Motor and Cognitive Outcomes in Nondisabled Low-Birth-Weight Adolescents

Early Determinants

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Objectives: To describe motor and cognitive outcomes in nondisabled low-birth-weight (LBW) adolescents and to determine the relation of specific prenatal, perinatal, and neonatal risk factors to these outcomes.

Design: A prospective epidemiological study.

Setting: An adolescent follow-up of a regional LBW (<2000 g) cohort born in or admitted to 3 hospitals between September 1, 1984, and June 30, 1987 (n=1105). Of 862 eligible survivors, 628 (72.9%) underwent assessment at a mean age of 16 years; of these, 33 had severe disability that precluded psychometric evaluation. The 474 nondisabled adolescents undergoing assessment at home had slightly less social risk at birth than did all other nondisabled eligible adolescents.

Participants: The 474 nondisabled LBW adolescents assessed at home.

Main Exposures: Basic birth characteristics (social risk, sex, fetal growth ratio, and gestational age), neonatal cranial ultrasound abnormalities, and other early medical complications.

Main Outcome Measures: Riley Motor Problems Inventory and Wechsler Abbreviated Scales of Intelligence.

Results: Nondisabled LBW adolescents had an excess of motor problems compared with the normative sample. The IQ scores, although within the normal range, were significantly lower than population norms. Independent predictors of total motor problems included male sex, white matter injury on neonatal ultrasound, and days of ventilation. Independent predictors of lower Full Scale IQ scores included social disadvantage, fetal growth ratio, and white matter injury on neonatal ultrasound.

Conclusions: Specific prenatal, perinatal, and neonatal risk factors influence motor and cognitive performance in nondisabled LBW survivors well into adolescence, even when controlling for social risk. Advances in maternal-fetal and neonatal care can substantially improve these long-term outcomes.

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Mounting evidence suggests that low birth weight (LBW) increases risk for not only major disabilities such as cerebral palsy and mental retardation, but also subtle motor and cognitive problems in nondisabled survivors by school age and, with some exceptions, even as late as adolescence. The most commonly studied prenatal, perinatal, and neonatal risk factors for motor and cognitive outcomes in nondisabled LBW adolescents are the basic birth characteristics that are readily available at or before birth: social disadvantage, sex, birth weight for gestational age, and gestational age. With rare exception, the relation of early medical complications to these subtle outcomes has not been examined, to our knowledge. Such information could help identify potential targets for preventive intervention with respect to long-term outcomes.

