

Cognition and Education Benefits of Increased Hemoglobin and Blood Oxygenation in Children

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Disclosures

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- Current employment in Genesis Research and former employee of PRECISIONheor, a life sciences research consulting firm paid by GBT to conduct this study
- Research funding: NHLBI, HRSA, PCORI, and ASH

Allison A. King

- Research funding: Global Blood Therapeutics

Andy Nguyen

- Current employment and current equity holder in a publicly traded company: Global Blood Therapeutics

Anuj Muyabi

- Current employee of PRECISIONheor, a life sciences research consulting firm paid by GBT to conduct this study. He owns no equity in PRECISIONheor

Irene Agodoa

- Current employment and current equity holder in a publicly traded company: Global Blood Therapeutics

Kim Smith-Whitley

- Current employment and current equity holder in a publicly traded company: Global Blood Therapeutics

Introduction

- Chronic anemia in individuals with sickle cell disease (SCD) has been associated with impaired intellectual functioning and lower academic achievement.¹⁻⁴
- Among these individuals, decreased hemoglobin (Hb) is associated with increased risk of stroke and lower oxygen saturation (SpO₂), which are both associated with lower intelligence quotient (IQ) scores.^{5,6}
- Thus, increasing Hb and SpO₂ in individuals with SCD may increase IQ and educational attainment.

1. Kawadler JM, et al. *Dev Med Child Neurol*. 2016;58(7):672-679. 2. Steen R, et al. *J Child Neurology*. 2005; 20(2):102-107. 3. Wang W, et al. *J Pediatr*. 2001;139(3):391-397. 4. Harris KM, et al. *Soc Work Publ Health*. 2019;34(6):468-482. 5. Ohene-Frempong K, et al. *Blood*. 1998;91(1):288-294. 6. King A, et al. *Am J Hematol*. 2014;89(2):162-167.

Hb, hemoglobin; IQ, intelligence quotient; SpO₂, oxygen saturation.

Objectives

- To model the link between increased hemoglobin/oxygenation and improvements in cognitive function, educational attainment, and incidence of stroke as a result of improved treatment for SCD

