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Children with Poor Linear Growth Are at Risk for Repeated Relapse to Wasting after Recovery from Moderate Acute Malnutrition

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Abstract

Background: Nutrition programs frequently approach wasting and stunting as 2 separate conditions with distinct causes and effects. Although several cross-sectional studies have identified an association between the 2 conditions, longitudinal studies are useful to quantify the risk of acute malnutrition based on the trajectory of linear growth.

Objective: We analyzed data from a longitudinal study to explore associations between linear growth and relapse to acute malnutrition in high-risk children during the year after recovery from moderate acute malnutrition (MAM).

Methods: This was a secondary data analysis from a cluster randomized trial involving 1487 Malawian children 6–62 mo old treated for MAM and enrolled upon recovery. Children were followed for 1 y, during which data were collected on anthropometric progress, symptoms of illness, and household food security. Multivariate fixed-effects logistic regression was used to identify associations between linear growth and relapse to acute malnutrition.

Results: Children who have recovered from MAM proved to be a high-risk population, with nearly half experiencing a decrease in height-for-age *z* score (HAZ) for 12 mo. Children whose HAZ was declining were more likely to relapse to MAM or SAM than were those whose linear growth rate maintained or increased their HAZ ($P < 0.001$). Mean changes of +0.15, −0.03, −0.17, and −0.53 in HAZ were observed for those who sustained recovery, relapsed to MAM once, relapsed to MAM multiple times, and developed SAM, respectively.

Conclusions: Our results add to the body of evidence suggesting that acute wasting is a harbinger of subsequent stunting. Children who experience poor linear growth after MAM are more likely to experience relapse. Given this bidirectional relation between wasting and stunting, supplementary feeding programs should consider both when designing protocols, aiming to optimize linear growth and achieve acute weight gain, as a means of reducing relapse. This trial was registered at clinicaltrials.gov as NCT02351687. *J Nutr* 2018;148:974–979.

Keywords: moderate wasting, supplemental feeding program, relapse, stunting, ready-to-use supplementary food

Introduction

Wasting and stunting in children under 5 y of age are frequently considered as 2 separate conditions with distinct causes, effects, and treatment outcomes (1, 2). Wasting, or acute malnutrition, defined as having a weight-for-height *z* score <−2 SD or a midupper-arm circumference (MUAC) of <12.5 cm (3), is a form of malnutrition characterized by rapid short-term weight loss. Stunting, a condition whereby poor linear growth over time leads an individual to have a height-for-age *z* score (HAZ) <−2 SD, is an indicator of chronic malnutrition. Acute and chronic malnutrition are often considered as contributing separately to poor child health outcomes (1, 2), with chronic malnutrition having negative implications for adult health and human capital, and acute malnutrition being associated with a more immediate risk of mortality. In emergency settings, operational agencies often screen children for wasting to identify those in need of immediate assistance; yet, children who are severely stunted have a mortality risk similar to that of moderate wasting (4, 5).

Despite different operational approaches, epidemiologic evidence has consistently demonstrated an association between the 2 forms of malnutrition with common causes and effects (6, 7). Causal factors typically attributed to wasting, such as seasonal food insecurity, repeated episodes of acute infection, and

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intrauterine growth retardation, are also risk factors for stunting (8). Thus, the descriptions "chronic" and "acute" are often an incomplete portrayal of the 2 forms of malnutrition (9). For example, "acute" malnutrition can persist for long periods of time, including periods longer than 7 mo, if untreated (10, 11). Even with effective treatment, many children will relapse repeatedly back to acute malnutrition after initial recovery (12, 13). Similarly, stunting, rather than being a condition that only slowly develops over time, can be exacerbated after an acute stressor (14–16); likewise, rapid catch-up growth, such as gaining height at 2–3 times the normal rate, is possible in young children (17, 18).

Poor linear growth both during and after an episode of acute malnutrition is common. Children with wasting between 6 and 17 mo are at an elevated risk for stunting between 18 and 24 mo of age (19). Poor linear growth and short stature are consistently seen when children are followed systematically during and after recovery from both moderate acute malnutrition (MAM) and severe acute malnutrition (SAM) (12, 20–23). This synergy between acute and chronic malnutrition was also demonstrated in an analysis using cross-sectional data which showed that children who are simultaneously wasted and stunted are at a higher risk for mortality than those with either condition alone (24).