The regional LBW cohort assembled for the Neonatal Brain Hemorrhage Study provides an unprecedented opportunity to examine the relation between specific early risk factors and adolescent motor and cognitive outcomes. This cohort is unique in the following respects: (1) it was geographically defined, representing nearly all infants with birth weights of less than 2000 g in a 3-county region during a 3-year period; (2) all members underwent neonatal cranial ultrasound (US) screening for evidence of neonatal brain injury; and (3) a large database of other prenatal, perinatal, and neonatal risk factors was collected systematically at birth on the entire cohort. The objectives of the present study were to describe motor and cognitive outcomes in nondisabled LBW adolescents and to determine the relation of specific prenatal, perinatal, and neonatal risk factors to these outcomes.
<table>
<thead>
<tr>
<th>Table 1. Risk Factors</th>
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<tr>
<td><strong>Basic Risk Variables</strong></td>
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<td>Maternal social disadvantage: Based on the Social Risk Index of Hack et al, this composite score is a count of the number of maternal risk conditions out of 5 (age &lt;19y, &lt;high school education, unmarried status, minority status, and receipt of public assistance) that were present at the time of the infant’s birth.</td>
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<td>Sex: Ascertained from physical examination at birth as recorded in the infant’s medical chart.</td>
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<td>Gestational age: Estimated using a hierarchical algorithm with data from multiple sources—prenatal ultrasound images (preferably before 20 weeks of gestation), prenatal and postnatal medical records, and postnatal maternal interview—with attention to consistency across records.</td>
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<td>Fetal growth ratio: Calculated as birth weight divided by median weight for gestational age according to Yudkin et al.</td>
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<td><strong>Early Medical Complications</strong></td>
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<td>Neonatal ultrasound abnormalities: Serial cranial ultrasound performed at 4 and 24 h and 7 d of life, according to a research protocol. Scans read independently by ≥2 radiologists blinded to all clinical information except birth weight; disagreements (only 6% of cases) resolved with a third reading. Two types of ultrasound abnormalities were identified: GMH/IVH: Isolated germinal matrix hemorrhage and/or intraventricular hemorrhage (GMH/IVH). PL/VE: Parenchymal lesions and/or ventricular enlargement with or without GMH/IVH.</td>
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<td>Other early medical complications: Maternal smoking: Maternal report of number of cigarettes smoked per day during pregnancy (log-transformed for analysis). Placental abruption: Determined from medical record; recorded as clinically evident. Chorioamnionitis: Determined from medical record; recorded as clinically evident. Active labor: According to Qi et al. 5-min Apgar score: Sum of 5 ratings (0-2, with 2 being best) at 5 min post partum. Base excess: Metabolic acid-base status, calculated from pH and bicarbonate ion concentrations in the first blood gas measurement after birth. Positive values indicate metabolic alkalosis; negative values indicate metabolic acidosis. In the immediate perinatal period, having more negative values (greater acidosis) indicates less adequate oxygen delivery to the tissues. Seizures: Any notation of seizure during the first 24 h of life in the infant’s medical chart. Thyroid status: Standardized z score derived from newborn blood thyroid and thyrotrophic screening results according to the criteria of Reuss et al. (There were no known cases of congenital hypothyroidism in our cohort,) Hypocapnia exposure: Time- and severity-weighted variable defined by Collins et al as the number of hours of exposure to ( \text{PO}_2 &lt; 35 \text{ mm Hg} ) ((&lt; 4.7)) multiplied by the number of millimeters of mercury of ( \text{PO}_2 &lt; 35 ) ((&lt; 4.7)); higher values indicate more prolonged and/or severe exposure. Hyperoxia exposure: Time- and severity-weighted variable defined by Collins et al as the number of hours of exposure to ( \text{PO}_2 &gt; 60 ) ((&gt; 8.0)) multiplied by the number of ( \text{PO}_2 ); units &gt;60; higher values indicate more prolonged and/or severe exposure. Low systolic blood pressure: Number of days with a systolic blood pressure &gt;2 SDs below the mean for that day as defined for this cohort by Hegyi et al. Peak bilirubin: Highest bilirubin level recorded during the first 8 neonatal days. Neonatal infection: Any positive blood, cerebrospinal fluid, or urine culture during the neonatal intensive care unit stay. Ventilator days: Number of days with any mechanical ventilation.</td>
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**METHODS**

**BIRTH COHORT**

Participants belonged to the Neonatal Brain Hemorrhage Study birth cohort. The original study prospectively enrolled 1105 consecutive infants with birth weights of less than 2000 g born in or admitted to 3 New Jersey hospitals between September 1, 1984, and June 30, 1987. During that period, the neonatal intensive care units at these hospitals provided neonatal care for 83% of all infants with birth weights of less than 2000 g and 90% of those with birth weights of less than 1300 g in 3 New Jersey counties. Compared with the nation as a whole, this 3-county region had a slightly higher per capita income and slightly lower proportion of minorities.

**SAMPLE AT 16 YEARS OF AGE**

The adolescent follow-up was approved by the institutional review board of the New York State Psychiatric Institute. Informed consent was obtained from legal guardians for all of the adolescents before participation. The mean±SD age at assessment was 16.0±0.5 years (range, 14.8-19.4 years). By age 16 years, 212 (19.2%) of the original birth cohort were known to have died and 31 (2.8%) had been adopted or were in foster care, leaving 862 enrollees who were potentially eligible for follow-up. Of the eligible enrollees, 628 (72.9%) participated in the 16-year follow-up, whereas 83 (9.6%) refused and 131 (17.5%) could not be located. Of the latter group, 68 (45.0%) had been lost to follow-up since hospital discharge.

