Interrelationship between Growth and Development in Low and Middle Income Countries

Reynaldo Martorell, Phuong Nguyen

Hubert Department of Global Health and Nutrition and Health Sciences Program, Emory University, Atlanta, GA, USA

Abstract

Early childhood growth failure is a significant public health problem in developing countries. We examine relationships between low birthweight and stunting with child development. Compared to children born with normal birthweight, low birthweight children have substantially poorer cognitive and schooling outcomes later in life. Linear growth failure leading to stunting mostly occurs before age 2 years, with stunting in older children reflecting growth failure in early life. Many studies show that stunting is associated with poor mental and motor development in infants and with low scores in cognitive tests, increased frequency of behavioral problems and poor school achievement in older children. Very few studies have assessed the relative importance for development of prenatal vs. postnatal growth failure and even fewer have done so using appropriate statistical techniques. The limited evidence to date suggests growth during the first 2 years of life is more important than growth at any other time, including the prenatal period, for predicting later cognitive development, schooling and educational achievement. In conclusion, children in settings of poverty who experience growth failure prior to age 2 years have reduced potential to succeed in school and to be productive members of society.

Introduction

Growth failure in early life is a significant public health problem in the developing world. Some 11% of term newborns are low birthweight (LBW; <2.5 kg), 20% (112 million) of children younger than 5 years old are underweight [weight-for-age z score (WAZ) <-2] and 32% (178 million) of children younger than 5 years old are stunted [height-for-age z score (HAZ) <-2] [1].
Early childhood growth retardation has varied adverse functional consequences such as increased childhood morbidity and mortality and reduced adult body size and work capacity. Also, growth retardation hinders motor, cognitive, and socioemotional development, which in turn affects schooling and individual and national income. The objective of this paper is to review studies from low and middle income countries of the relationship between growth failure and child development. Two key questions of this review are:

1. What is the relationship between LBW and stunting with child development?
2. What is the relative importance of prenatal vs. postnatal growth failure for child development?

Methods

Low Birthweight

LBW is usually defined as a birthweight less than 2.5 kg. Unlike in developed countries where the primary cause of LBW is prematurity (born before 37 weeks gestation), most LBW babies in developing countries are intrauterine growth retarded and born at term (completed 37 weeks of gestation). The prevalence of term LBW is highest in Asia (12.4%), followed by Africa (8.9%) and Latin America (5.3%) [2]. This review is focused exclusively on the consequences of term LBW.

Postnatal Growth

Height is the preferred anthropometric indicator of overall child health [2]. Stunting, or short stature for age, is defined as HAZ < –2. Stunting is a common problem in developing countries, affecting 40.1% (57 million) children under 5 years of age in Africa, 31.3% (112 million) in Asia and 16.1% (9 million) in Latin America [2]. Stunting is a cumulative process that begins in utero and continues to 2–3 years after birth [3]; the intense period of growth failure generally ends by 12–18 months of age [4]. This period has been referred to as ‘the window of vulnerability’ but also as the ‘window of opportunity’. The latter designation calls attention to the fact that nutrition interventions during this window will have the greatest impact in preventing child malnutrition. This review is focused on longitudinal studies of the consequences of postnatal growth failure.

Confounding Factors

The relationship between child growth retardation and child development is confounded by poverty [2, 5–7]. Poverty leads to both growth failure and to delayed child development. Therefore, analyses of the relationship between growth failure and child development must control for poverty indicators. The two most commonly used indicators of poverty in the child growth and development literature are family socioeconomic status (SES) and parental educational level.

Effect Size

Effect sizes provide a measure of the magnitude of associations and, for comparison of two samples, for example, LBW and normal birthweight newborns, are estimated as the difference between the two means divided by the pooled standard deviation. We estimated effect sizes and 95% confidence interval when possible.
LBW and Development

**LBW and Cognitive Functions and Schooling**

Table 1 summarizes studies [8–17] that compared developmental outcomes in children born term LBW or normal birthweight (NBW). In Jamaica, term LBW infants had poorer scores on problem solving ability at 7 months (cover test: 1.9 vs. 2.9; support test: 1.6 vs. 2.5) [13] and had lower scores on development quotients (DQ) at 15 months (109 vs. 112) and 24 months (94 vs. 98) [14].

In Brazil, mental and psychomotor development scores were compared between LBW and NBW children at several points of time: 6 months, 12 months, 2 years and 8 years. At 6 months, the LBW infants were 4.2 points lower in the Mental Development Index (MDI) and 7.3 points lower in the Psychomotor Development Index (PDI) compared to NBW infants [8]. Differences increased at 12 months (MDI 7.0 points lower; PDI 9.9 points lower) [8]. At 2 years, LBW infants had significantly lower mental (9.1 points lower) and motor scores (10.2 points lower) than NBW infants [9]. At 8 years, the LBW group had lower intelligent quotient (IQ) scores than NBW children on the Wechsler Intelligence Scale for Children (WISC; 5 points lower on the performance and 3 points lower in verbal) [10]. Another study in Brazil [11] showed that LBW children scored 6 points lower in cognitive scores compared to NBW children.

