12-1-2011

ASSOCIATION OF RACE AND ETHNICITY WITH COGNITIVE AND LANGUAGE TESTING AT 18-22 MONTHS IN EXTREMELY PRETERM INFANTS

Andrea Duncan

Andrea Freeman Duncan, MD
Candidate

Biomedical Sciences
Department

This thesis is approved, and it is acceptable in quality and form for publication:

Approved by the Thesis Committee:

Beth Tigges, PhD, RN Chairperson

Jean Lowe, PhD

Kristi Watterberg, MD

ASSOCIATION OF RACE AND ETHNICITY WITH COGNITIVE AND LANGUAGE TESTING AT 18-22 MONTHS IN EXTREMELY PRETERM INFANTS

BY

ANDREA FREEMAN DUNCAN

BA, UNIVERSITY OF TEXAS AT AUSTIN, 1998

MD, UNIVERSITY OF TEXAS SOUTHWESTERN MEDICAL CENTER AT DALLAS, 2002

THESIS

Submitted in Partial Fulfillment of the
Requirements for the Degree of

MASTER OF SCIENCE

BIOMEDICAL SCIENCE

The University of New Mexico
Albuquerque, New Mexico

December, 2011

ACKNOWLEDGMENTS

I heartily acknowledge Beth Tigges, PhD, RN the chair of my Committee of Studies and Jean Lowe, PhD and Kristi Watterberg, MD, my other Committee members, for their guidance and encouragement throughout the MSCR program in particular and in beginning my academic medicine career in general.

In addition, I must gratefully acknowledge the Eunice Kennedy Shriver National Institute of Child Health and Development, who supported this study.

EFFECT OF RACE AND ETHNICITY ON COGNITIVE AND LANGUAGE TESTING AT 18-22 MONTHS IN EXTREMELY PRETERM INFANTS

by

Andrea Freeman Duncan, MD

B.A., Humanities, University of Texas at Austin, 1998

M.D., University of Texas Southwestern Medical Center at Dallas, 2002

M.S., Biomedical Sciences,University of New Mexico, 2011

ABSTRACT

Objective(s) The objective of this study was to evaluate the relationship of race/ethnicity to cognitive and language scores on the Bayley Scales of Infant and Toddler Development 3rd edition (BSID-III) in extremely preterm toddlers (<28+0 weeks' estimated gestational age). **Study Design** Extremely preterm toddlers at NICHD Neonatal Research Network Centers evaluated at 18-22 months adjusted age from 3 race/ethnic groups (White, Black, and Hispanic-White) were included in this cohort study. Multivariable regression modeling was used to identify race/ethnic differences adjusting for medical and psychosocial factors. **Results** Children included 369 Whites, 352 Blacks and 144 Hispanic-Whites. Cognitive scores differed between groups in unadjusted analysis (p=<0.001), but not after adjusting for medical and psychosocial factors (p=0.13). Language scores differed in adjusted and unadjusted analyses. Whites scored higher than Blacks or Hispanic-Whites, and Blacks scored higher than Hispanic-Whites. **Conclusion(s)** A combination of medical variables and primary caretaker education accounted for differences in BSID-III cognitive scores between groups. Black and Hispanic-White toddlers had lower language scores than Whites, even after adjustment. Early intervention should be targeted to these identified risk factors. Assessment of early language development among minority groups may be warranted.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

Chapter 1

INTRODUCTION

Children born premature and extremely low birth weight (<1000 grams) are at high risk of developing intellectual and language difficulties.[1-3] These children are more likely to receive special educational assistance and/or repeat a grade than their normal birth weight peers.[4,5] Early childhood intervention has been shown to result in improvements in cognitive, academic, and social outcomes.[6,7] Early assessment of cognitive functioning in preterm children permits delivery of appropriate interventions to improve their cognitive and behavioral outcomes. In order to determine which interventions are needed, early assessment tools must identify the specific nature of developmental deficiencies.

Prior to 2005, the Bayley Scales of Infant and Toddler Development 2nd edition (BSID-II) was the standard tool for assessing outcomes for high risk infants at age two.[8] The BSID-II had several design weaknesses, including the fact that language skills were not evaluated separately from cognition, but were distilled into a single score, the Mental Developmental Index (MDI). We have demonstrated higher overall BSID-II MDI scores in White children than in Hispanic-White or Black children that were not explained by socioeconomic status or maternal education.[9] The cause of this difference is undetermined. A third edition of the Bayley Scales of Infant and Toddler Development (BSID-III) has been developed,[10] and is now being used exclusively throughout the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network (NRN) centers. The newer BSID-III has a separate language

composite score that is further subdivided into expressive and receptive components. This more detailed characterization of language development may allow better understanding of the development of cognitive function. However, the effect of race and ethnicity on BSID-III scores has not been described, and must be assessed in order to determine whether this may be a psychosocial factor associated with BSID-III scores, as was the case with the BSID-II. In addition, the inclusion of a separate language domain may affect the previously noted association between race/ethnicity and BSID scores, but this has yet to be determined.

The objectives of this study were to compare cognition and language scores in extremely preterm children at 18 to 22 months corrected age as measured by the BSID-III among different racial and ethnic groups while adjusting for various medical and psychosocial factors, including maternal education level. We hypothesized that 1) differences would be found between groups on the BSID-III composite scores of cognition and language at 18 to 22 months corrected age in children who were born <28+0 weeks estimated gestational age (EGA), 2) differences between groups would be found in the expressive language subtest, [11] and 3) identifiable medical and psychosocial factors would be associated with any observed racial and ethnic differences in cognitive and language skills measured on the BSID-III.