Methods

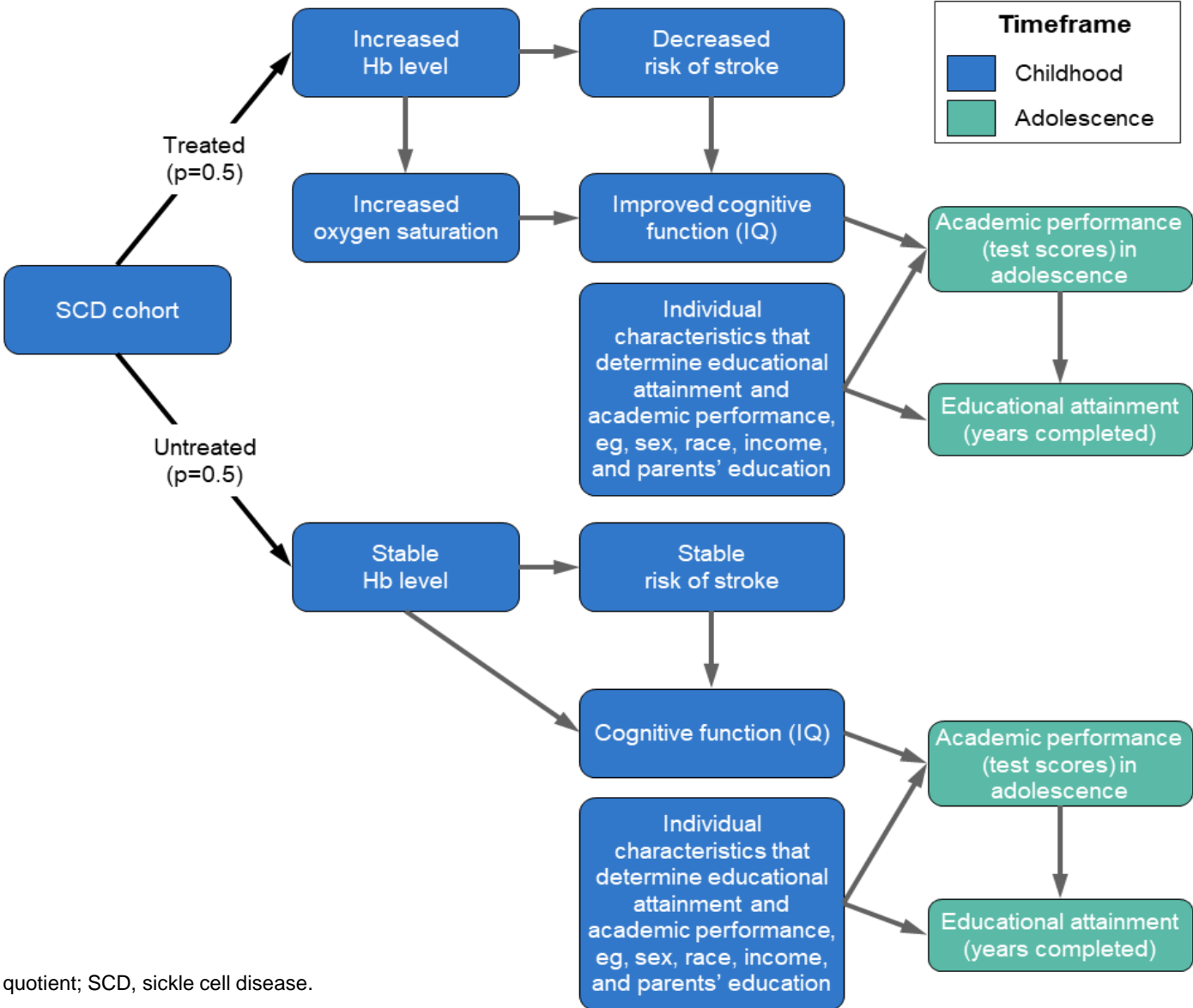
Model Design

- A cohort simulation model was built to reflect the pediatric SCD population and used to estimate how improvements in pediatric cognitive function, as measured by IQ, generated from randomized treatment for SCD, affect academic performance and educational attainment.
- The model contained two key stages: childhood (preschool and school age, <10 years) and adolescence (≥ 10 years). The model framework is shown in Figure 1.
 - In the first stage, children in the treated group had a mean Hb increase of 1.1 g/dL and increased SpO₂, which impacted IQ by directly increasing it and preventing deterioration of IQ over time. Hb increase also decreased the risk of stroke.
 - In the second stage, adolescence, IQ was a determinant of academic performance, as measured by the Armed Forces Qualification Test scores.¹
 - These scores and other individual characteristics, including pre-school attendance, parental educational attainment, and noncognitive skills (social skills, motivation, self-esteem, and self-control) were employed to model years of education completed.²
- Key model parameters were identified in the literature and are summarized in Table 1.