The relationship between LBW and cognitive development was also explored in Guatemala [12]. Compared to NBW infants, LBW infants had significantly lower scores on verbal but not memory scales at 36 months, but no significant differences were found at 48 months and 60 months for either scale.

A study in China [15] followed children until 16 years. The authors reported that LBW children had a lower DQ than NBW subjects through 3 years, lower IQ at 5 and 16 years, and lower scholastic achievement at 16 years. Results from this study should be interpreted with caution because there was no control for poverty measures.

LBW was significantly associated with neuropsychomotor development at 12 months in two Brazilian cohorts, 1993 and 2004 [17]. LBW children in the 1993 cohort were 3 times more likely to fail in the screening test for development compared to NBW children [16]. In addition, birthweight of women (but not men) predicted entry into the university [18].

The effect sizes for cognitive outcomes ranged from –0.98 to –0.14 (fig. 1).

LBW is also associated with less schooling. In an analysis of data from five prospective cohort studies from Brazil, Guatemala, India, The Philippines and South Africa [2], an additional 1 kg in birthweight (equivalent to about 2 z scores) was associated with an additional 0.3 years of schooling.
### Table 1. LBW and child development

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Age at assessment</th>
<th>Outcomes</th>
<th>LBW children</th>
<th>NBW children</th>
<th>Effect size</th>
<th>95% CI</th>
<th>Control for confounding</th>
<th>SES</th>
<th>schooling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grantham-McGregor et al., 1998 [8]</td>
<td>Brazil</td>
<td>6 months</td>
<td>PDI</td>
<td>102</td>
<td>102</td>
<td>-0.98</td>
<td>-1.27</td>
<td>-0.69</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MDI</td>
<td>102</td>
<td>102</td>
<td>-0.79</td>
<td>-1.07</td>
<td>-0.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>12 months</td>
<td>PDI</td>
<td>84</td>
<td>84</td>
<td>-0.95</td>
<td>-1.27</td>
<td>-0.63</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MDI</td>
<td>84</td>
<td>84</td>
<td>-0.67</td>
<td>-0.98</td>
<td>-0.35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eickman et al., 2002 [9]</td>
<td>Brazil</td>
<td>24 months</td>
<td>PDI</td>
<td>76</td>
<td>76</td>
<td>-0.61</td>
<td>-0.94</td>
<td>-0.29</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Emond et al., 2006 [10]</td>
<td>Brazil</td>
<td>8 years</td>
<td>MDI</td>
<td>76</td>
<td>76</td>
<td>-0.59</td>
<td>-0.92</td>
<td>-0.27</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Performance</td>
<td>83</td>
<td>81</td>
<td>-0.32</td>
<td>-0.63</td>
<td>-0.01</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Santos et al., 2008 [11]</td>
<td>Brazil</td>
<td>5 years</td>
<td>Verbal</td>
<td>83</td>
<td>81</td>
<td>-0.25</td>
<td>-0.56</td>
<td>0.06</td>
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</tr>
<tr>
<td>Gorman et al., 1992 [12]</td>
<td>Guatemala</td>
<td>3 years</td>
<td>Verbal</td>
<td>41</td>
<td>76</td>
<td>-0.41</td>
<td>-0.78</td>
<td>-0.04</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Memory</td>
<td>41</td>
<td>76</td>
<td>-0.23</td>
<td>-0.60</td>
<td>0.14</td>
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<tr>
<td>Gardner et al., 2003 [13]</td>
<td>Jamaica</td>
<td>7 months</td>
<td>Cover test</td>
<td>69</td>
<td>87</td>
<td>-0.53</td>
<td>-0.85</td>
<td>-0.20</td>
<td>Yes</td>
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<tr>
<td>Walker et al., 2004 [14]</td>
<td>Jamaica</td>
<td>15 months</td>
<td>DQ</td>
<td>68</td>
<td>94</td>
<td>-0.49</td>
<td>-0.81</td>
<td>-0.18</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>24 months</td>
<td>DQ</td>
<td>68</td>
<td>94</td>
<td>-0.49</td>
<td>-0.81</td>
<td>-0.18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Location</td>
<td>Age</td>
<td>Test</td>
<td>DQ</td>
<td>DQ</td>
<td>DQ</td>
<td>DQ</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Peng et al., 2005 [15]</td>
<td>China</td>
<td>6 months</td>
<td>DQ</td>
<td>85</td>
<td>60</td>
<td>-0.71</td>
<td>-1.05</td>
<td>-0.37</td>
<td>No</td>
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<tr>
<td></td>
<td></td>
<td>12 months</td>
<td>DQ</td>
<td>85</td>
<td>60</td>
<td>-0.71</td>
<td>-1.05</td>
<td>-0.37</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24 months</td>
<td>DQ</td>
<td>85</td>
<td>60</td>
<td>-0.71</td>
<td>-1.05</td>
<td>-0.37</td>
<td>No</td>
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<tr>
<td></td>
<td></td>
<td>3 years</td>
<td>DQ</td>
<td>85</td>
<td>60</td>
<td>-0.45</td>
<td>-0.78</td>
<td>-0.12</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 years</td>
<td>IQ</td>
<td>45</td>
<td>45</td>
<td>-0.73</td>
<td>-1.16</td>
<td>-0.30</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16 years</td>
<td>IQ</td>
<td>40</td>
<td>40</td>
<td>-0.78</td>
<td>-1.24</td>
<td>-0.32</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Harpen et al., 1996 [16]</td>
<td>Brazil</td>
<td>12 months</td>
<td>Denver II test</td>
<td>129</td>
<td>1,229</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Harpen et al., 2008 [17]</td>
<td>Brazil</td>
<td>12 months</td>
<td>Denver II test</td>
<td>1,364 (cohort 1993) and 3,907 (cohort 2004)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Barros et al., 2008 [18]</td>
<td>Brazil</td>
<td>23 years</td>
<td>University entry</td>
<td>2004</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>16 years</td>
<td>IQ</td>
<td>40</td>
<td>40</td>
<td>-0.78</td>
<td>-1.24</td>
<td>-0.32</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