Of the 628 adolescent participants, 33 (5.3%) had a severe major disability, defined as the inability to walk without assistance (n=24), an IQ score of less than 55 (>3 SDs below the population mean; n=28), or neurosensory impairment severe enough to preclude outcome testing (deaf or blind; n=4). Of the 595 nondisabled participants, 474 (79.7%) were assessed during home visits and 121 by telephone. Adolescents assessed by telephone were slightly older, on average, than those assessed in the home. The focus of this report is the 474 non-disabled adolescents assessed in the home.

**EARLY RISK FACTORS**

Table 1 gives the definitions of the risk factors used in this study.

**Basic Risk**

These variables, readily available at or before birth, are commonly used to predict later outcomes. It is not yet established, however, that they are related to outcome in nondisabled adolescents independently of neonatal brain injury and other early medical complications.

**Neonatal Brain Injury**

In view of the unique nature of the neonatal brain injury information in this cohort, US status was considered as a separate set of early medical complications. Ninety-eight percent of the cohort was scanned with US at least once in the first week.
Other Early Medical Complications

Early medical complications other than US abnormalities were selected from an extensive database that included information abstracted from prenatal, perinatal, and neonatal medical records and from a maternal interview conducted soon after birth. Some of these complications (hypothyroxinemia, hypocalcemia, hypocapnia, hypotension, hyperbilirubinemia, seizures, and ventilation days or indices of chronic lung disease) have previously been shown to predict major disability and might reasonably be expected to cause subtler problems as well. Others, such as metabolic acidosis, appear not to increase risk for major disability but might increase subtler problems.

Motor and Cognitive Assessment

All assessors were blinded to birth history and trained to reliability. Motor function was assessed with the Riley Motor Problems Inventory, which tests for oral, fine, and gross motor problems. Area scores are weighted counts of errors in performing an area’s tasks (3 tasks each for the oral and fine motor areas and 4 for the gross motor area), with errors weighted as 0 (no errors serious enough to be counted), 1, and 2. The maximum scores for the oral, fine, and gross motor areas are 6, 6, and 8, respectively. The total score is the sum of the 3 area scores (maximum, 20 points). The total score for persons 9 years or older has a median, upper tenth centile, and upper second centile, in the standardization sample, of 1, 5, and 7 points, respectively. For oral, fine, and gross motor area scores, these centiles are 3, 0, and 2 points, respectively. Full Scale, Verbal, and Performance IQ scores were assessed with the Wechsler Abbreviated Scales of Intelligence. For all 3 scales, mean ± SD is 100 ± 15.

STATISTICAL ANALYSIS

Bivariate relations were examined with Pearson product moment correlations (and with regressions, using k–1 dummy variables for categorical variables with more than 2 categories). However, multiple regression was the principal method used to evaluate the relation of predictors to outcomes.

To keep the number of predictors small relative to the number of cases in the sample, the prenatal, perinatal, and neonatal predictors used for this study were selected from a larger set that had been chosen on the basis of a priori theoretical interest or some indication in the literature that they were related to the studied outcomes. Selection for inclusion in these analyses was based on bivariate relations among predictors and between predictors and outcomes in this data set. Variables un-
related to any outcomes and those highly correlated or redundant with more meaningful ones were excluded. To maintain the sample size and power, missing values of predictors were replaced and dichotomous missing value indicators were included in regressions for predictors that were missing more than 3% of their values. The probability level (α criterion) for statistical significance was set at .01 for all analyses. We used SPSS and SAS statistical software.

RESULTS

STUDY SAMPLE

Except for having slightly less social risk at birth, the nondisabled adolescents assessed at home were similar to those nondisabled adolescents who were eligible for the study but were not assessed at home (Table 2).

