HHS Public Access

Author manuscript

J Dev Behav Pediatr. Author manuscript; available in PMC 2023 May 01.

Published in final edited form as:

J Dev Behav Pediatr. 2022 May 01; 43(4): 224–232. doi:10.1097/DBP.0000000000001011.

Sociodemographic and biomedical correlates of developmental delay in two- and four-year-olds with sickle cell disease

Jeffrey Schatz, Ph.D., **Laura Reinman, Ph.D.**, **Sarah Bills, M.A.**, **Julia Johnston, M.A.**

Department of Psychology, University of South Carolina, Columbia, SC

Abstract

Background: Developmental delay occurs frequently in sickle cell disease (SCD). Psychosocial and biomedical factors contribute to delays, but most studies have not examined the timing of risk factors and developmental delay. We examined sociodemographic and biomedical factors to evaluate if risks for developmental delay differed across two developmental periods.

Methods: We examined Ages and Stages Questionnaire, 2nd edition (ASQ-2) outcomes in two-year-olds ($n = 100$) and four-year-olds ($n = 101$) with SCD. ASQ-2 data was obtained from routine developmental screenings administered as part of health care between 2009 and 2016 at a single hematology clinic. Medical record reviews were used to identify sociodemographic and biomedical factors associated with positive screenings for developmental delay.

Results: Two-year-olds with positive ASQ-2 screenings ($n = 32$; 32%) were less likely to have private health insurance or to have been in formal daycare and more likely to have a severe SCD genotype. Four-year-olds with positive screenings ($n = 40$; 40%) were more likely to have a severe SCD genotype or an abnormal transcranial doppler ultrasound (TCD) exam indicating high stroke risk. The strength of the association between positive screenings and insurance status, severe genotypes, and TCD exams differed across the two age groups. Domain-level outcomes on the ASQ-2 also differed across the two age groups.

Conclusion: The cross-sectional data indicate biomedical and psychosocial risks are related to developmental delay, but the association with specific risk factors differs across age.

Keywords

sickle cell disease; child development; preschool children; neurodevelopmental disorders

Developmental delay occurs at a high rate among young children with sickle cell disease (SCD) with rates across published reports ranging from ~7–11% in 12-month-olds to ~46–50% in three-year-olds.[1–3] The risk factors associated with developmental delay have varied across studies, but include parental socioeconomic status, the quality of parent-child interactions and home environment, male gender, cerebral blood flow velocity (related to stroke risk), hospitalizations for vaso-occlusive pain episodes, and having a severe sickle cell genotype.[2–6] One limitation of most reports has been a lack of testing for age-specific

Correspondence should be directed to: Jeffrey Schatz, Department of Psychology, University of South Carolina, Columbia, SC (schatz@sc.edu).

associations with developmental risk and protective factors. The specific factors and their strength of impact may differ depending on the child's age. The goal of the present report was to assess the association of sociodemographic and biomedical risk factors with developmental delay in two-year-olds and four-year olds with SCD.

Sickle cell disease is a genetic blood disorder that leads to the production of abnormal (S-type) hemoglobin.[7] S-type hemoglobin has decreased oxygen-carrying capacity, has a shortened lifespan, and its cell wall undergoes changes under low oxygen concentration that makes the cells more viscous and gives the cells the "sickled" shape. These "sickled" cells more easily clump together to potentially block the microvascular supply and irritate the lining of blood vessels. Additionally, they are identified by the spleen as foreign bodies to be removed from the bloodstream, which adds further to anemia and taxes the immune system. The extent of abnormal hemoglobin production differs across specific genotypes that lead to SCD. Severe SCD genotypes (e.g., homozygous S (HbS/S), sickle cell beta-zero thalassemia (HbS/β-thal^0)) lead to a range of morbidities that vary from case-to-case, but include cerebrovascular complications, sleep disordered breathing, pain episodes, anemia, and decreased immune function.[7] There are also other relatively common genotypes of moderate severity (e.g., sickle cell hemoglobin C (HbS/C), sickle cell beta-plus thalassemia (HbS/β-thal$^+$)). Moderate genotypes are associated with variable, but typically milder or less frequent issues with pain episodes, anemia, and decreased immune function. Moderate genotypes have low rates of cerebrovascular complications in childhood relative to severe genotypes.[8–9]

The timing of measurement may be important for understanding how risk and protective factors impact developmental delay in SCD. For example, among social environmental factors exposure to poverty and the associated impacts on parent-child relationships has a differing degree of impact on child outcomes across developmental periods.[10–11] There are also age-related differences in the likelihood of biomedical impacts on development. Fetal hemoglobin typically decreases in production over the first two years of life; the production of fetal hemoglobin provides some protection from morbidity since it inhibits the "sickling" of S-type hemoglobin and reduces the severity of SCD.[12] Silent cerebral infarction (cerebral injury without clinical indications of stroke) begins to occur in the first two years of life in SCD and the prevalence increases steadily with older age .[13–14] Thus, social-environmental and biomedical risk factors should be examined in an age-dependent manner.