WPPSI-R = Wechsler Pre-School and Primary Scale of Intelligence Revised.

1 These studies were conducted in a cohort in the state of Pernambuco in Northeast Brazil.
2 These studies were conducted in a cohort in Kingston, Jamaica.
3 This study was conducted in a cohort in China.
4 These studies were conducted in a cohort in Pelotas, Brazil.
LBW and Behavioral Problems

LBW infants experienced more behavioral problems such as being less cooperative, happy, and active compared to NBW infants in Jamaica [13] and Brazil [8]. In addition, LBW infants were more inhibited than NBW infants [8]. Another study in Brazilian children [10] showed that LBW had an independent, adverse effect on coordination and selective attention after controlling for social background.

Postnatal Growth and Development

A summary of longitudinal studies [19–37] that assess stunting and child development is shown in table 2.
### Table 2. Longitudinal studies of physical growth and child development

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Age to measure outcomes</th>
<th>Outcomes</th>
<th>Stunted</th>
<th>Not stunted</th>
<th>Results</th>
<th>Control for confounding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mendez et al., 1999 [19]¹</td>
<td>Philippines</td>
<td>8–11 years</td>
<td>Cognitive tests</td>
<td>1,345</td>
<td>768</td>
<td>Stunted (especially severe) in the first 2 years, reduced cognitive performance at 8 (β = –0.14; 95% CI: –0.23 to –0.05) and 11 years (β = –0.05; 95% CI: –0.13 to 0.04).</td>
<td>Yes</td>
</tr>
<tr>
<td>Daniels et al., 2004 [20]¹</td>
<td>Philippines</td>
<td>18 years</td>
<td>School trajectory: age at entry, grade repetition, grades completed</td>
<td>1,345</td>
<td>768</td>
<td>Greater HAZ protected against late enrolment among both boys and girls. Taller children were less likely to repeat grades (girls OR = 0.78, 95% CI: 0.67–0.89; boys OR = 0.86, 95% CI: 0.74–0.99) and less likely to drop out (girls OR = 0.74, 95% CI: 0.61–0.91; boys OR = 0.79, 95% CI: 0.66–0.96)</td>
<td>Yes</td>
</tr>
<tr>
<td>Cheung et al., 2006 [21]</td>
<td>Indonesia</td>
<td>7 years</td>
<td>Cognitive tests</td>
<td>525 total</td>
<td></td>
<td>Weight gain from mid-infancy to around 7 years of age rather than mid-infancy weight was related to cognitive performance</td>
<td>No</td>
</tr>
<tr>
<td>Cheung et al., 2001 [22]</td>
<td>Pakistan</td>
<td>2 years</td>
<td>Motor development</td>
<td>1,014 total</td>
<td></td>
<td>Postnatal stunting had a linear inverse association with gross motor development (β = 0.96; 95% CI: 0.94–0.97).</td>
<td>Yes</td>
</tr>
<tr>
<td>Author</td>
<td>Country</td>
<td>Age to measure outcomes</td>
<td>Outcomes</td>
<td>Stunted</td>
<td>Not stunted</td>
<td>Results</td>
<td>Control for confounding</td>
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<tr>
<td>Berkman et al., 2002 [23]</td>
<td>Peru</td>
<td>9 years</td>
<td>WISC-R</td>
<td>46</td>
<td>97</td>
<td>Children with severe stunting in the 2nd year of life scored 10 points lower on the WISC-R test (95% CI: 2.4–17.5) than children without severe stunting</td>
<td>Yes, Yes</td>
</tr>
<tr>
<td>Alderman et al., 2006 [24]</td>
<td>Zimbabwe</td>
<td>18 years</td>
<td>Grades, age at entry</td>
<td>185</td>
<td>480</td>
<td>Children that were 3.4 cm taller in height for age at 3 years would have completed an additional 0.85 grades of schooling and would have commenced school 6 months earlier</td>
<td>No</td>
</tr>
<tr>
<td>Lasky et al., 1981 [25] 2,4</td>
<td>Guatemala</td>
<td>6, 15, 24 months</td>
<td>Composite infant scale</td>
<td>706 total</td>
<td></td>
<td>Changes in length or weight over time correlated with changes in behavioral performance.</td>
<td>Yes</td>
</tr>
<tr>
<td>Kuklina et al., 2004 [26] 3,4</td>
<td>Guatemala</td>
<td>15 months</td>
<td>Motor development scale</td>
<td>174 total</td>
<td></td>