Chapter 2

METHODS

Study Population

This study was a retrospective cohort study of children born at <28+0 weeks EGA and <1,000 grams at the sixteen centers of the NRN who were evaluated at 18 to 22 months adjusted age during the period of January, 2008 to June, 2009. Based on historic enrollment patterns in the NRN, we restricted this study to infants coded "White", "Black" and "Hispanic-White" to have an adequate sample size in each cell of >30 subjects. Sample size calculations indicated that a sample size of 369 Whites, 162 Blacks and 79 Hispanic-Whites would be adequate to detect a difference between groups of one-half standard deviation on each of the BSID-III cognitive and language composite scores with 90% power. Therefore, given past NRN enrollment patterns, the population anticipated to be evaluated January, 2008 to June, 2009 was considered more than adequate to evaluate the hypotheses proposed for this study. All subject data used was collected prospectively.

The study sample included all children born <28+0 weeks EGA in the three race and ethnic groups who were evaluated using the BSID-III examination and a neuromotor examination at 18 to 22 months corrected age. Children >28 + 0 weeks and with a birth weight >1,000 grams were excluded from this study, as were children meeting inclusion criteria who had missing values for BSID-III scores, missing values for race and ethnicity or children in race and ethnic groups containing ≤ 30 children as described above. Subject data were collected from the NRN Generic Follow-up Database.[12]

18-22 month Evaluations

Bayley Scales of Infant Development, 3rd edition[10]

The BSID-III cognitive scale, language composite scale, expressive language subtest and receptive language subtest were assessed. BSID-III scores range from 55-145 for the cognitive scale and 45-155 for the language composite scale, with scores of 100±15 representing the mean ± 1 SD for both. The receptive an expressive language scales range from 1-19 with scores of 10±3 representing the mean ± 1 SD. Internal consistency on the BSID-III was assessed using a split-half reliability method and shows reliability coefficients for the cognitive composite scale that range from 0.86 to 0.93. For the language composite scale, the split-half reliability coefficient ranged from .82-.98 and the language subscale coefficients ranged from .71-.97. Reliability coefficients for the special groups assessed (i.e. children born premature or with established diagnoses increasing the risk for developmental delay) are similar or higher than those of the normative sample, indicating that the BSID-III is equally reliable for children with clinical diagnoses or risk factors as for the general population. Test-retest reliability for the cognitive and language composite scales ranges from .75-.86, and the interval between the testing ranged from 2-15 days with a mean of 6 days in 197 children. Content validity of the test was assessed using expert consultation, literature review and an advisory panel. In addition, after several pilot studies, a confirmatory factor analysis using the norming sample scores supported a 3 factor structure (Cognitive, Language and Motor composite scales) based on the root mean square error of approximation as the goodness of fit index. For this study, the BSID-III cognitive and language composite and subscales were administered by experienced testers at each site who had been certified by

one of four NRN gold standard examiners. The BSID-III was administered in Spanish to those children whose primary language was identified as Spanish. In these instances, either a bilingual examiner administered the test or an interpreter was used to translate the test items.

BSID-III Cognitive scale: Cognitive function is assessed by examining the following cognitive constructs: 1) Sensorimotor development, 2) Exploration and manipulation, 3) Object relatedness, 4) Concept formation, 5) Memory, 6) Habituation, 7) Visual acuity, 8) Visual preference, and 9) Object permanence.

BSID-III Composite Language scale: Language development scores are composed of the combination of the expressive and receptive scores. The Expressive Language subtest measures the ability to communicate, either through words or gestures. The Receptive Language subtest tests the ability to comprehend and respond appropriately to words and requests.

Neuromotor Examination

The neuromotor examination is performed by a certified NRN examiner. The Gross Motor Function Classification System (GMFCS)[13] for cerebral palsy is a classification system that spans from 0-5 (0 = normal) and is based on self-initiated movement with emphasis on sitting (truncal control) and walking. Moderate to severe cerebral palsy is defined as a nonprogressive central nervous system disorder characterized by abnormal muscle tone in at least one extremity and abnormal control of movement and posture which interfered with or prevented age appropriate activities and a GMFCS score of ≥ 2.

Statistical Analysis

Primary outcome variables included the mean BSID-III Cognitive score, Composite Language score, Expressive Language score, and Receptive Language score. Race and ethnicity group was the primary independent variable. Key medical and psychosocial variables previously shown to adversely impact neurodevelopmental outcomes in at-risk children[14-16] were specifically chosen as covariates and were collected from the NRN database. Medical and psychosocial variables that were adjusted for included: gender, center, adjusted age at testing, primary caretaker education, birth weight, gestational age, multiple gestation, presence of culture positive nosocomial sepsis, bronchopulmonary dysplasia (BPD), Grade III or IV intraventricular hemorrhage (IVH) or cystic periventricular leukomalacia (PVL), postnatal steroid use, GMFCS Level ≥ 2, and blindness or deafness at 18-22 month follow-up (Table 1). Center was included as a covariate because each center may serve patients of in different socioeconomic strata, and clinical practices may differ at each center. Demographic characteristics of the three groups were compared using chi-square tests for categorical characteristics. BSID-III mean scores were first compared between groups using Analysis of Variance (ANOVA) with BSID-III score as the outcome variable and race and ethnicity category as the sole explanatory variable. Next, multivariable regression modeling using Analysis of Covariance (ANCOVA) was performed to examine the association of BSID-III score with race and ethnicity while controlling for medical and psychosocial variables. All medical and psychosocial variables were included in the ANCOVA for each BSID-III scale score. For each outcome measure, a linear regression model was created that included the multiple psychosocial and medical explanatory variables. The adjusted

