Influences on catch-up growth using relative versus absolute metrics: Evidence from the MAL-ED cohort study

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Abstract

**Background:** Undernutrition in early childhood has historically been considered irreversible after 2-3 years of age and has been associated with morbidity and mortality over the short-term and poor economic and cognitive outcomes over the long-term. We used longitudinal data to determine which factors are associated with positive changes in absolute and relative differences in height and weight from the WHO Growth Standards from 24 to 60 months of age.

**Methods:** Across six MAL-ED sites, 942 children had anthropometry data at 24 and 60 months, as well as information about socioeconomic status, maternal height, gut permeability (lactulose-mannitol z-score (LMZ)), dietary intake from 9-24 months, and micronutrient status. Anthropometric changes were categorized as positive changes in height- or weight-for-age z-score (HAZ, WAZ) or their absolute difference from the growth standard median (HAD (cm), WAD (kg)), as well as recovery from stunting/underweight. Outcomes were modeled using multivariate linear regression.

**Results:** Forty-three/34% of the children who were stunted/underweight at 24 months were no longer stunted/underweight at 60 months, Among the sites, 64-92% of children had positive changes in their HAZ, whereas 25-60% had positive changes in HAD. Linear regression models indicate that female sex (-0.21 HAZ (95% CI -0.27, -0.15); -0.75 HAD (-1.07, -0.43)) and mean LMZ (0-24 months) (-0.10 HAZ (-0.16, -0.04); -0.47 HAD (-0.73, -0.21)) were negatively associated with change in both metrics, and maternal height was positively associated with both (0.09 HAZ (0.03, 0.15); 0.45 HAD (0.15, 0.75)). Similar relationships were identified for change in WAZ and WAD. Dietary protein density was negatively associated with change in WAZ and WAD (-0.05 WAZ (-0.09, -0.01); -0.11 WAD (-0.21, -0.01)), and mean plasma transferrin receptor concentration was positively associated with change in WAZ and WAD (0.02 WAZ (0.0, 0.04); 0.04 WAD (0.0, 0.08)).

**Conclusions:** While children in the MAL-ED study demonstrated recovery from stunting and underweight from 24-60 months of age, they also lost additional centimeters and grams when compared to the WHO median references. Given the similarities in the factors associated with changes in HAZ and HAD (and WAZ and WAD), both can be used to characterize catch-up growth during childhood.

**Funding Sources:** The MAL-ED study was supported by the Bill & Melinda Gates Foundation, with grants to the Foundation for the NIH and NIH/FIC.

Background

Poor growth in early childhood is associated with increased risk of morbidity and mortality (1–4), as well as with longer-term negative effects on cognitive development and economic productivity (5–7). Scientific evidence over decades of research suggested that in early childhood, growth faltering can be reversed and catch-up growth can occur through improved nutrition and other inputs (e.g., reduced disease frequency), but after 2–3 years of age, such inputs are less likely to result in catch-up growth (8, 9). This research emphasized the need for prevention and control of linear growth faltering and stunting in the first 2 years of life, and this has led to a focus on "the first 1000 days", recognizing as well the importance of the maternal nutrition environment for child growth and development (10).

The literature documenting the reduced likelihood of catch-up growth after 2–3 years of age led many to consider that children who were stunted at age 2 would never exhibit catch-up growth and remain stunted at later ages. There
are now numerous studies published in which children with height-for-age z-scores (HAZ) < -2 (i.e., stunted) in early childhood were found to have HAZ > -2 later in childhood/adolescence (11–15), suggesting that the growth of some children does improve after the age of 2. Recently, Leroy et al (16) made the observation that because child growth is heteroscedastic (i.e., the variability of size (height or weight) increases with age), the absolute difference between the median and standard deviation quantiles increases with age. This means that as children age, their poor growth may continue but will appear to fall more within the limits of the distribution. Leroy et al (16) pointed out that in terms of the absolute difference in height-for-age from the median (HAD, in cm), children may still be losing ground, and thus, improvements in HAZ over time do not necessarily represent a recovery of centimetersforgone.

This contradiction between an apparent gain in HAZ concomitant with a loss in HAD complicates our understanding of catch-up growth, and our ability to ultimately interpret the impact of programs or other influences on child growth during the pre-school period. Since the publication by Leroy et al (16), researchers have compared differences in HAZ and HAD by age to evaluate this phenomenon (17, 18). Here, we use longitudinal data from the Etiology, Risk Factors, and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health and Development Project (MAL-ED) to evaluate child growth in terms of height and weight (HAZ, HAD, weight-for-age z-score (WAZ), and weight-for-age difference (WAD)) from 24 to 60 months, and to evaluate factors associated with catch-up growth based on relative versus absolute metrics. We ask the following questions: 1) what is the difference in catch-up growth from 24 to 60 months when considered in relative versus absolute terms?, and 2) are there differences in the early life factors associated with catch-up growth from 24 to 60 months, depending on how catch-up growth is specified?

