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Influence of Slight to Moderate Risk for Birth Hypoxia on Acquisition of Cognitive and Language Function in the Preterm Infant: A Cross-Sectional Comparison With Preterm-Birth Controls

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The cognitive and language performance of a group of 26 preterm-birth preschool and early school-age children with slight to moderate risk for perinatal hypoxia was compared with the performance of a preterm-birth comparison group of 26 children. Despite the relatively small discrepancy in degree of risk, the cognitive performance of the 2 groups diverged significantly. When data for children with known perinatal arterial pH were combined, a curvilinear (quadratic) regression model provided the best fit. Increasing acidosis was linearly related to decreases in cognitive skills, with the bend in the curve occurring well within the normal range of pH values. Hence, in the preterm infant, even minor risk for birth hypoxia may result in discernible deviation from the expected developmental trajectory.

Perinatal hypoxic–ischemic insult is thought to contribute not only to mortality and morbidity in the neonate (Gunn, Parer, Mallard, Williams, & Gluckman, 1992; Raz, Foster et al., 1994; Raz, Goldstein et al., 1994; Tejani & Verma, 1989; Williams, Gunn, Mallard, & Gluckman, 1992) but also to poor neurodevelopmental outcome (Brazy, Eckerman, Oehler, Goldstein, & O'Rand, 1991; Finer, Robertson, Richards, Pinnell, & Peters, 1981; Goldstein, Thompson, Oehler, & Brazy, 1995; Low et al., 1992; Palmer & Vannucci, 1993; Thompson et al., 1997). Exploration of the cognitive sequelae of birth asphyxia and its attendant risk for hypoxic–ischemic cerebral insult is crucial to the understanding of the nature of brain vulnerability during early development. The complexity of the processes involved in perinatal asphyxia is reflected in the terminology used in the extant literature. As noted by Blair (1993), although an initiating hypoxic or ischemic insult is considered necessary for the presence of birth asphyxia, the latter term has been used to refer to each of the components individually as well as any combination thereof. As hypoxia–ischemia may also occur antenatally, or during the neonatal period, it is important to determine its effects during each of these maturationally distinct periods. Whereas a recent study (Lauterbach, Raz, & Sander, 2001) focused on the respiratory distress syndrome, a condition associated with risk for neonatal hypoxia–ischemia, the present investigation focuses on birth-related hypoxic risk.

In this study, we sought to determine whether a relatively low risk for birth-related hypoxia explains a unique share of the variance in intellectual and language performance during the preschool and early school-age years. In an earlier study (Porter-Stevens, Raz, & Sander, 1999) designed to examine differences in cognitive development between term- and preterm-birth infants at birth-related hypoxic risk, a significant effect of gestational maturity on intellectual abilities was not observed. Because blood pH level is considered the biochemical standard of asphyxia (Carter, Haverkamp, & Merenstein, 1993), birth-related hypoxic risk was determined on the basis of arterial pH sampled shortly after birth. Nonetheless, in the total sample of term- and preterm-birth children at risk for hypoxia who had participated in the earlier study, we observed a relationship between initial arterial pH obtained within 3 hr of birth and cognitive development. Specifically, we found that within a group of children at slight to moderate birth-related hypoxic risk, an increase in the degree of risk was linked with a proportionate decline in cognitive performance. However, the study was not designed to evaluate the magnitude of the developmental change putatively associated with these lower risk levels. To that objective, we performed a comparison of cognitive and language function between preterm-birth children with history of slight to moderate perinatal hypoxia and preterm-birth children not considered at risk for this complication. For the latter group, determina-

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tion of reduced risk was based either on arterial pH values within the nonacidotic normal range (pH $\geq$ 7.3, according to criteria provided by Korones, 1981) or on improved clinical status at birth as reflected by absence of need for oxygen supplementation.

Method

Subjects

The sample was composed of 52 preterm-birth children who had been treated at the Neonatal Intensive Care Unit (NICU) at Baptist Memorial Hospital in Memphis, Tennessee, from 1986 to 1991. Two groups, one ($n = 26$) at risk for birth hypoxia and the other ($n = 26$) a comparison group not considered at risk, were recruited when the children reached preschool or early school age. The target group consisted of children born prematurely (gestational age $\leq$ 36 weeks according to maternal dates) whose initial arterial pH (within 2 hr after delivery) was below 7.3 (the lower cutoff for the normal range) and above 7.1 (the lower limits of moderate acidosis; Korones, 1981). Hence, perinatal hypoxic risk in the target group ranged from slight to moderate. Data about the intellectual performance of 25 of the 26 subjects was published in an earlier study (Porter-Stevens et al., 1999) that was designed to compare the cognitive performance of term- and preterm-birth infants at risk for perinatal hypoxia.

Because we were interested in studying the effects of hypoxic risk at birth, infants whose pH had recovered to normal but subsequently fell below 7.1 (the lower limits of moderate acidosis; Korones, 1981) were not included in the target group. We reasoned that a postrecovery drop in pH could have been linked to complications other than birth-related hypoxia (e.g., neonatal respiratory distress). In addition, infants who required supplemental oxygen for more than 1 week were excluded, as we wished to eliminate those with postnatal respiratory difficulty of sufficient severity to potentially influence cognitive outcome. Studywide exclusion criteria were chromosomal or genetic defects, placental abruption or previa, intrauterine growth retardation (defined according to the Colorado Intrauterine Growth Charts; Lubchenco, Hansman, & Boyd, 1966), retinopathy of prematurity, intracranial hemorrhage, and bronchopulmonary dysplasia. On the basis of maternal reports, none of the subjects had sustained a severe head injury and none had received a diagnosis of seizure disorder. In addition, none of the study participants had gross perceptual or motor handicaps. In brief, a unique feature of this at-risk early school-age sample was that we eliminated a variety of ante-, peri-, and postnatal conditions that could exert deleterious influences on cognitive or language function and thus confound the effects of birth-related hypoxic risk.

