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Silent cerebral infarction, income, and grade retention among students with sickle cell anemia

Allison A. King^{1,*}, Mark J. Rodeghier², Julie Ann Panepinto³, John J. Strouse⁴, James F. Casella⁴, Charles T. Quinn⁵, Michael M. Dowling⁶, Sharada A. Sarnaik⁷, Alexis A. Thompson⁸, Gerald M. Woods⁹, Caterina P. Minniti¹⁰, Rupa C. Redding-Lallinger¹¹, Melanie Kirby-Allen¹², Fenella J. Kirkham¹³, Robert McKinstry¹⁴, Michael J. Noetzel¹⁵, Desiree A. White¹⁶, Janet K. Kwiatkowski¹⁷, Thomas H. Howard¹⁸, Karen A. Kalinyak⁵, Baba Inusa¹⁹, Melissa M. Rhodes²⁰, Mark E. Heiny²¹, Ben Fuh²², Jason M. Fixler²³, Mae O. Gordon²⁴, and Michael R. DeBaun²⁵

¹Program in Occupational Therapy and Department of Pediatrics, Hematology/Oncology, Washington University School of Medicine, St. Louis, Missouri ²Rodeghier Consultants, Chicago, Illinois ³Division of Hematology/Oncology, Department of Pediatrics, Medical College of Wisconsin, Milwaukee, Wisconsin ⁴Division of Hematology/Oncology, Department of Pediatrics, Hematology/Oncology, Johns Hopkins University School of Medicine, Baltimore, Maryland ⁵Division of Hematology/Oncology, Department of Pediatrics, Cincinnati Children's Hospital Medical Center and University of Cincinnati, Cincinnati, Ohio ⁶Departments of Pediatrics, Neurology, and Neurotherapeutics, University of Texas Southwestern Medical School, Dallas, Texas ⁷Division of Hematology/Oncology, Department of Pediatrics, Wayne State University, Detroit, Michigan ⁸Division of Hematology/Oncology, Department of Pediatrics, Northwestern University, Chicago, Illinois ⁹Division of Hematology/Oncology, Department of Pediatrics, University of Missouri–Kansas City, Kansas City, Missouri ¹⁰National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, Maryland ¹¹Division of Hematology/Oncology, Department of Pediatrics, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina ¹²Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada ¹³Neurosciences Unit, Institute of Child Health, University College London, London, United Kingdom ¹⁴Department of Radiology, Washington University School of Medicine, St. Louis, Missouri ¹⁵Departments of Neurology and Pediatrics, Washington University School of Medicine, St. Louis, Missouri ¹⁶Department of Psychology, Washington University, St. Louis, Missouri ¹⁷Division of Hematology/Oncology, Department of Pediatrics, University of Pennsylvania, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania ¹⁸Division of Hematology/Oncology, Department of Pediatrics, University of Alabama at Birmingham, Birmingham, Alabama ¹⁹Department of Paediatrics, Evelina Children's Hospital, St Thomas' Hospital National Health Service Trust, London, United Kingdom ²⁰Division of Hematology/Oncology, Department of Pediatrics, The Ohio

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*Correspondence to: Allison King, Washington University School of Medicine, 660 South Euclid, Box 8505, St. Louis, MO 63110. king_a@wustl.edu.

Additional Supporting Information may be found in the online version of this article.

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State University, Columbus, Ohio ²¹Division of Hematology/Oncology, Department of Pediatrics, Indiana University–Purdue University Indiana, Indianapolis, Indiana ²²Division of Hematology/Oncology, Department of Pediatrics, Brody School of Medicine, Greenville, North Carolina ²³Division of Hematology/Oncology, Department of Pediatrics, Sinai Hospital, Baltimore, Maryland ²⁴Department of Ophthalmology and Visual Sciences, Biostatistics, Washington University School of Medicine, St. Louis, Missouri ²⁵Vanderbilt-Meharry Center of Excellence in Sickle Cell Disease, Division of Hematology/Oncology, Department of Pediatrics, Vanderbilt University, Nashville, Tennessee

