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Psychiatric Outcomes in Low-Birth-Weight Children at Age 6 Years: Relation to Neonatal Cranial Ultrasound Abnormalities

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Background: This study examined the relation of neonatal cranial ultrasound abnormalities to psychiatric disorder at age 6 years in a regional birth cohort of low-birth-weight children.

Methods: Neonatal cranial ultrasound abnormalities were classified as (1) isolated germinal matrix and/or intraventricular hemorrhage (suggestive of injury to glial precursors) or (2) parenchymal lesions and/or ventricular enlargement (suggestive of white matter injury) with or without germinal matrix–intraventricular hemorrhage. Psychiatric disorders by DSM-III-R at age 6 years were assessed by means of a structured parent interview. Children with severe mental retardation were excluded. Analyses were conducted first in the entire sample and then in children with normal intelligence.

Results: Twenty-two percent of the cohort had at least 1 psychiatric disorder, the most common being attention deficit hyperactivity disorder (15.6%). In the entire sample, parenchymal lesions and/or ventricular enlarge-

ment increased risk relative to no abnormality, independently of other biological and social predictors, for any disorder (odds ratio [OR], 4.4; 95% confidence interval [CI], 1.8-10.3; P<.001), attention deficit hyperactivity disorder (OR, 3.4; CI, 1.3-8.7; P=.02), and tic disorders (OR, 8.7; CI, 1.3-57.7; P=.02). In children of normal intelligence, parenchymal lesions/ventricular enlargement independently increased risk for any disorder (OR, 4.8; CI, 1.6-12.0; P<.01), attention deficit hyperactivity disorder (OR, 4.5; CI, 1.3-16.0; P=.02), and separation anxiety (OR, 5.3; CI, 1.1-24.8; P=.03). These effects were not ameliorated by female sex or social advantage. Isolated germinal matrix/intraventricular hemorrhage was not related to psychiatric disorder at age 6 years.

Conclusion: Neonatal cranial ultrasound abnormalities suggestive of white matter injury significantly increased risk for some psychiatric disorders at age 6 years in low-birth-weight children.

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THE INTRODUCTION, in the early 1980s, of ultrasonography (US) as a noninvasive means of imaging the brain in low-birth-weight (LBW; <2.5 kg) newborns brought an unprecedented opportunity to study the sequelae of perinatal brain injury. While a substantial body of literature now exists on the motor and cognitive sequelae of neonatal cranial US abnormalities in LBW infants,[1-3] the relation of these abnormalities to childhood psychiatric disorders has been relatively neglected. Such research is timely because the balance of evidence suggests that behavior problems,[4-8] in particular those found in attention deficit hyperactivity disorder (ADHD),[9-17] are an important aspect of the morbidity found among schoolage LBW survivors, whose numbers continue to grow as a result of improved techniques of newborn intensive care.[18] Such research is important be-

cause an estimated 6.5% of children who will become of school age in the United States in 1997 were LBW infants (Nigel Paneth, MD, written communication, August 1996), and because term infants of normal birth weight may sustain similar types of brain injury during the late second and early third trimesters.[19,20]

In LBW neonates, perinatal brain injury is most commonly subcortical, reflecting site-specific vulnerabilities of the developing fetal brain in the late second and early third trimesters.[21,22] One site of vulnerability is the germinal matrix. The germinal matrix proliferates neuroblasts and glioblasts during early and middle gestation and provides the protomap for the columnar organization of the cortex; it then involutes by 34 weeks of gestation. In response to metabolic and hemodynamic stress, the fragile capillaries of the germinal matrix can easily bleed, sometimes into the adjacent ventricle. Such

of the weight-for-gestational-age distributions compiled by Williams et al[42]. *Neonatal complications of prematurity* were indexed by fraction of inspired oxygen at the end of 24 hours,[43,44] and *neonatal chronic illness* by days receiving mechanical ventilation.[3] *Social disadvantage at age 6* was measured by means of 2 composite indexes. One index, "distal social disadvantage" (mean±SD, -0.02±0.68), was calculated as the sum of the standardized scores of the following variables: single-parent family, mother's education (reversed), household income (reversed), any income from welfare, and the Four Factor Index of Social Status (A. B. Hollingshead, PhD, unpublished data, 1975; scale reversed); if any of these variables were missing, the mean of the remaining variables was substituted. The second index, "proximal social disadvantage" (mean±SD, -0.03±0.69), was calculated similarly by means of the HOME[45] total score (reversed), the General Health Questionnaire,[46] and the Family Dysfunction Scale of the Family Health and Activity Questionnaire.[47]

CHILD OUTCOMES

Psychiatric Diagnoses at Age 6 Years

The Diagnostic Interview Schedule for Children–Parent version 2.1P (DISC 2.1P)[48] is a structured interview that assesses *DSM-III-R*[49] psychiatric disorders. The child version was not used because of the unreliability of self-report at this age.[50] The DISC 2.1P has been shown to have good sensitivity for rare disorders[48] and adequate test-retest reliability for common disorders in older children.[51]