**Methods**

The overall goal of the MAL-ED longitudinal multi-site birth cohort study was to evaluate the relationships between the child's environment and experience (dietary, illness, and pathogen exposure, among others) and growth and cognitive development from birth to two years of age (19). It was conducted in eight sites: Dhaka, Bangladesh (BGD); Fortaleza, Brazil (BRF); Vellore, India (INV); Bhaktapur, Nepal (NEB); Loreto, Peru (PEL); Naushero Feroze, Pakistan (PKN); Venda, South Africa (SAV), and Haydom, Tanzania (TZH). Each site enrolled at least 200 children within 17 days after birth who were born singleton to a mother who was at least 16 years of age, and weighed at least 1,500 g at birth. Children were first enrolled in November 2009, and due to additional funding, a follow-up of these children at 5 years of age was completed in February 2017. The protocols were reviewed by appropriate Institutional Review Boards (IRB) in each site and written consent was obtained from the family, both for the initial protocol, and for the follow-up. More detailed descriptions of the study protocol have been published (20–23); here we provide details most relevant for these analyses.

**Anthropometry**

Trained field workers visited the households monthly to measure child length and weight during the first two years of life and at least quarterly thereafter until five years of age (24). The length (≤ 24 months) or height (> 24 months), hereafter referred to as height, and weight measures were then converted to sex- and age-specific HAZ and WAZ using the WHO 2006 growth standards (25). Absolute HAD and WAD were calculated by subtracting the WHO reference median height or weight for a child of the same age and sex from the measured value. Changes in HAZ/HAD and WAZ/WAD were calculated by subtracting the 24-month value from the 60-month value. Field workers additionally measured maternal height two months after the child was enrolled in the study. The anthropometric data from PKN and BRF were not used for this analysis due to bias in the data collection in PKN,
and minimal stunting in BRF (<2%). For analyses, children were required to have HAZ and WAZ values at 0, 24, and 60 months of age, allowing for a ± 30-day window. Stunting is defined as HAZ<-2 and underweight is defined as WAZ<-2.

**Socioeconomic status**

In order to have a common measure of socioeconomic status across the sites, an indicator was developed combining information on Water and sanitation status, Assets, Maternal education, and Income (WAMI) (26). The WAMI index ranges from 0 to 1, with a higher value indicating a higher socioeconomic status. We calculated the mean WAMI score when the child was three to five years of age in order to best represent their socioeconomic status during the period of study.

**Illness surveillance**

Trained fieldworkers visited the homes bi-weekly during the first two years of life to query caregivers about signs and symptoms of morbidity for common illnesses (20). From this, the prevalence and incidence of diarrhea and respiratory illnesses were calculated. Stool samples were taken during each diarrheal episode and tested to determine etiology (27). Monthly surveillance stools were also collected and subjected to testing to evaluate pathogen carriage.

**Gut function**

The lactulose:mannitol (L:M) test (22) was performed at 3, 6, 9, and 15 months to assess the permeability and absorptive capacity of the gut during the first two years of life. We generated age and sex standardized z-scores for the L:M ratios (28) (LMZ) and calculated the mean value of these over the first two years of life for each child. A greater value indicates greater enteric dysfunction, using the BRF site as the reference. From each of the monthly (non-diarrheal) surveillance stools, three indicators of gut inflammation and permeability were also assessed: neopterin, myeloperoxidase, and alpha-1-antitrypsin (22).

**Diet**

From enrollment to 24 months, during the bi-weekly morbidity surveillance, caregivers were queried about breastfeeding and the feeding of other liquids and solids. From 9–24 months, trained field workers utilized a quantitative 24-hour recall questionnaire to quantify intakes of non-breast milk foods on a monthly basis (21). The food intakes were transformed into energy, macro- and micro-nutrients using study-created food composition databases. Due to co-linearity observed in the dietary data components, only energy and the protein density of the diet were included in our analysis. Using the residual method (29), we performed a regression of mean protein intake on mean energy intake and considered the residuals as an indicator of usual protein density.

**Micronutrient status**

Blood samples were taken by venipuncture at 7, 15, and 24 months of age to characterize iron, zinc, and vitamin A status of the child. Plasma concentrations of retinol and zinc were used to characterize vitamin A and zinc status, respectively. Plasma ferritin and plasma transferrin receptor (TfR) were assessed as indicators of iron status. At each time point, and at 5 years of age, hemoglobin concentration was obtained using the HemoCue method to detect anemia. Biochemical concentrations were adjusted for inflammation using plasma alpha-1-acid glycoprotein (30), and transformed using a square root function.

**Statistical methods**
The distributions of HAZ, HAD, WAZ, and WAD were plotted at 0, 24, and 60 months of age. The relationship between changes in HAZ and HAD (and WAZ and WAD) between 24 and 60 months were plotted and quantified with correlation coefficients (r). Children were identified as stunted or underweight at 24 and 60 months and cross-classified to identify persistence and recovery based on the cut-points for classification. We utilized 2 modeling approaches to evaluate factors associated with changes in HAZ, HAD, WAZ, and WAD from 24 to 60 months. First, we modeled the change in each of these four outcomes using linear regression with study site as an indicator variable. Second, we utilized logistic regression to evaluate characteristics associated with recovery from stunting and underweight (among the subset with values below −2 z-scores), and with positive changes in HAD and WAD (among all children) from 24 to 60 months. Based on previous analyses of factors related to growth (24, 31, 32), socioeconomic status (WAMI), child’s sex, maternal height, and the value of HAZ, HAD, WAZ or WAD at 24 months were also included in each base model. We used biologic rationale, data completeness, and stepwise selection (forward and backward improvements to the AIC) to identify other variables for inclusion. A list of the variables that were considered can be found in the supplemental materials (Supplemental Table 1). Models were run in R 3.4.3 (Foundation for Statistical Computing, Vienna, Austria).