<td>Growth in length during the 1st year of life predicted age of walking (β = 0.57, SE = 0.27)</td>
<td>Yes</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Age Range</td>
<td>Measured Outcomes</td>
<td>Sample Size</td>
<td>Results</td>
<td></td>
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<tr>
<td>Kuklina et al., 2006 [27]</td>
<td>Guatemala</td>
<td>6, 24, 36 months</td>
<td>PDI and MDI</td>
<td>404 total</td>
<td>Change in HAZ score from 0 to 24 months associated with MDI (β = 1.86; 95% CI: -0.02 to 3.73) and PDI (β = 5.05; 95% CI: 3.13–6.97) at 24 months</td>
<td></td>
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</tr>
<tr>
<td>Martorell et al., 1992 [28]</td>
<td>Guatemala</td>
<td>18 years</td>
<td>Cognition, literacy, numeracy and general knowledge</td>
<td>82 total</td>
<td>Stunting at 3 years is related to literacy and school attainment in boys at 18 years. Early postnatal growth (birth to 2 years) but not birth size or late postnatal growth was associated with women's education achievement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Li et al., 2004 [29]</td>
<td>Guatemala</td>
<td>20–29 years</td>
<td>Schooling, educational achievement</td>
<td>108 total</td>
<td>In an econometric analysis, stunting at 6 years was found to be a major determinant of adult cognitive skills. The impact on reading-comprehension scores of not being stunted at age 6 was equivalent to the impact of four grades of schooling.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Behrman et al., 2008 [30]</td>
<td>Guatemala</td>
<td>25–42 years</td>
<td>Reading-comprehension and nonverbal cognitive skills</td>
<td>1,448 total</td>
<td>Stunted children were 8.4 points lower in DQ score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grantham-McGregor et al., 1991 [31]</td>
<td>Jamaica</td>
<td>24 months</td>
<td>DQ measured by Griffith scale</td>
<td>33 total</td>
<td>Stunted control group had significantly lower score than nonstunted children groups in most tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grantham-McGregor et al., 1997 [32]</td>
<td>Jamaica</td>
<td>7–8 years</td>
<td>IQ measured by Stanford Binet test</td>
<td>32 total</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Country</td>
<td>Age to measure outcomes</td>
<td>Outcomes</td>
<td>Stunted</td>
<td>Not stunted</td>
<td>Results</td>
<td>Control for confounding</td>
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<tr>
<td>Walker et al., 2000 [33]</td>
<td>Jamaica</td>
<td>11–12 years</td>
<td>IQ-WISC, cognitive function</td>
<td>32</td>
<td>85</td>
<td>Stunted children had lower scores than nonstunted children on 10 of 11 tests</td>
<td>Yes</td>
</tr>
<tr>
<td>Walker et al., 2005 [34]</td>
<td>Jamaica</td>
<td>17–18 years</td>
<td>IQ-WRIS</td>
<td>105</td>
<td>64</td>
<td>Overall, stunted had significantly poorer scores than nonstunted on 11 of 12 cognitive and educational tests. Stunting in early childhood was associated with cognitive and educational deficits in late adolescence.</td>
<td>Yes</td>
</tr>
<tr>
<td>Gardner et al., 1999 [35]</td>
<td>Jamaica</td>
<td>12–24 months</td>
<td>Behavior</td>
<td>78</td>
<td>26</td>
<td>Stunted children showed significantly more apathy, and less enthusiasm and variety in exploring, were less happy and more fussy.</td>
<td>Yes</td>
</tr>
<tr>
<td>Chang et al., 2002 [36]</td>
<td>Jamaica</td>
<td>11–12 years</td>
<td>Behavior</td>
<td>116</td>
<td>80</td>
<td>Previously stunted children had more conduct difficulties at home and poorer educational attainment, regardless of their SES, than nonstunted children.</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Stunted participants reported significantly more anxiety and depressive symptoms, and lower self-esteem than nonstunted participants and were reported by their parents to be more hyperactive.