In the present sample, DISC 2.1P diagnoses showed reasonable agreement with standardized assessments of behavior problems. For example, children with ADHD, when compared with children with other diagnoses, had higher ratings of attention problems from parents on the CBCL/4-18[35] (mean±SD T score, 65.4±8.8 vs 57.7±6.2; $t[121]=4.79$, $P<.001$) and from teachers on the Teacher's Report Form[52] (mean±SD T score, 61.8±8.8 vs 57.2±11.1; $t[83]=2.08$, $P=.04$). Moreover, children with ADHD were more likely to be rated as inattentive (31.0%) or hyperactive (42.9%) by the study psychologist on the Test Behavior Checklist[53] than were children with other diagnoses (5.9% [$P<.01$] and 17.6% [$P=.01$], respectively) (additional data available on request).

Table 1 shows the specific disorders assessed, grouped into diagnostic clusters consistent with *DSM-III-R*. Some *DSM-III-R* disorders were not assessed because of their rarity at this age. "Any disorder" was defined as any 1 of the 19 disorders listed. Diagnoses were derived by means of algorithms (available on request) that implemented diagnostic inclusion criteria in the *DSM-III-R*.[49] Psychiatric exclusion criteria were not used; developmental exclusion criteria were used for the elimination disorders. Consistent with other studies,[54,55] a diagnosis of disorder was not assigned on the basis of symptoms alone. It was also necessary to have at least mild psychosocial impairment (defined by a nurse's rating of <71 on the Children's Global Clinical Assessment Scale).[55] The

diagnosis of ADHD, for example, was assigned only if the child had at least 8 of 14 possible symptoms of ADHD, each symptom had been present most of the time for at least 6 months, and the overall Children's Global Clinical Assessment Scale score was less than 71.

Other Child Characteristics

Intelligence at 6 years of age was defined as the composite score on the SB, and motor problems as the total score on the Riley Motor Problems Inventory.[56]

STATISTICAL ANALYSIS

The bivariate relations of US status to psychiatric outcomes were examined by means of logistic regression with 2 dummy variables as predictors, each encoding the comparison of 1 of the 2 US abnormality groups (GMH/IVH or PL/VE) with the NA group. The log odds of psychiatric disorder vs no disorder were the dependent variables. The bivariate relations of US status to other (non-US) predictors and the relations of diagnoses of disorders to non-US predictors and other child outcomes (eg, intelligence) were examined by means of χ^2 or Fisher exact tests for categorical variables and 1-way analyses of variance for continuous ones; the strength of these relations was assessed with correlations (ϕ, point-biserial, and product-moment, as appropriate).

Throughout this article, 2-tailed 5% significance levels were used. For the multivariate analysis, only diagnoses and diagnostic clusters having a bivariate relation to US status with a significance level of $P<.10$ were considered. When the number of cases of a given diagnosis was less than 10, the related diagnostic cluster was used instead, as long as it also showed a bivariate relation to US status. When the relation of a diagnostic cluster to US status was due primarily to 1 disorder in the cluster, that disorder was used. Explanatory variables were entered in 2 steps: first the US status variables and then the complete set of all non-US predictors. This strategy allowed evaluation of the robustness of the effect of US status when controlling for other potential risk factors. A subsequent logistic regression analysis included, in a third step, multiplicative terms representing the interaction of US status with sex and distal and proximal social disadvantage. Separate sets of logistic regressions were run for each interaction. The change in the -2 log likelihood (L^2) was used to evaluate the contribution of the interactions to the prediction of the outcome.[57] These analyses were repeated for a subsample of children with normal intelligence (SB composite scores ≥85) and for a subsample that excluded all children diagnosed at age 2 years with disabling cerebral palsy.[2]

To conserve cases and power, missing values were substituted with the sample mean or mode, while dummy-coded missing value indicators were added to equations.[58] None of the missing value indicators related significantly to any outcome.

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may be especially susceptible to injury from hypoperfusion. From a cellular standpoint, the immature oligodendroglia that form myelin appear to be extremely sensitive to oxidative stress and injury from free radi-

cal formation.[26] Perinatal white matter injury, which occurs in 5% to 10% of VLBW infants,[26] is frequently found in association with, and often on the same side as, germinal matrix hemorrhage (GMH) and/or intra-