The preterm comparison group was composed of 26 children. Sixteen of the comparison group children fulfilled criteria for the current study and for one of two additional ongoing studies, the first on the outcome of antenatal complications ($n = 11$; Raz et al., 2002) and the second ($n = 4$) on the cognitive sequelae of respiratory distress syndrome (Lauterbach et al., 2001). Six children qualified for the current study only. The remaining 5 children were added from an earlier investigation of sex differences for which data collection was completed in 1994 (Raz, Lauterbach, Hopkins, Glogowski, & Porter, 1995). It should be noted that recruitment of children for the comparison group spanned 3.5 years compared with 15 months for the target group, in part because of decreased availability for testing of preterm-birth children with initial arterial pH within the normal range and with improved clinical status at birth (see selection criteria below). Within the population of premature infants admitted to the NICU and available for evaluation, those with initial pH below 7.3 (our target group) were relatively more common than either those with normal pH or those with improved clinical status at birth (our comparison subgroups).

As mentioned above, two comparison subgroups were recruited. The first subgroup ($n = 15$) was selected on the basis of an initial arterial pH value greater than 7.3, the lower cutoff for the normal pH range (Korones, 1981). The second subgroup ($n = 11$) included children with improved neonatal status—as indicated by absence of need for oxygen supplementation—whose medical condition did not necessitate assessment of acid–base balance after delivery. Thus, perinatal pH values were unknown for members of the latter subgroup.

The decision to include two subgroups for comparative purposes was based on both practical and theoretical considerations. From a practical viewpoint, preterm neonates whose medical condition required assessment of acid–base status yet who were subsequently found to have initial arterial pH values within the normal range were difficult to obtain. From a theoretical perspective, it was important to include in the comparison group preterm-birth children whose improved medical condition at birth did not require evaluation of acid–base balance. Omission of these lower risk children with improved neonatal status would jeopardize ecological validity. Indeed, a comparison between the clinical characteristics of the two subgroups, presented in Table 1, reveals a small yet significant increase in the need for oxygen support as well as trends for lower Apgar scores and for a greater number of complications in the comparison subgroup with known arterial pH values. Nonetheless, because the two groups differed significantly only in the need for oxygen supplementation, they were combined in the remaining tables to simplify comparison with the target group.

The demographic and sociofamilial attributes of the group at risk for birth-related hypoxia and the preterm comparison group are presented in Table 2. These data reveal no significant differences between the two groups in age, parental education, socioeconomic status (SES), and maternal IQ. In addition, the groups did not differ in sex ratio, racial composition, or the singleton-to-twin births ratio.

Our analyses revealed that there were no significant differences between the group at risk for birth-related hypoxia and the preterm comparison group on presence of individual antenatal–obstetric complications such as Caesarean section, general anesthesia, breech presentation, forceps delivery, chorioamnionitis, nuchal or prolapsed cord, maternal diabetes, membranes ruptured more than 12 hr, toxemia–hypertension, or vaginal bleeding. The total number of antenatal–obstetric complications was also similar between the group at risk for birth-related hypoxia and the preterm group ($M = 1.81$, $SD = 1.20$, and $M = 1.73$, $SD = 1.22$, respectively), $t(50) = -0.23$, *ns*). A nonsignificant trend for a group difference was observed in parity (for the at-risk group, $M = 0.39$, $SD = 0.64$, and for the comparison group, $M = 0.89$, $SD = 1.14$), $t(50) = 1.95$, $p < .10$. The single significant difference between the groups was in maternal age, with higher age observed in the comparison group ($M = 27.58$, $SD = 4.93$, and $M = 30.58$, $SD = 4.97$ for the at-risk and comparison groups, respectively), $t(50) = 2.19$, $p < .05$.

Our analyses revealed no differences between the group at risk for birth-related hypoxia and the preterm comparison group in the total number of neonatal complications ($M = 3.08$, $SD = 1.02$, and $M = 2.73$, $SD = 1.15$, respectively), $t(50) = -1.15$, *ns*. In addition, no significant differences were observed when the two groups were compared in the frequency of individual neonatal

Table 1
Perinatal Characteristics of the Preterm Comparison Group Subdivided by Availability of Information on Perinatal Acid–Base Status

Characteristic	Initial arterial pH > 7.3 (n = 15)	Unknown acid–base balance (n = 11)
Apgar 1	6.80 ± 1.97	7.73 ± 0.65
Apgar 5†	8.40 ± 0.74	8.81 ± 0.41
Birthweight (g)	1,890.87 ± 533.83	2,061.64 ± 345.00
Gestational age (weeks)	32.80 ± 2.73	32.73 ± 1.74
Total obstetric complications	1.93 ± 1.22	1.73 ± 1.22
Total perinatal complications†	3.07 ± 1.34	2.27 ± 0.65
Total complications†	5.00 ± 1.89	3.73 ± 1.27
NICU days	21.00 ± 12.52	15.00 ± 5.80
Days on oxygen*	0.98 ± 1.57	0.01 ± 0.03[a]
Highest inspired oxygen (%)	42.20 ± 24.58	21.00 ± 0.00

Note. Tests for group differences were accomplished by a t test. NICU = neonatal intensive care unit.
[a] A single male infant from this group required oxyhood for 2 hr on room air (21% oxygen).
† $p < .10$. * $p < .05$.

complications, including anemia (hematocrit < 35%), apnea, hyaline membrane disease, hyperbilirubinemia (bilirubin levels > 12 mg/dl or greater), hypermagnesemia, hypoglycemia, hypocalcemia (calcium levels < 7 mg/dl), hypotension, necrotizing enterocolitis, patent ductus arteriosus, pneumothorax, neonatal seizures, sepsis, and tachypnea.

