Effect of Early Intervention on 8-Year Growth Status of Low-Birth-Weight Preterm Infants

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Objective: To examine the impact of early educational experience at age 8 years on child growth status. The Infant Health and Development Program has shown positive impacts to age 8 years on intelligence and adaptive functioning of larger preterm infants.

Design: Randomized controlled trial.

Setting: Home and center based.

Participants: Three hundred seventy-seven intervention (INT) and 608 nonintervention (NI) children, stratified by birth-weight categories 2001 to 2500 g and 2000 g or less.

Intervention: Educational intervention from nursery discharge until age 3 years.

Main Outcome Measures: Eight-year weight, height, head circumference, and body mass index.

Results: Complete data were available for 313 INT children and 491 NI children. Adjusting for child birth weight, birth-weight category, treatment group × birth-weight category interaction, sex, race, and Neonatal Health Index; maternal education and preconception weight; and site, the INT children at age 8 years were significantly taller (127.6 vs 126.6 cm; \( P = .02 \)) and had a larger head circumference (52.5 vs 52.1 cm; \( P < .001 \)) than the NI children. The prevalence of both overweight (9%) and underweight (4.5%) was the same in both treatment groups. Lighter low-birth-weight INT children had greater 8-year weight (28.0 vs 26.8 kg; \( P = .02 \)), larger head circumference (52.6 vs 52.1 cm; \( P < .001 \)), and larger height (127.6 vs 126.5 cm; \( P = .05 \)) compared with their counterparts in the NI group.

Conclusion: Low-birth-weight preterm children, specifically the lighter low-birth-weight group, who received the Infant Health and Development Program educational intervention were heavier and taller and had greater head circumference compared with NI children in the same birth-weight category.


Low-birth-weight preterm (LBWPT) infants are likely to demonstrate smaller size, more health problems, lower cognitive skills and academic achievement, and more behavioral problems at school age when compared with term normal-birth-weight peers.\(^1\) In a recent meta-analysis of studies that compared term infants with preterm infants at school age, term children had significantly higher cognitive scores.\(^2\) Although most LBWPT infants become normal size for age by school years, low-birth-weight (LBW) (particularly extremely LBW) children at school age are more likely to be shorter and lighter than children of normal birth weight.\(^5\) In sum, LBWPT infants are more likely to demonstrate deficits in both growth and development throughout infancy and childhood. A broad array of prenatal and perinatal clinical features, along with a range of perinatal and postnatal clinical characteristics, may contribute to these relative deficits.\(^11\) In addition, various sociodemographic and socioenvironmental characteristics of families have been shown to have significant long-term effects on the array of outcomes of LBWPT children.\(^13\)

Multiple experimental educational intervention programs for infants and toddlers have been implemented and assessed.\(^16\) These programs commonly focus attention on preschool children at increased risk because of their environmental circumstances. Most such programs provide educational stimulation for these children while working with parents, and their primary outcome of interest has been improved developmental/cognitive status. The favorable effects of these programs have been demonstrated into school years,\(^16\) adolescence, and young adult years.\(^19\)
Other interventions have focused on infants and toddlers who are at risk because of their biological status, such as LBWPT infants. The largest such comprehensive program that targeted LBWPT infants, the Infant Health and Development Program (IHDP), consisted of a multifaceted intervention that began at discharge from the nursery and continued until age 3 years. The children in the IHDP intervention (INT) group had significantly higher cognitive and behavioral status and somewhat higher minor morbidity when compared with a nonintervention (NI) group at age 3 years. There were no differences in length or body mass index (BMI) at age 3 years between INT and NI group children. By age 8 years, infants who were in the INT group and had a birth weight of 2000 g or less were not different from children of the same birth weight in the NI group in cognitive status or academic achievement. The preterm infants in the INT group with a birth weight of 2001 to 2500 g, compared with the infants who did not receive the intervention, showed significantly higher full-scale IQ and mathematic achievement scores. These differences persisted in the recently completed 18-year follow-up.