OR = Odds ratio; WRIS = Wechsler Intelligence Scale for Children.

1 These studies were conducted in a cohort in the Philippines.
2 These studies were conducted in a cohort in Guatemala.
3 These studies were conducted in a cohort in Jamaica.
4 These studies carried out continuous analyses and did not divide the sample into stunted and nonstunted groups.
Postnatal Growth and Cognitive Development

Growth retardation in early childhood had a linear, inverse association with gross and fine motor development in Pakistan [22] and Guatemala [26]. In Pakistan, compared to nonstunted children, stunted children had delayed age at independent walking (indicator of gross motor development) of 2.1 months and age at building a three-cube tower (indicator of fine motor development) of 0.7 months.

Several reports are available from the INCAP longitudinal cohort study in Guatemala. Growth in length or weight, rather than size at birth, predicted age at walking. Children who were 1 SD or more lower in their LAZ score during the 1st year of life started walking 0.6 months later [26]. In addition, gains in length and weight during the first 24 months were positively associated with child development at 36 months [27]. Associations between early childhood growth and cognitive function remained evident in late adolescence and adulthood. Height at 36 months was related to cognition, literacy, numeracy and general knowledge in children 18 years of age, and severely stunted males and females had 1.8 and 1 fewer years of schooling, respectively, than nonstunted subjects [28]. In an econometric analysis, preschool nutrition, as proxied by stunting at 6 years of age, was found to have a substantial impact on reading-comprehension and nonverbal cognitive skills in adults aged 25–42 years [30]. For example, the impact on reading-comprehension scores of not being stunted at age 6 was equivalent to the impact of four grades of schooling.

The relationship between stunting during the first 2 years of life and cognitive development later in childhood (age 8 and 11 years) was examined in a cohort of 2,198 Filipino children participating in the Cebu Longitudinal Health and Nutrition Study. Children stunted in the first 2 years had reduced cognitive performance [19], with a dose-response relationship between severity of stunting and cognitive scores. At age 8, children with severe and moderate early stunting had mean cognitive scores 0.61 SD and 0.25 SD, respectively, below the mean of nonstunted children [19]. The deficits in the stunted children's scores were less at age 11 than at age 8, but still were 0.3 SD lower than in nonstunted children.

Peruvian children with severe stunting in the 2nd year of life scored 10 points lower on the WISC-R test at age 9 years compared to children without severe stunting [23].

In a prospective cohort study of Jamaican children, stunted children at age 2 years had poorer cognitive scores in childhood and adolescence than children who were not stunted. At age 2 years, stunted children had 8.4 points less in DQ score compared to nonstunted children [31]. At ages 7 and 11 years, stunted children had poorer IQs and poorer cognitive function than children who were not stunted [32, 33]. The adverse effects of stunting on development remained evident in late adolescence; stunted children had significantly lower scores than the nonstunted children on 10 of 11 cognitive and educational tests at ages 17–18 years [34].
Effect sizes of cognitive deficits in later life associated with stunting in early childhood were calculated from data from the Philippines, Jamaica, Peru, Indonesia, Brazil and South Africa by Grantham-McGregor et al. [38]. Compared with nonstunted children, moderately or severely stunted had lower cognition scores, with effect sizes ranging from –0.4 to –1.05 SD (fig. 2).

Postnatal Growth and Schooling
The association between HAZ at 2 years and schooling trajectories was evaluated at age 18 years in the Philippines [20]. After adjustment for confounders, greater HAZ was significantly associated with earlier enrollment among boys (OR = 1.44; 95% CI: 1.04–1.98), less grade repetition (girls: OR = 0.78, 95% CI: 0.67–0.89, and boys: 0.86; 95% CI: 0.74–0.99), and less likelihood of dropping out of school (girls: OR = 0.74, 95% CI: 0.56–0.98, and boys: OR = 0.66, 95% CI: 0.51–0.84). In Guatemala, height and head circumference (HC) at 2 years (but not birth size) were positively associated with women’s education achievement at ages 20–29 years [29].

A study in Zimbabwe [41] estimated that if the median HAZ score at 3 years were shifted from the observed value of –1.25 to 0, the result would be that...
children would start school 6 months earlier and obtain an additional 0.85 grade of schooling. Results from analyses of five cohort studies from Brazil, Guatemala, India, the Philippines, and South Africa showed that, after controlling for confounding, HAZ and WAZ were strong predictors of schooling [2]. Each additional unit of HAZ or WAZ was associated with about 0.5 years of schooling.

Postnatal Growth and Behavior
Length and weight were the anthropometric variables most strongly correlated with behavioral development, with changes in length or weight over time correlated with changes in behavioral performance [25]. Results from Jamaica suggest that children who became stunted in early life had poorer emotional and behavioral outcomes in late adolescence compared to children who were never stunted [36]. The stunted participants reported significantly more anxiety (regression coefficient = 3.03; 95% CI: 0.99–5.08) and depressive symptoms (0.37; 95% CI: 0.01–0.72) and lower self-esteem (–1.67; 95% CI: –0.38 to –2.97) than nonstunted participants and were reported by their parents to be more hyperactive (1.29; 95% CI: 0.12–2.46) [37].