SUBJECTS AND METHODS

BIRTH COHORT AND ATTRITION

Birth Cohort

Participants were members of the Neonatal Brain Hemorrhage Study birth cohort.[25,33] That study prospectively enrolled 1105 consecutive infants with birth weights of 501 to 2000 g who were cared for in the neonatal intensive care units of 3 New Jersey hospitals between September 1, 1984, and June 30, 1987. Enrollees accounted for 83% of all neonates weighing less than 2000 g and for about 90% of all those weighing less than 1500 g born in 3 New Jersey counties during that period. According to a protocol described elsewhere,[33] the cohort was screened with cranial US scans obtained at 4 hours, 24 hours, and 7 days of life; 98% of the cohort was scanned at least 1 of these times and 47% were also scanned between the third and fifth hospital weeks and/or before discharge. Scans were read independently by at least 2 radiologists who were unaware of all clinical information except birth weight and were submitted to a third reader in cases of disagreement. In 94% of cases, diagnostic agreement by 2 readers was obtained.[33] A maternal interview and systematic chart abstraction provided other important prenatal, perinatal, and neonatal information.[33] At about 2 years of age, 86% of survivors were assessed for major neurodevelopmental impairments[2] and for behavior problems, by means of a standardized parent questionnaire, the Child Behavior Checklist for 2- to 3-year-olds (CBCL/2-3).[34]

Age 6 Years

By age 6 years, 207 infants had died, leaving 898 children eligible for follow-up, of whom 685 (76%) participated in the study at age 6 years. Of the 213 nonparticipants, 45 families (5% of those eligible) refused, 143 (16%) could not be located, and 25 children (3%) had been adopted. While nonparticipants had higher scores on an index of maternal social disadvantage[3] (mean risk count, 1.8 vs 0.9; P<.001), they did not differ from participants in birth characteristics, including US status, or on behavior problems at age 2 years (CBCL/2-3 Total Problem Score).[34] Of the 685 participants, 597 (87%) were assessed at home visits, representing 66.5% of the eligible sample; the remainder were assessed by telephone (85 subjects) or mail (3 subjects). Birth characteristics, maternal social disadvantage, and total behavior problems at 2 and 6 years of age (as measured with the CBCL for 4- to 18-year-olds)[35] did not differ by mode of assessment.

The present report was limited to the 564 children seen at home for whom the psychiatric diagnostic interview was obtained and considered valid. The interview was not obtained on 12 children because of time constraints or other factors and was considered invalid for 21 children too severely disabled to be tested with the Stanford-Binet Intelligence Scale, Fourth Edition (SB).[36] These latter 21 children had a mean (±SD) composite score on the Vineland Adaptive Behavior Scale[37] of 39.4±8.5, indicating that they were truly disabled rather than uncooperative. There were no sociodemographic differences between the children having psychiatric interview data and the 33 children without it.

PROCEDURES

All procedures were approved by the New York State Psychiatric Institute institutional review board. A pediatric nurse practitioner (C.T.) and a psychologist, both unaware of US status, conducted the home visits after obtaining written informed consent. The nurse obtained parental reports on child psychiatric disorder, behavior problems and adaptive functioning, family functioning, and parental mental health. She examined the child for motor problems and rated the child's level of socioemotional impairment and the home environment. The psychologist administered the child cognitive assessments and rated the child's behavior during testing. Teacher report on behavior problems was also requested.

PREDICTORS

Neonatal Cranial US Status

Ultrasound abnormalities are defined as follows. A GMH was defined by focal echodensity in the thalamocaudate groove, just lateral to the frontal horns of the lateral ventricles. An IVH was defined by an echodense focus or foci within the lateral, third, or fourth ventricles separate from, and at least as echodense as, the choroid plexus. A parenchymal lesion (PL) was defined by focal or confluent echodense and/or echolucent areas in the parenchyma. A ventricular enlargement (VE) was defined by at least moderate enlargement, as judged by the radiologist, of at least 1 lateral ventricle on the final scan obtained.

On postmortem examination, both GMH and IVH are associated with destruction of the germinal matrix and its glial precursor cells,[38,39] while PLs and VEs are associated with evidence of ischemic injury to white matter.[26,27] Thus, 3 mutually exclusive groups, more consistent with pathological findings than the widely used Papile classification,[40] were formed: (1) no abnormality (NA); (2) isolated GMH and/or IVH (GMH/IVH); and (3) PL and/or VE, with or without GMH or IVH (PL/VE).

