Constant	52.29	-	44.06 60.52	12.69	0.00**	-	-	-
	Total days	-	0.06	-0.01 0.13	1.66	0.10	-	-	-
	Parent education	-	-5.62	-13.02 1.79	-1.51	0.13	-	-	-
	intra thecal chemotherapy	-	6.16	0.53 11.78	2.18	0.033*	-	-	-

α, intercept; β, Standardized regression coefficient; 95%CI, 95% confidence interval; t, obtained t value; p, probability; R^2, proportional variance explained. Adjusted R^2, Adjusted variance. *p<0.05, **p<0.01,

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The Association of Neighborhood Poverty Status and Executive Functioning Among Childhood Cancer Survivors

Abstract:

Background: Childhood cancer survivors are at increased risk of developing executive dysfunction. Low socioeconomic status (SES) has been associated with poor executive functioning in childhood cancer survivors previously, but all the previous studies have used traditional measures of SES, based on parents' education level, family annual income and occupation.

Objective: The current study aims to understand the association of resource-limited environment, as measured by percentage of households in neighborhood of residence below the federal poverty level with executive functioning among children with cancer.

Methods: We used a retrospective cohort of 67 childhood cancer survivors. Relevant information was collected from the medical record, administrative data sets and parent-filled surveys. Address information was geocoded using ArcGIS 10.2 to obtain data on the neighborhood of residence (i.e. block group poverty status). A priori cut-points were set to represent neighborhoods with children living below poverty level at 0%, 0.1% to 9.9%, and ≥10.0%. Executive functioning were assessed through a parent-rated instrument, the Behavior Rating Inventory of Executive Functions (BRIEF). Multiple linear regressions were used to determine the relationship between neighborhood poverty status and the BRIEF scores.

Results: The mean scores for GEC, MI and BRI are not related to poverty status of neighborhood of residence. There was no statistically significant association seen between block group poverty status and executive functioning after adjusting for co variables in the final model.

Conclusion: Future prospective study with a bigger sample size, longer follow up period and more robust measures of the executive functioning like a clinician administered test are needed to understand the effect of neighborhood poverty status on executive functioning.

Background:

The incidence of pediatric cancer has been increasing steadily in the USA since 1975[3], and 10,380 new cases were projected to occur among children 0 to 14 years of age in 2016 in the USA (1). At the same time, advancements in cancer therapy and supportive care management have improved the survival of childhood cancer considerably. The 5-year relative survival rate increased from 58% in the mid 1970’s to 83% in the most recent time period (1). The increase in incidence of childhood cancer and the improved survival rate has led to a growing population of cancer survivors. Although, the majority of cancer survivors are healthy, 40% have at least one chronic medical condition and 20% have serious medical conditions following treatment (2, 3).

"Late effects" are complications, disabilities or adverse outcomes as a result of a disease process, the treatment or both (4). Common late effects of childhood cancer include neurocognitive, psychological, cardio-pulmonary, endocrine effecting growth and fertility, musculoskeletal, and secondary malignancies (4). In particular, the most frequently reported late effect among childhood cancer survivors is neurocognitive impairment (3) and many survivors of acute lymphoblastic leukemia (ALL) and CNS tumors require special education services (5). Neurocognitive functions has multiple domains, including attention, concentration, information processing speed, executive functioning, memory, language, spatial ability, and psychomotor ability (6). Survivors can have impairments in any area of neurocognitive functioning, but executive functioning is particularly vulnerable (7-10). Executive functioning is a combination of

[3] Population based registry started in USA in 1975

interrelated cognitive processes necessary for goal-directed behavior like emotional regulation, working memory, planning, and task flexibility (11) and are strongly associated with life milestones, such as living independently, marrying, achieving higher education, and becoming employed (8, 12-16).