In a prior study we examined outcomes of developmental screenings for 77 four-year-olds to test a hypothesis regarding syntactic processing and working memory skills as indicators of early cerebrovascular risk in sickle cell disease.[6] In that study children with severe genotypes or abnormal TCD exams (indicating stroke risk) showed lower scores for a measure of syntactic processing and working memory than children with moderate-severity genotypes or normal TCD exams, respectively. Contrary to our expectations, a similar pattern of findings was observed for outcomes on the Ages and Stages Questionnaire, 2nd edition (ASQ-2), a general screening tool for developmental delay. Positive ASQ-2 screenings were also noted to occur predominantly in the fine motor domain. The screening measure assessing syntactic processing and working memory was only available in a subset of the children screened at four years of age. In the present report we examined ASQ-2

outcomes in the full sample of four-year-olds who completed screenings and compared these data to ASQ-2 outcomes for two-year-olds who participated in the same developmental screening program.

The first goal of the present study was to examine specific risk factors associated with positive developmental screenings on the ASQ-2 within two-year-olds and four-year-olds. Given that many risks to child development cluster together, we also examined risk factors within each age group through multivariate analyses to identify associations with developmental screening outcomes that statistically control for overlapping variance among risk/protective factors. Second, we directly compared risk factors across groups to determine if the effects differed in magnitude across age groups. Finally, we compared which behavioral domains were leading to positive screenings across the two age groups.

Methods

Participants

The dataset for this study included two-year-olds (ages 24–35 months) and 101 four-year-olds (48–59 months) with SCD (confirmed by hemoglobin electrophoresis) who completed developmental screenings as part of their routine care at a pediatric hematology specialty clinic in the Southeastern United States between January 2010 and December 2016. Screenings were offered as part of routine care for all children and completed at the clinic either before or after the medical appointment.

Measures

Ages and Stages Questionnaire, 2nd edition (ASQ-2).—The ASQ-2 is a parent-reported developmental screening questionnaire for children ages 4 to 60 months designed to identify children who may have developmental delays.[15] Parents rate whether the child demonstrates specific developmental milestones (“yes”, “sometimes”, “no”) in the domains of Communication, Gross Motor, Fine Motor, Problem Solving, and Personal-social. Parents are encouraged to directly test items that they are uncertain about and provided with materials to do so. Norm-referenced cut-off scores are used to identify positive screenings at the domain-level based on the total score for each domain. In our method, we also attempt to directly test milestones from domains with positive screenings that the parent has not directly tested as an additional check on positive screenings. If children with positive screenings based on parent ratings do not cooperate with our attempt to test the milestone, we continue to consider it a positive screening. There are age-specific forms based on the chronological age of the child. The ASQ-2 has excellent reliability ($r > .90$) based on test-retest and inter-rater reliability as described in the test manual. Convergent validity with developmental assessments is also reported in the ASQ-2 manual with an overall agreement of 83%.

Medical Chart Review.—Details of the patient’s demographic characteristics, childcare history, routine blood lab data, history of disease complications, and developmental screening results were obtained through medical chart review using a medical chart coding sheet to provide a structured form for the review of electronic and paper medical charts.

Inter-rater reliability using a second coder has indicated kappa values of .88 to 1.0 for the variables coded with a median kappa of .97. Information on age at screening, gender, race/ethnicity, rural residence, and insurance status were collected for demographic descriptors. Race/ethnicity codes from the medical records were based on U.S. census categories. Rural residence was categorized based on zip code data from the Federal Office of Rural Health Policy, which provides zip codes in which more than 50% of the population resides in either a Non-Metro County and/or a rural Census Tract.[16]

Parents of preschool age children are asked routinely at medical appointments about the form of childcare currently being used by the family and this is noted in the medical record. Within the medical record, professional childcare provided outside of the home is referred to as “daycare” for children less than 48 months of age. For four-year-olds, professional childcare outside of the home is referred to as “preschool” (private childcare centers) or “4K kindergarten” (a public-school program offered in the state for children who have not yet begun 5K kindergarten). Within the state, 4K kindergarten serves both children with identified risk factors and children without such risk factors who enroll in available slots. However, clinicians reported being uncertain of whether they consistently differentiated between private and public childcare for this age range. We therefore refer to both “preschool” and “4K kindergarten” as a single category termed “preschool.”

Specific sickle cell genotypes were recorded and then dichotomized as either severe or mild-moderate.[7] Hemoglobin, white blood cell counts, and platelet counts were recorded from the routine blood lab data collected for the health maintenance visit at which the screening took place. History of hospitalizations over the past 12 months (sickle cell related or other causes) and prior treatment with therapeutic levels of hydroxyurea or chronic blood transfusion therapy was recorded.

TCD exams were completed by all patients with severe genotypes within the previous 12 months of the screening to assess for stroke risk. Outcomes of TCD exams were based on the STOP protocol method.[17] Abnormal exams are based on confirming an abnormal TCD screening with a second TCD exam. Occasionally, magnetic resonance angiography (MRA) was collected before the second TCD exam and chronic transfusion therapy to prevent stroke was started based on MRA results showing vessel occlusion; these cases were counted as abnormal TCD outcomes. Two children with abnormal TCD exams had concurrently completed the developmental screening and were not yet on chronic transfusion therapy. One child with an abnormal TCD exam was not on transfusion therapy due to objections based on religious beliefs and was started on hydroxyurea therapy. Children with mild or moderate genotypes do not receive TCD exams due to the rarity of stroke in these genotypes and all these cases were automatically coded as not having an abnormal TCD.