Non-US Predictors

Prenatal factors included maternal social disadvantage, defined by a composite index described elsewhere[3]; maternal tobacco use, measured by the average number of cigarettes smoked per day during this pregnancy (log transformed); and maternal alcohol consumption during pregnancy, scored as a 3-category variable (none; mild [1-6 drinks a week and <3 drinks on any occasion]; and severe [≥7 drinks a week or ≥3 drinks on any occasion]).[41] *Perinatal factors* included sex, 5-minute Apgar score, gestational age, and fetal growth ratio (birth weight relative to the median

hemorrhage occurs in up to 40% of very LBW (VLBW) neonates during the perinatal period.[23]

A second site of vulnerability is the developing subcortical white matter, which is especially sensitive to ischemic injury and metabolic insults before 32 weeks of gestation because of both vascular and cellular factors. From a vascular standpoint, the deep white matter has but a single arterial supply[24,25] and thus

Diagnosis	Entire Sample (N=562-564)	Ultrasound Status		
		NA (n=453-454)	GMH/IVH (n=77-78)	PL/VE (n=31-32)
Any disorder	22.0	20.3	21.8	46.9†
Any disruptive disorder	17.2	15.9	19.2	31.3‡
Attention deficit hyperactivity disorder	15.6	14.3	16.7	31.3‡
Oppositional defiant disorder	6.0	5.7	7.7	6.3
Conduct disorder	1.4	1.3	1.3	3.1
Any anxiety disorder	10.3	9.9	10.3	15.6
Obsessive-compulsive disorder	6.6	6.8	3.8	9.4
Separation anxiety	4.1	3.7	3.8	9.4
Overanxious disorder	1.4	0.9	2.6	6.3‡
Simple phobia	0.7	0.7	1.3	0.0
Avoidant disorder	0.4	0.4	0.0	0.0
Panic disorder	0.0	0.0	0.0	0.0
Any elimination disorder	7.1	6.6	7.7	12.5
Nocturnal enuresis	6.0	5.7	7.7	6.3
Diurnal enuresis	1.2	1.1	1.3	3.1
Encopresis	1.2	1.3	0.0	3.1
Any tic disorder	2.0	1.8	0.0	9.4‡
Transient tics	0.4	0.4	0.0	0.0
Motor tics	0.9	0.7	0.0	6.3‡
Vocal tics	0.4	0.2	0.0	3.2
Tourette syndrome	0.4	0.4	0.0	0.0
Other disorders				
Major depressive disorder	0.2	0.2	0.0	0.0
Elective mutism	0.4	0.4	0.0	0.0
Pica	0.4	0.2	0.0	3.1
Any disorder other than attention deficit hyperactivity disorder and tic disorders	17.2	16.5	16.7	28.1

*Prevalence is given as the percentage of the group having the relevant diagnosis. The effective number for each group varies by diagnosis because occasionally the answer to a question required for the assignment of a particular diagnosis was missing for a child. Missing answers were most common for transient tics, for which the effective numbers for the entire sample, and for groups with no abnormalitity (NA), germinal matrix hemorrhage/intraventricular hemorrhage (GMH/IVH), and parenchymal lesions and/or ventricular enlargement (PL/VE) were, respectively, 554, 448, 78, and 28. DISC 2.1P indicates Diagnostic Interview Schedule for Children–Parent Version 2.1P.
†P<.01 vs the NA group.
‡P<.05 vs the NA group.

ventricular hemorrhage (IVH) but probably represents a distinct pathophysiological process.[25] On postmortem examination, perinatal white matter lesions are correlated with ventricular enlargement[25,27] and with ischemic/infarctive lesions of the basal ganglia, brainstem, and cerebellum.[25,27] In premature neonates, unlike full-term neonates, cortical gray matter is limited in extent,[19] and distinct lesions of cortical gray matter are infrequently reported. However, cortical development might be adversely affected in preterms by both GMH/IVH and ischemic white matter injury

because of their effects on late migration, organization, and myelination.[28]

Thus far, only 4 studies have examined the relation of neonatal cranial US abnormalities to behavioral outcomes at school age in LBW children; all used relatively small samples from individual hospitals. While 3 of these studies[29-31] found no relation of US abnormalities to behavior, a fourth found that attention problems and/or hyperactivity were related to those types of US abnormalities suggestive of white matter injury.[32] However, this last study did not control for other behavioral predictors, and none of these studies examined the possible moderating role of sex or social disadvantage on the relation of US status to behavioral outcome.

The present study examines the relation of neonatal cranial US abnormalities to psychiatric disorder at age 6 years in a large, regional LBW cohort. A range of child psychiatric diagnoses was assessed by means of a structured diagnostic interview of the parent, and detailed information was collected on other predictors and outcomes. The following questions are addressed: Which, if any, types of US abnormalities are related independently of other predictors to psychiatric disorder at age 6 years? Is the relation diagnostically specific? Does the relation differ by sex or social disadvantage? Does any relation remain when the sample is restricted to children of normal intelligence?