Although much evidence relating wasting and stunting exists in the form of cross-sectional data, longitudinal data may provide more accurate and powerful information relating the development of acute malnutrition to the trajectory of linear growth. Furthermore, it remains unclear if linear growth after an episode of acute malnutrition is associated with subsequent relapses to wasting. Consistent poor linear growth and persistent stunting across a few studies that followed children after recovery from acute malnutrition led authors to hypothesize that children who experienced growth faltering may be at higher risk for subsequent relapse (20–23). Identifying such predictors of relapse would help program implementers better identify children who are likely to experience multiple anthropometric deficits and high risk of mortality (24). In this study, we analyze data from a longitudinal study in Malawi to test the hypothesis that there is an association between linear growth and repeated episodes of acute malnutrition in high-risk children, specifically those that have just recovered from an episode of MAM.

Methods

Study design. This was a secondary analysis of data obtained in the course of a prospective, cluster-randomized, controlled clinical effectiveness trial to assess the effectiveness of a package of health and nutrition services on post-recovery outcomes after treatment for MAM at a supplementary feeding program (SFP). Full methods have been described in detail previously (13).

Briefly, the research took place across 5 districts in southern Malawi among populations of subsistence farmers. Children aged 6–62 mo who were discharged from an SFP as recovered from MAM with an MUAC ≥12.5 cm and no bipedal edema (25) were recruited from 21 health clinics between April 2014 and June 2015. After recovery from MAM, caregivers were asked to bring their child back to the health clinic for reassessment visits at 1, 3, 6, and 12 mo after discharge from SFP and monthly during the rainy season (December to February). Caregivers were also encouraged to bring their child at any point during the 12-mo follow-up period if they were concerned about their child's nutritional status. At each of these visits, weight, length, and MUAC were measured. Kwashiorkor was diagnosed by examining for bilateral pitting edema. If children were identified as being malnourished at any point during the follow-up period, they received appropriate nutritional therapy according to the Malawian national guidelines. In the original study, during the follow-up period, each child was classified as having "sustained recovery", defined as having MUAC ≥12.5 cm without edema at every follow-up visit for 12 mo; "relapsed to MAM", defined as MUAC of 11.5–12.4 cm at any point during the follow-up period; "developed SAM", defined as MUAC <11.5 cm and/or bipedal edema (kwashiorkor) at any point during the follow-up period; "died"; or "lost to follow-up".

Only those who completed the full 12-mo follow-up period (including all scheduled follow-up visits) were included in this secondary data analysis, as anthropometric measurements could not be collected among children who died or were lost to follow-up and our main dependent variable of interest—change in HAZ—required such data. After excluding these children, data remained from 1368 children for final analysis. Given this total sample size and adjusting for clustering at the clinic level (intraclass correlation coefficient factor of 0.006), power was calculated retrospectively to be 83% with a significance level of 0.05 to detect an effect size of 10 percentage points in the main binary outcome variable regarding whether or not children experienced relapse. An effect size of 10 percentage points was chosen to be consistent with that of the original longitudinal study from which these data derived (13).

Statistical analyses. All statistical analyses were carried out using Stata Version 13.0 (StataCorp LP, College Station, TX). Anthropometric indexes were based on the WHO's 2006 Child Growth Standards (26), calculated using the WHO Anthro software (WHO, Geneva, Switzerland). Chi-squared and Student's *t* tests were used to test for differences in proportions and continuous variables, respectively, whereas ANOVA tests were used for categorical variables.

To take advantage of the longitudinal nature of the data (i.e., following the same children over 5 time points), a multivariate fixed-effects logistic regression model with cluster-robust SEs was developed to assess associations between linear growth rate, defined by change in HAZ, and relapse to acute malnutrition. This approach specifically captures change within the child over time by holding the average observed and unobserved time-invariant characteristics of each child constant and therefore removing omitted variable bias.