All children receive screenings for sleep apnea as part of routine hematologic health maintenance visits and children with positive screening results were referred for overnight polysomnography at a dedicated sleep lab ($n = 18$). The outcome of the overnight polysomnography exam was recorded to identify history of known sleep apnea based on standardized methods.[18] Finally, raw and norm-based cut-off scores from the ASQ-2 were recorded from medical records.

Procedures

Appropriate institutional board approval was obtained prior to medical chart review. After patients participated in a developmental screening, one of four coders reviewed the patients' electronic and paper charts to record study data as the primary coder. A second coder independently coded data for a random sample of 25% of the cases to compute reliability.

The ASQ-2 was collected as part of developmental screenings offered to parents for children at ages 24–35 months or 48–59 months to generally conform to recommended developmental screenings at ages 24 or 30 months and four years of age.[19] Screenings were performed in the context of the child's routine hematological health maintenance appointments.

Psychologists or doctoral-level psychology students with training in child and family assessment completed the screenings. Depending on parent preferences, screenings were conducted either before or after the child's physical examination by the hematologist. Parents completed the ASQ-2 either in the waiting room of the clinic while accompanied by their child or in the psychology office located within the hematology clinic while accompanied by their child. Parents were encouraged to complete items that they were confident they could rate and told to leave blank items they were unsure of how to rate. A psychology staff person would review the ASQ-2 with the parent to determine if there were any difficulties completing items. If parents were unsure of how to complete items, materials were provided to test the item with the child (e.g., given a pair of safety scissors and asked to cut paper). The screening measures were then scored. For domains with positive screenings we would determine if the parent directly tested the items, and if they did not, the examiner would attempt to have the child demonstrate the behavioral milestone(s) that led to a positive screen. Feedback about the results was provided to the parent.

For the ASQ-2, each domain has a cut-off score for a positive screening within that domain (a raw score 1.5 standard deviations below the mean score for the age group). Children with one or more positive domain-level scores are categorized as having a positive ASQ-2 screening for developmental delay. If a positive ASQ-2 screening occurred, two follow-up procedures were used. First, parents were given tip sheets for developmentally appropriate activities to promote development in the area of concern and the types of activities were reviewed with the parent. Second, sources of appropriate developmental services were reviewed with the parent and information about these services and/or a direct referral was provided depending on parent preferences.

Data Analyses

Potential risk/protective factors for positive screenings (i.e., age at screening, gender, race/ethnicity, rural residence, private health insurance, attending a formal daycare program, attending a formal preschool program, genotype severity, hospitalizations in past 12 months, hydroxyurea treatment, sleep apnea diagnosis, abnormal TCD exam) were first examined via correlation coefficients within each age group to assess for univariate associations. Given that screening outcomes were a dichotomous variable, Phi coefficients were computed for categorical risk/protective factors and point-biserial correlations were computed for

continuous risk/protective factors. For continuous variables, scatterplots for each correlation were reviewed visually to assess for outliers that might exert undue influence.

Multiple regression was used to evaluate all risk/protective factors that showed univariate associations with positive ASQ-2 screenings to determine if they showed a unique association with ASQ-2 outcomes. Collinearity diagnostics and residual statistics were examined for regression models to assess the appropriateness of each model for interpretation. For collinearity, condition index values of 15 or higher was set *a priori* as an indication of a problem with collinearity. Standardized residuals with a value greater than 3.0 was set as the *a priori* indication of a problem with outliers.

For risk/protective factors that showed univariate associations with ASQ-2 outcomes in either age group, we assessed if the degree of association differed between two-year-olds and four-year-olds using log linear analyses. Finally, we assessed for age-related differences in which ASQ-2 domain was rated as delayed through chi-square and Fisher's Exact tests. We set an alpha level of .05 for all analyses. Effect size estimates were provided via the correlation coefficients.

Results

Sample characteristics

The dataset for this study included 100 two-year-olds (M = 2.5 years; SD = 0.3) and 101 four-year-olds (M = 4.5 years; SD = 0.4). Descriptive data for the study sample is provided in Tables 1 & 2. All children were listed in the medical record as Black/African-American for race/ethnicity. Seventy-seven of the four-year-olds were described in a previous report.[6] In the prior report we noted that 100 four-year-olds were screened in this time frame; however, we subsequently identified one four-year-old child who received an ASQ-2 screening but was categorized as "not-screened" in the previous data set. One-hundred-twenty-eight two-year-olds (ages 24–35 months) and one-hundred thirty-two four-year-olds (ages 48–59 months) with SCD were seen for routine health maintenance visits during the study time frame (77% participation rate). Lack of time was the most common reason reported by parents for refusing the screening. The overall rate of positive ASQ-2 screenings was 32% (32/100) for two-year-olds and 40% (40/101) for four-year-olds, Fisher's Exact $p = .304$. Among those with positive screenings, the examiners were unable help confirm the results with direct behavioral testing in six of the two-year-olds (19%) and four of the four-year-olds (10%), Fisher's Exact $p = .323$.