RESULTS

SAMPLE DESCRIPTION

Of the 564 children in the present sample, 454 (80.5%) had no US abnormalities, 78 (13.8%) had GMH/IVH, and 32 (5.7%) had PL/VE. Of those with PL/VE, 15 also had GMH/IVH. Fifty-one percent (287/564) of the sample were male, 21% (119/564) were black, 16% (89/559) lived in single-parent households, 7% (39/564) had a caretaker who received welfare benefits, and 9% (48/555) of the mothers had not finished high school. The mean (±SD) age at follow-up was 6.3±0.28 years (range, 5.2-8.7 years). Many of the children were in kindergarten (58% [325/564]) or first grade (32% [181/564]). Consistent with most LBW samples,[39] general intellectual functioning (mean±SD, 102.3±13.4 on the SB) was close to the national average, while nearly 21% (116/564) had excessive motor problems as defined by scores in the top second percentile of the Riley Motor Problems Inventory standardization sample. As noted earlier, children too severely disabled to be psychometrically tested were excluded, but 14 children in the present sample had some type of impairment: 9 had mental retardation (4 mild and 5 moderate) as defined in a previous report[3]; 9 required assistance with walking because of disabling cerebral palsy as diagnosed at age 2 years[2]; and 4 children had both conditions.

PREVALENCE OF PSYCHIATRIC DISORDER

As shown in Table 1, slightly more than one fifth of the sample (22%) had at least 1 psychiatric disorder, the most

Table 2. Nonultrasound Predictors by Ultrasound Status*

		Ultrasound Status		
Predictors	Total (N=564)	NA (n=454)	GMH/IVH (n=78)	PL/VE (n=32)
Prenatal factors				
Social disadvantage at birth	0.9±1.2	0.9±1.2	0.8±1.2	1.0±1.3
Cigarettes per day (ln)	0.7±1.2	0.8±1.2	0.4±0.9	0.9±1.2
No.	491	397	64	30
Alcohol consumption				
No.	476	384	62	30
Mild	45.8 (218)	45.6 (175)	50.0 (31)	40.0 (12)
Severe	2.7 (13)	2.3 (9)	3.2 (2)	6.7 (2)
Perinatal factors				
Sex (male)	50.9 (287)	50.2 (228)	50.0 (39)	62.5 (20)
Fetal growth ratio†	0.9±0.2	0.9±0.2	1.0±0.2	1.0±0.2
No.	563	454	77	32
Gestational age,† d	221.7±21.6	224.5±21.0	211.4±20.7	206.0±18.2
Apgar score (5 min)†	7.9±1.4	8.0±1.3	7.6±1.5	7.1±1.4
No.	547	440	76	31
Neonatal complications of prematurity				
Fraction of inspired O_2, %†‡	37.4±19.5	35.3±17.7	41.4±23.5	48.6±21.6
Neonatal chronic illness				
Days receiving ventilator assistance†	5.6±13.4	4.6±12.7	7.8±14.1	13.9±17.8
Social disadvantage (measured at age 6 y)				
Distal	0.0±0.7	0.0±0.7	0.0±0.6	0.2±0.7
Proximal	0.0±0.7	0.0±0.7	0.0±0.7	0.1±0.8
No.	563	453	78	32

*The data are presented as percentage (number) for categorical variables and as mean±SD for continuous variables. NA indicates no abnormality; GMH/IVH, germinal matrix hemorrhage and/or intraventricular hemorrhage; PL/VE, parenchymal lesions and/or ventricular enlargement; and ln, natural legarithm.
†F or χ^2, $P<.001$ for a comparison among the 3 groups.
‡Valid only for children receiving oxygen.

common being ADHD (15.6%). More than two thirds of those with any disorder had more than 1. Boys were more likely than girls to have any disorder (28.9% vs 14.8%; $P<.001$), any disruptive disorder (23.8% vs 10.5%; $P<.001$), ADHD (22.0% vs 9.0%; $P<.001$), oppositional defiant disorder (8.0% vs 4.0%; $P<.001$), obsessive-compulsive disorder (8.7% vs 4.3%; $P=.04$), and nocturnal enuresis (9.4% vs 2.5%; $P<.001$).

RELATION OF US STATUS TO PSYCHIATRIC DISORDERS

The prevalences of several disorders and clusters of disorders were greater in the PL/VE than in the NA group, namely, any disorder (unadjusted odds ratio [OR], 3.5; 95% confidence interval [CI], 1.7-7.2; $P<.001$), any disruptive disorder (OR, 2.4; 95% CI, 1.1-5.3; $P=.03$), ADHD (OR, 2.7; 95% CI, 1.2-6.0; $P=.01$), overanxious disorder (OR, 7.5; 95% CI, 1.3-42.6; $P=.02$), any tic disorder (OR, 5.8; 95% CI, 1.4-22.9; $P=.01$), and motor tics (OR, 10.0; 95% CI, 1.6-62.15; $P=.01$); all $P<.05$. The GMH/IVH group did not differ significantly from the NA group for any psychiatric outcome. Of the disorders and clusters listed, 3 did not meet criteria for further consideration (see "Statistical Analysis" section): any disruptive disorder (because its relation to PL/VE was due primarily to ADHD) and overanxious disorder and motor tics (because of their low prevalence). For any disorder other than ADHD or tics, the comparison between the

PL/VE and NA groups was nearly significant (OR, 2.0; 95% CI, 0.9-4.4; $P=.10$). Thus, the 4 outcomes considered further are any disorder, ADHD, tic disorders, and any disorder other than ADHD or tics.