Results

Among the 1,635 children enrolled in the six MAL-ED sites included in these analyses, 1,040 (64%) had anthropometry at 0, 24, and 60 months of age, and the sample size decreased to 942 (58%) when we required that the children have at least one observation of key variables found to be associated with growth outcomes at 5 years: transferrin receptor, LMZ, maternal height, WAMI, and dietary intake (Supplemental Fig. 1). Mean HAZ values were −0.9 at enrollment, declined to -1.9 at 24 months and then increased to -1.4 at 60 months (Fig. 1 and Table 1). Children gained, on average, 0.2 to 0.8 HAZ from 24 to 60 months (Table 1). HAD values were similarly highest at enrollment (-1.7 cm), and decreased (Fig. 1); however, rather than improving from 24 to 60 months of age as was observed with HAZ, the deficit worsened by 0.9 to 1.5 cm from 24 to 60 months, except for SAV where the mean HAD was −4.9 cm at 24 months and −4.2 by 60 months.
Table 1
Characteristics of children with anthropometry at 0, 24, and 60 months of age in the MAL-ED study, including height-for-age z-score (HAZ), height-for-age difference (HAD), weight-for-age z-score (WAZ), and weight-for-age difference (WAD). Stunting is defined as HAZ<-2, underweight is defined as WAZ<-2.