Univariate associations between risk/protective factors and the ASQ-2

Univariate associations with ASQ-2 outcomes are shown in Table 3. For two-year-olds, children were less likely to have positive screenings for developmental delay if their parents had private health insurance or if they had attended professional daycare; they were more likely to have positive screenings if they had a severe SCD genotype. Among two-year-olds the association between ASQ-2 outcomes and gender was in the direction of females being more likely to have a positive screening, but this association was not statistically significant ($p = .093$). For four-year-olds, children were more likely to have a positive screening if they

had a severe SCD genotype or had an abnormal TCD exam indicating elevated stroke risk. Among four-year-olds the association between ASQ-2 outcomes and insurance status was in the same direction as for the two-year-olds, but not statistically significant ($p = .099$) and hospitalizations in the past year showed a similar degree of association with having a positive screening ($p = .072$).

Multivariate analysis of risk/protective factors

For the multiple regression analysis with two-year-olds, ASQ-2 screening outcome was the dependent variable and insurance status, professional daycare, and having a severe genotype were included as the independent variables. The overall regression model was statistically significant, $F(3, 96) = 6.37$, $p = .001$, $R^2 = .166$. Having private health insurance, $\beta = -.283$, $t(96) = -2.94$, $p = .004$, and attending professional daycare, $\beta = -.240$, $t(96) = -2.55$, $p = .012$, each accounted for independent variance in ASQ-2 outcomes and were associated with a lower likelihood of a positive screening. Having a severe genotype did not show a statistically significant association with ASQ-2 outcomes after statistically controlling for other variables in the regression, $\beta = .163$, $t(96) = 1.71$, $p = .090$.

For the multiple regression with four-year-olds, ASQ-2 screening outcome was the dependent variable and having a severe genotype and having an abnormal TCD exam were included as the independent variables. This analysis is important given that all abnormal TCD exams are among children with severe genotypes. The overall model was statistically significant, $F(2, 98) = 9.87$, $p = .0001$, $R^2 = .168$. Having a severe SCD genotype, $\beta = .272$, $t(98) = 2.90$, $p = .005$, and having an abnormal TCD exam, $\beta = .258$, $t(98) = 2.75$, $p = .007$, each increased the likelihood of a positive ASQ-2 screening outcome, indicating each factor accounted for unique variance in ASQ-2 screening outcomes after statistically controlling for shared variance.

Differences in the magnitude of associations across age groups

Loglinear analyses were run to examine if there were three-way interactions between age-group, positive screening outcomes, and risk/protective factors related to screening outcomes (i.e., having private health insurance, attending professional daycare, having a severe SCD genotype, having a positive TCD exam). The three-way loglinear analysis for insurance status (private insurance, no private insurance), ASQ-2 outcome (positive, negative), and age group (two-year-olds, four-year-olds) indicated that the three-way interaction was statistically significant, G^2 (4) = 14.27, $p = .006$. To break down this effect (and for subsequent analyses below), separate chi-square values for the combinations of the weighted logarithms were examined to determine the nature of the three-way interaction. The three-way interaction was due to a significant interaction between insurance status and screening outcomes among two-year-olds, G^2 (1) = 10.31, $p = .001$, whereas none of the other 2X2 effects were statistically significant (all p's > .08), indicating having private insurance was more strongly related to negative screening outcomes for two-year-olds than for four-year-olds. The three-way loglinear analysis for professional daycare (attended, never attended), ASQ-2 outcome (positive, negative), and age group (two-year-olds, four-year-olds) did not show a significant three-way interaction, G^2 (4) = 9.16, $p = .057$; therefore, potential age-related differences in these associations were not further examined.

The three-way loglinear analysis for genotype (severe genotype, mild-moderate genotype), ASQ-2 outcome (positive, negative), and age group (two-year-olds, four-year-olds) indicated a statistically significant three-way interaction, G^2 (4) = 17.50, p = .002. Separate chi-square analyses indicated the only statistically significant effects were for the interaction between genotype and screening outcomes among two-year-olds, G^2 (1) = 5.20, p = .023, and among four-year-olds, G^2 (1) = 11.06, p = .001 (all other p's > .19), indicating the strength of the effect differed across the two age groups with a stronger association between having a severe genotype and a positive screening among four-year-olds.

The three-way loglinear analysis for abnormal TCD exams (abnormal TCD; no abnormal TCD), ASQ-2 outcome (positive, negative), and age group (two-year-olds, four-year-olds) indicated that the three-way interaction was significant, G^2 (4) = 18.93, p = .001. Separate chi-square analyses indicated the only statistically significant effect was for the interaction between an abnormal TCD exam and screening outcomes among four-year-olds, G^2 (1) = 11.70, p = .001 (all other p's > .07), indicating the effect differed across the two age groups.

ASQ-2 domain-level outcomes

To clarify if there were domain-level differences in outcomes across the two age-groups, we compared the rate of positive domain-level outcomes (Communication, Gross Motor, Fine Motor, Problem Solving, Personal-social domains) between the two groups (two-year-olds, four-year-olds) with a Pearson chi-square test. These data are in Table 4. The analysis indicated the rate of positive domain scores differed across groups, X^2 (1) = 11.25, p = .001. Examination of standardized residuals for each cell indicated the only cell with an absolute residual of 1.5 or greater was the Personal-social domain for two-year-olds (standardized residual = 2.04), indicating a higher rate of positive domain scores for two-year-olds than for four-year-olds. Simple comparisons between age groups for each domain, which is a less stringent test for the source of the differences, also showed a higher rate of positive scores for the Fine Motor domain in four-year-olds than two-year-olds (see Table 4).

