Neurodevelopment and Recovery From Wasting

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abstract

BACKGROUND AND OBJECTIVES: Acute illness with malnutrition is a common indication for hospitalization among children in low- and middle-income countries. We investigated the association between wasting recovery trajectories and neurodevelopmental outcomes in young children 6 months after hospitalization for an acute illness.

METHODS: Children aged 2 to 23 months were enrolled in a prospective observational cohort of the Childhood Acute Illness & Nutrition Network, in Uganda, Malawi, and Pakistan between January 2017 and January 2019. We grouped children on the basis of their wasting recovery trajectories using change in mid–upper arm circumference for age z-score. Neurodevelopment was assessed with the Malawi Developmental Assessment Tool (MDAT development-for-age z-score [DAZ]) at hospital discharge and after 6 months.

RESULTS: We included 645 children at hospital discharge (mean age 12.3 months ± 5.5; 55% male); 262 (41%) with severe wasting, 134 (21%) with moderate wasting, and 249 (39%) without wasting. Four recovery trajectories were identified: high–stable, $n = 112$; wasted–improved, $n = 404$; severely wasted–greatly improved, $n = 48$; and severely wasted–not improved, $n = 28$. The children in the severely wasted–greatly improved group demonstrated a steep positive MDAT-DAZ recovery slope. This effect was most evident in children with both wasting and stunting (interaction wasted–improved × time × stunting: $P < .001$). After 6 months, the MDAT DAZ in children with wasting recovery did not differ from community children. In children who never recovered from wasting, there remained a significant delay in MDAT DAZ scores.

CONCLUSIONS: Neurodevelopment recovery occurred in parallel with wasting recovery in children convalescing from acute illness and was influenced by stunting.

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WHAT'S KNOWN ON THE SUBJECT Malnutrition is a key risk factor for acute illness and hospital admission in children in low-and middle-income countries. The relationship between the recovery of wasting and neurodevelopmental outcomes after an acute illness in young children is less clear.

WHAT THIS STUDY ADDS Neurodevelopment recovery mirrored wasting recovery in children convalescing from acute illness; the presence of stunting influenced this relationship. Our results indicate that the association between wasting and neurodevelopment delay may be reversible given sufficient time and adequate anthropometric recovery.

In low- and middle-income countries (LMICs), approximately 250 million children aged <5 years are at risk for not reaching their full developmental potential.[1] Improving early child development is stated as a priority of the Sustainable Development Goals.[2] Infancy is a unique period of high nutritional requirement because of accelerated physical growth coinciding with rapid anatomic and functional expansion of the brain.[3] Although the precise biological mechanisms remain unknown,[4] impairments in early childhood growth and neurocognitive development have been linked to chronic systemic inflammation experienced during the first 24 months of life. Such inflammation can derive from recurrent infections, which often occur in the context of malnutrition, especially in LMICs.

In young children, illness often precipitates, or is accompanied by, wasting (defined by a low weight-for-length z-score [WLZ] or low mid–upper arm circumference [MUAC]). Wasting can develop rapidly, whereas stunting (defined by a low length-for-age z-score [LAZ]) is seen as a form of chronic malnutrition.[5] Stunting has been strongly associated with adverse neurodevelopmental outcomes,[6] and limited studies have also reported long-term effects of severe wasting[7–9]; however, few studies have examined the impact of both wasting and stunting. Furthermore, it remains unclear if wasting recovery (eg, rapid recovery versus prolonged suboptimal recovery) is linked to differential impacts on early childhood neurodevelopment. Previous community-based studies have shown that malnutrition and recurrent infections are associated with neurodevelopmental outcomes in young children in LMICs.[10,11] However, there have been no previous longitudinal investigations to determine whether children discharged from hospital recover from wasting and, concurrently, show recovery trajectories in neurodevelopment outcomes.

The Childhood Acute Illness & Nutrition (CHAIN) Network cohort study offers a unique opportunity to examine the relationships between wasting recovery and neurodevelopmental outcomes in young children convalescing from severe illness (http://chainnetwork.org/).[12,13] The primary aim of this prospective CHAIN neurodevelopmental substudy was to investigate the association between wasting trajectories and neurodevelopmental outcomes in young children 6 months after a hospitalization for an acute illness. Our second aim was to examine the effect of stunting on this relationship. In LMICs, available resources to promote healthy development are scarce, and our approach is critical in identifying children most likely to benefit from interventions with targets to improve developmental outcomes after severe illness.

METHODS

Study Design and Setting

The CHAIN neurodevelopment substudy was conducted at 3 sites: Queen Elizabeth Central Hospital in Blantyre, Malawi; Mulago Hospital in Kampala, Uganda; and Civil Hospital in Karachi, Pakistan. Children between 2 and 23 months of age enrolled in the CHAIN prospective observational cohort were coenrolled in a neurodevelopment substudy from January 2017 to January 2019. Details of the CHAIN cohort were previously reported.[13] Anthropometric, clinical, and psychosocial measurements were collected at hospital admission, discharge, and at 45, 90, and 180 days after discharge. Wasting and stunting were defined as: severe wasting, WLZ <-3 and/or bilateral nutritional edema or an MUAC <11.5 cm if aged ≥6 months or MUAC <11 cm if aged <6 months; moderate wasting, WLZ <-2 and ≥-3 or an MUAC ≥11.5 to <12.5 cm if aged ≥6 months or ≥11.0 to <12.0 cm if aged <6 months; stunting was defined as LAZ <-2.[5,13]

Nutritional rehabilitation of children followed national and World Health Organization (WHO) guidelines.[14] Children with severe wasting were fed therapeutic milk and ready-to-use-therapeutic foods according to United Nation Children's Fund guidelines.[15] Once medically stable, children were discharged and referred to nutrition services for continued outpatient supplementary feeding according to national policy.[14] Community children were also recruited from the same community as the hospitalized children.[13] They underwent a 1 time assessment identical to that of inpatient children. Written, informed consent from a parent or guardian was obtained according to the International Conference on Harmonization clinical practice guidelines.