In his 2014 publication, *Developing Interventions for Cancer-Related Cognitive Dysfunction in Childhood Cancer Survivors*, Castlellino proposed that cancer therapy, tumor factors, and host factors contribute to cancer-related cognitive dysfunction (including executive dysfunction) in childhood cancer survivors (17). Castellino has operationalized tumor factors as CNS involvement of leukemia, primary brain tumor location, brain tumor size and brain metastasis; therapy factors as use of chemotherapy, cranial radiation field, cranial radiation dose, use of intracranial surgery; and host factors as age, pre-existing neurodevelopmental status, socioeconomic status (SES), learning environment, gender and genetics (17).

Socioeconomic factors are strongly associated with childhood cognitive and academic achievement, including intellectual abilities (18, 19), achievement test scores (20), grade retentions and functional literacy (21). This association is even stronger in children with chronic health conditions, like end stage renal disease (ESRD) requiring renal transplant (22). Low SES has been associated with poor executive functioning outcome in childhood cancer survivors previously (23, 24), but all of the previous studies have used traditional measures of the socioeconomic status (e.g. parents' education, family income and occupation). The current study examined the relationship between neighborhood economic status and executive functioning in childhood cancer survivors. Area based socioeconomic measures, like neighborhood poverty level, are deemed to be very useful in monitoring of social inequalities in health in the United States (25).

Statement of Purpose:

The current study focused on understanding the relationship between neighborhood poverty status and executive functioning of childhood cancer survivors. We hypothesize that childhood cancer survivors living in more impoverished neighborhoods will have more problems with executive functioning as compared to those living in less impoverished neighborhoods.

Methods:

Data: For the purpose of the study, we used a cohort of parents of 77 childhood cancer survivors, aged 6-18 years from Hasbro Children Hospital clinics; some were recruited during a medical appointment and some were recruited during a neurocognitive appointment. Out of the 77 patients, block group poverty status was able to be obtained for 67 (Fig 2.1). After obtaining signed consent for participation in the study, parents were asked to complete several surveys. Additional information was collected from the medical record and administrative data sets including: demographic data, utilization data, diagnosis and treatment.

Predictor variable: The predictor variable for this study is the block group poverty status of patient's home address; in other words, what percent of the households in the patient's block group have an income below the federal poverty level. Block Groups are divisions of census tracts and generally contain between 600 and 3,000 people (26). It is a feasible measure for routine monitoring of US socioeconomic inequalities in health using the strategy of characterizing population in relation to the poverty level of the block group in which individuals reside (25).

Address information was obtained from the administrative data sets and was geocoded using ArcGIS software to access the geographic variability. Geocoding allowed us to obtain data on the neighborhood of residence (e.g. block group poverty). This data comes from 2010-2014 American Community Survey; which provided data at the block group or track level. Geocoding has been used previously to represent the socioeconomic disparities in health (27-30). With 14.8% of its population living in poor households, Rhode Island is ranked 25th nationally among all states according to 2014 USA census bureau statistics. Once the block group poverty level was obtained, a priori cut-points were set to represent neighborhoods in which children living below poverty level equaled 0%, 0.1%-9.9%, and ≥10.0%.

Outcome: The outcome for this study is executive functioning of childhood cancer survivors. We assessed executive functioning of children through a parent-rated instrument, the Behavior Rating Inventory of Executive Functions (BRIEF).

The BRIEF has good validity and reliability for screening of executive functioning of children aged 5 to 18 years with Cronbach alpha coefficient of 0.80-0.98 for clinical and normative samples and parent teacher inter-rater agreement r=0.32 (range: 0.15-0.50; consistent with expectation for different environmental settings) (31). There are multiple versions of BRIEF instruments available, but for the purpose of this study, we used a parent rating scale which has 86 questions with a three-point scale answers (Never, Sometimes, Often) (31). There are eight subdomains of executive functioning; three subdomains, i.e. Inhibit, Shift, and Emotional Control together result in a composite Behavioral Regulation Index (BRI). The five other subdomains Initiate, Working Memory, Plan/Organize, Organization of Materials, and Monitor provide a composite Metacognition Index (MI). The combination of BRI and MI gives a Global Executive Composite (GEC) (31). The BRIEF has been shown to be a good screening tool to detect cognitive deficits, as well as problems with emotional and behavioral disorders, executive dysfunction, and poor health related quality of life in children treated for a brain tumor (32) and has been used previously to study late effects of brain cancer, leukemia and sarcomas in children (33-35).