Consistent with our group selection criteria, Table 3 shows multiple group differences on variables associated with birth-related hypoxic risk, including Apgar scores at 1 and 5 min, initial and lowest arterial pH, and initial base excess (Carter et al., 1993), an index of lactacidosis (Roth et al., 1992).

A comparison of the two groups on diagnostic and treatment procedures (see Table 4) reveals, in addition to the expected differences in need for supplemental oxygen, significant group differences in the frequency of antenatal administration of steroids to promote fetal lung maturation. In summary, the data presented here indicate that with the exception of variables related to our group assignment criteria, the preterm comparison group may be viewed as having a potential advantage on a single variable only—treatment with antenatal steroids.

Psychological Assessment

All children were tested at the University of Memphis Developmental Neuropsychology Laboratory. The assessments were completed in one or two sessions, depending on the examiner's judgment regarding the child's attention and cooperation during the session. The children included in the target group completed cognitive and language tests between August 1995 and October 1996, whereas children included in the comparison group were tested between January 1994 and May 1997. An informed consent form was signed by the parents or legal guardians of all subjects prior to the first testing session.

Table 2
Demographic and Sociofamilial Characteristics in a Group of Preterm-Birth Children at Risk for Birth-Related Hypoxia and in a Preterm Comparison Group

		Preterm comparison group	
Demographic characteristic	Risk group (n = 26)	Known and unknown pH (n = 26)	Known pH (n = 15)
Age (years)	5.91 ± 0.70	5.83 ± 0.91	6.10 ± 1.02
Sex (F:M)	15:11	10:16	7:8
Race (W:B)	19:7	20:6	14:1
Twin birth (singleton:twin)	20:6	20:6	11:4
Mother's education (years)	14.50 ± 1.89	13.62 ± 1.84	13.60 ± 1.99
Father's education (years)	14.27 ± 2.11	13.59 ± 2.53	13.97 ± 2.86
Socioeconomic status[a]	41.79 ± 8.52	39.00 ± 12.08	41.60 ± 11.91
Mother's IQ[b]	94.85 ± 13.17	97.44 ± 13.26	102.13 ± 14.78

Note. All differences were nonsignificant by a t test for continuous data or by a 2 × 2 chi-square test with Yates correction for discrete data. Frequencies are reported for discrete data, and means and standard deviations are reported for continuous data. F = female; M = male; W = White; B = Black.
[a] Computed according to Hollingshead's (1975) Four Factor Index of Social Status, on the basis of data obtained from the parent or legal guardian during the testing session. [b] Mother's IQ was prorated from three Verbal Scale subtests (Vocabulary, Similarities, and Information) from the Wechsler Adult Intelligence Scale—Revised (Wechsler, 1981). Calculations are based on 26 at-risk children and 25 comparison children, as IQs could not be obtained from one mother.

Table 3
Perinatal Characteristics of Group at Risk for Birth-Related Hypoxia and of Comparison Group

Perinatal variable	Risk group (n = 26)	Preterm comparison group: Known and unknown pH (n = 26)	Preterm comparison group: Known pH (n = 15)
Apgar 1	6.23 ± 1.64	7.19 ± 1.60*	6.80 ± 1.97
Apgar 5	8.08 ± 0.68	8.58 ± 0.64**	8.40 ± 0.74
Birthweight (g)	2,233.58 ± 646.71	1,963.12 ± 463.25†	1,890.87 ± 533.83†
Gestational age (weeks)[a]	33.42 ± 2.23	33.77 ± 2.32	32.80 ± 2.73
Initial arterial pH***	7.22 ± 0.05		7.36 ± 0.04
Age at initial sampling (min)	52.73 ± 20.31		138.36 ± 211.49[b]
Lowest arterial pH***	7.22 ± 0.05		7.34 ± 0.05
Initial base excess (mEq/L)[c]***	−6.02 ± 3.60		−1.09 ± 2.67[c]
Lowest base excess (mEq/L)[c]***	−6.88 ± 3.45		−2.44 ± 3.35[c]
NICU days	17.77 ± 11.20	18.46 ± 10.50	21.00 ± 12.52

Note. Group differences were accomplished by a t test. Means and standard deviations are reported. NICU = neonatal intensive care unit.
[a] Determined by maternal dates. [b] After removal of a single female subject whose initial blood gas sampling was completed at the age of 14 hr and 18 min, the mean age at initial sampling (±*SD*) drops to 83.00 ± 44.47 min for the comparison group. [c] Base excess is calculated from the pH, bicarbonate (HCO^-_3), and carbon dioxide (CO_2; see Loeppky, Fletcher, Roach, & Luft, 1993; Siggaard-Andersen, 1974).
† $p < .10$. * $p < .05$. ** $p < .01$. *** $p < .001$.

The intelligence testing was completed using the Wechsler Preschool and Primary Scales of Intelligence—Revised (WPPSI–R; Wechsler, 1989). The test was administered to all subjects with the exception of 2 subjects (1 boy) who completed the Wechsler Intelligence Scales for Children—Third Edition (WISC–III; Wechsler, 1991). The Preschool Language Scale—3 (PLS–3; Zimmerman, Steiner, & Pond, 1992) was also administered to obtain an index of language function, a critical component of cognitive skills in the preschool and early school years. The test yields Auditory Comprehension Scale (ACS) and Expressive Communication Scale (ECS) scores that summarize receptive and expressive language skills, respectively. Forty-five of the 52 participants, including 19 of the 26 comparison group subjects, completed the PLS–3. The tests were administered by graduate students at the University of Memphis Department of Psychology, who had been extensively trained in cognitive assessment in general and in psychological assessment of children in particular. They were unaware of the perinatal background of the subjects at the time of testing, and they were not briefed about the study hypotheses. All parents were asked to avoid discussion of the children's medical history with the examiners.