Abstract

Children with sickle cell anemia have a higher-than-expected prevalence of poor educational attainment. We test two key hypotheses about educational attainment among students with sickle cell anemia, as measured by grade retention and use of special education services: (1) lower household per capita income is associated with lower educational attainment; (2) the presence of a silent cerebral infarct is associated with lower educational attainment. We conducted a multicenter, cross-sectional study of cases from 22 U.S. sites included in the Silent Infarct Transfusion Trial. During screening, parents completed a questionnaire that included sociodemographic information and details of their child's academic status. Of 835 students, 670 were evaluable; 536 had data on all covariates and were used for analysis. The students' mean age was 9.4 years (range: 5–15) with 52.2% male; 17.5% of students were retained one grade level and 18.3% received special education services. A multiple variable logistic regression model identified that lower household per capita income (odds ratio [OR] of quartile 1 = 6.36, OR of quartile 2 = 4.7, OR of quartile 3 = 3.87; $P = 0.001$ for linear trend), age (OR = 1.3; $P < 0.001$), and male gender (OR, 2.2; $P = 0.001$) were associated with grade retention; silent cerebral infarct ($P = 0.31$) and painful episodes ($P = 0.60$) were not. Among students with sickle cell anemia, household per capita income is associated with grade retention, whereas the presence of a silent cerebral infarct is not. Future educational interventions will need to address both the medical and socioeconomic issues that affect students with sickle cell anemia.

Introduction

Children with poor health are at risk for poor academic attainment [1]. Higher absenteeism is associated with grade retention and limited academic attainment among children with chronic diseases, including sickle cell anemia [2], cancer [3,4], renal disease [5], and asthma [6]. Poor academic attainment among children limits future earnings and financial independence [1,7]. Other risk factors for poor academic attainment include male gender, African–American race/ethnicity, low socioeconomic status [8–10], single-parent households, lower parental academic attainment, lack of parental encouragement, poor self-esteem [11,12], and lack of health insurance [13]. Children with lower socioeconomic status as measured by family income or maternal education are more likely to exhibit poorer performance on cognitive testing, to be retained a grade level, or to not complete high school [14,15]. The strong correlation of socioeconomic status with future earning potential and quality of life underscores the importance of educational attainment [16–19].

Children with sickle cell anemia have an especially high risk for poor academic attainment as compared with other children because of the high prevalence of cerebrovascular disease. Approximately 30% of untreated children with this condition will experience a cerebrovascular event [20,21]; 80% of these events will result in significant cognitive deficits [22]. Chronic anemia is associated with lower levels of cognition among children and adults [23–25]. Among children with sickle cell anemia both with and without silent cerebral infarcts, we previously found that lower family income per capita and absence of the head of household's college education were associated with lower intelligence quotient scores [26]. We also found a grade-retention rate of 40% among 23 students with sickle cell anemia, cognitive deficits, and strokes [27]. Even students with sickle cell anemia and no stroke history had a 30% grade-retention rate [22]. Thus, grade retention among students with sickle cell anemia is common; causes are multifactorial and cannot be solely explained by the presence of strokes (Table I in Supporting Information).

Much literature regarding sickle cell anemia has focused on the prevention and treatment of cerebrovascular disease and anemia to address cognitive deficits and poor academic attainment. However, students with this chronic disease still face the same nonbiological issues as students without chronic disease: economic stress related to low income and reduced support from single-parent households or from parents with lower educational levels. On the basis of the observation that socioeconomic status is associated with poor academic performance, we explored the association between socioeconomic status as measured by household per capita income, silent cerebral infarcts, and educational attainment among students with sickle cell anemia. In light of our previous data [22], we conducted a cross-sectional analysis to test the hypothesis that among students with sickle cell anemia, those with a low household per capita income will have lower educational attainment as compared with students with a high household per capita income. Evidence to support that home environmental factors are associated with grade failure in children with sickle cell anemia will allow for resources to target the high-risk population to improve educational outcomes.