Control for Confounding in Studies of Growth and Development
Most of the studies that assessed the relationship between LBW, physical growth and child development attempted to control for possible confounding through variables such as SES and parental education. However, how this was done in practice varied greatly across studies. For example, some studies [8–10, 19, 20, 23] controlled for both mother and father’s schooling, while other studies [13, 14, 26–29, 31–34, 36] only controlled for mother’s literacy. The measures used for SES varied as well. For example, Filipino [19, 20], Brazilian [8–10] and Guatemalan studies [12, 26–30] used a variety of information in generating an index of SES, including family income, household amenities and assets, housing quality, and water and sanitation. A study in Pakistan [22], on the other hand, used residence (city, urban slum, periurban slum, village) as the single measure of SES.

Although both SES and growth were strongly associated with child development, the relationships with SES was of greater magnitude. For example, in a multiple linear regression analysis in a study in Brazil [9], SES explained 11 and 12%, respectively, of the variation in mental and motor indices, while the corresponding statistics for LBW were 3 and 5%, respectively, in children 24 months of age.

Controlling for SES and parental education often attenuated the effects of LBW or stunting on child development. In Brazil, the LBW group had lower IQ scores at 8 years of age than NBW children (difference = 5 points, p = 0.04) [10]. After controlling for SES, the association with birthweight was attenu-
ated (difference = 4 points, p = 0.10), whereas family income and maternal education remained strong, significant predictors [10]. In other studies, attenuation was observed but the associations remained statistically significant in adjusted models. In Peru, children with severe stunting in the 2nd year of life scored 13.2 points lower on the WISC-R test than children without severe stunting; this difference was reduced to 10 points after controlling for SES and parental education [23]. In the Philippines, taller boys and girls were less likely to repeat grades, 33 and 27% respectively, in unadjusted models; this difference was reduced to 22 and 14%, respectively, in adjusted models [20]. Also in the Philippines, stunted children had mean cognitive scores that were 0.40 SD lower than nonstunted children in an unadjusted model, but this was reduced to 0.14 SD in an adjusted model [19]. Attenuation of associations was also evident for several outcomes in Guatemala studies [26, 27, 29].

Controlling for confounding is important. When this is done, one observes slight to modest attenuation of associations but in many cases, the associations remain statistically significant. While this suggests an independent, true association, researchers must be concerned about residual confounding. It is possible that the measures of SES and education used were not perfect and that better measures of confounding would have attenuated the associations even more.

Relative Importance of Prenatal vs. Postnatal Growth for Child Development Outcomes

The evidence is overwhelming that both LBW and stunting are associated with large deficits in cognitive performance and schooling. Since birthweight influences postnatal growth and stunting reflects growth failure in utero and the first 2 years of life, this tells us little about the relative importance of prenatal vs. postnatal growth for developmental outcomes. The question is not trivial; understanding the relative importance of prenatal and postnatal growth helps define which periods in life are most critical for human capital outcomes such as cognitive development and schooling and helps guide the design and targeting of appropriate interventions to enhance human development.

Several studies [22, 39, 40] on this topic did not take the correlation between growth measures at different points in time into account and hence their conclusions are questionable. For example, a study by Horta et al. [40] included birthweight z score and WAZ at two different time points in the same regression model; this analysis may cause problems of multicollinearity (because birthweight and later weights are strongly correlated) and does not correct for the intercorrelation among weight measures over time. Other studies [39] used both birth measures and gains in infancy in the same model, which also has the problem of including a common error term.
Appropriate Analytic Approaches to Assess the Relative Importance of Growth across Periods

There are at least two methodological approaches that have been proposed to address the problem, Multiple Stage Least Square (SLS) [45] and Structural Equation Modeling (SEM). However, only one study [41] so far has used SEM.

SLS (such as 2-SLS or 3-SLS) refer to (1) a stage in which new dependent or endogenous variables are created to substitute for the original ones, and (2) a stage in which the regression is computed in ordinary least squares fashion, but using the newly created variables. Multiple SLS regression removes the bias that results due to correlation between measures of initial size and subsequent growth. It also addresses the problems of multicollinearity, common measurement error terms, and complicated interpretation of regression coefficients when compared to results from models in which both initial and subsequent size are simultaneously entered [42]. For example, if we have data at birth and at 2 years, we can partition the effects of prenatal (size at birth) and early postnatal growth (size at 2 years) on child development using a 2-SLS analysis. The first stage of 2-SLS involves the prediction of later size from initial size and the calculation of residuals that serve as better measures of subsequent growth because they are independent of initial size. In the second stage, child birth size and the residual are used as independent variables for assessing the relative importance of prenatal vs. postnatal effects in regression models.