means from these models were compared among groups and provide an estimate of the mean BSID-III scores by group for the average value of the specified medical and psychosocial confounders included in the model. Adjusted p-values comparing BSID-III score between race and ethnic groups were obtained from this second model. A p-value<0.05 determined statistical significance. Pairwise comparisons between race groups were adjusted for multiple comparisons using the Bonferroni correction. All p-values presented for race/ethnicity were obtained using the regression models described above. The p-value specifically is a test of the model parameter estimates associated with race/ethnicity. The test statistic was an F test statistic based on the type III sum of squares. When comparing race/ethnicities group by group, the regression model was also used and the test statistic obtained from the model was a t-test. Post-hoc, hypothesis-generating, exploratory analyses were conducted that included: 1) Evaluation of receipt of early intervention services between groups and exploration of the associations between early intervention receipt and BSID-III scores; 2) Regression modeling including and excluding various covariates to examine whether specific socioeconomic or medical covariates might be associated with the differences in scores between race/ethnicity groups and in an attempt to understand the possible factors accounting for the loss of significance between unadjusted and unadjusted p-values; and 3) Performing backwards selection starting from our initial model to come up with a 'prediction' model for cognitive score.

Table 1. Key Variables

VARIABLE	TYPE	DEFINITION
BSID-III Cognitive Score	**Dependent**	Cognitive function is assessed by examining the following cognitive constructs: 1) Sensorimotor development 2) Exploration and manipulation 3) Object relatedness 4) Concept formation 5) Memory 6) Habituation 7) Visual acuity 8) Visual preference 9) Object permanence. These constructs are measured through assessment of age-related skills including: 1)Counting 2) Visual and tactile exploration 3) Object assembly 4) Puzzle board completion 5) Matching colors 6) Comparing masses 7) Representational/pretend play
BSID-III Language Score	**Dependent**	Overall scores are classified as shown in Table 1 above. The composite score composed of the combination of the expressive and receptive scores.
BSID-III Expressive Language Score	**Dependent**	Overall scores are classified as shown in Table 1 above. The Expressive Language subtest tests the ability to communicate, either through words or gestures. Expressive communication is assessed through evaluation of the following age-related skills: 1) Preverbal communication (babbling, gesturing, joint referencing, turn-taking) 2) Vocabulary development (naming objects, pictures) 3) Morpho-Syntactic Development (using two-word utterances, plurals and verb tense)
BSID-III Receptive Language Score	**Dependent**	Overall scores are classified as shown in Table 1 above. The Receptive Language subtest tests the ability to comprehend and respond appropriately to words and requests. Receptive Language skills are assessed through evaluation of the following age-related skills: 1) Preverbal behaviors 2) Vocabulary development (identify objects & pictures) 3) Vocabulary related to morphological development (use of pronouns & prepositions) 4) Understanding of morphological markers (i.e, plurals, tense markings and possessives).

Table 2. Key Variables, continued

Race/Ethnicity	**Independent-Primary**	Race and Ethnicity are self-reported by the child's parents per Office of Management and Budget guidelines.
Birth Weight	**Independent-Medical**	Weight at birth measured in grams.
Gestational age	**Independent-Medical**	Infant gestational age at birth defined by the best obstetrical estimate. Obtained by chart review.
Intraventricular Hemorrhage	**Independent-Medical**	Moderate to severe Intraventricular Hemorrhage (IVH), defined by Grade 3 or Grade 4 as measured by head ultrasound.
Cystic Periventricular Leukomalacia	**Independent-Medical**	Yes or no categories. Brain injury that affects premature infants. The condition involves the death of small areas of brain tissue around fluid-filled areas called ventricles. Obtained by chart review
Blindness	**Independent-Medical**	Visual acuity of 20/200 or worse per parent report.
Deafness	**Independent-Medical**	Any hearing impairment requiring amplification measured by an audiological examination and reported by the parents.
GMFCS Level $\geq$ 2	**Independent-Medical**	The Gross Motor Function Classification System for cerebral palsy is based on self-initiated movement with emphasis on truncal control and walking. This is a 5 level classification system. Children are classified as follows prior to age 2: Level 1 Move in and out of sitting and floor sit with both hands free to manipulate objects, crawl, pull to stand and take steps holding on to furniture. Infants walk between 18 months and 2 years of age without the need for any assistive mobility device. Level 2 Maintain floor sitting but need to use their hands for support to maintain balance, creep on their stomach or crawl on hands and knees. Infants may pull to stand and take steps holding on. Level 3 Infants maintain floor sitting when the low back is supported. Infants roll and creep forward on their stomachs. Level 4 Have head control but trunk support is required for floor