Methods

Study design

We performed a multicenter, cross-sectional study ($N = 536$) of 22 study sites included in the silent infarct transfusion (SIT) Trial. The SIT Trial ([ClinicalTrials.gov: #NCT00072761](https://clinicaltrials.gov/ct2/show/study/NCT00072761)) is a randomized, controlled, interventional trial for children with sickle cell anemia between 5- and 14-years-old. For study definition, sickle cell anemia included hemoglobin SS and sickle β^0 -thalassemia. A detailed description of the study design has been published [28]. Institutional review boards at each institution approved the study. All participants and their guardians provided assent, consent, or both. The current article describes screened participants; the randomized trial is ongoing.

For the SIT Trial and this cross-sectional study, children with the following conditions were ineligible: sickle cell anemia with history of a focal neurologic event lasting more than 24 h; history of overt stroke; transcranial Doppler study of more than 200 cm/s; comorbid neurologic disorders; human immunodeficiency virus infection; pregnancy; impaired renal

function (i.e., creatinine >2_upper limit of normal); treatment with chronic blood transfusions; clinically significant alloimmunization; and metallic structures in the body that interfere with magnetic resonance imaging.

During screening, parents or guardians of children completed a comprehensive questionnaire with a section specifically created to complete this study. Sociodemographic information was obtained via questions from the National Health and Nutrition Examination Survey socioeconomic status measures [29]. Parents self-reported socioeconomic data as well as their children's academic statuses (e.g., special education resources, grade retention). Children's hematocrit levels were recorded from clinical records upon enrollment in the SIT Trial.

Initially, a total of 1,176 children met criteria for eligibility for the SIT Trial and completed screening. European children ($N = 226$) were excluded because those students are not retained in lower grades for poor performance. We excluded 135 American children because they were in kindergarten with no chance to repeat a grade level yet (or grade level was not recorded); 145 were then excluded because they did not have valid magnetic resonance imaging data; finally, 134 were missing data on covariates used in the model, chiefly household income (Fig. 1 in Supporting Information). An analysis of the differences between subjects with and without missing data is presented in Table II in the Supporting Information, showing no large or consistent differences.

Primary outcome

For the purpose of this report, academic attainment is measured as grade retention and receipt of special education services. Grade retention was defined as the student having repeated a grade level. Typically, children who have challenges in school that result in grade retention have an Individual Educational Program (IEP). An IEP provides special education services to meet a child's unique needs, offering educational benefit. Children with sickle cell anemia and educational challenges would meet IEP criteria under the category titled "Other Health Impairment" [30].

Covariates of interest

Data about the following covariates were collected for their known association with our primary outcome. Parents or guardians reported their own highest completed level of education, which was classified as "less than high school graduate," "GED/high school graduate," or "any amount of college." Marital statuses were collapsed into categories of "married" and "unmarried." Total family income was reported in \$5000 increments; the midpoint of each increment was divided by the total number of people in the household to create a per capita income variable. Type of health coverage was recorded as "Medicaid" (Medicaid or State Children's Health Insurance Plan), "private insurance," or "no coverage."

Educational attainment

Grade retention was defined as the student having repeated a grade level. Receipt of an IEP constituted special education services. Receipt of a 504 Plan was recorded but not considered special education services. Section 504 is an antidiscrimination, civil rights

statute (Rehabilitation Act of 1973) that requires the needs of students with disabilities be met as adequately as those of children without disabilities [31]. Children with sickle cell anemia may have a 504 Plan in place to provide more frequent restroom breaks, the chance to carry a water bottle, an extra set of books at home to reduce the physical burden of transporting books, or extra time to complete assignments as a result of fatigue.

Statistical analysis

Demographic features of the students with and without histories of grade retention were analyzed with the *t*-test for continuous variables and with the χ^2 test or Fisher's exact test for discrete variables, or the Mann–Whitney *U* for ordinal variables or those with skewed distributions. Multivariable logistic regression was used to model the risk of grade retention or receipt of an IEP. We used a combination of sociodemographic measures (i.e., household per capita income, level of education of head of household, age, gender, and type of health coverage) that was based on previously published studies [8–12] as well as biologically plausible measures, including silent cerebral infarcts, pain event rates, and hematocrit levels.