The binary outcome variable was whether the child relapsed to acute malnutrition (defined as relapsed to MAM or developed SAM) or sustained recovery (defined as maintaining an MUAC ≥12.5 cm from discharge to that follow-up visit) at each time point throughout the study. The main independent variable included in the model was poor linear growth rate, defined as experiencing negative monthly change in HAZ. This was calculated by dividing the absolute difference in HAZ from the prior visit to the current visit, divided by the number of months between visits. Other covariates included age; whether or not the child was moderately stunted (HAZ ≥−3 and <−2); whether or not the child was severely stunted (HAZ <−3); whether or not the child had fever in the 2 wk prior to the visit; whether or not the child had diarrhea in the 2 wk prior to the visit; degree of household food insecurity (as measured by the Household Food Insecurity Access Scale) (27); and whether or not the visit occurred during the rainy/lean season (defined as December to May). *P* values <0.05 were considered statistically significant.

Ethical oversight. The study was approved by the University of Malawi's College of Medicine Research and Ethics Committee, Washington University's Human Research Protection Office, and Tufts University's Institutional Review Board. Permission to conduct the study

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Abbreviations used: HAZ, height-for-age *z* score; MAM, moderate acute malnutrition; MUAC, midupper arm circumference; SAM, severe acute malnutrition; SFP, supplementary feeding program.

TABLE 1 Characteristics of 1368 children aged 6–62 mo at the time of discharge from SFP and enrolled in the study[1]

Characteristic	($n = 1368$)
Female, *n* (%)	839 (62)
Age, mo	17.6 ± 9.1
6–11, *n* (%)	455 (33)
12–17, *n* (%)	406 (30)
18–23, *n* (%)	211 (15)
24–35, *n* (%)	230 (17)
36–59, *n* (%)	66 (5)
Type of treatment food, *n* (%)	
Whey RUSF	230 (17)
Soy RUSF	266 (19)
RUTF	871 (64)
Household food security, *n* (%)	
Food secure	149 (11)
Mild food insecurity	46 (4)
Moderate food insecurity	203 (15)
Severe food insecurity	933 (70)
Upon discharge from SFP	
MUAC, cm	12.8 ± 0.3
WHZ	−0.9 ± 0.7
HAZ	−2.7 ± 1.2
Length, cm	72.1 ± 6.8
Weight, kg	7.8 ± 1.3
Days to recovery	31.8 ± 20.7

[1] Values are means ± SDs unless otherwise indicated. HAZ, height-for-age *z* score; MUAC, midupper arm circumference; RUSF, ready-to-use supplementary food; RUTF, ready-to-use therapeutic food; SFP, supplementary feeding program; WHZ, weight-for-height *z* score.

was obtained by each site's District Health Officer and/or District Nutritionist.

Results

Children were enrolled in the study after treatment for MAM and subsequent discharge from an SFP from April 2014 to June 2015. Full results regarding the effectiveness of the intervention and detailed relapse rates are presented elsewhere (13). Characteristics of children included in the final analysis are described in Table 1.

Forty-five percent of the children experienced a decrease in HAZ from the time of SFP discharge to the end of the 12-mo follow-up period. The proportion of children who experienced this decline was highest among those who experienced the worst outcomes with respect to acute malnutrition: 36% among those who sustained recovery, compared with 44% of those who relapsed to MAM once, 58% of those who relapsed to MAM multiple times, and 67% of those who developed SAM ($P < 0.001$) (Table 2). The proportion of severely stunted children (HAZ <−3) was also higher among those with the poorer outcomes ($P = 0.004$), whereas those who were moderately stunted did not vary with respect to their acute malnutrition outcomes (Table 2). The mean change in HAZ across outcomes was +0.16, −0.03, −0.16, and −0.53 for those who sustained recovery, relapsed to MAM once, relapsed to MAM multiple times, and developed SAM, respectively ($P < 0.001$) (Figure 1). The differences in HAZ change between groups were statistically significant for all pairwise comparisons. No statistically significant differences in HAZ change were observed at any of the follow-up points between children who received ready-to-use therapeutic food compared with a ready-to-use supplementary food during treatment.