These early developmental intervention programs focused little attention on growth status or growth rate as an outcome measure. Although many early intervention programs provided nutritional education to families and offered snacks and meals at their centers, we are aware of no such early intervention program that evaluated growth as an outcome measure. Since growth status and growth rates are considered important markers of a child’s well-being, particularly for LBWPT children who are at increased risk for long-term health, growth, and developmental problems, we evaluated the effects of the multifaceted IHDP intervention on longer-term growth status. The IHDP intervention offered a unique opportunity to evaluate the impact on long-term growth because this cohort was followed up in a standardized study protocol longitudinally until age 8 years, and a broad array of high-quality data were carefully collected, which allowed us to control for many important confounding variables. We examined the following research questions: Does the growth status of LBWPT children who received the multifaceted IHDP intervention differ from the NI group in 8-year weight, length, head circumference, and BMI, while controlling for important child clinical and parent variables? Do these 8-year effects vary based on birth-weight category?

### METHODS

Detailed descriptions of IHDP recruitment and subjects, study design, and intervention have been published in detail elsewhere and are reviewed briefly herein. All participating IHDP universities received required institutional review board approval at all data collection points. The University of Arkansas for Medical Sciences institutional review board approved the analyses described herein.

### SAMPLE

Infants were eligible for the IHDP study if they had a birth weight of 2500 g or less, had a gestational age of 37 weeks or less, resided in the catchment area, and did not have severe medical illness or neurological impairment. Unhealthy infants were included unless they had conditions (eg, neural tube defects, severe sensory deficits) or neurological dysfunction that were recognized before nursery discharge and were judged to be so severe as to preclude participation in the intervention. Only 61 such infants were excluded. The infants were enrolled from October 1984 through August 1985. A total of 985 infants constituted the primary analysis group. These infants were randomly assigned to the INT group (n=377) or the NI group (n=608) at discharge from the nursery using a design with 2 birth-weight strata: lighter LBW (LBW) (<2000 g [n=623]) and heavier LBW (HLBW) (2001-2500 g [n=362]). All children assigned to the INT group, regardless of their compliance with intervention, were included in the analyses as INT children.

### DATA COLLECTION

Infants in both INT and NI groups received the same periodic medical, developmental, and social assessments through 8 years of age. Clinical staff at each site typically included a pediatrician and a nurse clinician and social worker. All measurements were collected by standardized protocol after careful training. All children were assessed at 40 weeks’ postconceptual age and at 4, 8, 12, 18, 24, 30, and 36 months’ gestation-corrected age and at 4, 5, 6.5, and 8 years of age.

### INTERVENTION

The intervention program began at discharge from the neonatal nursery and continued until October 1988, when each child was at least 36 months of age, corrected for degree of prematurity. The intervention consisted of home visits (birth to age 3 years), attendance at a center for education intervention (age 1-3 years), and parent group meetings (age 1-3 years). Children were eligible to attend the child development center 5 days per week for approximately 6 hours per day for 2 years. Children received 2 meals per day. There was no nutrition focus in the IHDP and no nutrition data were collected. Clinicians provided general care instructions during all follow-up clinic visits to INT and NI children, including nutrition advice as needed. After the intervention ended, the sites attempted to find appropriate community education programs for children in both INT and NI groups. Within sites, there were no differences between the INT and NI groups in maternal reports of child enrollment in education programs at age 4 years.

### 8-YEAR SAMPLE AND DATA

Of the original 985 in the primary analysis group, 878 children (89%) were evaluated at 8 years of age. The percentage of children retained within the INT and NI groups was similar, both overall and within sites; 89.7% of the INT group and 88.8% of the NI group were available and 90.5% of the LLBW and 86.7% of HLBW were available at 8 years. Eight-year growth status was assessed by clinic staff who had access to the child’s treatment group assignment and history. All growth measures were collected by standard protocol after appropriate training procedures. The following measures were used for the clinical analyses: weight; height; head circumference; and BMI (calculated as weight in kilograms divided by height in meters squared).