Results

Demographics

A total of 536 students, average age 9.4 years, were evaluated. Almost 48% were female, 98% were self-reported African Americans, 1.5% were Hispanic, 98.2% had hemoglobin SS, 17.5% had a history of grade retention, and 18.3% received an IEP. Students who were retained a grade level were more likely to be male ($P = 0.002$), to have slightly larger households ($P = 0.05$), to have lower per capita household income ($P < 0.001$), to be on Medicaid ($P = 0.001$), and to have a head of household with lower education ($P = 0.01$). There were no differences in the rate of grade failure by presence of silent cerebral infarct ($P = 0.47$) or pain event rate ($P = 0.26$), but hematocrit was lower in this group ($P = 0.007$) (Table I).

As household income was reported in ranges, for purposes of the logistic regressions, household income per capita was divided into quartiles (<\$2999, \$3000–\$5834, \$5835–\$11,250, and >\$11,251). There was a correlation between household per capita income and Medicaid ($r = 0.49$; $P = 0.001$).

Almost half of the students with a history of grade retention received educational support from school systems. A total of 47.9% (45 of 94) of students with grade retention had IEPs, and ~9.3% (50 of 536) of all students had 504 Plans. With regard to 504 Plans, there was no difference between those who had a history of grade retention as compared with those who did not.

Multivariable model of risks for grade retention

The multivariable logistic regression was conducted in two steps. First, a model was constructed with all characteristics and a significance of $P < 0.20$ was used to screen for inclusion in a reduced model. A second model was run with the screened set of characteristics.

In the first stage, three characteristics met the screening criterion: age ($P < 0.001$), gender ($P = 0.001$), and household per capita income ($P = 0.002$). None of the biological factors, including silent cerebral infarct, met the screening criterion. In the reduced model with these three, all remained significantly associated with grade retention (model chi square = 56.0, 5 df, $P < 0.001$): male gender (OR 2.23, 95% CI 1.37–3.65, $P = 0.006$), age (OR 1.30, 95% CI 1.16–1.44), and household per capita income ($P < 0.001$). Specifically, as compared with those in the highest quartile of household per capita income ($> \$11,251$), those with household per capita incomes of \$5835 to \$11,250 (third quartile) had an OR of 3.87 for grade retention; those with household per capita incomes of \$3000 to \$5834 (quartile 2) had an OR of 4.70; and those in the lowest quartile ($< \$2999$) had an OR of 6.36 (Table II). Figure 1 displays the predicted probability of grade retention for males based on the final model. By age 14 the model predicts an instance of grade retention is more likely than not for males in the lower three quartiles of income.

Multivariable model of risks for individual education plan

In the first stage, three characteristics met the screening criterion: age ($P = 0.001$), grade retention ($P < 0.001$), and silent cerebral infarct ($P = 0.12$). In the reduced model, only two variables were significantly associated with IEP (model chi square = 69.6, 3 df, $P < 0.001$): age (OR 1.21, 95% CI 1.08–1.35, $P = 0.001$) and grade failure (OR 5.80, 95% CI 3.50–9.60, $P < 0.001$). Silent infarct was not ($P = 0.120$) (Table III).

Discussion

Sickle cell anemia is an inherited disease that most commonly occurs among people of African descent living in North America. Previous studies have documented lower levels of socioeconomic status among patients with this disease, but none have presented the overwhelming evidence of disparity as the current study [32–34]. A report from the Cooperative Study of Sickle Cell Disease showed that increasing age, lower reading achievement and lower family cohesion were associated with grade retention in 204 children with sickle cell disease [35]. By examining the largest sample of school-aged children with sickle cell anemia among a more recent cohort, our findings describe the striking educational challenges that these students face.