Table 4
Diagnostic and Treatment Procedures by Presence of Hypoxic Risk in Preterm-Birth Children

Diagnostic and treatment method	Risk group (n = 26)	Preterm comparison group: Known and unknown pH (n = 26)	Preterm comparison group: Known pH (n = 15)
Cranial ultrasound	22	23	13
Surfactant	2	2	2
Prenatal steroids[a]	4	15**	8**
Days on oxyhood	1.48 ± 1.86	0.41 ± 0.87**	0.70 ± 1.07†
Continuous positive airway pressure	0.08 ± 0.32	0.01 ± 0.03	0.01 ± 0.03
Days on ventilator	0.43 ± 1.11	0.17 ± 0.61	0.29 ± 0.80
Days oxygenation[b]	2.00 ± 2.25	0.58 ± 1.28***	0.99 ± 1.57†
Highest inspired oxygen (%)	54.65 ± 19.66	33.23 ± 21.27***	42.20 ± 24.57†

Note. Group differences were accomplished by a t test for continuous data, 2 × 2 chi-square test with Yates correction for categorical data, or Fisher's exact probability test for cell frequency of 5 or less. Frequencies are reported for discrete data, and means and standard deviations are reported for continuous data.
[a] Betamethasone administered to mothers to promote fetal lung maturity. [b] Includes respiratory support via oxyhood, continuous positive airway pressure, ventilator, or binasal cannula.
† $p < .10$. ** $p < .01$. *** $p < .001$.

The WPPSI–R or WISC–III IQ scores were calculated on the basis of 8 subtests out of the 10 subtests included in the standard battery in attempt to minimize potential difficulties with attention span in our at-risk population. Thus, a prorated Performance IQ (PIQ) score was obtained on the basis of 4 Performance Scale subtests (Object Assembly, Picture Completion, Block Design, and Mazes), and a prorated Verbal IQ (VIQ) score was obtained on the basis of 4 VIQ subtests (Vocabulary, Comprehension, Information, and Similarities). The prorating procedures used to compute the VIQ and PIQ scores are described in the WPPSI–R manual (Wechsler, 1989, p. 187). The choice of the 8 subtests was dictated by both practical and psychometric considerations. From the 5 Performance Scale subtests, we did not include the Geometric Design, as this subtest does not have a parallel in the WISC–III—a test administered to our older subjects. From the Verbal Scale subtests, the 4 subtests with the highest reliability (split-half coefficients) were included, thus Arithmetic was removed (see Sattler, 1992, p. 980).

Because we excluded only 2 of the 10 WPPSI–R subtests from the standard battery, we believe neither reliability nor validity were substantially affected. Indeed, a short form composed of only 4 of the 8 subtests included in our battery (i.e., Block Design, Picture Completion, Information, and Vocabulary) yields a reliability coefficient of .93 and a validity coefficient of .91 (Sattler, 1992). This is hardly surprising because the correlations between standard and prorated IQ scores in our sample, using data from 14 of 52 children who completed a full 10-subtest WPPSI–R battery, were very high ($r = .97$, $p < .001$, and $r = .93$, $p < .001$, for the standard 5 subtest VIQ and the prorated 4 subtest VIQ and for the standard 5 subtest PIQ and the prorated 4 subtest PIQ, respectively).

Results

Group Comparisons: Children at Relatively Small Risk Versus Children Not Considered at Risk for Birth Hypoxia

To evaluate the effects of birth-related hypoxic risk on cognitive and language function in children born prematurely, we conducted a multivariate analysis of covariance with several predictors and covariates. The PIQ and VIQ were the dependent variables, whereas the grouping factor, presence of slight to moderate perinatal hypoxic risk, was the main predictor of interest. Variables on which there were systematic group differences in favor of the comparison group and variables that correlated with our outcome measures were selected as covariates. Thus, SES was entered as a covariate to control for variance in cognitive and language performance that is associated with family income and education level (Pearson's $r = .43$, $p < .001$, $N = 52$, for SES and Full Scale IQ). Maternal IQ was not entered because it moderately correlated with SES (Pearson's $r = .58$, $p < .001$) and because these data were not available for all subjects (see Table 2). As the target and comparison groups differed in oxygen supplementation needs, $t(50) = -2.81$, $p < .01$, this variable was also entered as a covariate to account for neonatal respiratory difficulties that might confound the effects of birth-related hypoxic risk. Antenatal steroid administration to promote fetal lung maturation, a variable on which the two groups differed significantly, was also entered as a covariate. We wished to adjust for a potential treatment advantage (de Zegher et al., 1992; Johnson, Munson, & Thompson, 1981) in favor of the preterm comparison group—or perhaps a disadvantage, as claimed by others (e.g., Modi et al., 2001). The grouping factor, presence of hypoxic risk, and the three covariates (SES, number of days on supplemental oxygen, and antenatal steroid administration) were entered simultaneously into the equation. Prior to data analyses, we examined all interactions between the categorical predictor of interest (hypoxic risk) and the covariates. As none of these interactions were significant, we used the reduced model without the interactions.

The analyses revealed that the effect of group affiliation on the linear combination of the VIQ and PIQ, a global index of intelligence, approached significance, Wilks' $\Lambda = .89$, $F(2, 46) = 2.93$, $p < .06$. After removal of a single multivariate outlier, a male subject with near normal pH (7.28) whose VIQ fell 2.4 standard deviations above his group mean, the effect was substantially enhanced, Wilks' $\Lambda = .82$, $F(2, 45) = 4.81$, $p = .01$. Univariate analyses further revealed associations between group affiliation and both the VIQ and the PIQ, $F(1, 46) = 7.94$, $p < .01$, and $F(1, 46) = 5.89$, $p < .02$, respectively.