Table 3. Key Variables, continued

		sitting, can roll to supine and may roll to prone. Level 5 Physical impairments limit voluntary control of movement. Infants are unable to maintain antigravity head and trunk postures in prone and sitting and require assistance to roll. The GMFCS level is determined by examination performed by a certified NRN examiner.
Gender	**Independent-Medical**	Male or female; obtained by chart review
Adjusted Age at Testing	**Independent-Medical**	Calculated by examiner by subtracting the gestational age from 40 and then subtracting the result from the chronological age at testing.
Multiple gestation	**Independent-Medical**	Number of infants carried during the pregnancy. Obtained by chart review.
Culture positive nosocomial sepsis	**Independent-Medical**	Yes or no categories; obtained by chart review.
Bronchopulmonary Dysplasia	**Independent-Medical**	Yes or no category; obtained by chart review. Defined by National Institute of Health consensus conference on bronchopulmonary dysplasia.
Postnatal steroid receipt	**Independent-Medical**	Yes or no category; obtained by chart review.
Center	**Independent--Medical**	The NRN center where follow-up occurred.
Early Intervention	**Independent--Medical**	Parental report at the time of 18-22 examination. Response options: receiving, not received or discontinued.
Primary Caretaker Education	**Independent--Psychosocial**	Caretaker report of the highest level of education completed at the time of follow-up: 1) < 7th grade 2) 7th to 9th grade 3) 10th to 12th grade 4)High school degree 5)Partial college 6) College degree 7) Graduate degree 8)Unknown
Primary Language	**Independent-Psychosocial**	Self-reported by parents as English or Other.

Chapter 3

RESULTS

The study population consisted of 865 extremely preterm children. Population characteristics are shown in Figure 1 and Tables 2-4.

Cognitive Scale

The mean BSID-III cognitive score was significantly lower than the expected mean of 100 in all three groups. However, the score was significantly higher in the White group than in either the Black or Hispanic-White groups when no adjustment was made for medical or psychosocial covariates (Table 5). When cognitive scores were adjusted for either medical or psychosocial covariates alone, this difference remained. However, adding medical and psycho-social factors *together* resulted in loss of significance between groups. Backward selection was then performed, retaining only factors at $p \leq 0.05$ level. In this model, birth weight, gender, primary caretaker education, postnatal steroids, grade III or IV IVH, nosocomial sepsis, multiple gestation, blindness, and GMFCS ≥ 2 appeared to jointly account for the loss of significance in scores between groups. In the final model obtained using backward selection for cognitive scores, $R^2 = .41$. Thus 41% of the variation in cognitive scores was explained by the remaining medical and psychosocial variables (Table 6).

Language Scales

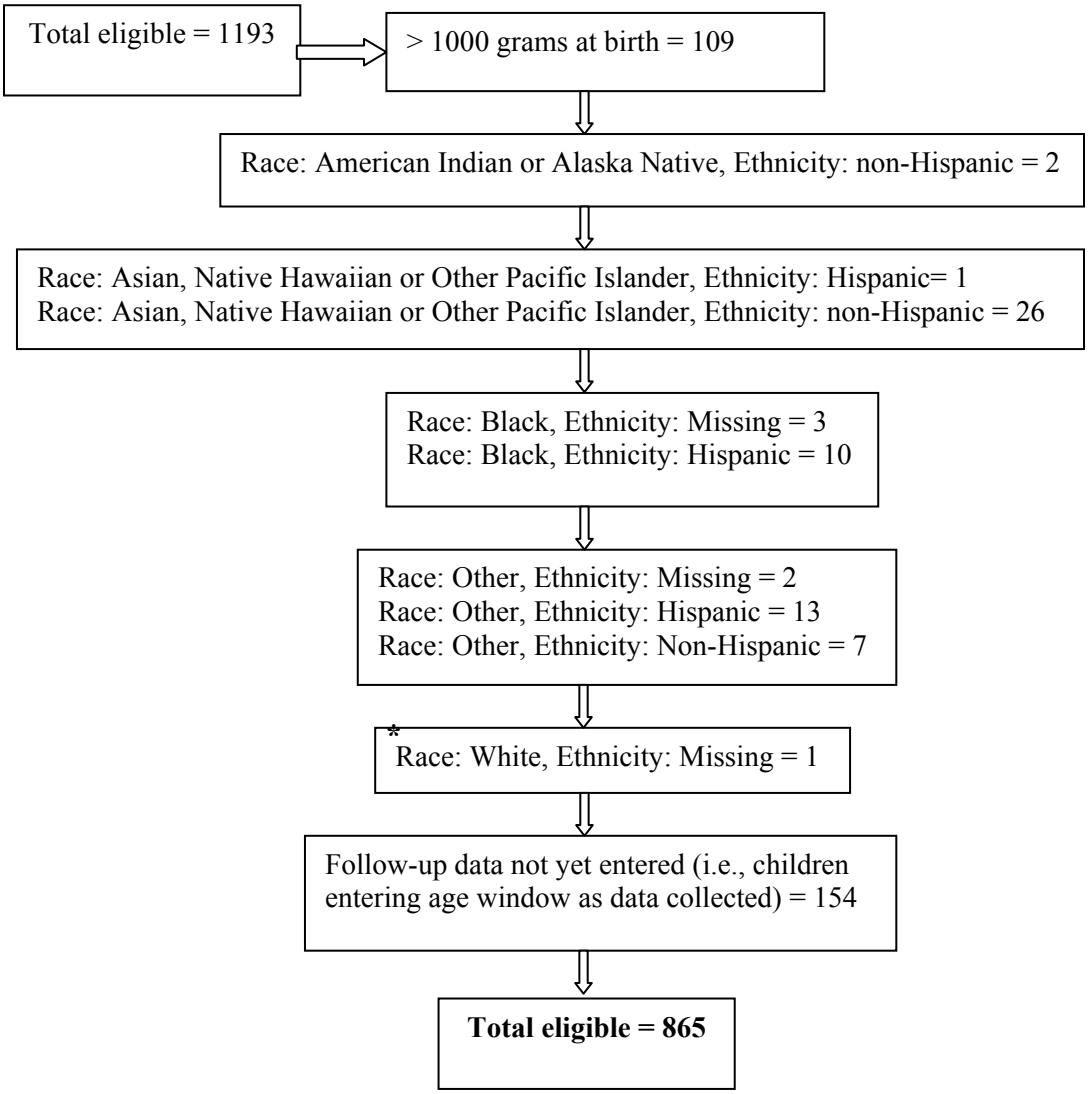
The mean BSID-III composite language score was significantly lower than the expected mean of 100 in all three groups. Analyses showed that both the mean composite language score and the receptive and expressive language scale scores were significantly