The BRIEF is normed with a mean T-score of 50 with a standard deviation of 10; and children with executive dysfunction score higher. By convention, the score of 65 or higher is considered to represent significant problems with executive functioning (31, 36).

Co-variables: All of the parents participating in the study were asked to complete several surveys and information was obtained for co-variables including age at the time of study participation, age at the time of diagnosis, gender, race, ethnicity, education level of the parent, intrathecal chemotherapy given, any chemotherapy given, CNS radiation given, annual house hold income and child's diagnosis from the parent-filled survey. These variables were selected based on previous similar studies (22-24, 37). For analyses, race was collapsed into three groups: Caucasian, African-American and others. Similarly, cancer diagnosis was categorized based on the parent-reported cancer types; (1) brain tumor, (2) leukemia and (3) others, including Wilm's Tumor, Osteosarcoma, hepatoblastoma, Hodgkin's lymphoma, rhabdomyosarcoma, nasopharyngeal carcinoma, neuroblastoma and fibrosarcoma. Moreover, reported annual household income was collapsed into tertiles: <\$60,000, \$60,000-\$99,999 and ≥ \$100,000. Time since diagnosis is a derived variable, calculated as the difference in age at the time of the study and the age at the time of the diagnosis.

Data Analysis: We used Stata statistical software, version 11.2 SE (Statacorp, College Station, TX) for our statistical analysis. In addition to descriptive statistics, mean group differences were examined by t-tests or ANOVA's. Correlations between variables were also assessed. The primary question was evaluated with a linear regression model. We used a forward stepwise method for building the model. We added variable one at a time to the model and retained any confounders that were significant at p=0.2 level.

Results:

Table 2.1 shows the descriptive demographic, socioeconomic, diagnostic and therapeutic characteristics of all children included in the study. The mean age at the time of study participation was 10.8 years while the mean patient age at the time of the diagnosis was 5.6 years and mean time from the diagnosis 5.4 years. The study participants were evenly distributed by gender (52% female vs 48% male), and were predominantly Caucasians (91%) and non-Hispanic (92.5%). A variety of oncologic diagnoses were represented, with most having had leukemia, followed by brain tumors. The mean GEC, MI, and BRI scores for the study participants were 54.1, 53.4 and 54.3, respectively, falling generally in the average range. Nevertheless, 23.9%, 22.4% and 20.9% of the children in the study had GEC, MI and BRI in the abnormal range (above 65) respectively, as compared to 6.68% expected in a normally distributed sample.

As mentioned previously, a total of 77 children consented to participate in the study, but out of those 77, we were able to geocode only 67. The reasons for this inability to geocode 10 children were that patients lived out of state (n=4), or had a P.O. box instead of a valid home address (n=2) or other (n=4) (Fig 2.1). We limited the analysis for the purpose of the study to the children for whom we had neighborhood poverty status data (n=67). We have compared the GEC, MI, and BRI scores according to the demographic, socioeconomic, diagnostic, and therapeutic characteristics for full cohort of 77 children against subset of children included in the analysis (n=67) and found that they were similar on 35 out of 36 measures. The only significant differences seen are the following: in the full cohort, family income is significantly associated with MI score while in the subset of the children included in the data analysis for this study (n=67), this effect is not significant.

Table 2.2 shows the mean GEC, MI and BRI scores and correlation coefficients for the study cohort according to the socioeconomic and treatment variables. Problems with MI component of the executive functioning worsens with time since diagnosis r^2=0.31** (p=0.01). Otherwise, there was no statistically significant correlation or statistically significant difference in the mean GEC, MI or GEC scores by other demographic, socioeconomic or treatment characteristics like block group poverty status, gender, grade school age, race, ethnicity, parents' education level, family income, cancer type, CNS radiation, any chemotherapy or intrathecal chemotherapy.