RELATION OF NON-US PREDICTORS TO US STATUS

As shown in **Table 2**, the US groups did not differ by sex, by social disadvantage at birth or at age 6 years, or by maternal alcohol use during pregnancy. In general, the NA group tended to be at less perinatal and neonatal risk, having greater gestational age, higher 5-minute Apgar scores, lower fractions of inspired oxygen, and fewer ventilator days than either the GMH/IVH or PL/VE group. The lower fetal growth ratio in the gestationally more mature NA group, as compared with the other 2 groups, results from using birth weight to define the sample.[60]

PSYCHIATRIC OUTCOMES— MULTIVARIATE ANALYSIS

Effects of US Status on Psychiatric Disorder Controlling for Non-US Predictors

Table 3 presents the results of regression analysis with all non-US predictors included. The adjusted ORs comparing the PL/VE with the NA group were strikingly similar to the unadjusted ones given above. The

Table 3. Adjusted ORs and Confidence Intervals for Selected Disorders: Full Model*

Predictors	Any Disorder (N=564)		ADHD (N=563)		Tic Disorders (N=563)		Any Disorder Other Than ADHD or Tic Disorders (N=564)	
	OR	95% Confidence Interval	OR	95% Confidence Interval	OR	95% Confidence Interval	OR	95% Confidence Interval
US status								
GMH/IVH	1.4	0.7-2.7	1.5	0.7-3.3	0.0	0.0-∞	1.1	0.5-2.2
PL/VE	4.4†	1.8-10.3	3.4‡	1.3-8.7	8.7‡	1.3-57.7	2.1	0.8-5.3
Prenatal factors								
Social disadvantage at birth	1.0	0.8-1.2	0.9	0.7-1.2	0.4	0.1-1.1	1.1	0.9-1.4
Cigarettes per day (ln)	1.5†	1.2-1.8	1.5†	1.2-1.9	2.0‡	1.0-3.8	1.3‡	1.0-1.6
Alcohol consumption (mild)	0.6	0.4-1.1	0.5‡	0.3-1.0	0.3	0.0-2.0	0.8	0.5-1.4
Alcohol consumption (severe)	1.4	0.4-4.9	0.2	0.0-1.7	3.4	0.2-54.4	1.7	0.4-6.3
MVI alcohol consumption	0.0	0.0-∞	0.0	0.0-∞	0.0	0.0-∞	0.0	0.0-∞
MVI smoking	664.9	0.0-∞	911.0	0.0-∞	5456.2	0.0-∞	436.1	0.0-∞
Perinatal factors								
Sex (male)	2.6†	1.7-4.2	3.4†	2.0-5.8	2.9	0.6-13.6	2.4†	1.5-4.0
Fetal growth ratio	0.8	0.2-3.4	0.6	0.1-3.0	0.1	0.0-5.1	0.8	0.2-3.7
Gestational age	1.0	1.0-1.0	1.0	1.0-1.0	0.9‡	0.9-1.0	1.0	1.0-1.0
Apgar (5 min)	1.0	0.8-1.2	1.0	0.8-1.3	1.5	0.8-2.7	1.1	0.9-1.3
MVI Apgar	2.6	0.5-13.9	2.7	0.3-22.5	109.4	0.3-35 205.9	3.7	0.5-26.8
Neonatal complications of prematurity								
Fraction of inspired O₂	1.0	1.0-1.0	0.6	1.0-1.0	1.0	0.9-1.0	1.0	1.0-1.0
MVI fraction of inspired O₂	0.7	0.4-1.2	1.0	0.6-1.8	1.7	0.3-9.2	0.7	0.4-1.2
Neonatal chronic illness								
Days receiving ventilatory assistance	1.0§	1.0-1.0	1.0	1.0-1.0	1.0	1.0-1.0	1.0	1.0-1.0
Social disadvantage (measured at age 6 y)								
Distal	0.8	0.5-1.3	0.9	0.5-1.5	1.7	0.4-8.0	0.7	0.5-1.2
Proximal	2.3†	1.6-3.3	2.1†	1.4-3.1	1.1	0.3-3.7	2.2†	1.5-3.1
MVI proximal	2128.6	0.0-∞	7808.8	0.0-∞	0.0	0.0-∞	4072.9	0.0-∞
Constant	0.0‡	0.0-0.4	0.0	0.0-1.5	86 933.6	0.0-∞	0.0	0.0-1.4

*ADHD indicates attention deficit hyperactivity disorder; OR, odds ratio; US, ultrasound; GMH/IVH, germinal matrix hemorrhage and/or intraventricular hemorrhage; PL/VE, parenchymal lesions and/or ventricular enlargement; and MVI, missing value indicator. The infinity sign (∞) stands for an extremely large number.
†$P<.001$.
‡$P<.05$.
§$P<.01$.

presence of PL/VE still significantly increased the risk for any disorder, ADHD, and tic disorders, while GMH/IVH again did not affect risk for any psychiatric outcome.