Review of Studies That Used Appropriate Methods for Assessing the Relative Importance of Prenatal vs. Postnatal Growth on Child Development

There are very few studies in developing countries that look at the relative importance of child growth at different periods of child development and that do so using appropriate methods. A study in Guatemala [29] examined the long-term relationship of growth in early life with educational achievement in adulthood (at ages 20–29 years). The authors used a 2-SLS approach to partition the variances of size at 2 years into two components: the prenatal and early postnatal (0–2 years) components and a 3-SLS approach to partition the variances of adult height into three components: prenatal, early, and late postnatal (2 years to adulthood). Results indicate that early childhood growth is a significant predictor of women’s educational achievement, even after adjusting for SES and age at follow-up. In particular, growth during the early postnatal period (birth to age 2 years) but not the prenatal or the late postnatal period was the only variable predictive of women’s educational achievement. For each 1 SD increment in length in the early postnatal period,
the odds of having higher education achievement were 1.5 (95% CI: 1.05–2.2) [29].

In another study from Guatemala, the authors used 2 SLS methods to assess the relative effect of prenatal and postnatal growth on child development. Birth size was significantly associated with child development at 6 and 24 months. Gain in length and weight during the first 24 months was positively associated with child development, whereas growth from 24 to 36 months of age was not associated with child development at 36 months. HC gain after 6 months was not a significant predictor of child development at 24 and 36 months [27].

Similar studies are also rare in developed countries. Two studies in the UK [43, 44] used the SLS method to investigate the relationship between HC growth (indicator of brain growth) during different periods and cognitive function in children at 8–9 years of age. One study [43] suggested that postnatal brain growth is more important than prenatal brain growth for cognitive function. For each SD increase in HC at 9 months and 9 years of age, IQ at age 9 years rose by 1.98 points (95% CI: 0.34–3.62) and 2.87 points (95% CI: 1.05–4.69), respectively. However, there was no relationship between IQ and HC at 18 weeks’ gestation or at birth [43]. In the second study [44], the association between HC at birth, 1 year, 4 years and 8 years and cognitive performance at 4 and 8 years was evaluated. HC growth during infancy but not thereafter was associated with IQ at 4 and 8 years. For each SD increase in HC between birth and 1 year, full-scale IQ at 4 and 8 years was increased by 1.97 (95% CI: 0.68–3.26) and 1.56 (95% CI: 0.11–3.01) points, respectively [44].

**Possible Mechanisms Liking Growth Retardation and Poor Development**

Various mechanisms, none mutually exclusive, have been proposed to explain the interrelationship between malnutrition (or its indicator, growth failure) and poor development (fig. 3). The oldest idea posits that the relationship is mediated through changes in the structure or biochemistry of the brain that impair the functioning of the central nervous system [45], but there are several plausible mechanisms of a more subtle nature [46]. Malnutrition delays motor development [22, 26] and this in turn reduces children's interaction with the environment and affects skills acquisition. Deficiencies in some nutrients, such as zinc, increase the incidence of diarrheal diseases and pneumonia [47]. These common illnesses are usually accompanied by apathy, withdrawal and days in bed. During these episodes of illness, there is diminished exploration of the environment, which in turn delays intellectual development. Malnourished children are stunted and thus appear younger; this may shape the interaction with others, particularly adults. Stunted children
may be less likely to be challenged to explore and expand their capabilities by care-takers and teachers.

**Conclusions**

Growth retardation in early childhood is linked to delayed cognitive development, reduced schooling and behavioral problems in children and adults. The relative importance of prenatal and postnatal growth on development is not well understood, but it would appear that the adequacy of growth during the first 2 years of life is the critical factor, perhaps even more important than intrauterine growth. The prevention of malnutrition during pregnancy and early childhood is an important strategy for improving cognitive and schooling outcomes.

**References**

Interrelationship between Growth and Development


Discussion

Dr. Mobarak: How did you measure school failure? And how did you measure cognitive development in children under 2 years, especially very small children, because in the Columbia University study we studied 4,000 children and we had a lot of difficulties in performing cognitive and hearing assessments in children under 2 years. About 66% of the children could not be tested because they were either very shy or didn't turn up.
Dr. Martorell: School failure measures are derived from schooling histories. In the analyses of our five cohorts, we defined school failure as ever fail a grade because that was a variable that we had in all sites. Your question about measuring developmental outcomes in young children identifies a challenge for researchers. How do you get young children to cooperate, because tests typically demand a lot of interaction between the tester, child and mother. I am not a psychologist, but I have collaborated with psychologists in many studies. In all cases, we have collected the data in a quiet setting, specially accommodated for testing and centrally located. We use testers that are familiar with the local culture, and that are trained to gain the trust of the child and mother. Sometimes, as you say, it’s impossible on a given day to test a child and you have to re-schedule him. It is difficult, but it can be done.