Household per capita income—not silent cerebral infarct or frequent painful episodes—was the dominant risk factor associated with grade retention among students with sickle cell anemia. Previous studies presented associations among silent cerebral infarcts, cognitive deficits, and poor academic achievement (i.e., grade retention and receipt of IEP or 504 plan); however, they failed to quantify the associations with household per capita income [22,35,36]. Recently, we published results from the SIT Trial that predicted lower intelligence scores with lower household income per capita, lower levels of head of household education, and increasing age of the child [26]. In fact, a lack of college education was associated with a decrease of 6.2 points while the presence of silent cerebral infarcts was associated with a 5.2 point decrease in intelligence quotient. These results may also be contributing to the increased risk of grade retention among the older children.

Multiple studies have documented lower intelligence quotient scores among children with silent cerebral infarcts as compared with sibling controls [22,36–38] and age-expected norms. Lower intelligence quotient scores have been documented among children with sickle cell anemia and overt strokes [22,36–38]. As a result of these sequelae, primary and secondary prevention of cerebral infarcts is a major component of care for children with sickle cell disease. Our data suggest that the focus on only preventing cerebral infarcts (primary or secondary) may not address the multifactorial issues that lead to poor educational attainment among these students.

An unexpected finding of the study was the degree of poverty of these children. According to the 1999 census, the average household per capita income in the United States was \$21,587 [39]. Families that provided annual income information for our study had a median household per capita income of \$6250. A total of 82% of families reported their annual incomes, and these reports skewed toward lower incomes. These data are correlated with the children's health insurance coverage. Only 12 children (1.6%) had no health coverage at all, and the majority received health insurance from Medicaid (69%). Previous studies involving large national hospital databases estimated that 60–70% of children with sickle cell anemia have Medicaid coverage [40,41]. In 2009, the Department of Health and Human Services set the poverty guideline for the income of a family of four at \$22,050 (i.e., \$5512 per person) [39]. We believe that the household per capita income data obtained for this study are likely representative of the population of children with sickle cell anemia in the United States.

An inherent limitation of this study is that no temporal relationship can be established between household per capita income and academic attainment. Only one time-point is available, so we do not know when the silent cerebral infarcts occurred or the duration of the morbidity caused by cerebral ischemia. The average age of a child with a silent cerebral infarct in the Cooperative Study of Sickle Cell Disease cohort ($n = 46$) was 8 years (i.e., 6 years in girls, 10 years in boys). The mean age of children diagnosed with silent cerebral infarcts in the current study was 9.6 years. Given the similar age at diagnosis for silent cerebral infarcts in both cohorts, we believe the students in this study are representative of the population of children with sickle cell anemia in the United States with regard to this complication. The report from the Cooperative Study of Sickle Cell Disease found a similar rate of grade retention as our more modern cohort [35]. We were unable to obtain source documents for family income or school records. However, the data are consistent with previously published results among demographically similar families. For example, we confirmed previous findings that males are more likely to have lower levels of educational attainment than females. No clear etiology is identified in the literature, but self-esteem is less associated with academic performance among boys versus girls [42]. In addition, our previous work predicts a decrease in IQ for each year of age among students with sickle cell anemia [26]. The decreases in cognition may also contribute to the gradually increasing risk of grade retention and increasing age.

Another limitation of the study design included the inability to determine household income over time. Thus, we could not measure the length of exposure to silent cerebral infarct or to poverty. African Americans who are born into poverty tend to remain in or near poverty [43], so the exposure to poverty was likely longer than the exposure to the silent cerebral

infarct. The U.S. Department of Education found that, among African-American students from kindergarten through eighth grade, 22.9% of those who were poor (<100% of poverty level), 10.9% of those who were near poor (100–199% of poverty level), and 5.1% of the nonpoor (200% of poverty level) had a history of grade retention [44]. When we categorized our family income data into these categories of poor, near poor, and nonpoor, 20%, 16.7%, and 5.9% of the groups, respectively, had failed a grade. These results are similar to those of Schatz's study, which demonstrated a correlation of cognitive scores with lower socioeconomic status for both children with sickle cell anemia and controls; however, there was a "basement effect" of poverty for both groups [45].