Effects of Non-US Predictors on Psychiatric Disorder

Several of the non-US predictor variables were related independently to the 4 psychiatric outcomes of interest. Maternal smoking elevated risk for all 4 outcomes. Male sex and proximal (but not distal) social disadvantage predicted 2 of the outcomes: any disorder and ADHD. For both, the odds of disorder increased by a little more than 2 times for each unit increase in the scale for proximal social disadvantage. Days receiving mechanical ventilation, maternal alcohol use, and gestational age were each related to a single outcome.

Moderating Effect of Sex and Distal and Proximal Social Disadvantage on the Relation of US Abnormalities to Psychiatric Outcomes

Neither sex nor proximal social disadvantage modified the effect of US status on any psychiatric outcome. How-

ever, distal social disadvantage actually reduced the risk for ADHD associated with PL/VE (OR, 0.2; Wald $\chi^2=5.0$; $df=1$; $P=.05$).

Relation of US Status to Psychiatric Disorder Among Children of Normal Intelligence

In the sample as a whole, intelligence was negatively related to psychiatric disorder (point-biserial $r=-0.35$, $P<.001$, for any disorder with the SB composite). Intelligence was also associated with US status; as reported elsewhere,[3] children in the PL/VE group had significantly lower SB composite scores than children in the NA group.

To address the possibility that the association between US status and psychiatric disorder might be influenced by the children with low intelligence in the sample, all analyses were repeated with the sample restricted to children of at least normal intelligence. In this subsample (n=521), as in the full sample, GMH/IVH (n=72) was not related to any psychiatric outcome. Also as in the full sample, PL/VE (n=20) was significantly related to any disorder (unadjusted OR, 3.0; 95% CI, 1.2-7.7; $P=.02$). Now, PL/VE was also sig-

nificantly related to separation anxiety disorder (unadjusted OR, 4.9; 95% CI, 1.3-18.4; $P=.02$) but not to tic disorders. While the bivariate relation of PL/VE to ADHD was not significant, it did meet the .10 criterion for further examination (unadjusted OR, 2.5; 95% CI, 0.9-7.1; $P=.09$).

With all other predictors controlled, PL/VE was related to any disorder (adjusted OR, 4.8; 95% CI, 1.6-12.0; $P<.01$), ADHD (adjusted OR, 4.5; 95% CI, 1.3-16.0; $P=.02$), and separation anxiety disorder (adjusted OR, 5.3; 95% CI, 1.1-24.8; $P=.03$). Non-US predictors were related to any disorder and to ADHD among the children with normal IQ in essentially the same way as in the sample as a whole (data available on request). Also as in the intact sample, distal social advantage reduced the risk associated with PL/VE for ADHD (OR, 0.04; Wald $\chi^2=5.6$; $df=1$; $P=.04$). No other significant interactions between US status and sex or social disadvantage were found. When the sample was restricted to those who had not been diagnosed (at age 2 years) as having disabling cerebral palsy (n=530), the results were essentially identical to those obtained in this subsample of children with normal IQ.

COMMENT

This study examined the relation of perinatal brain injury, as detected on neonatal cranial US, to psychiatric disorder in LBW children at early school age. The study has several methodological strengths: children with neonatal US abnormalities were prospectively identified based on screening of a large regional birth cohort; a structured parent interview was used to diagnose a range of child psychiatric disorders at age 6 years; and detailed information was available on other social and biological predictors and other child outcomes.

Although the study has some limitations, these do not pose major threats to the validity of the findings. While our pathological studies[27] as well as those of others[61] have shown that US is not completely sensitive to milder forms of white matter injury, this limitation would lead to an underestimation of the effects of PL/VE on outcomes. Although the sample was limited to children seen on home visits, comprising only two thirds of those eligible to be seen at age 6 years, the effective sample remained reasonably representative, as discussed in the section on the birth cohort and attrition. Finally, although psychiatric diagnoses were based solely on parental interviews, parent, teacher, and psychologist ratings of behavior were in reasonable agreement.

The finding that isolated GMH/IVH did not increase risk for psychiatric disorder at age 6 years was surprising given that in most LBW infants, the germinal matrix is still proliferating (primarily glioblasts) at the time of birth.[62] It must be underscored that isolated GMH/IVH may have behavioral effects at age 6 years that are not captured by diagnosable psychiatric disorder or may be related to disorders that typically emerge later.