### ANALYSES

Baseline demographic characteristics (based on a sample of 878 subjects who participated in the 8-year data collection) were compared using either t tests for continuous variables or χ² tests for categorical variables.
Table 1. Infant Health and Development Program Age 8 Years Sample

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Birth Weight = 2000 g</th>
<th>Birth Weight = 2001-2500 g</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>INT (n=318)</td>
<td>NI (n=346)</td>
</tr>
<tr>
<td>Birth weight, g, mean (SD)</td>
<td>1551</td>
<td>1522</td>
</tr>
<tr>
<td>Birth length, cm, mean (SD)</td>
<td>41.2</td>
<td>40.6</td>
</tr>
<tr>
<td>Birth head circumference, cm, mean (SD)</td>
<td>28.4</td>
<td>28.3</td>
</tr>
<tr>
<td>Male</td>
<td>50.5</td>
<td>46.5</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>33.0</td>
<td>37.0</td>
</tr>
<tr>
<td>Black</td>
<td>57.3</td>
<td>52.9</td>
</tr>
<tr>
<td>Hispanic</td>
<td>9.6</td>
<td>10.1</td>
</tr>
<tr>
<td>Neonatal Health Index, mean (SD)</td>
<td>101.1</td>
<td>100.3</td>
</tr>
<tr>
<td>Maternal education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;High school</td>
<td>38.5</td>
<td>36.7</td>
</tr>
<tr>
<td>High school</td>
<td>28.9</td>
<td>29.8</td>
</tr>
<tr>
<td>&gt;High school</td>
<td>32.6</td>
<td>33.5</td>
</tr>
<tr>
<td>Maternal height, in, mean (SD)</td>
<td>63.6</td>
<td>63.7</td>
</tr>
<tr>
<td>Maternal preconception weight, lb, mean (SD)</td>
<td>127.5</td>
<td>134.1</td>
</tr>
</tbody>
</table>

Abbreviations: INT, intervention group; NI, nonintervention group.

a Adjusted for birth weight, birth-weight category, treatment × birth-weight category interaction, sex, race, and Neonatal Health Index; maternal education (at time of entry into study) and preconception weight; and site.

Table 2. 8-Year Growth Status

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intervention (n=314)</th>
<th>Nonintervention (n=491)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight, kg</td>
<td>28.0 (0.39)</td>
<td>27.3 (0.34)</td>
<td>.07</td>
</tr>
<tr>
<td>Height, cm</td>
<td>127.6 (0.42)</td>
<td>126.6 (0.36)</td>
<td>.02</td>
</tr>
<tr>
<td>Head circumference, cm</td>
<td>52.5 (0.15)</td>
<td>52.1 (0.14)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BMI</td>
<td>17.1 (0.21)</td>
<td>16.9 (0.18)</td>
<td>.96</td>
</tr>
</tbody>
</table>

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

For the 8-year analysis, complete data on all control variables and 8-year growth measures (weight, height, BMI, BMI percentile, and head circumference) were available for 314 INT children and 491 NI children. Comparative analyses of all 8-year growth variables were performed between INT and NI groups for the full sample and within the 2 birth-weight categories. Linear mixed models were used to compare the 8-year growth measures means between the INT and NI children, adjusting for covariates. Predictors included a site effect (only random effect), treatment group (INT or NI), child birth weight, child birth-weight category (<2000 g or ≥2000 g), treatment group by birth-weight category interaction, sex, race (white/other, black, or Hispanic), maternal education at time of entry into the study (<high school, high school, or >high school), preconception weight of the mother, and Neonatal Health Index. The Neonatal Health Index is a marker of severity of neonatal course calculated based on length of stay in the neonatal nursery, adjusted for birth weight and standardized to a mean of 100, with higher scores indicating better health. The models were fit using the MIXED procedure of SAS (SAS Inc, Cary, North Carolina). Individual model effects were evaluated for statistical significance using the Type III F statistics. Although a treatment group × birth-weight category was postulated, the interactions did not reach statistical significance for any of the measures. Post hoc least squares means comparisons based on t tests were used to compare treatment group differences by birth-weight category.