<table>
<thead>
<tr>
<th></th>
<th>BGD</th>
<th>INV</th>
<th>NEB</th>
<th>PEL</th>
<th>SAV</th>
<th>TZH</th>
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<td>125</td>
<td>152</td>
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<td>0.8</td>
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<td>(0.1)</td>
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<td>0.6</td>
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<td>(0.5)</td>
<td>(0.4)</td>
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<td>151.2</td>
<td>149.7</td>
<td>150.2</td>
<td>158.9</td>
<td>156.1</td>
<td>152.2</td>
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<tr>
<td>(5.0)</td>
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<td>(4.9)</td>
<td>(5.4)</td>
<td>(6.5)</td>
<td>(5.9)</td>
<td>(6.5)</td>
<td></td>
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<td>Mean energy intake(^3), kcal/d (SD)</td>
<td>504.8</td>
<td>883.8</td>
<td>614.2</td>
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<td>1000.3</td>
<td>1077.4</td>
<td>838.0</td>
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<td>(290.5)</td>
<td>(311.4)</td>
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<td>(360.8)</td>
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<td>16.6</td>
<td>24.4</td>
<td>31.9</td>
<td>29.9</td>
<td>23.3</td>
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<td>(7.1)</td>
<td>(9.0)</td>
<td>(8.3)</td>
<td>(8.2)</td>
<td>(10.6)</td>
<td>(6.0)</td>
<td>(10.5)</td>
<td></td>
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<tr>
<td>Mean transferrin receptor(^4), mg/L (SD)</td>
<td>6.6</td>
<td>4.8</td>
<td>9.1</td>
<td>7.3</td>
<td>4.0</td>
<td>4.5</td>
<td>6.0</td>
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<tr>
<td>(2.8)</td>
<td>(2.9)</td>
<td>(3.5)</td>
<td>(2.0)</td>
<td>(2.0)</td>
<td>(1.9)</td>
<td>(3.1)</td>
<td></td>
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<tr>
<td># stunted at 0 mo (%)</td>
<td>29</td>
<td>31</td>
<td>13</td>
<td>22</td>
<td>15</td>
<td>20</td>
<td>130</td>
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<tr>
<td>(15.6)</td>
<td>(14.7)</td>
<td>(10.4)</td>
<td>(14.5)</td>
<td>(10.6)</td>
<td>(15.7)</td>
<td>(13.8)</td>
<td></td>
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<tr>
<td># stunted at 24 mo (%)</td>
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<td>94</td>
<td>32</td>
<td>61</td>
<td>53</td>
<td>96</td>
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<td>(48.4)</td>
<td>(44.5)</td>
<td>(25.6)</td>
<td>(40.1)</td>
<td>(37.6)</td>
<td>(75.6)</td>
<td>(45.2)</td>
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<td># stunted at 60 mo (%)</td>
<td>59</td>
<td>61</td>
<td>30</td>
<td>28</td>
<td>20</td>
<td>58</td>
<td>256</td>
</tr>
<tr>
<td>(31.7)</td>
<td>(28.9)</td>
<td>(24.0)</td>
<td>(18.4)</td>
<td>(14.2)</td>
<td>(45.7)</td>
<td>(27.2)</td>
<td></td>
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<tr>
<td>Mean HAZ at 0 mo (SD)</td>
<td>-1.0</td>
<td>-1.0</td>
<td>-0.7</td>
<td>-1.0</td>
<td>-0.8</td>
<td>-1.0</td>
<td>-0.9</td>
</tr>
<tr>
<td>(1.0)</td>
<td>(1.0)</td>
<td>(1.0)</td>
<td>(1.0)</td>
<td>(1.0)</td>
<td>(1.2)</td>
<td>(1.0)</td>
<td>(1.0)</td>
</tr>
<tr>
<td>Mean HAZ at 24 mo (SD)</td>
<td>-2.0</td>
<td>-1.9</td>
<td>-1.4</td>
<td>-1.9</td>
<td>-1.7</td>
<td>-2.7</td>
<td>-1.9</td>
</tr>
<tr>
<td>(0.9)</td>
<td>(1.0)</td>
<td>(0.9)</td>
<td>(0.9)</td>
<td>(0.9)</td>
<td>(1.1)</td>
<td>(1.0)</td>
<td>(1.0)</td>
</tr>
<tr>
<td>Mean HAZ at 60 mo (SD)</td>
<td>-1.6</td>
<td>-1.5</td>
<td>-1.2</td>
<td>-1.3</td>
<td>-0.9</td>
<td>-2.0</td>
<td>-1.4</td>
</tr>
<tr>
<td>(0.9)</td>
<td>(0.9)</td>
<td>(0.9)</td>
<td>(0.8)</td>
<td>(1.0)</td>
<td>(0.9)</td>
<td>(0.9)</td>
<td>(0.9)</td>
</tr>
<tr>
<td>Change HAZ 24 to 60 mo (SD)</td>
<td>0.4</td>
<td>0.4</td>
<td>0.2</td>
<td>0.6</td>
<td>0.8</td>
<td>0.7</td>
<td>0.5</td>
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<tr>
<td>(0.5)</td>
<td>(0.5)</td>
<td>(0.4)</td>
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<td>(0.7)</td>
<td>(0.7)</td>
<td>(0.6)</td>
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</tr>
<tr>
<td>Change HAD 24 to 60 mo (cm)</td>
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<td>-1.4</td>
<td>-1.5</td>
<td>-1.0</td>
<td>0.7</td>
<td>-0.9</td>
<td>-1.0</td>
</tr>
<tr>
<td>(2.4)</td>
<td>(2.2)</td>
<td>(2.1)</td>
<td>(2.2)</td>
<td>(3.0)</td>
<td>(2.7)</td>
<td>(2.5)</td>
<td></td>
</tr>
<tr>
<td># underweight at 0 mo (%)</td>
<td>37</td>
<td>47</td>
<td>17</td>
<td>15</td>
<td>9</td>
<td>5</td>
<td>130</td>
</tr>
<tr>
<td>(19.9)</td>
<td>(22.3)</td>
<td>(13.6)</td>
<td>(9.9)</td>
<td>(6.4)</td>
<td>(3.9)</td>
<td>(13.8)</td>
<td></td>
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<tr>
<td># underweight at 24 mo (%)</td>
<td>62</td>
<td>75</td>
<td>17</td>
<td>13</td>
<td>14</td>
<td>21</td>
<td>202</td>
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<tr>
<td>(33.3)</td>
<td>(35.5)</td>
<td>(13.6)</td>
<td>(8.6)</td>
<td>(9.9)</td>
<td>(16.5)</td>
<td>(21.4)</td>
<td></td>
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<tr>
<td># underweight at 60 mo (%)</td>
<td>57</td>
<td>62</td>
<td>14</td>
<td>7</td>
<td>14</td>
<td>30</td>
<td>184</td>
</tr>
<tr>
<td>(30.6)</td>
<td>(29.4)</td>
<td>(11.2)</td>
<td>(4.6)</td>
<td>(9.9)</td>
<td>(23.6)</td>
<td>(19.5)</td>
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</table>
Similarly, mean WAZ values were greater at enrollment at most sites than they were at either 24 or 60 months, with the exception of the PEL site where mean WAZ increased over time, and for the NEB site, where mean WAZ remained approximately constant (Fig. 1, Table 1). Three of the sites had a positive change in WAZ from 24 to 60 months, and all of the sites had a negative change in WAD from 24 to 60 months (-0.1 to -1.6 kg).

Just under half of the children included in this analysis were stunted at 24 or 60 months, except for TZH where the prevalence was 76% at 24 months (Table 2). Approximately a quarter of the children were underweight at 24 or 60 months. Children who were not stunted or underweight at 24 months were unlikely to develop stunting or be underweight at 60 months (Table 2 and Table 3). Forty three percent of those who were stunted at 24 months were no longer stunted at 60 months, and 34% of those who were underweight at 24 months were no longer underweight at 60 months.
Table 2
Summary of transitions between stunted and non-stunted status, and underweight and non-underweight status at 24 and 60 months in the cohorts, by site. Stunting is defined as height-for-age z-score (HAZ) <-2, underweight is defined as weight-for-age z-score (WAZ) <-2.