By constrast, PL/VE, which is indicative of ischemic injury to white matter,[27] increased by 4-fold the risk for having at least 1 psychiatric disorder, even after control for other predictors. However, the relation of PL/VE to any disorder was accounted for by its relation to specific disorders, most strongly and consistently ADHD. This study extends an earlier finding[32] to a rigorously diagnosed and population-based sample, while controlling for other predictors. As in other schoolage LBW cohorts[11,13,15] and among 6-year-olds in the general population,[63] ADHD was the most common disorder. The relation of PL/VE to ADHD was unlikely to have resulted from its greater frequency, however, because some other common disorders (eg, oppositional defiant disorder) were not related to PL/VE. Neither birth weight nor gestational age increased risk for ADHD independent of US status, suggesting that recent reports of elevated rates of ADHD in LBW cohorts[11,13,15] may reflect the higher rates of PL/VE likely to have been present in such groups.

Here, as in other other recent studies,[64-66] maternal smoking during pregnancy adversely affected childhood behavior; the present study shows this effect to be independent of PL/VE and social disadvantage. A recent review[66] of the effects of nicotine on the fetal brain points to functional alteration of receptors within the basal ganglia as a possible mechanism for this effect.[67] However, postnatal maternal smoking, a factor not assessed here, might also have played a role.

As in other population-based studies of childhood psychiatric disorder,[63] male sex independently predicted increased risk for ADHD, a finding that has been attributed to sex differences in the development of the dopaminergic system.[68-70] The advantage of female sex was constant across brain injury groups, however, and was not particularly pronounced in the presence of perinatal brain injury.

In the present study, proximal social disadvantage was an independent predictor of ADHD; previous studies on this point have been inconsistent.[71] Distal social disadvantage actually reduced the risk of ADHD among children with PL/VE; findings from a recent study[72] raise the possibility that this effect may result from selective mortality among LBW infants born to severely disadvantaged mothers.

From a theoretical standpoint, the findings of the present study are not consistent with the widely accepted interactional model of biological and social risk.[73-75] According to that model, among children who are not severely disabled, higher rates of psychiatric disorder would be expected with greater social disadvantage, and perinatal brain injury per se would have an effect only among socially disadvantaged children. Among advantaged children, inherent "self-righting tendencies" would counteract any adverse effects of perinatal risk factors,[73] including presumedly those of perinatal brain injury. Instead, in this study both PL/VE and social disadvantage raised the risk of psychiatric disorder independently of one another, and social advantage did not protect children with PL/VE from increased risk for psychiatric disorder. Of course, an interaction suggesting a protective effect of social advantage in the presence of some other aspects

of perinatal risk might still exist. However, it does appear from the present results that the relation of PL/VE to psychiatric disorder at age 6 years is more consistent with a main effects model than an interactional model.

Consistent with modern neurodevelopmental models of psychiatric disorders, such as that proposed by Weinberger for schizophrenia,[76] the effects of PL/VE on ADHD, tic disorders, and separation anxiety disorder at age 6 years may reflect an effect of perinatal ischemic injury on brain maturational events that occurs at this age, in particular maturation of the striatum (caudate and putamen) of the basal ganglia. Maturation of the striatum is thought to play an important role in the improvement of behavioral inhibition that normally occurs in middle childhood[77] but is notably deficient in ADHD, tic disorders, and anxiety disorders.[78,79] In a postmortem study in this cohort,[25] ischemic/infarctive white matter lesions were statistically associated with ischemic/infarctive lesions of the basal ganglia, probably because they share with deep white matter the distinction of having only 1 arterial supply and thus are especially vulnerable to hypoperfusion.[24] Structural and functional brain imaging studies of children with ADHD[80-83] and tic disorders[84,85] have found abnormalities in the basal ganglia, specifically the corpus striatum (caudate and putamen), while subtle motor impairments in a subset of children with anxiety disorders[86] also suggest basal ganglia abnormalities. The striatum receives substantial dopaminergic input from the substantia nigra,[87] and dysregulation of the dopaminergic system has been implicated in both ADHD[78,88] and tic disorders.[78,89] Alterations of the dopaminergic system have been shown to accompany ischemic brain injury in human neonates[90] and in rats.[91] The striatal dopaminergic system appears to be more vulnerable to ischemic injury than other striatal neurotransmitter systems (eg, serotonin),[92] perhaps because, in the striatum, dopamine synapses are closely juxtaposed with glutamate synapses,[93] which are thought to play a key role in mediating the neurotoxic effects of ischemia.[94] As the cohort undergoes puberty, which is accompanied by cortical maturation[95] and synaptic pruning,[96-99] it is possible that PL/VE will increase risk for disorders that typically have a later onset and in which abnormalities of cortical–basal ganglionic circuits have been implicated, such as mood disorders,[100] obsessive-compulsive disorder,[101] and schizophrenia.[93,100,102,103] Certainly, further longitudinal follow-up of this cohort will be of great interest.

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