Dr. Mobarak: In terms of child development, we have seen that a lot of children were vitamin A deficient, and also a lot of children had hearing deficits because of post-otitis media. These children were not attending school properly due to visual and hearing problems, not cognitive problems. So there were a lot of confounding factors in the school failure in our study.

Dr. Martorell: That’s another good point that there are some children that for a number of reasons are not typical. In cases with chronic conditions, usually identified through pediatric examinations, we code these children as atypical and deal with this information in the analysis. We do not usually find very many children that are atypical. If a child is ill with common problems, such as diarrhea, we re-schedule the visit.

Dr. Boey: I would like to mention what both you and Dr. Cooke stated this morning about the problem of interpreting the effect of nutritional factors on growth and development due to confounding factors such as socioeconomic factors, poverty, mother’s education and many other factors. My concern is that these factors are so varied that in spite of even the best statistical methods sometimes we can get quite different results and sometimes even opposing results. Are you concerned about this, and how do you think we can overcome this and get some meaningful objective answers.

Dr. Martorell: As I said in the presentation, we included only those studies that included control for confounding. There are some very good studies that have gone to great lengths to control for confounding and that find robust relationships between growth failure and developmental outcomes. We have also been using econometric methods that control for endogeneity and that are reputed by economists to control for confounding. Our own study in Guatemala is a follow-up of individuals who participated as children in a community randomized nutrition trial. We have shown that the nutrition intervention reduced stunting in early life and improved schooling, cognitive outcomes and wages in adults [1–4]. What is re-assuring is that the nutrition intervention only reduced stunting when provided prior to 3 years of age, and that similarly only exposure to improved nutrition prior to 3 years of life impacted on adult human capital outcomes. Finally, the Chinese famine of 1959–1961, associated with the Great Leap Forward, led to shorter adult heights and reduced incomes and wealth in adults that were born during the famine compared to those exposed to the famine at older ages or born after the famine [5].

Dr. Adair: We have talked about evidence that recovery or catch-up can improve morbidity and mortality outcomes. Is there evidence that recovery or catch-up can improve the outcomes that you have been talking about and if so what’s the window, is it the same as for these other outcomes?

Dr. Martorell: The best data I know come from children who are adopted, and of these some of the most interesting were carried out in the 1970s by Winick et al. [6] and Winick [7]. They studied children from Korean orphanages who were adopted by US families. IQ was tested at school age in the US and the sample was divided by degree of malnutrition on admission to the orphanage (based on weight: severe,
moderate and none) and timing of adoption (before of after 2 years of age). They found that as a whole, the children had IQs that were slightly above normal for US children, despite the early history. There was a difference of about 5 IQ points between children adopted before and after 2 years of age. Also, there was a difference of about 10 IQ points between the extreme categories of malnutrition (severe vs. no malnutrition) in both the children adopted before and after 2 years of age. There are more recent adoption reports that also show that the ability of children to recover from adverse early beginnings is great but that more is gained if the children are adopted before the age of 2 years [8].

Dr. Gillman: I have a specific question and a general question. I missed what you said about length earlier and whether in the observational studies and cohort studies increasing length or weight-for-length or both gave the same beneficial educational outcomes. The more general question is about comparing prenatal with postnatal growth. We have heard a number of speakers say that postnatal growth is more important for certain outcomes, and I am asking this question out of concern that we diminish the importance of prenatal interventions. I guess the question is how do we really compare postnatal with prenatal growth, number one because we often use just the size at birth to represent a growth parameter prenatally, and number two because you have the mother and the placenta as well as the fetus, so can we really compare them, how do we compare them, what does it mean for inferences and implications for intervention?

Dr. Martorell: Your first question about length, weight for length and weight, clearly depends on the outcome. If you are looking at outcomes like future obesity, I think weight for length is really quite important, but for these educational outcomes and human capital outcomes the key variable is length. In a paper of the 2008 Lancet series on maternal and child undernutrition, we categorically state that length is the best predictor of human capital [9]. Your second question about the relative importance of prenatal vs. postnatal growth is a difficult issue. Few people use methods that remove the correlation between prenatal status and postnatal growth, which is necessary to properly answer the question. When we do that, we find that growth is more important for schooling outcomes than prenatal growth, but birthweight, however imperfect a measure of prenatal growth it may be, is still related to schooling. What's interesting is that growth after 2 years has no relationship, so at least we know that beyond that point there is no longer a relationship between growth and schooling.

Dr. Ziegler: We discuss prenatal and postnatal growth failure as if they were a continuum, as if they were the same thing that can happen before or after birth. Postnatal growth failure is almost always a lack of nutrients, energy and/or protein, whereas prenatal growth failure is predominantly a lack of oxygen. With different causes, the consequences could very well be different. So I don't find it surprising that you and others find that postnatal growth failure has more severe consequences than prenatal growth failure.

References

Interrelationship between Growth and Development