To examine the growth of all growth variables over time between the INT and NI children, linear mixed models were used to model the heights, weights, and head circumferences at 24, 36, 48, 60, 78, and 96 months of age, controlling for the same variables noted earlier. Fixed effects were evaluated using Type III F tests. Post hoc least squares means comparisons based on t tests were used to compare treatment group differences for each period. All available data were used at each period.

Baseline demographic characteristics of the 878 subjects who participated in the 8-year data collection are shown within birth-weight categories by intervention group status (Table 1). Birth weight, length, and head circumference did not vary between INT and NI groups within either birth-weight category. The mothers of the NI group weighed on average more than 6 lb more (P = .02) than the INT group in the LLBW sample. There were no other significant differences between the baseline variables by intervention group within birth-weight categories. We compared these baseline variables between the full original sample and those who completed the 8-year evaluation (data not shown). There were no differences in any of these baseline variables, except the mothers of the children who completed the eighth-year evaluation were more

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Birth Weight = 2001-2500 g

For the LLBW group, there was no difference in BMI, weight, or height between treatment groups. The difference in head circumference was statistically significant at age 36 months, and these differences persisted and increased until age 8 years. The difference in height for the INT and NI LLBW infants became statistically significant at age 78 months and persisted until age 8 years. The difference in head circumference was statistically significant at age 36 months, and these differences persisted and increased until age 8 years.

Eight-year growth status is shown in Table 3 by intervention group category within birth-weight categories. Within the LLBW sample, the 8-year weight was significantly heavier for the INT group (by 1.2 kg; P = .02) and had significantly larger head circumference (by 0.4 cm; P < .001). The children in the INT group on average weighed 700 g greater than the NI group but this did not reach statistical significance. There was no difference between the groups in 8-year BMI. The percentage of children with a BMI greater than 95% or less than 5% did not differ between INT and NI groups.

Eight-year growth status is shown in Table 4 by intervention group category within birth-weight categories. The children in the INT group were taller and had significantly higher body mass index (by 1.2 kg; P = .02), height (mean [SD], INT, 0.18 [0.09]; NI, −0.05 [0.08]; P = .02), and had a significantly larger head circumference (by 0.4 cm; P < .001). While all 8-year anthropometric variables were larger for the HLBW infants in the INT group, none of these differences between treatment groups reached statistical significance. There were no differences in BMI for either birth-weight category. The percentage of children with a BMI greater than 95% or less than 5% did not differ between INT and NI groups.

Table 3. 8-Year Growth Status by Birth-Weight Category

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Birth Weight ≤ 2000 g</th>
<th>Birth Weight = 2001-2500 g</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>INT (Mean, SD)</td>
<td>P Value</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>28.0 (0.47)</td>
<td>.02</td>
</tr>
<tr>
<td>Height, cm</td>
<td>127.6 (0.5)</td>
<td>.05</td>
</tr>
<tr>
<td>Head circumference, cm</td>
<td>52.6 (0.17)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BMI</td>
<td>17.1 (0.24)</td>
<td>.07</td>
</tr>
</tbody>
</table>

Table 4. z Scores for 8-Year Weight, Length, and BMI

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Full Sample</th>
<th>LLBW</th>
<th>HLBW</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>INT (Mean, SD)</td>
<td>NI (Mean, SD)</td>
<td>INT (Mean, SD)</td>
</tr>
<tr>
<td>Weight</td>
<td>0.20 (0.08)</td>
<td>0.04 (0.06)</td>
<td>0.05 (0.08)</td>
</tr>
<tr>
<td>Length</td>
<td>−0.09 (0.07)</td>
<td>−0.26 (0.06)</td>
<td>−0.29 (0.08)</td>
</tr>
<tr>
<td>BMI</td>
<td>0.28 (0.08)</td>
<td>0.16 (0.07)</td>
<td>0.25 (0.1)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); INT, intervention group; NI, nonintervention group.

