

Mental Retardation and Learning Disability in Survivors of Childhood Cancer Diagnosed in Infancy

A Report from the Childhood Cancer Survivor Study

Marc H. Bornstein and O. Maurice Haynes
NICHD

INTRODUCTION

A major limitation of studies of the psychosocial consequences of childhood cancer is that they usually do not recruit numbers of participants which allow reliable cell sizes to address issues of the potential impact of patient age at onset/diagnosis controlling also for different types of cancer, different treatments, varied psychosocial factors (such as family income, ethnicity, gender, etc.). Our aim is to begin to fill this developmental gap in the existing literature by focusing on cancers diagnosed and treated in infancy (0-1 years) versus later years (2-4 years, 5-10 years, 10+ years). We used the Childhood Cancer Survivor Study (CCSS) to examine the effects of specific periods in childhood of the onset or diagnosis of cancers for psychosocial sequelae. The main questions are two:

- Controlling for medical and psychosocial factors, is cancer in infancy still a specific risk factor for further cognitive development?
- If so, would that be a specific cognitive risk covering only hardwired cognition (i.e., leading to mental retardation) or would that be a wide-spectrum effect, covering also learning and academic achievement problems?

We also identified which types of cancer in infancy may predict the worst outcomes and in controlling for problems in cognitive functioning in our survivors' sample by comparing their outcomes with the outcomes of a control group of siblings.

METHOD

Participants

The CCSS is a multi-institutional study, funded by the National Cancer Institute, of individuals who survived five or more years following treatment for cancer, leukemia, tumor or similar illness diagnosed during childhood or adolescence. Members of the CCSS cohort younger than 8 years at the follow-up survey, and those who had been diagnosed with Hodgkin's Disease, non-Hodgkin Lymphoma, or bone cancer, were not included in the study. Table 1 presents the demographic, diagnostic, and treatment data for the 9,981 survivors and 3,825 siblings with complete data who were used in the study.

Procedures

Outcome Measures of Mental Retardation and Learning Disability.

- Whether members of the study cohort had ever been diagnosed as having had mental retardation or having been in a learning disabled or special education program.
- Responses were encoded 0 = "No" and 1 = "Yes."
- The measure of learning disability was recoded to exclude those respondents who had identified themselves as both mentally retarded and learning disabled.

Predictors of Mental Retardation and Learning Disability.

- Group membership (survivor or sibling).
- The age of initial diagnosis of cancer.
- The type of tumor,
- Treatment by chemotherapy or treatment by radiotherapy.

Table 1 presents the data for these predictors as well as gender, household income, ethnicity, and age at follow-up which were used as covariates.

Analytic Plan

- All models were fit using binary logistic regression.
- Final models met the assumptions of additivity, linearity, and no influential outliers and included only the significant two-way interactions of the focal predictor with other predictors and the interaction of Age at follow-up x Income.
- Predictive ability of models was assessed, and all models were validated using enhanced bootstrapping with 500 resamples. Predictive ability of the models was generally acceptable: Nagelkerke R^2 ranged from .085 to .15, D_{xy} ranged from .367 to .555, and Brier ranged from .027 to .173.
- Validation statistics indicated minimal to little overfitting in the original models with minimal differences in the statistics for the validation model and the original model.

Table 1. Demographic, diagnostic, and treatment data

Table 2. Prediction of mental retardation in survivors vs. siblings, N=12,227.