<table>
<thead>
<tr>
<th>Site</th>
<th>Not stunted at 24 or 60 mo (%)</th>
<th>Not stunted at 24, not stunted at 60 mo (%)</th>
<th>Stunted at 24, not stunted at 60 mo (%)</th>
<th>Stunted at both 24 and 60 mo (%)</th>
<th>Not underweight at 24 or 60 mo (%)</th>
<th>Not underweight at 24, underweight at 60 mo (%)</th>
<th>Underweight at 24, not underweight at 60 mo (%)</th>
<th>Underweight at both 24 and 60 mo (%)</th>
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<tbody>
<tr>
<td>BGD</td>
<td>94 (50)</td>
<td>2 (1)</td>
<td>33 (18)</td>
<td>57 (31)</td>
<td>110 (59)</td>
<td>14 (8)</td>
<td>19 (10)</td>
<td>43 (23)</td>
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<tr>
<td>INV</td>
<td>113 (54)</td>
<td>4 (2)</td>
<td>37 (18)</td>
<td>57 (27)</td>
<td>128 (61)</td>
<td>8 (4)</td>
<td>21 (10)</td>
<td>54 (26)</td>
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<tr>
<td>NEB</td>
<td>89 (71)</td>
<td>4 (3)</td>
<td>6 (5)</td>
<td>26 (21)</td>
<td>104 (83)</td>
<td>4 (3)</td>
<td>7 (6)</td>
<td>10 (8)</td>
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<td>PEL</td>
<td>89 (59)</td>
<td>2 (1)</td>
<td>35 (23)</td>
<td>26 (17)</td>
<td>139 (91)</td>
<td>0 (0)</td>
<td>6 (4)</td>
<td>7 (5)</td>
</tr>
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<td>SAV</td>
<td>87 (62)</td>
<td>1 (1)</td>
<td>34 (24)</td>
<td>19 (14)</td>
<td>121 (86)</td>
<td>6 (4)</td>
<td>6 (4)</td>
<td>8 (6)</td>
</tr>
<tr>
<td>TZH</td>
<td>29 (23)</td>
<td>2 (2)</td>
<td>40 (32)</td>
<td>56 (44)</td>
<td>87 (68)</td>
<td>19 (15)</td>
<td>10 (8)</td>
<td>11 (9)</td>
</tr>
<tr>
<td>All</td>
<td>501 (53)</td>
<td>15 (2)</td>
<td>185 (20)</td>
<td>241 (26)</td>
<td>689 (73)</td>
<td>51 (5)</td>
<td>69 (7)</td>
<td>133 (14)</td>
</tr>
</tbody>
</table>

Table 3
Number (%) of children with positive changes in growth (linear and ponderal), defined as positive change in height-for-age z-score (HAZ) / weight-for-age z-score (WAZ), height-for-age difference (HAD) / weight-for-age difference (WAD), and recovery from stunting (HAZ<-2) / underweight (WAZ<-2). Change in values was calculated as the value at 60 months minus the value at 24 months of age.

<table>
<thead>
<tr>
<th>Site</th>
<th>Positive change in HAZ (%)</th>
<th>Positive change in HAD (%)</th>
<th>Recovery from stunting (%)</th>
<th>Positive change in WAZ (%)</th>
<th>Positive change in WAD (%)</th>
<th>Recovery from underweight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BGD</td>
<td>152 (82)</td>
<td>49 (26)</td>
<td>33/90 (37)</td>
<td>98 (53)</td>
<td>20 (11)</td>
<td>19/62 (31)</td>
</tr>
<tr>
<td>INV</td>
<td>161 (76)</td>
<td>52 (25)</td>
<td>37/94 (39)</td>
<td>117 (56)</td>
<td>20 (10)</td>
<td>21/75 (28)</td>
</tr>
<tr>
<td>NEB</td>
<td>80 (64)</td>
<td>31 (25)</td>
<td>6/32 (19)</td>
<td>57 (46)</td>
<td>20 (16)</td>
<td>7/17 (41)</td>
</tr>
<tr>
<td>PEL</td>
<td>129 (85)</td>
<td>47 (31)</td>
<td>35/61 (57)</td>
<td>97 (64)</td>
<td>58 (38)</td>
<td>6/13 (46)</td>
</tr>
<tr>
<td>SAV</td>
<td>124 (88)</td>
<td>84 (60)</td>
<td>34/53 (64)</td>
<td>55 (39)</td>
<td>35 (25)</td>
<td>6/14 (43)</td>
</tr>
<tr>
<td>TZH</td>
<td>117 (92)</td>
<td>45 (35)</td>
<td>40/96 (42)</td>
<td>45 (35)</td>
<td>13 (10)</td>
<td>10/21 (48)</td>
</tr>
<tr>
<td>ALL</td>
<td>763 (81)</td>
<td>308 (33)</td>
<td>185/426 (43)</td>
<td>469 (50)</td>
<td>166 (18)</td>
<td>69/202 (34)</td>
</tr>
</tbody>
</table>

Shown in Fig. 2 are the patterns of mean HAZ and HAD amongst those who were never stunted, those who remained stunted and those who recovered from stunting. A figure capturing these same relationships for WAZ/WAD is also shown. Among those who were stunted / underweight throughout, the mean HAD / WAD continued to decrease until nearly 5 years of age for those who remained stunted / underweight, but flattened out at around 24 months of age for those who were no longer stunted / underweight at 5 years of age. Changes in HAZ and HAD between 24 and 60 months were highly correlated (r = 0.80), as were differences in WAZ and WAD (r = 0.77) (Fig. 3).
The percentage of children with improvement in linear growth differed depending on the definition used. Between 64–92% of children had a positive change in their HAZ from 24 to 60 months, whereas far fewer (33% overall) had a positive change in their HAD (Table 3). In general, positive changes in WAZ and WAD were less common than for HAZ and HAD.