different among the three race and ethnic groups both with and without adjustment for medical and psychosocial covariates. Post-hoc analyses showed that White children had higher scores than the other two groups on all three scales. Composite and expressive language scores were not different between Blacks and Hispanic-White. Although Blacks scored higher than Hispanic-Whites on the receptive language subscale this difference was not significant once adjustment was made.

Early Intervention

In our study population, 63.4% of White infants, 55.1% of Black infants and 54.9% of Hispanic-White infants were reported as needing early intervention (p-value=0.0471 based on chi-square test). For White infants, 57.8% were receiving early intervention at 18-22 months and an additional 17.9% had received early intervention at some point but discontinued prior to their 18-22 month visit. For Black infants, 43.8% were still receiving early intervention while 16.8% had received early intervention but discontinued. For Hispanic-White infants, 47.5% were still receiving early intervention while 20.8% had received early intervention but discontinued. The p-value for comparing receipt of early intervention (yes or no) between race/ethnicity groups was <0.001. Furthermore, infants that received early intervention at any point (discontinued or still receiving) tended to have lower cognition scores than those who had not while infants that were still receiving early intervention at 18 to 22 months tended to have lower scores for all language outcomes than those who were not still receiving early intervention. As a post-hoc analyses, we included receipt of early intervention in the models described above as an additional covariate. The inclusion of this variable did not change the relationship between race and ethnicity and the cognitive or language scores.

Figure 1. Sample Population



*Eligibility defined as EGA <28 + 0/7 weeks.

Table 2. Study Population Demographic and Baseline Characteristics During Hospitalization

	White (N=369)	Black (N=352)	Hispanic-White (N=144)	Total (N=865)	P-value
Gestational age at birth (weeks)					
n	369	352	144	865	0.1061
Mean (StdDev)	25.5 (1.12)	25.3 (1.24)	25.4 (1.09)	25.4 (1.16)	
Range	23-27	22-27	22-27	22-27	
Multiple gestation: n (%)					
No	251/369 (68.0)	274/352 (77.8)	105/144 (72.9)	630/865 (72.8)	0.0125
Yes	118/369 (32.0)	78/352 (22.2)	39/144 (27.1)	235/865 (27.2)	
Birth weight (g)					
n	369	352	144	865	0.0145
Mean (StdDev)	811.0 (172.70)	777.0 (162.25)	809.5 (158.57)	796.9 (166.83)	
Range	440-1276	410-1250	510-1230	410-1276	
Gender: n (%)					
Female	181/369 (49.1)	178/352 (50.6)	68/144 (47.2)	427/865 (49.4)	0.7857
Male	188/369 (50.9)	174/352 (49.4)	76/144 (52.8)	438/865 (50.6)	
BPD: n (%)					
No	160/365 (43.8)	188/348 (54.0)	78/142 (54.9)	426/855 (49.8)	0.0103
Yes	205/365 (56.2)	160/348 (46.0)	64/142 (45.1)	429/855 (50.2)	
Postnatal steroids: n (%)					
No	312/362 (86.2)	311/348 (89.4)	125/144 (86.8)	748/854 (87.6)	0.4177
Yes	50/362 (13.8)	37/348 (10.6)	19/144 (13.2)	106/854 (12.4)	
Grade III or IV IVH: n (%)					
No	316/368 (85.9)	306/349 (87.7)	119/143 (83.2)	741/860 (86.2)	0.4193
Yes	52/368 (14.1)	43/349 (12.3)	24/143 (16.8)	119/860 (13.8)	
Cystic PVL: n (%)					
No	352/369 (95.4)	334/351 (95.2)	136/144 (94.4)	822/864 (95.1)	0.9041
Yes	17/369 (4.6)	17/351 (4.8)	8/144 (5.6)	42/864 (4.9)	
Nosocomial sepsis: n (%)					
No	250/369 (67.8)	187/352 (53.1)	88/144 (61.1)	525/865 (60.7)	0.0003
Yes	119/369 (32.2)	165/352 (46.9)	56/144 (38.9)	340/865 (39.3)	

Table 3. Study Population Demographic and Baseline Characteristics at 18-22 Month Follow-up