1. Borghans L, et al. *Proc Natl Acad Sci U S A*. 2016;113(47):13354-13359. 2. Heckman JJ, Raut LK. *J Econom*. 2016;191(1):164-175.

IQ, intelligence quotient; SCD, sickle cell disease; SpO₂, oxygen saturation.

Figure 1. Model Diagram



Hb, hemoglobin; IQ, intelligence quotient; SCD, sickle cell disease.

Table 1. Key model parameters

Model Parameter	Value	Sources
Treatment effect on hemoglobin	1.10 g/dL increase (95% CI: 0.9-1.4)	Vichinsky et al. (2019) ¹
Treatment effect on oxygen saturation	3.10 percentage point increase per 1 g/dL increase in Hb	Blyden et al. (2018) ²
Relative stroke risk (infarctive)	1.85 (95% CI: 1.32-2.59) per 1 g/dL decrease in Hb	Ohene-Frempong et al. (1998) ³
Reduction in IQ score in stage 1 resulting from stroke	-15.86	Kawadler et al. (2014) ⁴
Reduction in IQ score in untreated state between stages 1 and 2 independent of stroke/infarct status	-5.00	Wang et al. (2001), ⁵ King et al. (2014) ⁶
Increase in IQ score per 1 percentage point increase in SpO2	0.75	King et al. (2014) ⁶
Baseline initial IQ	Mean 89.18 (95% CI: 86.36-92.00)	Kawadler et al. (2014) ⁴
Baseline initial stroke risk	Mean 7.20% (SD 0.7)	DeBaun et al. (2014) ⁷
Probability of being female	52.00%	Farber et al (1985) ⁸