Multivariable linear regression models indicate that HAZ or HAD at 24 months, child’s sex, maternal height, and mean LMZ were associated with change in HAZ and HAD from 24 to 60 months in multivariable linear regression models (Table 4). The relationship between size at 24 months and change in HAZ was negative, indicating that children with higher HAZ at 24 months had more negative changes in their HAZ from 24 to 60 months; however, the opposite was true for HAD. Higher HAD (i.e., height values that were closer to or greater than the WHO median height for a child of that age and sex) at 24 months was associated with a more positive change in HAD from 24 to 60 months. Greater average LMZ, a marker of intestinal permeability, was associated with a negative change in both HAZ and HAD from 24 to 60 months. Results were similar, although not always statistically significant for the logistic regression models considering positive changes in HAZ or HAD as the outcome variable (Table 5). Only HAZ at 24 months was statistically significantly associated with recovery from stunting.

### Table 4

<table>
<thead>
<tr>
<th>Δ 24 to 60mo (n = 942)</th>
<th>ΔHAZ</th>
<th>ΔHAD</th>
<th>ΔWAZ</th>
<th>ΔWAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAZ at 24 mo</td>
<td>-0.25 (0.02)***</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAD at 24 mo</td>
<td></td>
<td>0.12 (0.03)***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WAZ at 24 mo</td>
<td></td>
<td></td>
<td>-0.26 (0.02)***</td>
<td></td>
</tr>
<tr>
<td>WAD at 24 mo</td>
<td></td>
<td></td>
<td></td>
<td>0.33 (0.04)***</td>
</tr>
<tr>
<td>WAMI (SES score) 3-5y (10% increase)</td>
<td>0.01 (0.01)</td>
<td>0.03 (0.06)</td>
<td>0.04 (0.02)*</td>
<td>0.09 (0.04)*</td>
</tr>
<tr>
<td>Boys 0, Girls 1</td>
<td>-0.21 (0.03)***</td>
<td>-0.75 (0.16)***</td>
<td>-0.16 (0.04)***</td>
<td>-0.48 (0.09)***</td>
</tr>
<tr>
<td>Maternal height (per 10 cm)</td>
<td>0.09 (0.03)**</td>
<td>0.45 (0.15)**</td>
<td>0.10 (0.04)*</td>
<td>0.22 (0.09)*</td>
</tr>
<tr>
<td>Mean Lactulose:Mannitol z-score</td>
<td>-0.10 (0.03)***</td>
<td>-0.47 (0.13)***</td>
<td>-0.13 (0.03)***</td>
<td>-0.28 (0.08)***</td>
</tr>
<tr>
<td>Mean energy intake 9−24 mo</td>
<td>0.01 (0.02)</td>
<td>0.07 (0.08)</td>
<td>-0.02 (0.02)</td>
<td>-0.02 (0.05)</td>
</tr>
<tr>
<td>Protein density 9−24 mo</td>
<td>-0.01 (0.02)</td>
<td>-0.03 (0.08)</td>
<td>-0.05 (0.02)*</td>
<td>-0.11 (0.05)*</td>
</tr>
<tr>
<td>Mean transferrin receptor, inflammation adjusted(30)</td>
<td>0.00 (0.01)</td>
<td>0.01 (0.03)</td>
<td>0.02 (0.01)*</td>
<td>0.04 (0.02)*</td>
</tr>
</tbody>
</table>

*** p < 0.001, ** p < 0.01, * p < 0.05
Logistic regression with the outcomes of positive change in height-for-age z-score (HAZ), positive change in height-for-age difference (HAD), recovery from stunting, positive change in weight-for-age z-score (WAZ), and positive change in weight-for-age difference (WAD) change between 24 and 60 months as a function of anthropometry at 24 months and other child and household factors in six sites from the MAL-ED study (BGD, INV, NEB, PEL, SAV, TZH).