	White (N=369)	Black (N=352)	Hispanic-White (N=144)	Total (N=865)	P-value
Adjusted age for BSID-III cognitive subscale (months)					
n	368	351	144	863	0.0986
Mean (StdDev)	19.7 (1.38)	19.5 (1.39)	19.5 (1.35)	19.6 (1.38)	
Range	18-22	18-22	18-22	18-22	
Adjusted age for BSID-III receptive language subscale (months)					
n	366	346	141	853	0.1297
Mean (StdDev)	19.7 (1.38)	19.5 (1.39)	19.5 (1.36)	19.6 (1.38)	
Range	18-22	18-22	18-22	18-22	
Adjusted age for BSID-III expressive language subscale (months)					
n	362	348	139	849	0.0885
Mean (StdDev)	19.7 (1.38)	19.5 (1.39)	19.5 (1.37)	19.6 (1.38)	
Range	18-22	18-22	18-22	18-22	
Weight at testing (kg)					
n	369	352	143	864	0.4282
Mean (StdDev)	10.7 (1.34)	10.8 (1.50)	10.6 (1.32)	10.7 (1.40)	
Range	7-15	7-16	8-15	7-16	
Length at testing (cm)					
n	369	351	143	863	0.7787
Mean (StdDev)	81.1 (3.58)	80.9 (3.97)	80.8 (3.14)	81.0 (3.68)	
Range	71-92	67-91	72-91	67-92	
Head circumference at testing (cm)					
n	369	352	143	864	0.0807
Mean (StdDev)	47.1 (1.94)	46.8 (2.06)	47.1 (1.84)	47.0 (1.98)	
Range	36-54	36-55	44-54	36-55	
GMFCS ≥2: n (%)					
No	351/369 (95.1)	330/352 (93.8)	138/144 (95.8)	819/865 (94.7)	0.5692
Yes	18/369 (4.9)	22/352 (6.3)	6/144 (4.2)	46/865 (5.3)	
Blind: n (%)					
No	368/369 (99.7)	347/352 (98.6)	142/144 (98.6)	857/865 (99.1)	0.2231
Yes	1/369 (0.3)	5/352 (1.4)	2/144 (1.4)	8/865 (0.9)	
Hearing Impaired: n (%)					
No	360/369 (97.6)	336/352 (95.5)	139/143 (97.2)	835/864 (96.6)	0.2690
Yes	9/369 (2.4)	16/352 (4.5)	4/143 (2.8)	29/864 (3.4)	

Table 4. Maternal/Primary Caretaker Characteristics For Study Population

	White (N=369)	Black (N=352)	Hispanic-White (N=144)	Total (N=865)	P-value
Maternal age (years)					
N	369	352	144	865	<.0001
Mean (StdDev)	28.5 (6.39)	26.0 (6.31)	27.8 (6.67)	27.4 (6.50)	
Range	16-48	12-43	16-42	12-48	
Primary caretaker education: n (%)					
< 7th grade	1/349 (0.3)	2/331 (0.6)	17/135 (12.6)	20/815 (2.5)	<.0001
7th to 9th grade	7/349 (2.0)	7/331 (2.1)	21/135 (15.6)	35/815 (4.3)	
10th to 12th grade	24/349 (6.9)	63/331 (19.0)	22/135 (16.3)	109/815 (13.4)	
High school degree	82/349 (23.5)	111/331 (33.5)	31/135 (23.0)	224/815 (27.5)	
Partial college	102/349 (29.2)	96/331 (29.0)	25/135 (18.5)	223/815 (27.4)	
College degree	89/349 (25.5)	39/331 (11.8)	9/135 (6.7)	137/815 (16.8)	
Graduate degree	43/349 (12.3)	10/331 (3.0)	6/135 (4.4)	59/815 (7.2)	
Unknown	1/349 (0.3)	3/331 (0.9)	4/135 (3.0)	8/815 (1.0)	
Primary language used in household: n (%)					
English	358/369 (97.0)	342/352 (97.2)	43/144 (29.9)	743/865 (85.9)	<.0001
Other	11/369 (3.0)	10/352 (2.8)	101/144 (70.1)	122/865 (14.1)	

Table 5. Association Between Race/Ethnicity and BSID III Score

	White (N=369)	Black (N=352)	Hispanic-White (N=144)	Total (N=865)	P-value [1]
BSID-III					
Cognitive					
Mean (StdDev)	91.9 (14.50)	88.2 (14.38)	88.2 (14.37)	89.8 (14.53)	0.0009
Range	54-140	54-130	54-120	54-140	
Adjusted Mean (StdErr)	68 (2.7)	66 (2.7)	65 (2.7)		0.1293
Language					
Mean (StdDev)	89.7 (17.54)	81.8 (16.08)	79.2 (16.88)	84.7 (17.39)	<.0001
Range	46-144	46-118	46-135	46-144	
Adjusted Mean (StdErr)	61 (3.5)	55 (3.4)	53 (3.4)		<.0001
Expressive					
Mean (StdDev)	8.3 (2.96)	7.4 (2.78)	6.9 (2.86)	7.7 (2.92)	<.0001
Range	1-17	1-14	1-16	1-17	
Adjusted Mean (StdErr)	6 (0.5)	5 (0.5)	4 (0.5)		0.0003
Receptive					
Mean (StdDev)	8.4 (3.04)	7.0 (2.50)	6.2 (3.01)	7.5 (2.95)	<.0001
Range	1-18	1-13	1-17	1-18	
Adjusted Mean (StdErr)	6 (0.5)	5 (0.5)	4 (0.5)		0.<0.0001

[1] P-values for 'Mean (StdDev)' rows obtained from an ANOVA model with the score of interest as the outcome and Race/Ethnicity as the explanatory variable. Adjusted means and the corresponding p-values obtained from an ANCOVA model with the score of interest as the outcome, Race/Ethnicity as the explanatory variable and controlling for medical and socioeconomic factors.