1. Vichinsky E, et al. *N Engl J Med.* 2019;381(6):509-519. 2. Blyden G, et al. *Am J Hematol.* 2018. doi:10.1002/ajh.25139. 3. Ohene-Frempong K, et al. *Blood.* 1998;91(1):288-294. 4. Kawadler JM, et al. *Dev Med Child Neurol.* 2016;58(7):672-679. 5. Wang W, et al. *J Pediatr.* 2001;139(3):391-397. 6. King A, et al. *Am J Hematol.* 2014;89(2):162-167. 7. DeBaun MR, et al. *N Engl J Med.* 2014;371(8):699-710. 8. Farber M, et al. *J Chronic Dis.* 1985;38(6):495-505.

Hb, hemoglobin; IQ, intelligence quotient; SpO2, oxygen saturation.

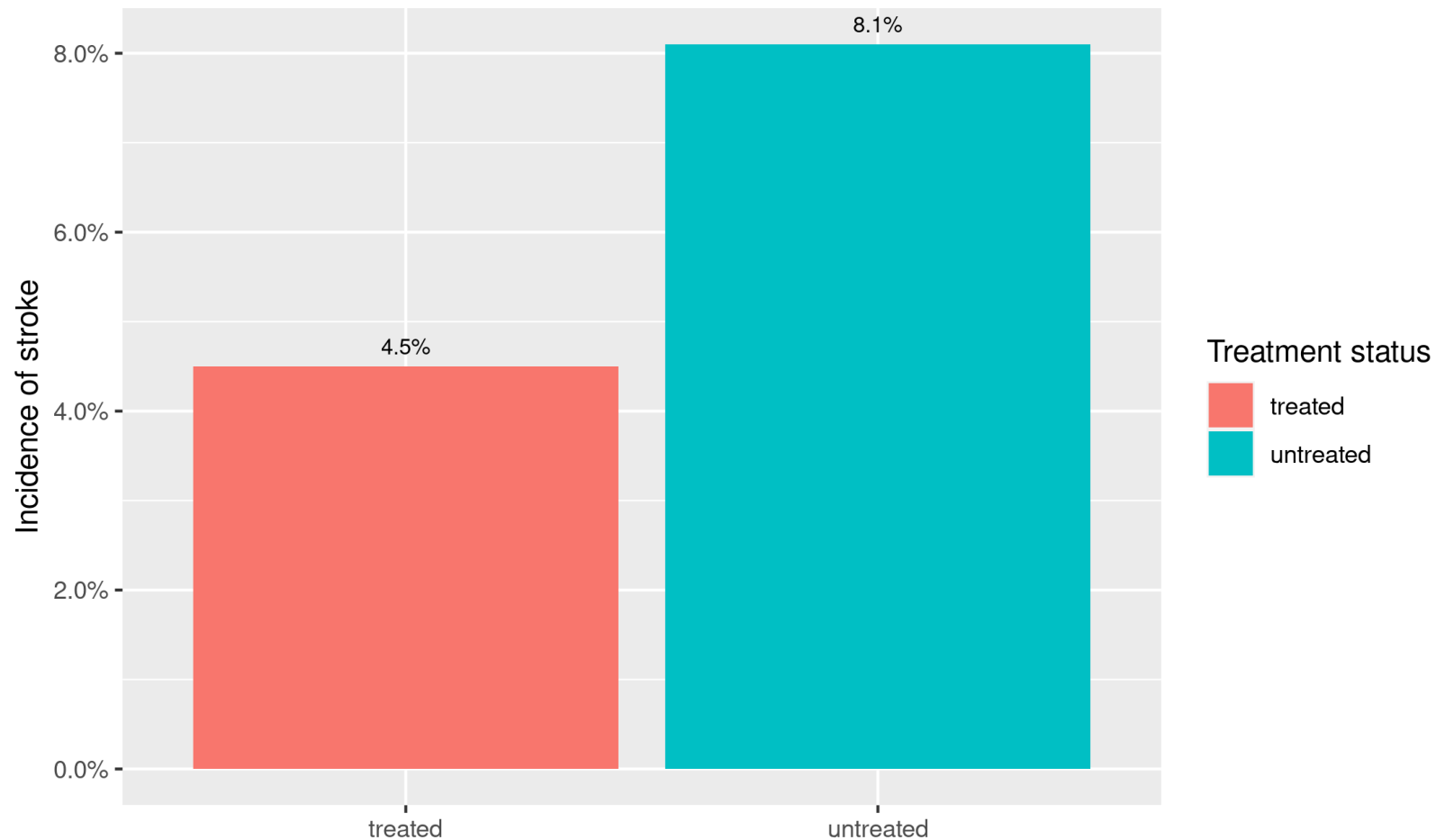
Model Scenarios

- **Baseline**
 - Individuals in the treated group receive a boost in Hb and SpO₂, which affects IQ both directly—increasing it and preventing the deterioration of IQ over time—and indirectly, by decreasing the risk of stroke.
- **Only treatment varies between cohorts**
 - All individuals in the cohort had the same baseline levels of socioeconomic variables including noncognitive skills, mother's education, father's education, and preschool attendance.
 - Isolates the impact of cognitive skills on educational attainment.
- **Treatment impacts noncognitive skill development as well as**
 - Explores the potential impact of allowing treatment to affect noncognitive skills, which in turn impact educational outcomes.
 - Treatment increased the probability that the socialization, self-concept, and motivation noncognitive skills were present by 10%.