<table>
<thead>
<tr>
<th></th>
<th>Positive change in HAZ (n = 942)</th>
<th>Positive change in HAD (n = 942)</th>
<th>Recovery from stunting (n = 426)</th>
<th>Positive change in WAZ (n = 942)</th>
<th>Positive change in WAD (n = 942)</th>
<th>Recovery from underweight (n = 202)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAZ at 24 mo</td>
<td>-0.83 (0.12)**</td>
<td>2.55 (0.31)**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAD at 24 mo</td>
<td>0.11 (0.03)**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WAZ at 24 mo</td>
<td></td>
<td>-0.86 (0.09)**</td>
<td></td>
<td>3.11 (0.59)**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WAD at 24 mo</td>
<td></td>
<td></td>
<td>0.58 (0.09)**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WAMI (SES score) 3-5y (10% increase)</td>
<td>0.00 (0.07)</td>
<td>0.01 (0.06)</td>
<td>0.15 (0.10)</td>
<td>0.06 (0.06)</td>
<td>0.09 (0.08)</td>
<td>-0.07 (0.15)</td>
</tr>
<tr>
<td>Boys 0, Girls 1</td>
<td>-0.90 (0.19)**</td>
<td>-0.63 (0.15)**</td>
<td>-0.43 (0.25)</td>
<td>-0.50 (0.15)**</td>
<td>-0.69 (0.19)**</td>
<td>-1.13 (0.39)**</td>
</tr>
<tr>
<td>Maternal height (per 10 cm)</td>
<td>0.31 (0.18)</td>
<td>0.31 (0.14)*</td>
<td>0.37 (0.24)</td>
<td>0.36 (0.14)**</td>
<td>0.04 (0.17)</td>
<td>0.34 (0.37)</td>
</tr>
<tr>
<td>Mean Lactulose:Mannitol z-score</td>
<td>-0.43 (0.16)**</td>
<td>-0.25 (0.12)*</td>
<td>-0.14 (0.22)</td>
<td>-0.32 (0.12)**</td>
<td>-0.40 (0.16)*</td>
<td>-1.43 (0.40)**</td>
</tr>
<tr>
<td>Mean energy intake 9–24 mo</td>
<td>0.03 (0.10)</td>
<td>0.07 (0.08)</td>
<td>0.21 (0.13)</td>
<td>-0.08 (0.07)</td>
<td>0.05 (0.10)</td>
<td>0.00 (0.21)</td>
</tr>
<tr>
<td>Protein density 9–24 mo</td>
<td>-0.08 (0.09)</td>
<td>-0.01 (0.07)</td>
<td>0.02 (0.12)</td>
<td>-0.13 (0.07)</td>
<td>-0.13 (0.09)</td>
<td>-0.19 (0.19)</td>
</tr>
<tr>
<td>Mean transferrin receptor</td>
<td>0.00 (0.03)</td>
<td>0.01 (0.03)</td>
<td>-0.00 (0.05)</td>
<td>0.01 (0.03)</td>
<td>0.04 (0.04)</td>
<td>0.08 (0.06)</td>
</tr>
</tbody>
</table>

Similarly, changes in WAZ and WAD from 24 to 60 months were associated with WAZ and WAD at 24 months, child's sex, maternal height and LMZ (Table 4). In addition, higher mean TfR in the first two years of life was associated with more positive changes in WAZ and WAD, whereas the average protein density from complementary foods was negatively associated with changes in WAZ and WAD from 24 to 60 months. WAMI (socioeconomic status) was positively associated with changes in WAZ and WAD, but when the binary outcomes were considered (positive change in WAZ or WAD, recovery from underweight), the associations with WAMI were not statistically significant (Table 5). Similar to the linear regression findings, higher LMZ were associated with lower odds of a positive change in WAZ, WAD, and underweight status and taller mothers were more likely to have children with more positive changes in WAZ, but protein density of the diet and TfR status were not statistically significantly associated with the binary weight outcomes.
Discussion

Populations with a high prevalence of stunting tend to have height distributions that are negatively shifted, rather than skewed, compared with the standard WHO distribution. This suggests that the entire population, rather than a subset, is not growing to their potential (33). In these data, from 24 to 60 months of age, the distribution of HAZ shifted to the right, indicating a positive shift in height, and in some cases, recovery from stunting. However, as has been demonstrated in other studies (16, 18), the HAD distribution shifted to the left from 24 to 60 months of age, indicating that children had greater absolute height deficits at 60 months than they had at 24 months when compared with the WHO reference median. For weight, the distribution of WAZ at 24 and 60 months was very similar, whereas the WAD distribution shifted more to the left from 24 to 60 months, indicating greater weight deficits at 60 months.

As discussed earlier, the apparent contradiction between relative and absolute height and weight deficits stems from the increasing variance of the cross-sectional WHO z-score calculations. Leroy et al. (16) have suggested that HAD is a more meaningful way to measure catch-up growth in a population, whereas Victora et al. (34) argued that changes in HAZ and HAD are both meaningful ways to express changes in linear growth in children, and that they give complementary information. Here we have shown that in low-income settings, children who show positive changes in HAD are a subset of those who show positive changes in HAZ, and are more likely to be those with greater positive changes in HAZ. This is also true for WAZ and WAD, except that positive changes in WAD are much less likely to be observed, and unlike for height, many children who were not underweight at 24 months are found to be underweight at 60 month. Because of the overall high correlation between the changes in the indicators from 24 to 60 (as shown in Fig. 3) it is not surprising that during analyses, we did not identify factors in early life that distinguish between these two types of changes over time. Given the similarity of the factors associated with change in HAZ and HAD from 24 to 60 months that we identified (child sex, maternal height, and LMZ), and with the binary outcomes of positive change in HAZ or HAD (child sex and LMZ), it is likely that these changes, using either metric, reflect the same underlying process, and both are informative to assess changes over time in the growth of children.