Despite the associated reduction in the number of degrees of freedom, the findings remained essentially the same when only data from children with known initial pH were considered in examining the relationships between group affiliation and global cognitive abilities, Wilks' $\Lambda = .75$, $F(2, 34) = 5.59$, $p < .01$. Again, univariate analyses revealed significant associations between presence of acidosis and both the VIQ and the PIQ: $F(1, 35) = 9.28$, $p < .01$, and $F(1, 35) = 6.07$, $p < .02$, respectively. The relationship of the subjects' VIQs and PIQs with presence of risk for perinatal hypoxia is depicted in Figure 1.

Because group affiliation was significantly linked to both the VIQ and PIQ, we proceeded with post hoc analyses to determine whether one or more of the eight WPPSI–R or WISC–III administered subtests were differentially associated with level of perinatal risk for hypoxia. Analyses revealed that none of the four Performance Scale subtests was differentially linked to hypoxic-risk status after Bonferroni adjustment of the critical alpha level for the number of comparisons to .0125: Block Design, $F(1, 46) = 2.97$, $p < .09$; Object Assembly, $F(1, 46) = 6.40$, $p < .02$; Picture Completion, $F(1, 46) = 1.34$, $p < .30$; and Mazes, $F(1, 46) = 1.99$, $p < .17$. Similarly, none of the four Verbal Scale subtests administered was differentially linked to perinatal hypoxic risk status after adjustment for multiple comparisons: Vocabulary, $F(1, 46) = 0.50$, $p < .48$; Comprehension, $F(1, 46) = 5.95$, $p < .02$; Information, $F(1, 46) = 1.53$, $p < .22$; and Similarities, $F(1, 46) = 3.04$, $p < .09$.

The same predictor and three covariates were used to analyze the PLS–3 performance data from the 45 subjects who completed the test. The results did not reveal any association between group affiliation and the linear combination of the ACS and ECS, Wilks' $\Lambda = .96$, $F(2, 39) = 0.78$, *ns*. When children with unknown perinatal pH

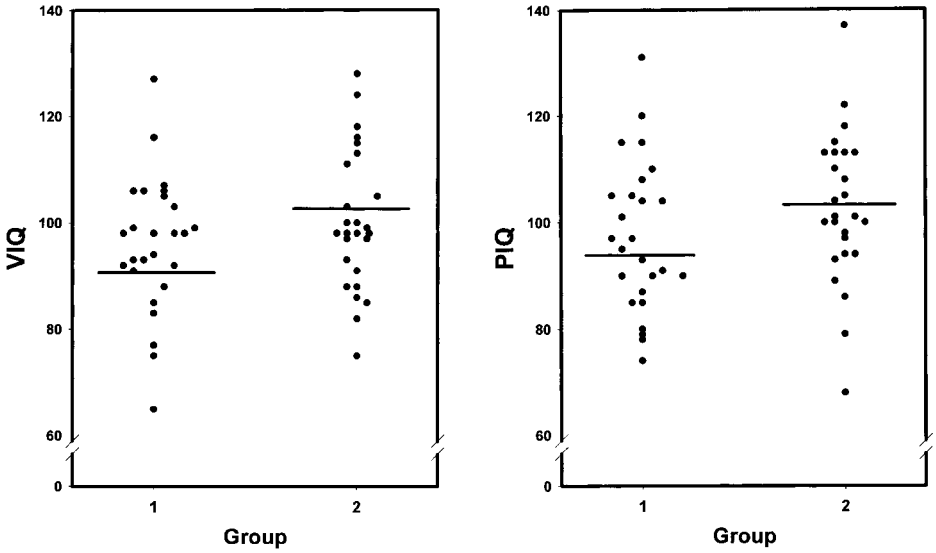


Figure 1. The Verbal IQ (VIQ; left) and Performance IQ (PIQ; right) of preterm infants classified by presence of risk for hypoxia. Adjusted means (± *SE*) were 92.35 ± 2.28 versus 102.47 ± 2.23 for the VIQ and 94.00 ± 2.59 versus 105.19 ± 2.54 for the PIQ, for the target and comparison groups, respectively. Adjusted means were computed without a multivariate outlier (a male subject with near normal pH whose VIQ fell 2.4 standard deviations above his group mean). Group 1 = risk group (pH < 7.3); Group 2 = comparison group.

were removed from the preterm comparison group, the effect remained nonsignificant, Wilks' $\Lambda = .87$, $F(2, 30) = 2.18$, $p = .13$.

Initial pH and Outcome: Comparing Linear and Curvilinear Models

The addition of 15 preterm-birth children with normal acid–base balance from the current sample to the pool of preterm children with subnormal pH values from a previous study (Porter-Stevens et al., 1999) facilitated examination of the relationships between various biochemical indices of birth-related asphyxia and cognitive outcome. Table 5 depicts the zero-order correlations between various biochemical indices of perinatal asphyxia and measures of intellectual function in the 41 preschool and early school-age children whose blood gas data were obtained at the NICU. The table reveals that the only variable consistently related to cognitive outcome was pH, whether it was the initial or the lowest value obtained during NICU stay. Initial base excess, an index of metabolic acidosis (Carter et al., 1993; Roth et al., 1992), was highly correlated with initial arterial pH (Pearson's $r = .80$, $p < .001$), yet its correlations with intellectual outcome measures did not attain conventional statistical significance level. Overall, perinatal oxygen and carbon dioxide partial pressures were not linked to intellectual outcome as consistently as a general index of acidosis—initial arterial pH. Perhaps these indices are more reactive to the effects of neonatal resuscitation efforts. Such efforts may mask the influence of birth-related distress. It is noteworthy that the zero-order correlations between initial or lowest pH values and indices of intellectual functioning reached statistical significance despite the restriction on the range of possible pH values in arterial blood. In our sample, pH ranged from 7.11 to 7.44, thus not including values in the severe and profound range of acidosis. Hence, the obtained correlations probably underestimate the strength of the relationship between perinatal pH—the most widely used biochemical index of birth asphyxia—and cognitive outcome.