Table 2.3 compares annual household income with Block Group Poverty status. Spearman's rank correlation coefficient shows that the annual house hold income and block group poverty status are independent of each other (Spearman's rho = 0.14, prob =0.25). Similarly, table 2.4 compares care giver's education level with Block Group Poverty status and shows that these two are independent of each other (Spearman's rho = -0.02, prob =0.84).

Time interval since diagnosis, gender, grade school age group, race, ethnicity, parent education, annual household income, cancer type, intracranial radiation, any chemotherapy and intrathecal chemotherapy were included in three forward stepwise models to examine relative relationships with BRIEF scores and neighborhood poverty status. All co-variables that were significant at a predetermined level (p=0.2) were included in the final model (table 2.5). Among the childhood cancer survivors, block group poverty was not associated with more problems with a global measure (GEC) or metacognitive functioning (MI) after adjusting for the interval since diagnosis and annual household income level. Similarly, neighborhood poverty status was not associated with emotional-behavioral index (BRI) after adjusting for parent education, race, or use of intrathecal chemotherapy among the childhood cancer survivors. The children from households with annual income >$100,000 are reported to have better metacognitive functioning (MI), as compared to children from lower income households (t(64)=-2.05, p=0.04*[4]), and children further away from diagnosis had worse MI outcomes (t(64)=3.52, p=0.001**).

Discussion:

Childhood cancer survivors have problems with executive functioning later on in life (7-10). In contrast to our initial hypothesis, the poverty status of the neighborhood of childhood cancer survivors is not associated with their reported executive functioning. The current study shows that executive functioning for cancer survivors from more impoverished neighborhood were not statistically significantly different from children from less impoverished neighborhoods. The effect of the neighborhood poverty status on executive functioning among childhood cancer survivors has not been studied previously, but it has been shown to be associated with worse outcomes in several other health related measures (27-30).

There are a several limitations in this study. As mentioned previously, a total 77 children consented to participate in the study, but out of those 77, we were able to geocode only 67. We limited the analysis for the purpose of the study to the children for whom we had the neighborhood poverty status data (n=67). Limiting the sample size from 77 to 67 children decreased the power enough that association of the household income on the MI is not significant. It is possible that the effect of the neighborhood poverty status on executive functioning is statistically significant, but we do not have enough power to see the difference.

The parent reported BRIEF is a parent reported scale and is a reliable and valid instrument for screening for executive functioning, but it is not comparable to a functional test done in a clinical setting. BRIEF is limited to what parents perceive rather than the actual executive functioning for the child.

[4] *p<0.05, **p<0.01,

Children start developing executive functioning early in life, but they continue to develop and refine throughout childhood into the early adulthood (38). As the childhood cancer survivors grow older, they lag behind their peers in executive functioning. Our study shows that the reported metacognitive difficulties are greater for children with longer time interval since diagnosis. Mean time since diagnosis in this study was 5.4 years, and if these children are followed over a longer period of time, they may show more pronounced problems with executive functioning in general and in relation to neighborhood poverty status specifically.

Conclusion:

Future prospective study with a bigger sample size, longer follow up period and more robust measures of the executive functioning like a clinician administered test are needed to understand the effect of neighborhood poverty status on executive functioning.

Table2.1. Socioeconomic and treatment characteristics of all patients (n=77)