Recently, we published analyses of factors in early childhood that influence anthropometric status at 60 months(24). Here we extend those findings by evaluating factors associated with catch-up growth from 24 to 60 months. Maternal height was positively and mean LMZ was negatively associated with HAZ at 60 months, and here were also associated with change in HAZ and HAD from 24 to 60 months. Further, mean LMZ (from multiple assessments between 3 and 15 months) was associated with decreased likelihood of a positive change in HAZ or HAD. Some variables that were associated with HAZ at 60 months that were not retained in the final change in HAZ/HAD models included bacterial detection rates in stools, mean plasma ferritin concentrations, and mean stool concentrations of alpha-1-antitrypsin. These were not included here based on the initial semi-univariate results that did not show associations with the outcomes (see Supplemental Table 1). Of note, the mean WAMI between 6 to 24 months was positively associated with HAZ at 60 months, but the mean WAMI between 36 and 60 months was not associated with changes in HAZ/HAD, after adjusting for HAZ/HAD at 24 months. In terms of our prior findings with respect to WAZ at 60 months, both mean WAMI and mean TfR concentration (assessed at 7, 15 and 24 months) were associated with change in WAZ/WAD in the current analyses.

The longitudinal data collected during MAL-ED allow for detailed analysis of growth in early childhood across six sites with high rates of stunting. The extensive data on risk factors collected during the study allow for evaluation of risk factors for growth across different categories, measured in a common way across the sites. However, there are
community-level factors that likely affect all of the children at a site, as well as other unmeasured risk factors, and those contribute to the unexplained variance of our models. In addition, the gaps in funding for the follow up study led to inconsistencies in data collection across sites depending on whether sites could maintain field activities during the gap period. Thus, our analyses necessarily focus on factors assessed during the first 2 years of life, and it may be that longitudinal data sets with more extensive data from 24 to 60 months may be able to identify factors which allow for positive changes in HAD amongst those with positive changes in HAZ over time.

Conclusions

In six MAL-ED sites, almost half (43%) of the children who were stunted at 24 months of age were no longer stunted at 60 months of age, indicating some degree of recovery in linear growth from two to five years of age, and very few children developed stunting after 24 months of age. Most of the children demonstrated some improvement in HAZ, and except for SAV, only about 30% had improvement in HAD. Fewer children had a positive change in WAZ, and most of the children with a positive WAD were in the sites in Peru and South Africa. Given the high correlation and the similarity in factors associated with changes in z-scores or absolute difference, we conclude that both approaches can be used to understand catch-up growth during the preschool years.

List Of Abbreviations

BRF: Fortaleza, Brazil
HAD: height-for-age difference
HAZ: height-for-age z-score
INV: Vellore, India
LAZ: length-for-age z-score
LMZ: lactulose:mannitol z-score
NEB: Bhaktapur, Nepal
PEL: Loreto, Peru
PKN: Naushero Feroze, Pakistan
SAV: Venda, South Africa
TfR: transferrin receptor
TZH: Haydom, Tanzania
WAMI: Water, Assets, Maternal education, and household Income
WAD: weight-for-age difference
WAZ: weight-for-age z-score
Declarations

Ethics approval and consent to participate

Ethical approval was obtained from each of the collaborating institutions as appropriate. These were: Institutional Review Board, Johns Hopkins University; PRISMA Ethics Committee; Health Ministry, Loreto (Peru); Health, Safety and Research Ethics Committee, University of Venda; Department of Health and Social Development, Limpopo Provincial Government (South Africa); Medical Research Coordinating Committee, National Institute for Medical Research; Chief Medical Officer, Ministry of Health and Social Welfare (Tanzania); Ethical Review Committee, ICDDR, B; (Bangladesh); Institutional Review Board, Christian Medical College, Vellore; Health Ministry Screening Committee, Indian Council of Medical Research (India); Institutional Review Board, Institute of Medicine, Tribhuvan University; Ethical Review Board, Nepal Health Research Council; Institutional Review Board, Walter Reed Army Institute of Research (Nepal). Informed written consent was obtained from the parent or legal guardian of each participating child enrolled in the original study and for the follow-up study.

Consent for publication

Not applicable

Availability of data and materials

The datasets analyzed during the current study are available on the ClinEpiDB platform (https://clinepidb.org).

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

SAR, BJJM, LEMK, and LEC designed the research, contributed to the analysis and interpretation of results, and wrote the manuscript. SAR performed the statistical analysis. TA, GK, EM, ES, MNK, SKS, and PB conducted the research. SAR and LEC have primary responsibility for final content, and all authors reviewed the manuscript. A full listing of all MAL-ED Network Investigators is provided at the end of the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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**Figures**
Figure 1

Distributions of height-for-age z-scores (HAZ), weight-for-age z-scores (WAZ, and weight-for-height z-scores (WHZ) at 0, 24 and 60 months in the MAL-ED cohort study sites.
Figure 2

Average z-score (left y-axis, dashed line) and height/weight-for-age difference (right y-axis, solid line) by month of age, among children who were stunted / underweight at 24 and 60 months (red), >-2 at 24 months and <-2 at 60 months (orange), stunted / underweight at 24 months and not stunted / underweight at 60 months (blue), and not stunted / underweight at either 24 or 60 months (green).

Figure 3

Difference in height/weight-for-age z-scores and height/weight-for-age centimeters/kilograms between 24 and 60 months of age at six MAL-ED cohort study sites.

Supplementary Files
This is a list of supplementary files associated with this preprint. Click to download.

- SuppMaterials.pdf