The addition of a subsample with normal pH values, thereby shifting the upper end of the pH range from 7.29 to 7.44, expanded the continuum of initial arterial pH values by 83%. This expansion permitted a more accurate and detailed characterization of the "dose–response" curve, il-

Table 5
Zero-Order Correlations Between Blood Chemistry Indices Obtained at the NICU and Intellectual Performance in 41 Children

Blood chemistry	Initial values recorded within 2 hr of delivery		Least optimal values recorded at NICU	
	VIQ	PIQ	VIQ	PIQ
pH	.40**	.38**	.39*	.31*
Base excess	.27†	.24	.19	.05
P_{O_2}	−.16	−.15	−.27	−.13
P_{CO_2}	−.28†	−.26†	.25	−.30*

Note. NICU = neonatal intensive care unit; VIQ = Verbal IQ; PIQ = Performance IQ; P_{O_2} = partial oxygen pressure; P_{CO_2} = partial carbon dioxide pressure.
† $p < .10$. * $p < .05$. ** $p < .01$.

lustrating the relationships between hypoxic risk and cognitive–language outcome. To establish whether a linear or curvilinear regression model provided the best fit for our data, we used as dependent measures the Verbal and Performance Scaled scores from the age-appropriate Wechsler battery (WPPSI–R or WISC–III) of all subjects whose initial pH was available ($n = 41$). The predictors of interest were initial pH and the combination of the Apgar scores at 1 and 5 min, both indices of hypoxic risk. It should be noted that the correlation between pH and the combined Apgar score was not sufficiently high to result in multicollinearity (Pearson's $r = .38$, $p < .02$). The highest arterial partial pressure of carbon dioxide observed at the NICU was significantly correlated with the PIQ (see Table 5), yet it was also correlated highly with the initial pH (Pearson's $r = .70$, $p < .001$, $n = 41$). To avoid multicollinearity, we did not use this variable as a third index of asphyxia. The same three covariates used in the preceding analyses were entered to the equation: SES, antenatal administration of steroids, and days of oxygen support. Univariate mixed linear model analyses revealed a significant association between pH and both the VIQ and the PIQ: $F(1, 35) = 9.68$, $p < .004$, and $F(1, 35) = 12.79$, $p < .001$, respectively. The models accounted for 33% and 45.3% of the total variance in VIQ and PIQ, respectively. The relationship between pH and cognitive outcome was significantly strengthened when a second order trend (pH^2) was added as a predictor. The resulting polinomial equations accounted for 44.3% and 52.4% of the variance in VIQ and PIQ, respectively. The addition of a quadratic component resulted in net increments of 11.3% and 7.1% to the explained VIQ and PIQ variance: $F(1, 34) = 6.90$, $p < .01$, and $F(1, 34) = 5.07$, $p < .05$, respectively. The curvilinear relationships between initial pH level, the VIQ, and the PIQ are depicted in Figure 2.

The same two indices of hypoxia and three covariates were used in analyzing language outcome data from the 36 children for whom information about acid–base status and language performance data were available. Univariate analyses revealed that the association between initial pH and the ECS score was significant, $F(1, 30) = 7.56$, $p = .01$. The model accounted for 33.6% of the variance in ECS scores. The association between pH and the ACS score, though in the same direction, did not reach a conventional statistical significance level, $F(1, 30) = 2.50$, $p < .15$. The presence of curvilinear relationships between pH and language performance was examined by adding a second-order trend (pH^2) as a predictor. The resulting polinomial equation accounted for 41.4% of the variance in the ECS. Addition of a quadratic component resulted in a net increment of 7.8%, revealing a trend for a curvilinear (quadratic) relationship between initial arterial pH and the ECS, $F(1, 29) = 3.86$, $p < .07$. The relationships between initial pH level, the ECS, and the ACS are depicted in Figure 3.

Discussion

In an earlier investigation (Porter-Stevens et al., 1999), a linear relationship was documented between perinatal arterial pH and cognitive outcome in a heterogeneous group of term- and preterm-birth children at mild to moderate hypoxic risk. The inclusion of a group of preterm-birth children with normal pH at birth in the current study permitted characterization of the relationships between perinatal hypoxic risk and intellectual or language development along a broader risk continuum in comparison with the earlier study. Our analyses revealed that a quadratic regression model provided the best fit for the data within the broader continuum of risk studied here. Specifically, a linear relationship between pH and verbal or visuospatial skills may be observed throughout the spectrum of pH levels ranging from the lower end of moderate acidosis to the lower end of normal acid–base balance, whereas the bend in the curve occurs only well within the normal range between initial