MOTOR PROBLEMS AND IQ SCORES IN THE NONDISABLED SAMPLE

The means for the total, oral, fine, and gross motor problem scores (Table 3) place the sample of nondisabled adolescents as a whole between the median and upper tenth centile of the standardization sample. Total motor problem scores were 5 or greater for 22.4% of these adolescents, placing them in the top 10% of the standardization sample, and 7 or greater for 11.3%, placing them in the top 2%.

Although the mean IQ scores in Table 3 were all within the average range, the distributions were shifted downward. The means for the Full Scale and Performance IQ scores were significantly lower than those for the population norm (t−3.96 and t−6.91, respectively; both P<.001).

MULTIPLE REGRESSIONS

The standardized partial regression coefficients in Table 4 show the relation of each risk factor to outcome after controlling for all other risk factors. These coefficients indicate how much of a change in outcome (in standard deviation units) is uniquely associated with 1 SD of change in the risk factor.

Basic Risk

Greater maternal social risk at birth was significantly associated with lower Full Scale, Verbal, and Performance IQ scores, but not with any type of motor problem. For each additional condition of maternal social risk, the IQ scores were depressed by 3.6 points on the Full Scale IQ, 3.6 points on the Verbal IQ, and 2.6 points on the Performance IQ. Male sex was significantly associated with more total, oral, and fine motor problems, but not with lower IQ. Gestational age was not associated with any aspect of motor problems or IQ score, whereas a lower fetal growth ratio was significantly associated with lower Full Scale and Performance IQ scores.

Neonatal Cranial US Abnormalities

Compared with those who had no US abnormalities, nondisabled adolescents with germinal matrix and/or intraventricular hemorrhage (GM/IVH) had higher scores on the oral motor problems scale by half a point, whereas those with parenchymal lesions and/or ventricular enlargement (PL/VE) had higher scores on the total, oral, fine, and gross motor problem scales by 3.7, 0.8, 0.9, and 2.0 points, respectively, and lower Full Scale and Performance IQ scores by 1.6 and 2.2 points, respectively.

OTHER EARLY MEDICAL COMPLICATIONS

Except for placental abruption and ventilator days, the independent relations of these risk factors to motor problems were nonsignificant. The average fine motor problems score was 0.7 points higher among those with placental abruption. For every additional week of mechanical ventilation, total and oral motor problem scores were higher by 0.33 and 0.14 points, respectively. Other medical complications had no independent relation to IQ scores.

RELATIONS OF RISK TO IQ SCORE AMONG NONDISABLED LBW ADOLESCENTS OF NORMAL INTELLIGENCE

To determine whether the relations described in Table 4 were primarily due to the inclusion of adolescents with Full Scale IQ scores in the mildly retarded or borderline range (55-84), analyses were repeated excluding those adolescents. In this sample (n=385), the following 5 relations between risk factors and intelligence scores dropped below the significance threshold, although they differed only minimally in magnitude from those in the less restricted sample: age at test with Full Scale IQ (β=−0.12) and Verbal IQ (β=−0.16), fetal growth ratio with Full Scale IQ (β=0.11), and PL/VE with Full Scale IQ (β=−0.08) and Performance IQ (β=−0.11). Other significant relations with IQ scores in Table 4 remained, and a new relation emerged between low thyroid levels and lower Full Scale IQ scores (β=0.16; P<.01).

COMMENT

The finding that nondisabled LBW adolescents had an excess of motor problems relative to the normative sample is consistent with results of 2 case-control studies of motor skills.