Results

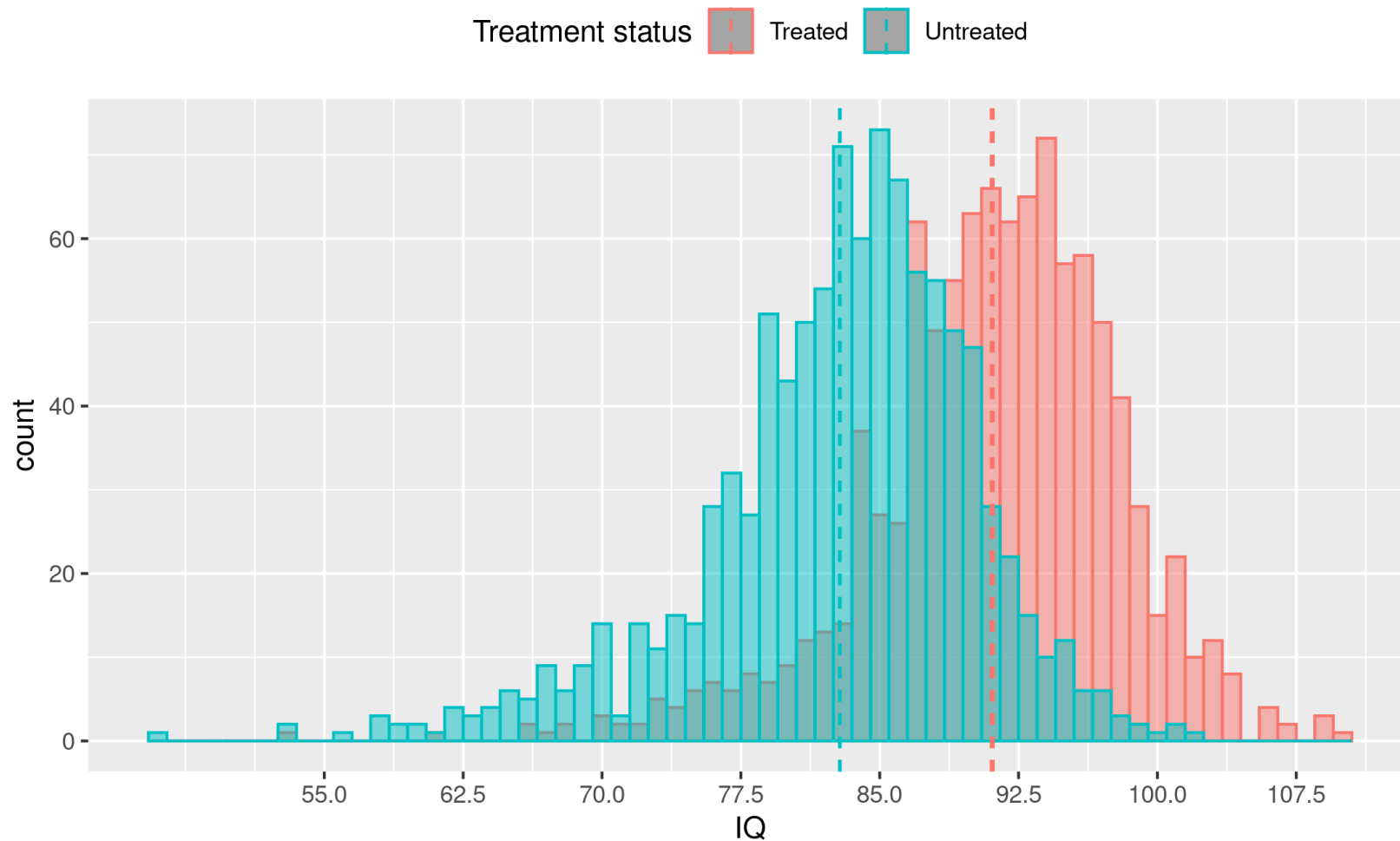
44.4% Lower Incidence of Stroke Among Treated Group in Model

- The model predicted that 4.5% of the treated group would have a stroke versus 8.1% of the untreated group