	All patients (n=77)	Study cohort (n=67)
Mean age, years (mean, 95% CI)	11.0 (3.6-18.4)	10.8 (3.6-18)
Mean age at time of diagnosis, years (mean, 95% CI)	5.7 (0-13.3)	5.6 (0-12.8)
Mean years from dx to consent (mean, 95% CI)	5.6(0-11.6)	5.4 (0-11.2)
Gender, %(n)		
Female	50.7% (39)	52.0% (35)
Male	49.4% (38)	48.0% (32)
Race, %(n)^		
Caucasian	92.1%(70)	90.9%(60)
African American	4.0% (3)	4.6% (3)
Other	4.0% (3)	4.6% (3)
Ethnicity, %(n)		
Hispanic	7.8% (6)	7.5% (5)
Non-Hispanic	92.2 (71)	92.5% (62)
Diagnosis, %(n)		
Leukemia (ALL, AML)	48.1% (37)	52.2% (35)
Brain Tumor	14.3% (11)	11.9% (8)
Others (all others)@	37.7% (29)	35.8% (24)
Education of primary caregiver, %(n)		
High School or less	15.6% (12)	14.9% (10)
More than high school	84.4% (65)	85.1% (57)
Family income, %(n)		
< $60,000	29.9% (23)	32.8% (22)
$60,000 to $99,999	35.1% (27)	32.8% (22)
≥ $100,000	35.2% (27)	34.3% (23)
CNS Radiation, %(n)		
Yes	22.0% (17)	19.4% (13)
No	78.0% (60)	80.6% (54)
Intra-thecal chemotherapy, %(n)^		
Yes	54.0% (41)	57.6% (38)
No	46.0% (35)	42.4% (28)
Any Chemotherapy, %(n) ^		
Yes	93.4% (71)	95.4% (63)
No	6.6% (5)	4.5% (3)
BRIEF scores (mean, 95% CI)		
GEC	53.7 (29.1-78.3)	54.1 (29.1-78.3)
MI	53.2 (28.8-77.6)	53.4 (28.8-77.6)
BRI	53.5 (29.7-77.3)	54.3 (29.7-77.3)
Patients with Elevated BRIEF scores, %(n)		
GEC	23.4% (18)	23.9 %(16)
MI	22.1 %(17)	22.4% (15)
BRI	18.2 %(14)	20.9%(14)
Hospital Services Utilization (mean, 95% CI)		
ED visits	6.8 (0-19.4)	7.6 (0-20.2)
Total hospital days (inpatient days and ED visits)	58.4 (0-139.2)	57.3 (0-138.1)

^Information regarding race, intrathecal chemotherapy and any chemotherapy were missing for 1 patient each.
@: Wilm's Tumor, Osteosarcoma, hepatoblastoma, lymphoma, rhabdomyosarcoma, nasopharyngeal carcinoma, neuroblastoma, fibrosarcoma

Table2.2: Un-adjusted mean (95%CI) and correlation coefficients for BRIEF GEC, MI and BRI scores according to treatment and socioeconomic characteristics (N = 67)