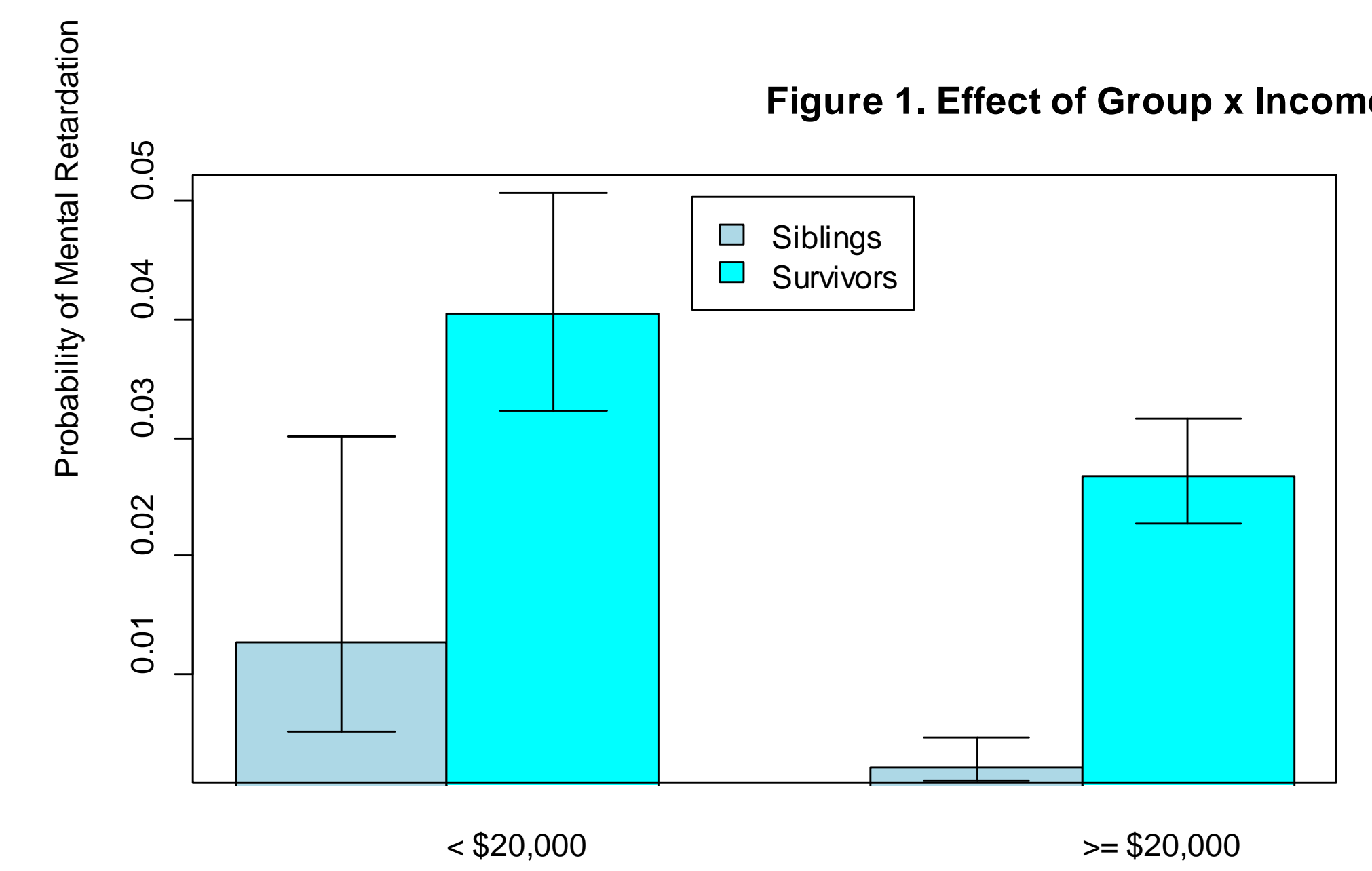


Figure 1. Effect of Group x Income

Separate models of the prediction of mental retardation in the two income groups indicate that in both income groups the odds of mental retardation for survivors were significantly greater compared to siblings (Figure 1).

Table 3. Prediction of mental retardation in survivors by diagnosis and treatment, N=7,383.

	B	S.E.	Wald χ^2	df	p.	Odds Ratio	95.0% CI for Odds Ratio	
							lower	upper
Intercept	-3.924	0.154	652.601	1	<.000	0.020		
Gender (males)	-0.128	0.127	1.019	1	.313	0.880	0.686	1.128
Age at follow-up	-0.008	0.015	0.260	1	.610	0.992	0.963	1.023
Household income (< \$20,000)	0.214	0.160	10785	1	.182	1.239	0.905	1.697
Ethnicity (other than white non-Hispanic)	0.025	0.182	0.019	1	.892	1.025	0.717	1.466
Age at diagnosis (vs. 1st year)			39.978	3	<.000			
2-4 years	-0.512	0.170	9.038	1	.003	0.599	0.429	0.837
5-10 years	-1.185	0.223	28.119	1	<.001	0.306	0.197	0.474
> 10 years	-2.254	0.397	32.254	1	<.001	0.105	0.048	0.228
Type of tumor (vs. CNS)			68.783	4	<.001			
Leukemia	-2.016	0.359	31.470	1	<.001	0.133	0.066	0.269
Wilms	-2.413	0.415	33.870	1	<.001	0.090	0.040	0.202
Sarcoma	-1.859	0.363	26.179	1	<.001	0.156	0.076	0.318
Neuroblastoma	-1.644	0.365	20.322	1	<.001	0.193	0.094	0.395
Chemotherapy (vs. none)			4.094	2	.129			
Not intrathecal	0.195	0.192	1.040	1	.308	1.216	0.835	1.770
Intrathecal	0.751	0.374	4.041	1	.044	2.119	1.019	4.406
Radiotherapy (vs. none)			12.906	2	.002			
Not to the brain	-0.381	0.311	1.504	1	.220	0.683	0.372	1.256
To the brain	0.495	0.159	9.717	1	.002	1.641	1.202	2.240
Number of new or recurrent malignancies	0.415	0.184	5.098	1	.024	1.5147	1.056	2.171
Age at diagnosis x Type of tumor	0.017	0.016	1.175	1	.278	1.018	0.986	1.050
Age at follow-up x Income	0.075	0.026	8.628	1	<.001	1.078	1.025	1.134