When controlling for other factors in a multivariable fixed-effects logistic regression model, children who had a negative change in HAZ were more likely to experience a relapse to MAM or SAM (OR = 1.72 ± 0.20, $P < 0.001$) (Table 3). Whether the child was moderately stunted at the time of the follow-up visit was not found to be associated with relapse ($P = 0.374$), yet being severely stunted had a marginally significant association with relapse ($P = 0.080$). Other significant associations with relapse included younger age ($P = 0.031$), having fever ($P < 0.001$) or diarrhea ($P < 0.001$), and seasonality (i.e., having the visit occur during the rainy or lean season) ($P < 0.001$). Household food security at the time of the follow-up visit was not associated with relapse.

Discussion

In this secondary analysis of data from a cluster-randomized controlled trial following children for 1 y after successful treatment for MAM, we found a strong statistical association between poor linear growth and relapse to acute malnutrition. The association between poor linear growth (or negative change in HAZ) and relapse to acute malnutrition was seen across all age groups and types of relapses, with the worst linear growth rates associated with multiple and more severe relapses, whereas those with better linear growth were more likely to sustain recovery. Our results may indicate a direct causal relation between wasting and stunting; however, the exact direction and mechanisms are still unclear. These data add to the body of evidence hypothesizing that acute wasting may be a harbinger of subsequent stunting; conversely, children recovering from MAM may be suffering from a process of stunting that is in turn largely predictive of a subsequent relapse.

Nonetheless, these findings strengthen the evidence that links poor linear growth with acute malnutrition, which has been questioned in some corners (7). Particularly, our results support other studies that demonstrate poor linear growth and short stature in children after recovery from MAM and SAM. We have shown previously that higher HAZ upon admission to MAM treatment was associated with greater likelihood of sustained recovery for 12 mo; conversely, a lower HAZ was predictive of developing SAM and death during the follow-up period (12). Although our current study did not find stunting or change in HAZ *during* MAM treatment to be associated with relapse (13), the time spent in SFPs can be quite short (as few as 2–4 wk), and thus, too brief a period for differences in linear growth to be captured.

Evidence indicates that linear growth can improve in response to treatment for acute malnutrition (28, 29). Some improvement occurs during initial treatment (28) and some may also occur only after children reach a certain weight gain threshold (29). Still, a more recent study that followed children with SAM observed no such catch-up growth after recovery (22), and our results show only 55% of children experiencing a positive change in HAZ after MAM recovery. This brings into question what other factors may be influencing how and when linear growth can improve after recovery from acute malnutrition. Overall, the trajectory of linear growth seems to be interrupted by the process of becoming wasted and possibly the recovery from wasting.

Although causal pathways explaining the association between wasting and poor linear growth are unknown, one

TABLE 2 Length, stunting, and linear growth among children who sustained recovery, relapsed to MAM once, relapsed to MAM multiple times, and relapsed to SAM during a year-long follow-up period after recovery from MAM[1]

Anthropometric measurement	Sustained recovery ($n = 754$)	Relapsed to MAM once ($n = 324$)	Relapsed to MAM multiple times ($n = 217$)	Relapsed to SAM ($n = 73$)
Length, cm***	81.98 ± 5.93	80.38 ± 5.73	79.37 ± 5.16	77.81 ± 5.03
Change in length, cm***	9.15 ± 2.34	8.99 ± 2.20	8.67 ± 2.04	7.31 ± 3.06
HAZ***	−2.59 ± 1.06	−2.69 ± 0.96	−2.86 ± 1.00	−3.37 ± 1.11
Stunted (HAZ <−2)*	540 (72)	222 (69)	169 (78)	60 (82)
Moderately stunted (HAZ ≥−3 and <−2)	285 (38)	103 (32)	73 (34)	22 (30)
Severely stunted (HAZ <−3)**	255 (34)	119 (37)	96 (44)	38 (52)
Change in HAZ***	0.16 ± 0.62	−0.03 ± 0.64	−0.16 ± 0.56	−0.53 ± 0.93
Growth faltering (negative change in HAZ)***	268 (36)	143 (44)	126 (58)	49 (67)

[1]Values are means ± SDs or *n* (%). *$P < 0.05$, **$P < 0.005$, and ***$P < 0.001$. HAZ, height-for-age *z* score; MAM, moderate acute malnutrition; SAM, severe acute malnutrition.