	BRIEFGEC		BRIEFMI		BRIEFBRI	
	Mean(95% CI)	**p**	**Mean(95% CI)**	**p**	**Mean(95% CI)**	**p**
BG poverty level		0.81		0.83		0.82
0%	53.95 (47.87-60.04)		53.85 (47.72-59.99)		53.05 (47.21-58.88)	
0.1-9.9%	53.29 (48.94-57.63)		52.32 (47.85-56.79)		54.54 (50.39-58.68)	
≥10%	55.72 (49.04-62.40)		54.44 (48.45-60.43)		55.56 (48.41-62.69)	
Gender		0.50		0.60		0.29
Male	55.22 (50.77-59.67)		54.19 (49.91-58.47)		56.0 (51.30-60.69)	
Female	53.17 (48.88-57.47)		52.63 (48.32-56.93)		52.83 (48.87-56.78)	
School grade group		0.85		0.55		0.98
Elementary	53.41 (49.33-57.48)		52.19 (48.19-56.18)		54.56 (50.44-58.69)	
Middle	54.2 (47.99-60.4)		53.05 (47.76-58.33)		54.35 (47.49-61.21)	
High School	55.66 (47.90-63.43)		56.33 (47.78-64.88)		53.87 (47.59-60.14)	
Race		0.58		0.65		0.56
Caucasian	54.68 (51.53-57.83)		53.85 (50.72-56.98)		54.85 (51.73-57.97)	
African American	47.33 19.86- 74.81)		48.33 (19.54-77.12)		47.0 (21.06-72.93)	
Other[@]	51.67 (0.81-104.15)		49.67 (3.50-95.83)		54.0 (2.37-105.63)	
Hispanic		0.36		0.44		0.87
Yes	59.0 (44.26-73.74)		57.4 (46.91-67.88)		55.2 (36.61-73.79)	
No	53.76 (50.60-56.91)		53.05 (49.9-56.19)		54.27 (51.18-57.37)	
Parents' Education		0.22		0.28		0.14
High school or less	58.6 (50.32-66.87)		57.2 (49.69-64.7)		59.6 (49.96-69.23)	
More than high school	53.37 (50.07-56.67)		52.7 (49.41-55.99)		53.4 (50.25-56.59)	
Family income		0.09		0.08		0.22
Less than 60,000	56.77 (50.24-63.30)		55.18 (49.47-60.89)		56.68 (49.73-63.63)	
60-99,999	56.27 (50.89-61.53)		56.23 (50.61-61.85)		55.77 (50.71-60.83)	
≥ 100,000	49.61 (45.78-53.8)		48.91 (44.6-53.22)		50.74 (47.08-54.39)	
Cancer types		0.48		0.45		0.63
Brain Tumors	57 (48.81-65.19)		57.36 (49.33-65.42)		54.75 (45.81-63.68)	
Leukemia	55.11 (50.42-59.81)		53.88 (49.4-58.34)		55.57 (50.89-60.25)	
OTHERS	51.79 (47.09-56.48)		51.29 (46.37-56.21)		52.42(47.84- 56.98)	
CNS Radiation		0.78		0.78		0.7
Yes	55.0 (47.35-62.65)		54.23 (46.66-61.79)		53.15 (46.10-60.2)	
No	53.94 (50.55-57.33)		53.16 (49.84-56.49)		54.63 (51.22-58.04)	
Intrathecal Chemotherapy		0.22		0.46		0.09
Yes	56.02(51.58-60.47)		54.58 (50.41-58.75)		56.76 (52.23-61.29)	
No	52.28 (48.39-56.19)		52.36 (48.0-56.71)		51.68 (48.19-55.17)	
Any Chemotherapy		0.86		0.62		0.71
Yes	54.38 (51.23-57.53)		53.48 (50.37-56.58)		54.73 (51.62-57.84)	
No	55.67 (48.07-63.25)		57.0 (54.51-59.48)		52.0 (29.92-74.08)	
	Correlation coefficient	**p**	**Correlation coefficient**	**p**	**Correlation coefficient**	**p**
Time from diagnosis	r^2= 0.19	0.11	r^2= 0.31	0.01**	r^2= 0.03	0.78

*p<0.05, **p<0.01
@: Wilm's Tumor, Osteosarcoma, hepatoblastoma, lymphoma, rhabdomyosarcoma, nasopharyngeal carcinoma, neuroblastoma, fibrosarcoma

Table 2.3: Comparison of Block Group Poverty Status with Annual Household Income.

	0 % Block group poverty	0.1-9.9% Block group poverty	≥10 % Block group poverty	Total	Spearman Rho	*p*
	-	-	-	-	0.14	0.25
<$60,000	6	11	5	22	-	-
60,000-$99,999	6	5	11	22	-	-
≥100,000	9	12	2	23	-	-
Total	21	28	18	67	-	-

Table 2.4: Comparison of the block group poverty status with care giver education level

	0 % Block group poverty	0.1-9.9% Block group poverty	≥10 % Block group poverty	Total	Spearman Rho	*p*
	-	-	-	-	-0.02	0.84
High school or less	3	4	3	10	-	-
More than High school	18	24	15	57	-	-
Total	21	28	18	67	-	-

Table 2.5: Results of forward stepwise model multiple regression on GEC, MI and BRI scores using block group poverty as lock term