Table 3. Motor Problems and Cognitive Ability in Nondisabled LBW Adolescents

<table>
<thead>
<tr>
<th>Domain (Outcome Measure)</th>
<th>No. of Adolescents</th>
<th>Mean ± SD Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor problems*</td>
<td>464</td>
<td>3.58 ± 3.27</td>
</tr>
<tr>
<td>Total</td>
<td>464</td>
<td>0.75 ± 1.22</td>
</tr>
<tr>
<td>Oral</td>
<td>464</td>
<td>1.80 ± 1.48</td>
</tr>
<tr>
<td>Fine</td>
<td>464</td>
<td>1.03 ± 1.65</td>
</tr>
<tr>
<td>Gross</td>
<td>464</td>
<td>97.27 ± 14.57</td>
</tr>
<tr>
<td>Cognitive performance†</td>
<td>474</td>
<td>99.56 ± 14.57</td>
</tr>
<tr>
<td>Full Scale</td>
<td>468</td>
<td>95.21 ± 14.57</td>
</tr>
<tr>
<td>Verbal</td>
<td>468</td>
<td>97.27 ± 14.57</td>
</tr>
<tr>
<td>Performance</td>
<td>468</td>
<td>99.56 ± 14.57</td>
</tr>
</tbody>
</table>

Abbreviation: LBW, low-birth-weight.
*Scores from the Rily Motor Problems Inventory.
†IQ scores from the Wechsler Abbreviated Scales of Intelligence.
in nondisabled very-LBW adolescents. In this LBW cohort, with lower overall adaptive functioning (A.H.W., unpublished data, November 2005). The finding that the IQ scores of these nondisabled LBW adolescents were in the average range is consistent with studies of extremely LBW and very LBW adolescents. Here, this finding is extended to a broader range of birth weight. In this sample, as in the studies just cited, however, the slight downward shift of the means indicates an extra public health burden when these findings are extrapolated to the general population.

When other risk factors were controlled for, gestational age alone was not an independent predictor of adolescent motor or cognitive outcomes. This finding runs counter to the view that, in the absence of medical complications, premature exposure to the extraterrestrial environment per se alters brain development in LBW infants. Major independent determinants of motor outcomes in these LBW adolescents without severe disabilities were male sex, evidence of white matter injury on neonatal brain US, and number of ventilation days. The finding of an adverse effect of male sex, despite control for so many other risk factors, suggests a need to look beyond the association of maleness with greater prevalence and severity of neonatal complications to explain this male vulnerability effect. One possibility is that hormonal differences between the sexes affect acute response to and long-term recovery from brain injury. Although gestational age appeared to have a protective effect on motor outcomes, this effect is an artifact of the inverse relation of maleness with greater prevalence and severity of neonatal complications to explain this male vulnerability effect. One possibility is that hormonal differences between the sexes affect acute response to and long-term recovery from brain injury. Although gestational age appeared to have a protective effect on motor outcomes, this effect is an artifact of the inverse relation of maleness with greater prevalence and severity of neonatal complications to explain this male vulnerability effect. One possibility is that hormonal differences between the sexes affect acute response to and long-term recovery from brain injury.
parently localized lesion on US. Evidence from magnetic resonance imaging studies, however, suggests that focal white matter injury may also be a marker for diffuse white matter injury and may be related to minor motor impairments. Abernethy et al44 found that preterm school-age children without major neurodisability had, in addition to visible lesions on magnetic resonance images, a diffuse abnormality of cerebral white matter (manifested as an increase in T2 relaxation time) that was highly related to minor motor impairment but not to Full Scale IQ scores. The finding that GM/IVH was related selectively to oral motor problems is consistent with the location of this injury near the head of the caudate nucleus, which is now being implicated in oromotor control.12

Of the other early medical complications, only placental abruption and ventilator days were independently related to motor outcomes. Placental abruption has been widely reported to be associated with cerebral palsy; thus, an association with fine motor problems is not surprising. The relation of ventilator days could be explained by the duration of mechanical ventilation being considered a marker for severity of illness; this could explain its disappearance as a factor when the adolescents with below-normal IQ scores were deleted from the sample. Duration of mechanical ventilation could also be associated with an increased risk of exposure to some ventilation-related practice that itself is detrimental. (Hypocapnia and hyperoxia might be reasonable candidates for such exposure.)25 This hypothesis is attractive because it suggests that, if we could identify the practice and modify it, outcome could be improved.