hypothesis is that wasting interrupts proper linear growth due to the role that fat stores play in regulating bone growth through the hormone leptin. Fat tissues produce leptin, which triggers linear growth by stimulating: *1*) appropriate energy balance, *2*) the production and secretion of growth hormones from the hypothalamus, and *3*) proper endochondral ossification at the growth plates (30). One small study followed 30 children for 6 mo after treatment for MAM and found that catch-up growth was only observed in children with an increase in leptin concentrations (31). Larger trials are needed to verify these early findings. Also, stunted children often have an insufficient intake of essential amino acids (32). A deficiency in amino acid intake leading up to and during an episode of acute malnutrition may lead to poor linear growth through the inactivation of the mammalian target of rapamycin complex 1 pathway, which regulates the growth of bone, skeletal muscle, and whole-body energy balance (33). Future studies assessing the impact of improved amino acid intake on linear growth are warranted.

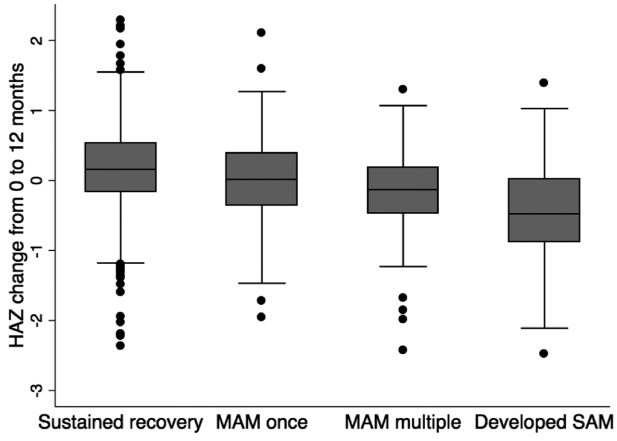

FIGURE 1 Change in HAZ in children from 0 to 12 mo after initial recovery from MAM. Shaded boxes represent medians (IQRs), with the middle line at median value and top and bottom lines at 75th and 25th percentiles, respectively. Whiskers represent the minimum and maximum, with points beyond representing outliers (at 3 × IQR). HAZ change among those who sustained recovery was −0.16, +0.16, and +0.53 for the 25th, 50th, and 75th percentiles, respectively. HAZ change among those who relapsed to MAM once was −0.37, +0.01, and +0.38 for the 25th, 50th, and 75th percentiles, respectively. HAZ change among those who relapsed to MAM multiple times was −0.47, −0.13, and +0.19 for the 25th, 50th, and 75th percentiles, respectively. HAZ change among those who developed SAM was −0.93, −0.48, and +0.02 for the 25th, 50th, and 75th percentiles, respectively. HAZ, height-for-age *z* score; MAM, moderate acute malnutrition; SAM, severe acute malnutrition.

Although evidence supports the hypothesis that wasting interrupts the mechanisms for optimal linear growth and stunting, causal mechanisms could also be the reverse, such that poor linear growth preceded and caused the repeated episodes of wasting. With the current lack of physiologic understanding of the causal relations between linear growth and wasting, it is difficult to disentangle the exposure from the outcome. In addition to a direct causal relation, it is likely that both conditions are the result of biological abnormalities due to a cascade of nutritional deficits and persistent infections.

Excessive intestinal inflammation plays a major role in the relation between MAM and poor linear growth, and may be particularly powerful in settings such as that found in this study, in which children are vulnerable to repeated episodes of weight loss from reoccurring acute infections (34). Repeated infectious diseases in Guatemalan children have been shown to be an important cause of both weight loss and poor linear growth (35). Children with MAM have elevated inflammatory immune markers, even without any manifest clinical symptoms of illness during and after treatment for MAM (36, 37). Studies in Peru have shown that children whose growth is suppressed during and shortly after illness experience rapid catch-up growth after the illness is resolved (14). However, in our study, half of the children continued to experience poor linear growth as well as repeated episodes of acute malnutrition, possibly indicating that for these children, a full physiologic and immunologic recovery

TABLE 3 Multivariable fixed-effects logistic regression model regressing poor linear growth on whether or not a child relapsed to either MAM or SAM at any given follow-up visit during a year-long follow-up period after recovery from MAM[1]