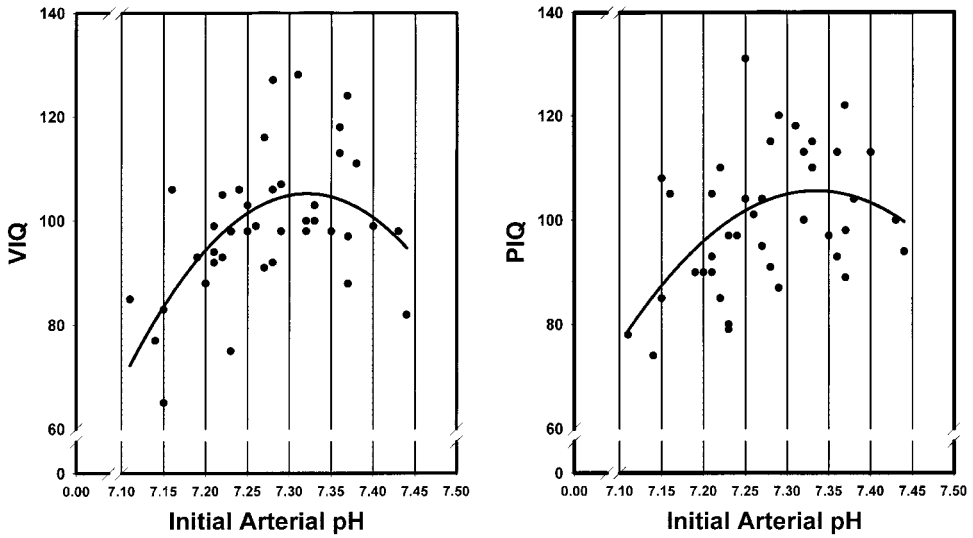


Figure 2. The relationships between initial arterial pH and the Verbal IQ (VIQ; left) and Performance IQ (PIQ; right) in a group of preschool and school-age children born prematurely.

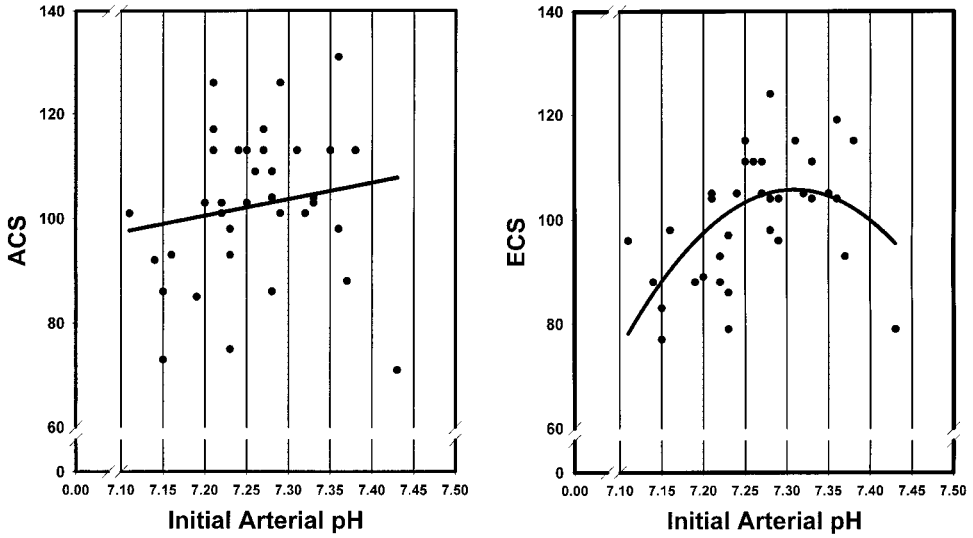


Figure 3. The relationships between initial pH and the Auditory Comprehension Scale (ACS; left) and the Expressive Communication Scale (ECS; right) in a group of preschool and school-age children born prematurely.

arterial pH values of 7.30 and 7.35 (see Figure 2). These characteristics of the curve are consistent with the notion that even minor risk for birth hypoxia may exert discernible influence on the course of cognitive development. Although we were able to document a linear relationship between initial pH and expressive language skills, it is likely that the trend for a curvilinear (quadratic) relationship did not attain conventional statistical significance because of the smaller number of subjects who completed the language evaluation.

Despite the close resemblance in sociodemographic and perinatal attributes between the two preterm-birth groups, the group differences observed on cognitive outcome measures were rather large, about two thirds of a standard deviation on the standardization samples of the WPPSI–R or the WISC–III. A pH value that falls between 7.0 and 7.1 (i.e., two standard deviations below the mean arterial pH at birth) has often been cited as a cutoff for severe and profound birth asphyxia (for a review, see Nagel et al., 1995). The findings from the current study suggest that a relatively small risk for birth-related hypoxia, defined as a pH value falling above the established critical level, is by no means too negligible to exert an appreciable influence on intellectual outcome.

Our findings are commensurate with results from a twin study (Raz et al., 1998) in which moderate intrapair differences in perinatal hypoxic risk—indexed by Apgar scores and need for respiratory support—were found to be associated with significant intrapair gaps in motor performance. However, a similar relationship was not observed between intrapair differences in perinatal risk and cognitive measures. It is possible that the unavailability of acid–base balance data to index hypoxic risk precluded demonstrating the link between the latter variable and cognitive outcome in the twin study.

Because of the reduced availability of children who fit our selection criteria for the preterm-birth comparison group, children included in this group were recruited and tested over 3 years, a period more than twice as long as that required for the testing of the target group. We do not believe this resulted in any bias on the part of the examiners because they were unaware of the children's perinatal status and because the comparison group children were mixed with children at perinatal risk from several ongoing studies. Furthermore, our analyses revealed that neither the year of birth nor the year of testing were correlated with outcome measures (Pearson's $r = .22$ and .09, both *ns*, for year of birth and the VIQ and the PIQ, respectively; Pearson's $r = .01$ and $-.27$, both *ns*, for year of psychological assessment and the VIQ and the PIQ, respectively). It should also be noted that because our preterm-birth comparison group was recruited exclusively from the pool of NICU graduates, preterm-birth infants with improved neonatal status who remained in the well baby nursery were not included in this study. If anything, the omission of the latter group of infants (who are expected to have better outcome) may have resulted only in underestimation of the reported effects of mild to moderate hypoxic risk on cognitive abilities.