Average IQ 9.9% Higher Among Treated Group in Model

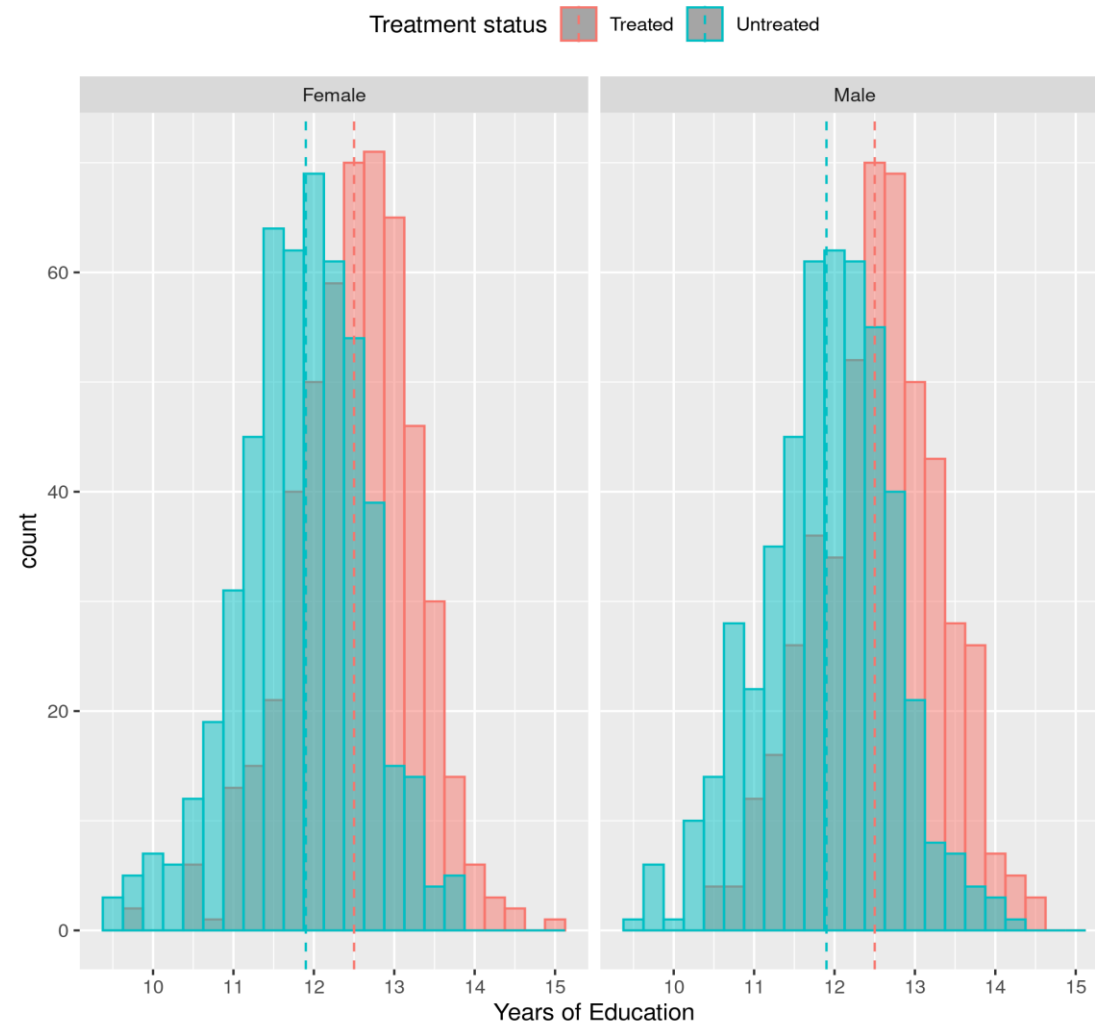
- Average IQ was estimated to be 91.1 in the treated group vs 82.8 in the untreated group



IQ, intelligence quotient.

High School Completion 64.7% Higher Among Treated Group in Model

- 76.1% of the treated group were projected to complete 12+ years of school vs 46.2% of the untreated group



Model Results

Predicted Outcome	Group		Difference		
	Untreated	Treated	Absolute	Relative	P-value
Panel A: Baseline					
Stroke incidence	8.1%	4.5%	-3.6%	-44.4%	0.001
IQ score	82.85	91.08	8.23	9.9%	<0.001
Years of education	11.87	12.53	0.65	5.5%	<0.001
% completing ≥12 years of education	46.2%	76.1%	29.9%	64.7%	<0.001
Panel B: Scenario 1					
Stroke incidence	8.3%	4.3%	-4.0%	-48.2%	<0.001
IQ score	82.72	91.03	8.30	10.0%	<0.001
Years of education	11.50	12.17	0.66	5.8%	<0.001
% completing ≥12 years of education	18.7%	65.0%	46.3%	247.6%	<0.001
Panel C: Scenario 2					
Stroke incidence	6.9%	4.9%	-2.0%	-29.0%	0.058
IQ score	82.96	90.94	7.99	9.6%	<0.001
Years of education	11.86	12.55	0.69	5.8%	<0.001
% completing ≥12 years of education	44.9%	75.2%	30.3%	67.5%	<0.001

IQ, intelligence quotient.

Limitations

The model does not capture the following impacts/relationships:

- Improved cognitive function on noncognitive function
- Improved cognitive function and increased educational attainment on employment
- Improved cognitive function and increased educational attainment on life expectancy
- Stroke on educational attainment and academic achievement (only captured indirectly through IQ)

Conclusions

In this simulation model, children with SCD with increased Hb and SpO2 were estimated to have better cognitive function (IQ) and lower risk of stroke.

Our model predicts that an average 1.1 g/dL improvement in Hb may be associated with improved neurocognition and educational outcomes.

These improvements may also generate benefits not captured by our model, including improved quality of life, employment, and income among individuals with SCD.

Acknowledgments

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