Although silent cerebral infarcts were not a significant risk factor for grade retention in this model, their impact on cognition should not be discounted. Rather, our data suggest that silent cerebral infarcts alone may not be responsible for poor academic performance or even be the primary cause among this population. The impact of poverty on school systems is known. As minority enrollment and poverty increases, teacher quality decreases [46]. School districts with lower quality teachers are less likely to have students who are ready for college [47]. Perhaps the effect of poverty on educational attainment is so strong that the influence of other factors is difficult to detect.

In summary, the results of this study indicate that, among students with sickle cell anemia, a low household per capita income is associated with grade retention; whereas, the presence of a silent cerebral infarct is not. The majority of children with sickle cell anemia who receive care at 22 academic medical centers are living below or just above the poverty threshold. When designing studies to assess the medical determinants of cognition in children with sickle cell anemia, family household factors, and social determinants of health—including poverty—must be included. In all likelihood, only a multidisciplinary approach will allow us to make progress in our efforts to support these families. Our work and others suggest that interventions that target parenting skills and student specific health and educational issues are needed. The level of educational attainment is associated with the future earning potential and quality of life of these children [16–19]. Thus, the task of maximizing children's educational attainment is an important public responsibility.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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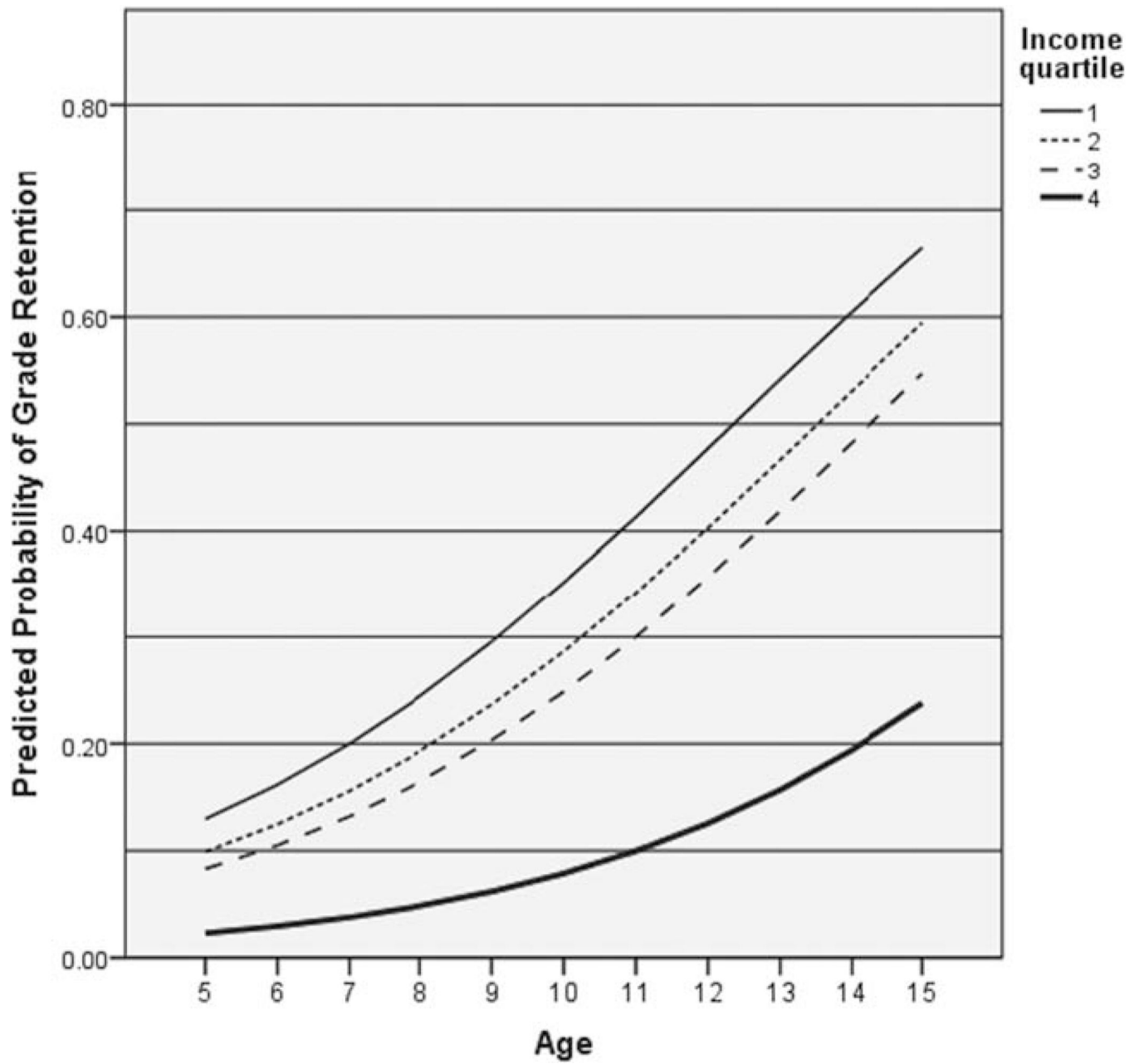