Table 6. Final Multivariate Prediction Model for BSID-III Cognitive Scores Obtained via Backwards Selection

Parameter	Parameter Estimate (b)	SE (b)	95% CI	Standardized Estimates (β)	P-value
Birth weight (g)	0.01	0.003	0.01, 0.02	0.12	0.0001
Male (vs. Female)	-4.03	0.821	-5.64, -2.41	-0.14	<0.0001
Education:					0.0014
7th to 9th grade (vs. < 7th grade)	-9.58	3.30	-16.06, -3.11	-0.14	
10th to 12th grade (vs. < 7th grade)	-6.00	2.95	-11.78, -0.22	-0.14	
High school degree (vs. < 7th grade)	-7.55	2.85	-13.14, -1.96	-0.24	
Partial college (vs. < 7th grade)	-5.46	2.85	-11.06, 0.14	-0.17	
College degree (vs. < 7th grade)	-3.58	2.92	-9.31, 2.16	-0.09	
Graduate degree (vs. < 7th grade)	-2.21	3.15	-8.41, 3.98	-0.04	
Unknown (vs. < 7th grade)	-3.85	5.67	-14.99, 7.29	-0.03	
Postnatal steroids (vs no use)	-3.88	1.33	-6.50, -1.26	-0.09	0.0037
Grade III or IV IVH (vs. no occurrence)	-4.44	1.21	-6.82, -2.06	-0.11	0.0003
Nosocomial sepsis (vs. no occurrence)	-2.42	0.881	-4.15, -0.69	-0.08	0.0062
Multiple birth (vs. single birth)	-2.35	0.933	-4.18, -0.52	-0.07	0.0120
Blind (vs. no occurrence)	-18.30	4.62	-27.36, -9.24	-0.12	<0.0001
GMF >= Level 2 (vs. no occurrence)	-25.77	1.95	-29.60, -21.93	-0.40	<0.0001

Chapter 4

DISCUSSION

In this study we have shown for the first time that race and ethnicity are associated with cognitive and language scores on the BSID-III. While differences in the cognitive scores were explained by a combination of medical and psychosocial factors, these factors did not account for the differences identified in language scores. The identification of specific medical and psychosocial factors associated with increased risk for cognitive impairment may allow more targeted early intervention. Our finding that language differences were sustained in minority groups regardless of other risk factors provides a compelling argument for focusing early intervention programs on the attainment of language in these groups. In addition, as BSID-III scores were below expected in *all three* race and ethnic groups included, this study highlights the continued need for monitoring and provision of early intervention in all at-risk groups.

Difficulties with cognition, attention and self-regulation seen in children born at lower birth weights can persist throughout childhood and are associated with an increased incidence of learning difficulties.[1-5] Because early childhood intervention results in improvements in developmental and social outcomes,[6,7] early assessment of cognitive functioning in these children is extremely important. We have shown that cognition and language scores were lower for infants receiving early intervention. Receipt of early intervention identified infants in our database that were likely to have lowered cognitive/language scores. It is thus likely that infants that receive early intervention are selected to receive this intervention because caretakers believe they are predisposed to have developmental deficits.

In the current study, we found that BSID-III cognitive scores were no longer different between race and ethnic groups after adjustment for a combination of psychosocial and medical factors. In our previous study using the BSID-II, however, race and ethnic differences remained even after adjustment.[9] This difference may be due to the inclusion of a separate language domain in the BSID-III. Ethnic and cultural influences may be of less concern for cognitive development than previously believed, and our results highlight the importance of conducting future studies of assessment of language development in this population.

In a recent meta-analysis, Aylward[1] found that expressive language skills, such as verbal production and mean length of utterances, were lower in preterm children, and that these skills were susceptible to environmental influences. The BSID-III language scales now provide us with a tool to look specifically at language skills in preterm children, and separate out receptive and expressive language skills. Because receptive language skills were lower in Hispanic-White children than Black children, we speculate that non-English primary language may contribute to this finding. However, language scores were lower in both Black and Hispanic-White children compared to Whites, indicating that language delays may be more prevalent in both groups, but this requires further study.

This study had several important limitations that should be addressed in future studies. First, defining race and ethnicity is often difficult due to the variability in reporting of the measure. For instance, race and ethnicity may be collected via subject self-report, direct observation of the subject, proxy report, or extraction from medical records. This variability may decrease the reliability and validity of the measure. Self-report is the most reliable method of collecting race and ethnicity information, and is thus

preferred for data collection and study;[17] this is the method which we utilized. In addition, the Office of Management and Budget has defined minimum acceptable standards for collecting and presenting race and ethnicity data, and we have met those standards.[17] Though we have used the most reliable method of measurement of race/ethnicity, the risk of error in this measurement still exists, and the influence of such an error on the study results is unknown. In addition, the use of race and ethnicity as an explanatory variable may be limited by the fact that race and ethnicity may be proxies for socioeconomic status. We have attempted to limit the effect of this possible confounding by including socioeconomic status as a separate variable in the analysis.