Low-birth-weight preterm children who were assigned to the IHDP intervention to age 3 years were taller and had larger head circumference at age 8 years compared with children who did not receive the intervention. The greater impact on growth was seen in the smaller LLBW group with a birth weight of 2000 g or less as compared with the group with a birth weight of 2001 to 2500 g. In this group,

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**COMMENT**

The evolution of weight, height, and head circumference for the LLBW preterm infants who were assigned to the IHDP intervention to age 3 years was taller and had larger head circumference at age 8 years compared with children who did not receive the intervention. The greater impact on growth was seen in the smaller LLBW group with a birth weight of 2000 g or less as compared with the group with a birth weight of 2001 to 2500 g. In this group,
the INT infants weighed 1.2 kg more than the NI group, were 1.1 cm taller, and had larger head size by 0.5 cm. These differences were noted before age 8 years. The weight was significantly larger for the LLBW INT group infants by age 4 years and persisted until age 8 years. The head circumference was significantly larger by age 3 years in this group and this difference persisted until age 8 years. There was no difference in BMI, or the percentage of children with a BMI greater than 95% or less than 5%, between NI and INT groups for the full sample or the LLBW or HLBW groups. These analyses controlled for site, birth size, neonatal course, and maternal size and demographic variables. There were no differences between the INT and NI groups within birth-weight categories in baseline birth weight, birth head size, or birth length, the Neonatal Health Index, and most maternal growth variables. In fact, the mothers of the NI infants in the LLBW group weighed on average more than 6 lb more than the INT mothers ($P = .02$).

Are these differences in growth patterns resulting from the IHDP intervention of clinical significance? Greater growth attainment in term infants has been shown to be associated with higher cognitive abilities.28,29 Larger head circumference is associated with higher intelligence,30,31 and taller children and adults have higher IQ, academic achievement, and, ultimately, job attainment and income.32-34 While all LBWPT children are at greater risk to

Figure 1. z Scores at 8 Years. LLBW indicates lighter-low-birth-weight category (birth weight $\leq 2000$ g); HLBW, heavier-low-birth-weight category (birth weight $> 2000$ g and $\leq 5000$ g).

Figure 2. Weight by treatment group for lighter-low-birth-weight children from 24 to 96 months. Lighter low birth weight=birth weight $\leq 2000$ g.

Figure 3. Height by treatment group for lighter-low-birth-weight children from 24 months to 96 months. Lighter low birth weight=birth weight $\leq 2000$ g.
remain small in all growth variables, when compared with normal-birth-weight peers into young adult years, extremely LBWPT children are at greatest risk to remain small in all growth variables.\textsuperscript{7,35-37} Long-term problems in intellectual development are more likely in LBWPT children who demonstrate atypical growth in weight and head circumference, particularly in the early years of life.\textsuperscript{38,39} In addition, early poor head circumference growth, after which slow compensatory growth occurs, is associated with later lower intelligence.\textsuperscript{40-42} Low-birth-weight preterm children with later cognitive impairment have been shown to have smaller head circumference at ages 4 and 15 years, even after adjusting for growth restriction and socioeconomic status at birth.\textsuperscript{43} Within the full IHDP sample, 8-year head circumference was positively and significantly correlated with measures of 8-year Wechsler Intelligence Scale for Children III full-scale IQ ($r=0.22; P<.001$) and Woodcock-Johnson Tests of Achievement in math ($r=0.21; P<.001$) and reading ($r=0.17; P<.001$). It is thus feasible to speculate that the improvements in growth that resulted from the IHDP intervention may have some long-term benefits in the development of these children, although no benefits were noted at age 8 years on cognitive skills or academic achievement in the LLBW infants who received this intervention.