Figure 1. Logistic regression predicted probabilities for grade retention for males, by age and household income.

TABLE I

Demographics of Children with Sickle Cell Anemia Screened in the Silent Infarct Transfusion Trial

Variable	History of grade retention (N = 94)	No history of grade retention (N = 442)	P-value
Age of child at registration in years	10.4	9.2	<0.001
Gender (male, %)	(67.0)	(49.1)	0.002 ^a
Silent infarct (%)	(28.7)	(32.6)	0.466 ^a
Hematocrit level	22.2	23.2	0.007
Pain event rate (episodes per 3 years)	0.59	0.55	0.260 ^b
Last grade that the child completed in school (median)	3	2	0.095 ^b
IEP in place (%)	(47.9)	(12.0)	<0.001 ^a
504 Plan in place (%)	(7.4)	(9.8)	0.486 ^a
Medicaid health care coverage for child (%)	(82.8)	(64.5)	0.001 ^a
Marital status of parents: unmarried (%)	(68.1)	(58.6)	0.088 ^a
Age of mother in years	34.6	34.6	0.962
Age of father in years	38.4	37.2	0.225
Number of people in household	4.9	4.5	0.052
Yearly household per capita income in U.S. dollars	5668	9365	<0.001
Yearly household per capita income in U.S. dollars (median)	(IQR 5 5833)	(IQR 5 8929)	<0.001 ^b
Head of household education (overall test)			0.010 ^a
Less than high school graduation (%)	24.5	14.3	
High school diploma or GED (%)	36.2	31.0	
Any amount of college (%)	39.4	54.8	

IEP, individualized education program; GED, general education development.

^a Chi-square test.

^b Mann-Whitney *U* test.

TABLE II

Logistic Regression Model of Risk Factors for Grade Retention Among Children with Sickle Cell Anemia Screened in the Silent Infarct Transfusion Trial

Covariate	Odds ratio	95% CI for odds ratio		P-value
		Lower	Upper	
Age at registration	1.30	1.16	1.44	<0.001
Gender (male)	2.23	1.37	3.65	0.001
Household per capita income—Quartile 1 ^a	6.36	2.80	14.41	<0.001
Household per capita income—Quartile 3	4.70	2.08	10.62	<0.001
Household per capita income—Quartile 3	3.87	1.69	8.85	0.001

^aHousehold per capita income in US dollars; reference category is Quartile 4.

TABLE III

Logistic Regression Model of Risk Factors for Special Education Among Children with Sickle Cell Anemia Screened in the Silent Infarct Transfusion Trial

Covariate	Odds ratio	95% CI for odds ratio		P-value
		Lower	Upper	
Age at registration	1.21	1.08	1.35	0.001
Grade failure	5.80	3.50	9.60	<0.001