Exploratory analyses were run in which we computed Phi coefficients between the outcome for each of the five ASQ-2 domains and the four factors related the overall ASQ-2 outcomes (i.e., having private health insurance, attending professional daycare, having a severe SCD genotype, having a positive TCD exam). The purpose of this exploratory analysis was to determine if domain-level ASQ-2 outcomes yielded similar associations as the overall ASQ-2 screening outcome. For two-year-olds, having private health insurance was correlated with the Problem Solving domain, but in the opposite of the expected direction, with a positive correlation indicating a higher risk for a positive score for those with private health insurance, r = .20, p = .044. For two-year-olds, having attended private day care was associated with a lower risk for a positive screening due to the Personal-social domain, r = −.20, p = .047. For four-year-olds, having a severe genotype was associated with greater likelihood of a positive domain score for the Fine Motor domain, r = .26, p = .009. Finally, for four-year-olds a history of an abnormal TCD exam was associated with a greater likelihood of a positive score for the Communication, r = .20, p = .044, Gross Motor, r = .20, p = .048, Fine Motor, r = .33, p = .001, and Problem Solving, r = .28, p = .005, domains. Overall, specific domains appeared more likely to be related to risk and protective factors

within age groups; however, these exploratory analyses are vulnerable to Type I errors and yielded one counter-intuitive association.

Discussion

In the present cross-sectional study, we found that sociodemographic factors and biomedical factors were both associated with developmental delay in young children with SCD; however, the magnitude of the association and statistical significance differed across the two age groups studied. Overall, findings were consistent with sociodemographic factors showing a larger relationship with developmental delay in two-year-olds and biomedical factors showing a larger relationship with delay in four-year-olds. One interpretation of the pattern of results is that environmental factors and disease severity both are important in 2-year-olds, but with increasing age, the intensification of disease symptoms becomes the predominant determinant of developmental delay in 4-year-olds. Caveats to this interpretation are discussed below. The results of the present study also may explain, in part, the reason for inconsistencies across prior studies in the specific risk/protective factors identified in relation to developmental delay in SCD since many studies have included a wide age-range of children.

For sociodemographic factors, having a parent with private health insurance or attending a professional daycare were each associated with a lower risk for developmental delay among two-year-olds. The direction of the association was consistent with these variables functioning as protective factors. The strength of the association between insurance status and developmental delay was significantly different across the two age groups with only two-year-olds showing a statistically significant association. The association between attending professional daycare and developmental delay was also statistically significant in the two-year-olds, but no age differences in the magnitude of this effect was observed. It is possible that both variables are surrogate markers for socioeconomic status or alternately that daycare may provide age-appropriate developmental experiences that mitigate the risk for developmental delay. Professional daycare centers are used most often by parents who are working full-or part-time outside of the home such that this could be a surrogate marker for families in which all adults in the household work outside the home.[20] The potential for age-appropriate developmental experiences in professional childcare settings to serve as a protective factor is another possibility, although the extent to which daycare serves as a protective factor is dependent on the quality of care.[21] The observed associations are consistent with prior studies indicating socioeconomic status and the social environment impact the risk for developmental delay in SCD.[4,22]

The failure to observe any specific sociodemographic relationships with developmental delay in four-year-olds should not be taken to imply that social-environmental factors are not relevant at this age. The present study relied on sociodemographic factors that could be extracted from the medical record, such as a binary measure of socioeconomic status, which captures limited variability in this dimension. The social indicators available also provided only a limited window into the full range of social-environmental factors that are important for early childhood development, which is a study limitation. There are a wide range of negative (e.g., child abuse/neglect, parent stress, low parent mental health, parent substance

abuse) and positive (parent education, cognitive stimulation in the home) features of the social environment which were not included in the present study that are well established risk/protective factors for developmental delay across early childhood.[23–24] Although these risk and protective factors often are related to socioeconomic status, they also account for differences in child outcomes independent of this association. However, the increasing rate of cerebrovascular complications with age in SCD also represents a different context within which to evaluate social-environmental factors compared with studies of children without such neurologic risks.

For biomedical variables, having a severe genotype was associated with a higher risk for developmental delay at both ages and having an abnormal TCD exam was associated with an elevated risk for developmental delay in four-year-olds. It is notable that the overall rate of positive ASQ-2 screenings was not significantly higher in four-year-olds than two-year-olds, but the factors associated with the positive screenings were significantly different for the two age groups. This data pattern suggests a shift in the predominant risk/protective factors for developmental delay across the two ages, rather than progressive disease effects simply being added to ongoing social-environmental risks.

Having a severe genotype did not show an association with developmental delay in the multivariate analysis of risk/protective factors for two-year-olds, but these two variables were associated in the bivariate correlations. We suspect that this may be due, in part, to a sampling factor since there was an over-representation of two-year-olds with mild-moderate genotypes whose parents had private health insurance (see Table 2). This over-representation could lead to shared variance between these factors, lessening our ability to detect unique associations. Thompson and colleagues also found an association of severe genotypes with lower Mental Development and Psychomotor Development scores in 24-month-olds with SCD using the Bayley Scales of Infant Development- II.[3] Alternately, prior studies of children less than four years of age have failed to detect an association between severe genotypes and developmental delay with sample sizes comparable to the present study.[2,5] The inter-correlation of insurance status and genotype in the present study may have created a spurious univariate relationship among two-year-olds. Overall, the body of research to-date does not suggest that SCD genotype severity is a reliable marker of risk for developmental delay in very young children. Additional genetic disease modifiers or phenotypic indicators of biomedical risk should be examined in future research.