Major independent predictors of intelligence were social disadvantage at birth, fetal growth ratio, and white matter injury as seen on neonatal US images of the brain. Although this latter factor was no longer significant in the smaller sample (those with an IQ score at or above 85), the magnitude of its association with cognitive outcome was only minimally reduced. An adverse effect of early social disadvantage on intelligence that occurs as late as adolescence in LBW survivors is a well-replicated finding.43 On the other hand, the finding that biological risk factors also predicted adolescent cognitive outcome suggests that effects of early biological insult are not completely overwhelmed by the environment over time.

The finding that slow growth in utero (as indexed by fetal growth ratio) was highly associated with intelligence in adolescence—in particular with the Performance IQ score—is consistent with findings from a population cohort study of Swedish men showing that all studied indices of slow fetal growth were independently associated with increased risk of poor cognitive performance at 18 to 19 years of age.45 The present finding is inconsistent with that of an earlier literature review,46 which concluded that, by adolescence and adulthood, the deleterious effect of intrauterine growth retardation sometimes found at earlier ages was inconsequential compared with environmental influences. In the present study, low fetal growth ratio was highly correlated with fetal head circumference ratio; 77.7% of the infants in the sample who were small for gestational age also had a head circumference ratio that was in the lowest tenth percentile for age. Thus, it is not possible to discern from these data whether the effect on cognition was related to fetal growth ratio in general or rather, more specifically, to fetal head growth retardation. This issue requires further exploration.

Several caveats apply to these findings. First, although only a few of the early medical complications examined were independently related to motor or cognitive outcomes, their possible importance to these outcomes in adolescence cannot be dismissed. It may well be that several of these early complications share the same determinative path, and thus account for similar aspects of motor problems and/or cognitive performance. In consequence, any independent relation of these risk factors to outcome would be precluded. Second, inasmuch as the present regression findings apply to entire distributions of exposures, they do not rule out an effect of being at the extreme of the distribution for some risk factor (eg, <26 weeks of gestation). In addition, interactions between medical complications (eg, between Apgar scores and mechanical ventilation) cannot be ruled out. Third, although subject loss was within the expected range for such a long-term follow-up in a population-based sample, some bias might be expected. In particular, the caretakers of infants with identified problems are more likely to participate in follow-up visits, thereby possibly inflating the estimates of dysfunction.47

The strengths of this study remain (1) the use of a regional birth cohort, (2) the prospective and systematic ascertainment of a rich set of early medical complications, (3) the rigor of the US protocol, and (4) the inclusion of a wider spectrum of LBW survivors than is usually examined in modern follow-up studies.

The finding that, independent of social risk, specific prenatal, perinatal, and neonatal biological risk factors are associated with cognitive and motor outcomes as late as adolescence runs counter to the view that, absent severe disability, early biological risk factors are of little importance in later life.43,48 The prevention of white matter injury and the need for mechanical ventilation may be key to improving motor outcomes, whereas the prevention of intrauterine growth retardation (or perhaps impaired head growth) and white matter injury may be key to improving cognitive outcomes. Taken together, these findings suggest that enhanced maternal-fetal and neonatal care have the potential to substantially improve cognitive and motor outcomes for nondisabled LBW adolescents.

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Author Contributions: Drs Whitaker and Feldman had full access to all of the data in the study and take full responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Whitaker, Feldman, Lorenz, Shen, McNicholas, Pintomartin, and Paneth. Acquisition of data: Whitaker, McNicholas, Nieto, McCulloch, and Paneth. Analysis and interpretation of data: Whitaker, Feldman, McNicholas, Lorenz, Shen, and Paneth. Drafting of the manuscript: Whitaker, Feldman, Lorenz, Nieto, and Paneth. Critical revision of the
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