It has been suggested that birth asphyxia may be a qualitatively distinct state, or a threshold phenomenon, with brain injury being dramatic in nature and occurring only when duration and severity of hypoxia and ischemia have surpassed unspecified, though apparently substantial, levels (Johnston, Trescher, & Taylor, 1995). The ensuing functional sequelae are presumed to be grave (e.g., cerebral palsy alone or in combination with mental retardation and epilepsy) and are thought to occur only in the most extreme cases of the insult (see American Academy of Pediatrics Committee on Fetus and Newborn, 1986). Such conceptualization presumes dose–response relationships characterized by a clearly defineable threshold, or breaking point, at which all adverse sequelae emerge simultaneously. This essentially categorical model of asphyxial insult is not eas-

ily sustainable. In all likelihood, the relationship between the dose of the insult and the dire behavioral response may be best described by an inverted U-shaped curve, in which both increasing acidosis and increasing alkalosis are associated with decline in cognitive performance. Alkalosis, a condition associated with hypocapnia (hypocarbia), is followed by immediate and sustained cerebral vasoconstriction and significant reduction in cerebral blood flow (Cartwright, Gregory, Lou, & Heyman, 1984) that may, in turn, lead to ischemic brain damage. Despite the paucity of information about the developmental effects of perinatal alkalosis in the premature infant, support for this model may be found in studies documenting increased risk for cystic periventricular leukomalacia in preterm infants with pH $>$ 7.5 within first 24 hr of life (Fujimoto et al., 1994) as well as increased risk for sensorineural hearing loss in preterm infants with maximum pH $>$ 7.6 (Leslie, Kalaw, Bowen, & Arnold, 1995).

The model of relationships between hypoxia–ischemia and cerebral injury suggested by the findings of our two-phase investigation is consistent with Casaer, de Vries, and Marlow's (1991) notion that "there is a continuum of brain injury in asphyxia, rather than the 'all or none' concept which had previously prevailed" and that this continuum "clearly connects perinatal events to performance in middle-childhood" (p. 158). This model is also supported by experimental studies of the fetal sheep brain during the midthird trimester, a period of gestation corresponding to the degree of gestational maturity in many preterm-birth infants. Following transient ischemia ranging from mild to severe, Williams et al. (1992) observed selective neuronal necrosis that was directly proportionate in its severity and extent in all affected regions to the length (i.e., severity) of the inflicted insult.

The neonatal cranial ultrasound evidence did not reveal any structural abnormalities despite the suboptimal pH at birth in the group at perinatal hypoxic risk. A follow-up clinical imaging study with computerized tomography on a single female subject from the higher risk group revealed bilateral occipital encephalopathy. In the absence of perinatal evidence for morphological cerebral changes in the preponderance of subjects who had experienced slight to moderate perinatal acidosis (n = 23, see Table 5), how can the poorer intellectual outcome of this subgroup be explained? Recent studies have revealed that subtle hypoxic–ischemic cerebral lesions are not readily detectable by the cranial sonogram obtained during the neonatal period. Skranes et al. (1997), who analyzed the magnetic resonance imaging (MRI) scans of 20 low birth weight children without cerebral palsy, observed in 50% of the children periventricular gliosis in the centrum semiovale or the central occipital white matter, whereas 30% of the children manifested delayed myelination. The follow-up MRI was performed when the study participants, none of whom had an abnormal cranial sonogram at birth, were 6 years of age. The findings suggest that a great proportion of preterm infants with neither perinatal evidence of brain abnormalities nor gross neurological deficits may have suffered perinatal cerebral insult. The major area of predilection appears to be the periventricular white matter.

To explain their findings, Skranes et al. (1997) proposed that a graded spectrum of periventricular white matter lesions (i.e., periventricular leukomalacia), in which discrete foci are undetectable by neonatal cerebral ultrasound, become manifest on follow-up MRI scans as gliosis. Indeed, postmortem studies reveal that less than a third of nonhemorrhagic hypoxic and ischemic lesions that are observed during necropsy had been identified by ultrasound during life (Gaffney, Squier, Johnson, Flavell, & Sellers, 1994) and that minor lesions are readily missed by cranial ultrasonography (Hope et al., 1988). It is possible that the emerging use of MRI for the study of infants and older children with history of birth complications (e.g., Barkovich et al., 1998; Coskun et al., 2001; Fujii et al., 1992) will help shed light on the structural brain changes that follow perinatal asphyxial insult.

The likelihood of delayed manifestation of perinatal hypoxic–ischemic lesions in our at-risk group is supported by the evidence summarized above. However, one should not overlook the possibility that the putative cerebral damage in the group with slight to moderate perinatal acidosis may not be observable at the gross morphological level even at school age. The hypothesized brain response accounting for the relatively reduced intellectual performance in the group at risk may involve permanent alterations in cerebral micromorphology or biochemistry. With the advent of functional neuroimaging and magnetic resonance spectroscopy (MRS), it may be possible to document both early and delayed pathological cerebral changes even in those at relatively minor risk for birth hypoxia. Recent MRS studies suggest that changes in cerebral metabolic activity that occur within the first few days of birth in asphyxiated infants may be predictive of infant and preschool age outcome (Barkovich et al., 1999; Hanrahan et al., 1999; Roth et al., 1997; Shu, Ashwal, Holshouser, Nystrom, & Hnshaw, 1997). The relationship between indices of neonatal cerebral metabolism and biochemical or clinical indices of birth asphyxia is an important focus of study (e.g., Pavlakis et al., 1999). The relative merit of these indices for prediction of cognitive and neuropsychological performance in preschool and school-age children at different levels of risk for perinatal asphyxia has yet to be determined.

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