The finding of a statistically significant increase in the association between severe genotypes or abnormal TCD exams with developmental delay in four-year-olds compared with two-year-olds is consistent with the concept that the increased prevalence of cerebrovascular effects over time is a key factor in developmental delays.[22] Although other medical factors, such as hospitalizations for pain episodes, have also been described as risk factors for developmental delay these associations have replicated less often across studies, whereas risks for cerebrovascular disease or identified cerebrovascular disease have been more consistently related to developmental or cognitive delay in preschoolers and school-age youth.[22] Thus, the absence of statistically significant findings for biomedical variables in two-year-olds may reflect the low rate of cerebrovascular effects at younger ages.

It may also be that general developmental screening or assessment tools are not sensitive to the behavioral effects of cerebral vascular disease in infants and toddlers. Data has indicated that developmental delay based on the Bayley Scales of Infant Development- II was not typically evident in infants and toddlers with silent cerebral infarction, but high rates of cognitive deficits (70%) and academic difficulties (75%) became evident when these children were followed over time.[25–26] A caveat for all findings related to abnormal TCD exams in the present study is that the results are based on a small number of children with abnormal TCD exams. In addition, the study did not have sleep studies available for all participants and only a small proportion of the cases had been treated with hydroxyurea. Thus, the null findings for sleep apnea and hydroxyurea treatment may reflect characteristics of our data set, rather than the underlying nature of these as risk and protective factors.

Research on developmental delay and neurocognitive deficits in SCD has often studied groups of children that are heterogenous in age and therefore examined risk and protective factors as if they are constant across different points of development. This is understandable given the relative rarity of SCD but may contribute to inconsistent ability to identify important risk and protective factors. The results of the present study indicate that risk and protective factors for developmental delay in SCD differ in their magnitude across timepoints in early childhood. Future studies should consider longitudinal monitoring of the stability or change in developmental status to understand factors associated with failure to make typical developmental progress or the amelioration of delays. Evaluating modifiable risk and protective factors at specific ages would be useful for testing prevention approaches. For example, the current study suggests a focus on social environmental factors may be of primary importance early in development (e.g., parenting interventions for toddlers) with increasing importance of interventions to reduce neurologic risk as toddlers become preschoolers.[27–29]

Acknowledgments

Conflicts of Interest and Source of Funding: Portions of this work were supported by Grant Number T32-GM081740 from NIH-NIGMS, which provided support to the third author. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIGMS or NIH. For the remaining authors, none were declared.

References

1. Armstrong FD, Elkin TD, Brown RC, et al. Developmental function in toddlers with sickle cell anemia. Pediatrics 2013;131(2): e406–e414. doi:10.1542/peds.2012-0283 [PubMed: 23296434]
2. Aygun B, Parker J, Freeman MB, et al. Neurocognitive screening with the Brigance preschool screen-II in 3-year-old children with sickle cell disease. Pediatric Blood & Cancer 2011;56(4):620–624. doi:10.1002/pbc.22833 [PubMed: 21298749]
3. Thompson RJ Jr, Gustafson KE, Bonner MJ, et al. Neurocognitive development of young children with sickle cell disease through three years of age. J Pediatr Psychol 2002;27(3):235–244. 10.1093/jpepsy/27.3.235 [PubMed: 11909931]
4. Drazen CH, Abel R, Gabir M, et al. Prevalence of developmental delay and contributing factors among children with sickle cell disease. Pediatric Blood & Cancer 2016;63(3):504–510. doi:10.1002/pbc.25838
5. Glass P, Brennan T, Wang J, et al. Neurodevelopmental deficits among infants and toddlers with sickle cell disease. J Dev Behav Pediatr 2013;34(6):399–405. doi:10.1097/DBP.0b013e31829c3c48 [PubMed: 23838585]