We are aware of no early intervention programs that focused on children at biological or social risk in a country that report longer-term effects of intervention on growth status. There have been several intervention studies in developing countries that have provided nutritional supplementation and psychosocial stimulation to mothers and children with malnutrition or who were at risk for malnutrition. In a study of malnourished children identified between the ages of 9 and 24 months in Jamaica, a 2-year intervention was implemented, including both nutritional supplementation and psychosocial stimulation. There were no benefits on height, weight, or head circumference found at age 11 to 12 years in these children, although positive benefits on IQ and academic achievement were noted at age 11 to 12 years and 17 to 18 years.\textsuperscript{44,45} A group of Colombian children judged to be at risk for malnutrition because of poverty received food supplementation and home visitation from birth until age 3 years. At age 3 years, the children were significantly taller and heavier. Positive effects on weight and height persisted to age 6 years, 3 years after the interventions were discontinued. The authors concluded that both more positive family functioning and biological mechanisms accounted for these benefits.\textsuperscript{46}

One can only speculate regarding the mechanism that resulted in the positive effects of the IHDP intervention on the growth of these LBWPT infants. Children in the IHDP intervention were provided 2 meals per day for 2 years. Perhaps this longer-term growth effect is a direct result of the food provided at these meals. This is not likely the complete explanation, as the IHDP sample consisted of families of a broad array of socioeconomic backgrounds, not just impoverished children, and they were in general likely to provide adequate diets to their children. There were no differences in the incidence of failure to thrive noted between the IHDP INT and NI groups, as noted in a previous publication.\textsuperscript{22} It is also possible that the positive effects on growth were a reflection of improved parenting. The IHDP intervention has been shown to improve the quality of mother-child interaction and the children’s home environment in the first 3 years of life.\textsuperscript{47,48} Perhaps the children came to learn mealtimes to be both a biological event in which they received nutrition and a social event for mutual exchange between adults and children. This could lead to increased nutrition and nurturance over the years, which could ultimately improve growth status. Another pathway that might have resulted from the IHDP intervention is the reduction of stress for both parent and child. There is evidence that excessive stress during infancy, including prolonged stays in neonatal intensive care units in early childhood, may have negative consequences on growth via neuroendocrine stress system response.\textsuperscript{49} Perhaps the benefits of the intervention on the child and parent together minimized the neuroendocrine effect of stress on these preterm infants. This latter speculation may also partially explain why the greater effects on growth were noted in the lighter LBWPT infants who were more likely to have had prolonged stays in the neonatal intensive care units. An alternative explanation, of course, is that these results may not be the consequence of the IHDP intervention, but rather due to some variable not measured by the IHDP protocol.

There is substantial evidence that adverse circumstances, such as being born at a low birth weight and premature or poor parenting practices, can have negative impacts in nearly every domain of development. As negative consequences accumulate in one domain of development, they are likely to compromise development in other domains as well; that is, there is interconnectedness in adaptive functioning across domains. Broad-based interventions, such as the IHDP intervention, aimed at stemming the negative consequences of LBW and its cofactors are likely to produce a variety of positive outcomes for children even when the primary goal of the intervention may be to increase intellectual development and school readiness. Although our study is limited because direct measures of nutrition and maternal feeding practices are not available, the IHDP intervention, with its broad focus of supporting both parents and children, ap-
pears to have benefited these premature LBWPT children in a variety of ways, including growth.

In summary, LBWPT children who received the IHDP intervention to age 3 years were taller and had larger head circumference at age 8 years. The greater impact of this intervention was seen in the LLBW children born at a weight of 2000 g or less. The prevalence of overweight status did not differ between treatment groups. These results vary from the previously reported cognitive outcomes since only the HLBW infants (birth weight 2001-2500 g) demonstrated positive beneficial effects on cognitive scores at age 8 years. The mechanisms and long-term significance of these results are not clear.

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Yet the car can be an occasion of serious trouble when a boy and a girl go out for a ride in a car and then decide to park in some dark lane or corner so as to be able to give themselves over to... necking and prolonged kissing.

—From the educational pamphlet Teenagers and the Automobile by Ernest Miller, 1964