Model	Predictor variable	α	β	95%CI	t	p	R^2	adjusted R^2	Model Probability
GEC	-	-	-	-	-	-	0.15	0.07	0.088
	Constant	48.46	-	39.09 57.82	10.35	0.00**	-	-	-
	BG poverty 0.1%-9.9% ≥10%	-	 0.17 -0.24	 -6.78 7.12 -8.50 8.03	 0.05 -0.06	 0.96 0.95	-	-	-
	Interval	-	1.32	0.26 2.39	-0.06	0.95	-	-	-
	Income <60K ≥100K	-	 2.73 -6.09	 -4.94 10.41 -13.45 1.28	 0.71 -1.65	 0.48 0.10	-	-	-
MI	-	-	-	-	-	-	0.22	0.16	0.008**
	Constant	46.59	-	37.80 55.39	10.60	0.00**	-	-	-
	BG Poverty 0.1%- 9.9% ≥10%	-	 -0.87 -1.33	 -7.40 5.65 -9.09 6.43	 -0.27 -0.34	 0.79 0.73	-	-	-
	Interval	-	1.76	0.76 2.77	3.52	0.001**	-	-	-
	Income <60K ≥100K	-	 1.91 -7.09	 -5.30 9.12 -14.01 -0.17	 0.53 -2.05	 0.59 0.04*	-	-	-
BRI	-	-	-	-	-	-	0.14	0.05	0.17
	Constant	43.46	-	27.68 59.24	5.51	0.00**	-	-	-
	BG Poverty 0.1-9.9% ≥10%	-	 2.49 2.91	 -4.57 9.55 -5.45 11.27	 0.71 0.70	 0.48 0.49	-	-	-
	Parent education	-	-8.64	-17.35 0.76	-1.98	0.052	-	-	-
	intra thecal chemotherapy	-	5.68	-0.37 11.73	1.88	0.06	-	-	-
	Race Caucasians Others	-	 12.48 14.28	 -8.63 33.59 -0.78 29.34	 1.18 1.90	 0.24 0.06	-	-	-

α, intercept; β, Standardized regression coefficient; 95%CI, 95% confidence interval; t, obtained t value; p, probability; R^2, proportional variance explained. Adjusted R^2, Adjusted variance. *p<0.05, **p<0.01,

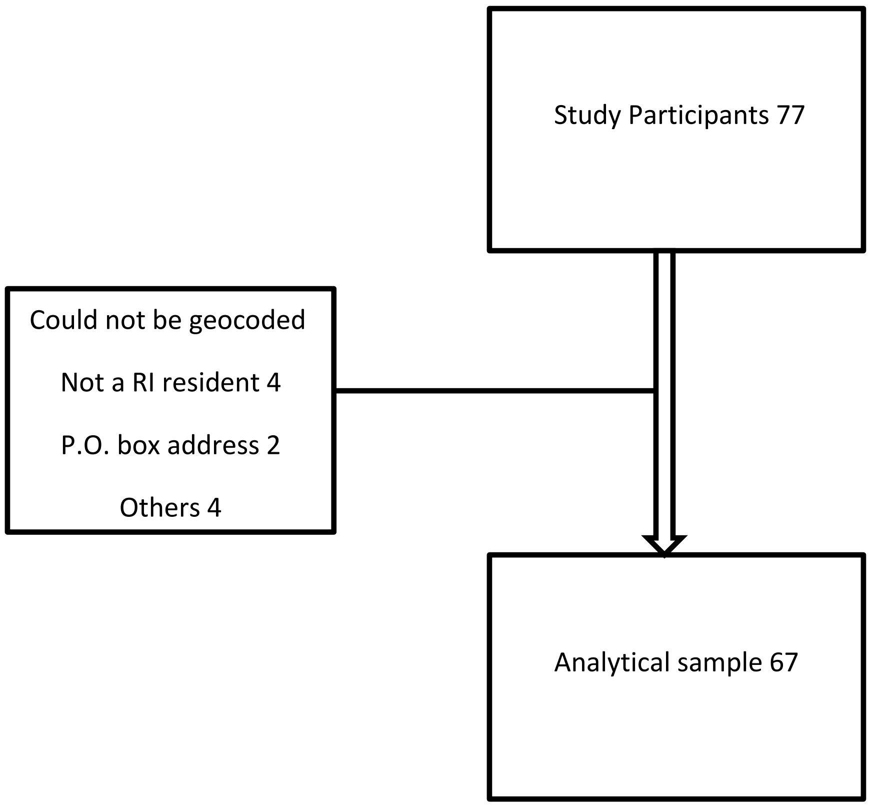

Fig 2.1: Analytical Sample

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