6. Schatz J, Schlenz A, Reinman L, et al. Developmental screening in pediatric sickle cell disease: Disease-related risk and screening outcomes in 4-year-olds. J Dev Behav Pediatr 2017; 38(8), 654–662. 10.1097/DBP.0000000000000486 [PubMed: 28816916]
7. Rees DC, Williams TN, Gladwin MT. Sickle-cell disease. Lancet 2010; 376(9757):2018–31. doi: 10.1016/S0140-6736(10)61029-X. [PubMed: 21131035]
8. Moser FG, Miller ST, Bello JA, et al. (1996). The spectrum of brain MR abnormalities in sickle-cell disease: a report from the Cooperative Study of Sickle Cell Disease. AJNR Am J Neuroradiol 1996; 17(5): 965–972. [PubMed: 8733975]
9. Prengler M, Pavlakis SG, Prohovnik I et al. Sickle cell disease: The neurological complications. Ann Neurol 2002; 51: 543–552. 10.1002/ana.10192 [PubMed: 12112099]
10. Allhusen V, Belsky J, Booth-LaForce C, et al. Duration and Developmental Timing of Poverty and Children's Cognitive and Social Development from Birth Through Third Grade. Child Dev 2005; 76(4): 795–810. 10.1111/j.1467-8624.2005.00878.x [PubMed: 16026497]
11. Conger RD & Donnellan MB. An interactionist perspective on the socioeconomic context of human development. Annu Rev Psychol 2007; 58: 175–199 [PubMed: 16903807]
12. Akinsheye I, Alsultan A, Solovieff N, et al. (2011). Fetal hemoglobin in sickle cell anemia. Blood 2011; 118(1): 19–27. doi: 10.1182/blood-2011-03-325258 [PubMed: 21490337]
13. Kassim AA, Pruthi S, Day M. et al. Silent cerebral infarcts and cerebral aneurysms are prevalent in adults with sickle cell anemia. Blood 2016; 127(16): 2038–2040. doi: 10.1182/blood-2016-01-694562 [PubMed: 26941400]
14. Kwiatkowski JL, Zimmerman RA, Pollock AN, et al. Silent infarcts in young children with sickle cell disease. Br J Haematol 2009;146(3):300–305. [PubMed: 19500105]
15. Squires J, Potter L, Bricker D. The ASQ User's Guide, 2nd ed. Baltimore, MD: Paul H. Brookes Publishing Co; 1999.
16. Federal Office of Rural Health Policy. Federal Office of Rural Health Policy (FRHP) Data Files [Health Resources and Services Administration web site] September 15, 2020. Available at: https://www.hrsa.gov/rural-health/about-us/definition/datafiles.html. Accessed September 22, 2020.
17. Adams RJ. TCD in sickle cell disease: an important and useful test. Pediat Radiol 2005; 35: 229–234. [PubMed: 15703904]
18. American Thoracic Society. Standards and indications for cardiopulmonary sleep studies in children. Am J Respir Crit Care Med 1996; 153: 866–878. [PubMed: 8564147]
19. American Academy of Pediatrics Council on Children with Disabilities. Identifying infants and young children with developmental disorders in the medical home: an algorithm for developmental surveillance and screening. Pediatrics 2006;118(1): 405–420 [PubMed: 16818591]
20. West J, Wright D & Germino-Hausken E. Child care and early care and education participation of infants, toddlers, and preschoolers Washington DC: U.S. Department of Education (NCES 95–824); 1995.
21. Cost, Quality, and Child Outcomes Study Team. Cost, quality, and child outcomes in child care centers Denver, CO: Department of Economics, University of Colorado at Denver; 1995.
22. Prussien KV, Siciliano RE, Ciriegio AE et al. , Correlates of cognitive function in sickle cell disease: A meta-analysis, J Pediatr Psychol 2020; 45(2): 145–155. 10.1093/jpepsy/jsz100 [PubMed: 31968106]
23. Brooks-Gunn J & Duncan G The effects of poverty on children. Future Child 1997; 7(2): 55–71. doi:10.2307/1602387 [PubMed: 9299837]
24. Walker SP, Wachs TD, Grantham-McGregor S, et al. Inequality in early childhood: Risk and protective factors for early child development. Lancet 2011; 378(9799): 1325–1338. 10.1016/S0140-6736(11)60555-2. [PubMed: 21944375]
25. Cancio MI, Helton KJ, Schreiber JE, et al. Silent cerebral infarcts in very young children with sickle cell anaemia are associated with a higher risk of stroke. Br J Haematol 2015, 171: 120–129. 10.1111/bjh.13525 [PubMed: 26058476]
26. Wang WC, Pavlakis SG, Helton KJ, et al. (2008) MRI abnormalities of the brain in one-year-old children with sickle cell anemia. Pediatric Blood & Cancer 2008; 51: 643–646. [PubMed: 18478575]

27. Fields ME, Hoyt-Drazen C, Abel R, et al. A pilot study of parent education intervention improves early childhood development among toddlers with sickle cell disease. Pediatr Blood Cancer 2016; 63: 2131–2138. 10.1002/pbc.26164 [PubMed: 27509845]

28. Puffer E, Schatz J, Roberts CW. The association of oral hydroxyurea therapy with improved cognitive functioning in sickle cell disease. Child Neuropsychology 2007;13(2):142–154. 17 18. [PubMed: 17364571]

29. Partanen M, Kang G, Wang WC, et al. Association between hydroxycarbamide exposure and neurocognitive function in adolescents with sickle cell disease. British Journal of Haematology 2020;189(6):1192–1203. [PubMed: 32103506]

Table 1.

Descriptive Information for Study Sample.