Factors at the time of follow-up	Adjusted OR ± Robust SE
Poor linear growth** (1 = negative monthly HAZ change; 0 = positive monthly HAZ change)	1.72 ± 0.20
Stunted	
Severely stunted (1 = HAZ <−3; 0 = HAZ >−3)	2.41 ± 1.21
Moderately stunted (1 = HAZ ≥−3 and <−2; 0 = HAZ ≥−2)	1.33 ± 0.44
Age, mo*	0.96 ± 0.02
Fever in the prior 2 wk**	1.18 ± 0.04
Diarrhea in the prior 2 wk**	1.29 ± 0.06
HFIAS score	1.02 ± 0.01
Whether the follow-up visit occurred during rainy/lean season (Dec–May)**	2.87 ± 0.29

[1]Values are ORs ± SEs. *$P < 0.05$ and **$P < 0.001$. HAZ, height-for-age *z* score; HFIAS, Household Food Insecurity Access Scale; MAM, moderate acute malnutrition; SAM, severe acute malnutrition.

was not achieved at the time of SFP discharge based on standard anthropometric criteria.

In this study, we show significant associations between symptoms of illness and relapse back to acute malnutrition during the year after anthropometric recovery from MAM. These findings suggest that underlying infections during MAM contribute to both subsequent poor linear growth and relapse. A recent review of the impact of malnutrition on host defense mechanisms highlights that protein and micronutrient deficiencies affect the hematopoietic and lymphoid organs and compromise both innate and adaptive immune functions, whereas changes in intestinal microbiota contribute to growth faltering and dysregulated inflammation and immune function (38). Markers of immune function such as white blood cells, acute phase proteins, complement proteins, lymphocytes, and antibody concentrations seem to be more affected in children with SAM than in children with MAM, but unfortunately much of the research in immunodeficiency among malnourished children is relatively outdated (37). A rigorous understanding of the various types of immunodeficiency during and after MAM could facilitate enhanced treatment protocols that go beyond the promotion of short-term weight gain to include a reversal of underlying immunologic deficiencies, ultimately improving the sustainability of recovery and promoting linear growth.

Although previous analysis has shown that type of food provided during MAM treatment may reduce relapse rates (12, 13), we did not observe any difference in linear growth during the follow-up period among children who received different supplementary foods during initial MAM treatment. These findings are consistent with a study in Niger which compared children who received ready-to-use therapeutic food with those who received corn-soy blend during MAM treatment and found no difference in height or HAZ gains between the 2 groups at 6 mo post-discharge (39). Also, extending the provision of supplementary feeding beyond SFP discharge does not directly have an impact on reducing relapse or improving linear growth (12, 13, 40). Clinical trials involving new formulations of supplementary foods that might promote optimal linear growth are warranted.

Given that children with both wasting and stunting have a higher risk of death than do those with either condition alone (24), more programmatic attention should be provided to targeting both wasting and stunting simultaneously. This includes incorporating routine monitoring of children after anthropometric recovery from MAM. Innovative solutions, such as teaching mothers to monitor their own children's anthropometric status using MUAC tapes (41) or expanding the treatment of acute malnutrition at the community health worker level (42), may help keep costs low while increasing coverage of monitoring and services. Policies should include the treatment of acute malnutrition as a critical step to facilitate the reduction of stunting. Our findings contradict recent recommendations by WHO to avoid treating children with MAM in efforts to prevent overweight and obesity (43). Rather, our findings support the need to improve the treatment of MAM to reduce repeated episodes of wasting and reverse poor linear growth that leads to stunting; both of which have long-term associations with overweight, obesity, and other noncommunicable diseases (44, 45).

Further research is needed to better understand the causal pathways underlying the associations between acute malnutrition and poor linear growth in the form of longitudinal studies that follow individual children prior to, during, and after treatment for acute malnutrition. Studies must go beyond collecting only anthropometric measurements, to include body composition parameters, biomarkers of immune function, growth factors, amino acid concentrations, microbiota, and other markers of inflammation. The strong association between poor linear growth and repeated relapses after treatment for MAM highlights the need for the initial treatment to aim for a more holistic recovery that goes beyond weight gain alone, but rather leads to a full physiologic and immunologic recovery.

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