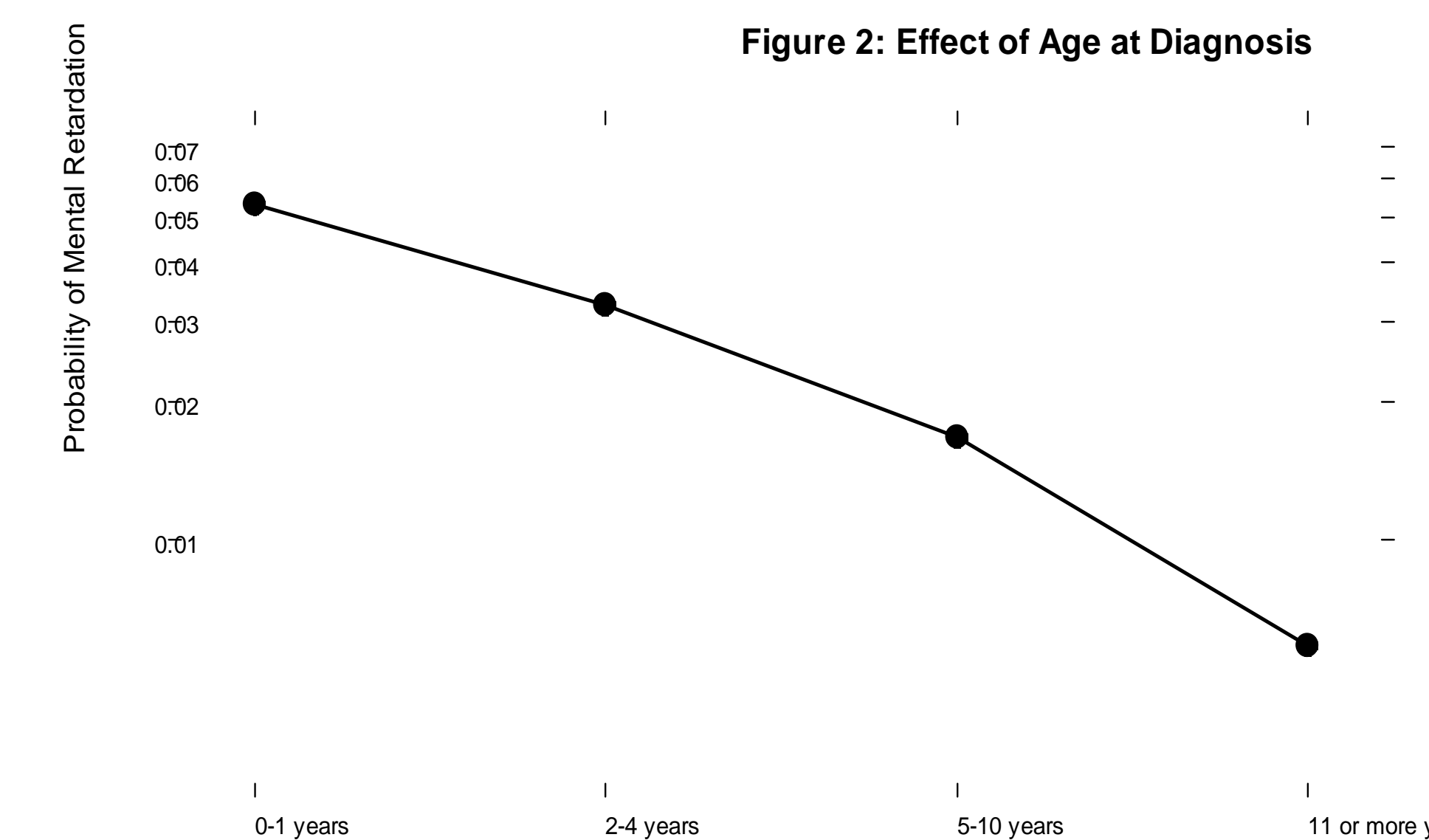


Figure 2: Effect of Age at Diagnosis

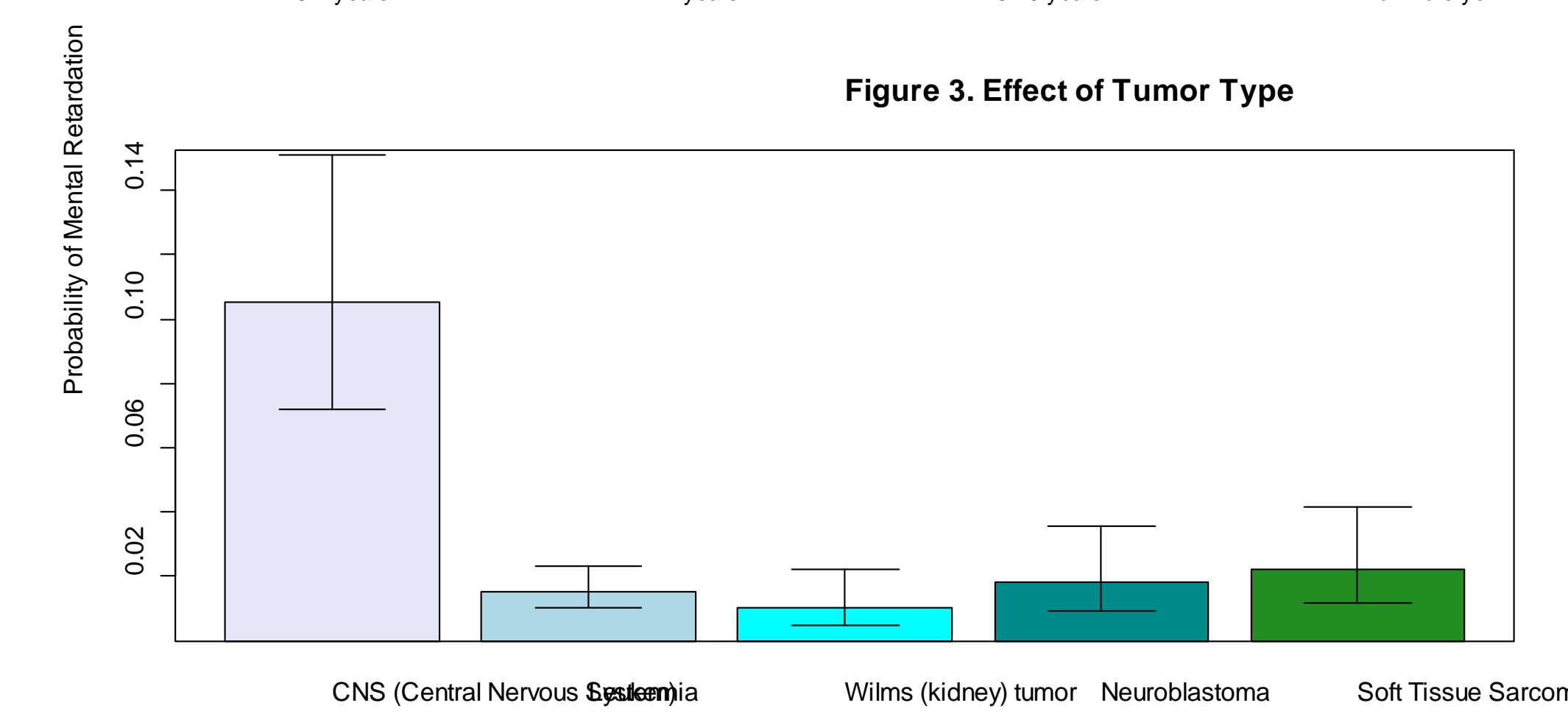


Figure 3: Effect of Tumor Type

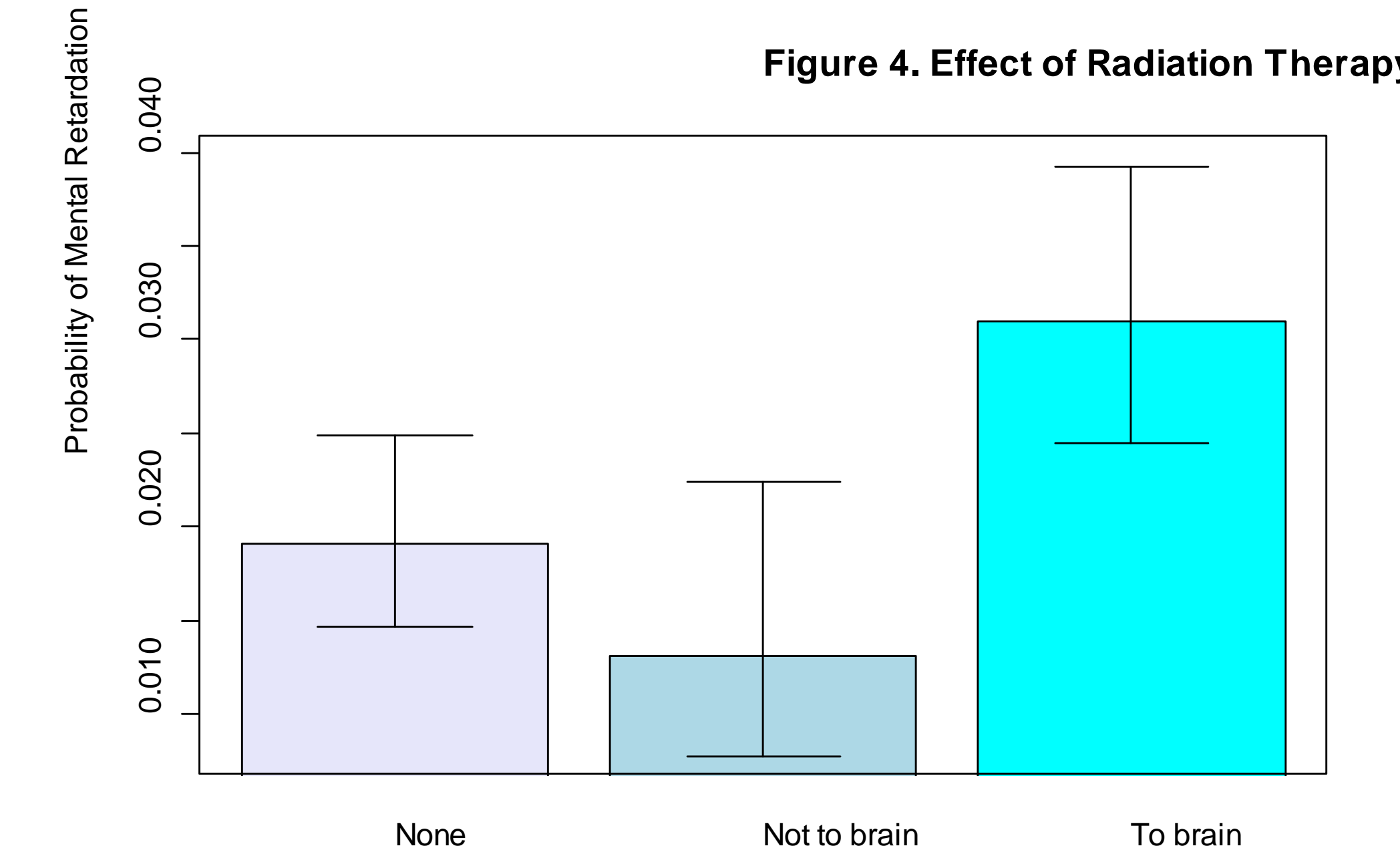


Figure 4: Effect of Radiation Therapy

Table 4. Prediction of learning disability in survivors vs. siblings, N=10,751.

	B	S.E.	Wald χ^2	df	p.	Odds Ratio	95.0% CI for Odds Ratio	
							lower	upper
Intercept	-1.476	0.046	1033.979	1	<.001	0.228		
Group (survivors)	1.140	0.074	238.407	1	<.001	3.128	2.707	3.615
Gender (males)	0.488	0.073	45.076	1	<.001	1.629	1.413	1.879
Age at follow-up	-0.041	0.004	88.311	1	<.001	0.959	0.951	0.968
Household income (< \$20,000)	0.633	0.059	116.599	1	<.001	1.883	1.678	2.112
Ethnicity (other than white non-Hispanic)	-0.018	0.067	0.072	1	.789	0.982	0.861	1.120
Group x Gender	-0.514	0.145	12.523	1	<.001	0.598	0.450	0.795
Age at follow-up x Income	0.025	0.009	83412	1	.004	1.026	1.008	1.043



For more information, address correspondence to:
Marc H. Bornstein, Child and Family Research,
NICHD, NIH, Suite 8030, 6705 Rockledge Drive,
Bethesda MD 20892-7971, U.S.A.
Email: Marc_H_Bornstein@nih.gov.