Variable	Two-year-olds (n = 100)	Four-year-olds (n = 101)	Test statistic^
Demographics			
Gender (M:F)	61:39 (61% Male)	67:34 (66% Male)	$p = .465$
Private health insurance (*n*)	19 (19%)	21 (21%)	$p = .860$
Rural residence (*n*)	29 (29%)	36 (36%)	$p = .366$
Childcare history			
Attended professional daycare (*n*)	21 (21%)	31 (31%)	$p = .147$
Clinical History			
Severe SCD genotype *(n)*	67 (67%)	64 (64%)	$p = .658$
-HbS/S *(n)*~	65	62	
-HbS/C *(n)*	24	25	
-HbS/β^+-thalassemia *(n)*	7	12	
-HbS/β^0-thalassemia *(n)* ~	1	1	
-HbS/O-Arab *(n)* ~	1	1	
-HbS/HPFH *(n)*	1	0	
Hospitalizations in past year	0.8 ± 1.15	0.8 ± 1.0	$t(199) = -0.21$
Hydroxyurea treatment (*n*)	9 (9%)	16 (16%)	$p = .199$
Sleep apnea diagnosis (*n*)	2 (2%)	11 (11%)	$p = .018$
Abnormal TCD exam (*n*)	1 (1%)	6 (6%)	$p = .118$
Routine blood labs			
Hemoglobin (gr/dL)	9.1 ± 1.6	9.2 ± 1.6	$t(199) = 0.50$
White blood cells (k/uL)	13.5 ± 9.1	12.4 ± 4.8	$t(199) = -1.08$
Platelets (k/uL)	352.2 ± 134.3	396.8 ± 162.3	$t(199) = 2.12$*

Notes: Continuous variables are presented as M ± SD.

^ p-values are for the Fisher Exact test;

~ categorized as a severe genotype[7]; TCD = transcranial doppler ultrasound;

* $p < .05$

Table 2.

Descriptive information for mild-moderate versus severe sickle cell genotypes.

Variable	Two-year olds (n = 100)		Genotype comparison^	Four-year olds (n = 101)		Genotype comparison^
	Mild-moderate genotypes	Severe genotypes		Mild-moderate genotypes	Severe genotypes	
n	33	67		37	64	
Demographics						
Age	2.5 ± 0.3	2.59 ± 0.3	$t = -0.39$	4.5 ± 0.4	4.5 ± 0.3	$t = 0.08$
Gender (M:F)	23:10 (70% male)	38:29 (57% male)	$p = .277$	24:13 (65% male)	43:21 (67% male)	$p = .830$
Private health insurance (*n*)	10 (30%)	9 (13%)	$p = .058$	7 (19%)	14 (22%)	$p = .803$
Rural residence (*n*)	11 (33%)	18 (27%)	$p = .640$	13 (35%)	23 (36%)	$p = .999$
Childcare history~						
Attended professional daycare (*n*)	7 (21%)	14 (21%)	$p = .999$	11 (30%)	20 (31%)	$p = .999$
Attended professional preschool (*n*)	n.a.	n.a.		27 (73%)	45 (70%)	$p = .823$
Clinical history						
Hospitalizations in past 12 months	0.6 ± 1.5	0.9 ± 1.0	$t = -0.94$	0.4 ± 0.6	1.1 ± 1.1	$t = -3.22^{**}$
Hydroxyurea treatment (*n*)	0 (0%)	9 (13%)	$p = .028$	0 (0%)	16 (25%)	$p = .001$
Sleep apnea diagnosis (*n*)	0	2	$p = .999$	2 (5%)	9 (14%)	$p = .320$
Routine Blood Labs						
Hemoglobin	10.7 ± 0.9	8.4 ± 1.3	$t = 9.32^{**}$	10.9 ± 0.8	8.4 ± 1.0	$t = 13.88^{**}$
White blood cells	8.7 ± 2.3	15.9 ± 10.27	$t = -4.09^{**}$	9.7 ± 4.0	13.9 ± 4.6	$t = -4.65^{**}$
Platelets	294.1 ± 93.4	380.8 ± 142.6	$t = -3.17^{**}$	306.1 ± 124.9	449.2 ± 158.9	$t = -4.70^{**}$

Notes:

^ *p*-values are for the Fisher Exact test; M = male; F = female;

~ daycare refers to attending a formal childcare program between birth and 47 months of age; preschool refers to enrollment in a preschool/kindergarten program beginning at 48 months of age;

* $p < .05$;

** $p < .01$;

Table 3.

Correlation coefficients for positive ASQ-2 screenings in relation to sociodemographic and biomedical variables.

Variable	Two-year-olds(n = 100)	Four-year-olds(n = 101)
Sociodemographic		
Age^	−.15	−.06
Gender	−.17	−.11
Private health insurance	−.29**	−.17
Rural residence	.07	.07
Attended professional daycare (birth to 47 months)	−.20*	−.10
Attended professional preschool (48 to 59 months)	n.a.	−.07
Biomedical		
Severe SCD genotype	.22*	.32**
Hospitalizations past 12 months^	.02	.18
Hydroxyurea treatment	.08	.15
Sleep apnea diagnosis	.05	.17
Abnormal TCD exam	.14	.31**

Notes: Screening outcomes were coded with 0 as a negative screen and 1 as a positive screen; Associations are described in Phi values except when noted;

^ Point-biserial correlation;

* $p < .05$;

** $p < .01$; TCD = transcranial doppler ultrasound

Table 4.

Number of positive domain-level scores on the ASQ-2

Domain	Two-year-olds(n = 100)	Four-year-olds(n = 101)	Fisher Exact
Communication	11 (11%)	19 (19%)	$p = .165$
Gross Motor	9 (9%)	10 (10%)	$p = .999$
Fine Motor	11 (11%)	26 (26%)	$p = .010$
Problem Solving	12 (12%)	13 (13%)	$p = .999$
Personal-social	13 (13%)	4 (4%)	$p = .024$

Notes: The totals within each column are higher than the total number with overall positive ASQ-2 screenings due to some children having positive screenings in more than one domain.