Perhaps the greatest limitation of this study is the fact that there is not a standardized Spanish version of the BSID-III, and there is thus no evidence that the BSID-III administered to Spanish-speaking children in the manner that we have described is valid or reliable. There may have been differences in interpretation between test administrators, and the effect of this is unknown. In addition, it is not known whether those children for whom their primary language was identified as Spanish were bilingual Spanish/English speakers or monolingual Spanish speakers. This heterogeneity could bias our results and makes interpretation of the language score data difficult. Further study on how language use during BSID-III administration influences test results is greatly needed. The association between race and ethnicity and language score should not be completely discounted, however, as Black children also scored significantly lower than Whites on the language portion of the BSID-III, and this difference is unexplained by non-English language, as there was only one child in the study identified as Black for whom the primary language was identified as Spanish.

The use of backward selection in our secondary post-hoc analyses may also be a limitation of this study, and in future studies a cross-validation approach might be more useful in identifying predictive factors. The inclusion of receipt of early intervention may also be a limitation of the study, as there was no control for the *type* of early intervention given; our data collection included only whether or not the child received any early intervention. Early intervention services may be extremely heterogeneous, and future studies should consider comparison of intervention types in at-risk children of different races and ethnicities. Finally, though we have shown important associations between psychosocial factors such as race and ethnicity and medical morbidities with BSID-III scores, our study design does not allow causal inference based upon our results. Though we have attempted to address this by adjusting for medical and psychosocial factors, it is impossible to know whether we have adjusted for all potentially important covariates or confounders. The degree and direction of any bias in our results due to this is unknown. Future studies should be designed to specifically assess whether there is differential prediction of developmental outcomes between groups.

Conclusions

In conclusion, the racial and ethnic group differences on the BSID-III cognitive scale observed in this study were explained by a combination of medical and psychosocial factors. Black and Hispanic-White children were at greater risk for delayed language than White children, highlighting the need for further study and possibly specific programs focused on language skills in these groups. This study provides an important step in better understanding the impact of race and ethnicity on the newly revised BSID-III and has important implications for the refinement of early intervention

strategies among children with a history of preterm birth by delineating modifiable factors underlying race and ethnic disparities in neurodevelopmental test results in these children.

REFERENCES

1. Aylward GP. Cognitive and neuropsychological outcomes: More than IQ scores. Ment Retard Dev DR 2002; 8: 234-40.
2. Anderson PJ, Doyle LW. Executive Functioning in School-Aged Children Who Were Born Very Preterm or With Extremely Low Birth Weight in the 1990s. Pediatrics 2004; 114: 50-57.
3. Moster D, Lie RT, Markestad R. Long-term medical and social consequences of preterm birth. New Engl J Med 2008; 359: 262-73.
4. Saigal S, den Ouden L, Wolke D, Hoult L, Paneth N, Streiner DL et al. School-age outcomes in children who were extremely low birth weight from four international population-based cohorts. Pediatrics 2003; 112:943-50.
5. Hack M, Taylor HG, Drotar D, Schlucter M, Cartar L, Wilson-Costello D et al. Poor Predictive Validity of the Bayley Scales of Infant Development for Cognitive Function of Extremely Low Birth Weight Children at School Age. Pediatrics 2005; 116: 333-341.
6. Nordhov SM, Ronning JA, Dahl LB, Ulvund SE, Tunby J, Kaaresen PI. Early intervention improves cognitive outcomes for preterm infants: randomized controlled trial. Pediatrics 2010; 126: e1088.
7. Ramey CT, Campbell FA, Burchinal M, Skinner ML, Gardner DM, Ramey SL. Persistent effects of early childhood education on high-risk children and their mothers. Applied Developmental Science 2000; 4:2 -14.
8. Bayley, N. Bayley scales of infant development- 2nd edition. San Antonio, TX: The Psychological Corporation; 1993.

9. Lowe J, MacLean P, Shaffer P, Watterberg K. Early working memory and cognition in a cohort of ethnically diverse infants born extremely low birth weight at 18-22 months. J Child Neurol 2009; 24: 410-15.
10. Bayley, N. Bayley scales of infant development-3rd edition. San Antonio, TX: The Psychological Corporation; 2006.
11. Leung AK, Kao CP. Evaluation and management of the child with speech delay. Am Fam Physician 1999; 59: 3121-8.
12. Stoll BJ, Hansen NI, Bell EF, Shankaran S, Laptook AR, Walsh MC et al., Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Neonatal Outcomes of Extremely Preterm Infants From the NICHD Neonatal Research Network. Pediatrics 2010; 126:443-56.
13. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and validation of a gross motor function classification system for children with cerebral palsy. Dev Med Child Neurol 1997; 39: 214–23.
14. Taylor HG, Klein N, Drotar D, Schluchter M, Hack M. Consequences and risk of <1000 g birth weight for neuropsychological skills, achievement, and adaptive functioning. J Dev Behav Pediatr 2006; 27: 459-69.
15. Doyle LW, VICS Study Group. Outcome at 5 years of age of children 23-27 weeks' gestation: refining the prognosis. Pediatrics 2001; 108:134-41.
16. Laucht M, Esser G, Schmidt MH. Developmental outcome of infants born with biological and psychosocial risks. J Child Psychol Psyc 1997; 38:843-53.
17. Egede LE. Race, ethnicity, culture, and disparities in health care. J Gen Intern Med 2006; 2: 667–69.