Outcome: Neurodevelopment Assessment

Neurodevelopment was assessed with the Malawi Developmental Assessment Tool (MDAT) at hospital discharge and at 6 months postdischarge. The MDAT is culturally validated and one of the few instruments developed specifically for LMICs.[4,16,17] Through direct observation of the child and responses to questionnaires, the MDAT examines 4 developmental domains of: (1) gross motor skills, (2) fine motor skills, (3) language, and (4) social skills. It also has evaluations of cognitive capacity embedded within the fine motor and language domains. The 144 items (36 in each domain) are scored as "pass," "fail," or "unknown" in cases where the child is uncooperative. The MDAT has good construct validity and sensitivity (97%) in predicting

moderate to severe developmental delay in children from birth to 6 years of age.[16] Domain-specific neurodevelopment delay is defined as a domain specific z-score < -1.64 on the MDAT.[16] An overall development-for-age z-score (DAZ) was calculated using the original MDAT collected in a Malawian standard population.[16]

The MDAT was adapted for use in both Uganda and Pakistan under the direct guidance of the original designer of the MDAT (M. Gladstone). Research assistants with backgrounds in early child development underwent regular and extensive training in the standardized administration of the MDAT and subsequently performed all MDAT assessments.

Exposure: Anthropometry

Weight, supine length, and MUAC were measured by trained clinical assistants. MUAC was recorded to the nearest millimeter using a nonstretch insertion tape (TALC, St. Albans, United Kingdom); body length was recorded to the nearest millimeter (Seca 416 infantometer, Birmingham, United Kingdom); and body weight was recorded to the nearest 10 g (Seca 825 electronic scale, Birmingham, United Kingdom, calibrated monthly). MUAC-for-age z-scores (MUACz), LAZ, and WLZ were calculated according to 2006 WHO growth standards using the "*zscorer*" R package.[18] The MUACz and WLZ scores were used to create wasting recovery trajectories (see analysis section below).

Covariates

On the basis of literature, the following covariates related to child development outcomes were considered:[19]

1. medical history: suspected or known chronic cerebral palsy, epilepsy, or prematurity;

2. indication for hospitalization: diagnosis including pneumonia,

confirmation of suspected sepsis, gastroenteritis, meningitis, or malaria (determined by rapid diagnostic testing or blood smears);

3. biological variables: hemoglobin at hospital discharge, HIV-reactivity (ie, infection or exposure status in children aged <18 months determined by rapid diagnostic testing);

4. sociodemographic factors: caregiver highest level of education, and an asset index derived from principal component analysis of variables obtained from a comprehensive household wealth survey[13,20];

5. maternal mental health: measured with the Patient Health Questionnaire (PHQ)-9[21] at admission and day 45 follow-up; the PHQ-9 is a 9-item scale widely used in the screening of depression in LMICs[22,23]; and

6. stimulation in the home: play items and interactions at home were evaluated using the Family Care Indicator (FCI) from the Multiple Indicator Cluster Survey.[24]

Statistical Analysis

First, we identified different patterns of wasting recovery in children after hospital discharge using latent class mixed models (LCMMs). MUACz and WLZ were modeled across 4 time points (hospital discharge, day 45, day 90, day 180). LCMMs are an extension of linear mixed-effect modeling that can evaluate heterogeneity in the growth trajectories of children and classify them into latent groups.[25] All children with at least 1 MUACz or WLZ measurement after discharge were included in the LCMM clustering. Previous studies have shown that having few measured observations per cluster did not lead to notable bias when estimating random effects.[26] However, children not showing recovery (ie, those who still met

criteria for severe wasting at 6 months' follow-up) were excluded a priori from the LCMM analysis (Supplemental Fig 5). We evaluated the subdivision of MUACz and WLZ growth trajectories into 1 to 5 latent groups (K-class models, K = 1.5) with either a linear or quadratic fit. Model selection was based on Bayesian information criterion, Akaike information criterion, differences in Lo-Mendell-Rubin adjusted likelihood ratio test (eg, comparing model of K classes to that of K-1), and clinical interpretability.[25] As in other relevant studies,[27] we used a less-restrictive criterion of 1% group membership, with each participant assigned to only 1 growth trajectory on the basis of the highest posterior probability. For this, the LCMM R package was used.[25]

We fitted linear mixed models to determine the association between the wasting recovery trajectories and the change in MDAT DAZ score or individual domain scores. Four models were assessed for both MUACz and WLZ:

1. unadjusted;

2. adjusted for only child factors (sex, age at admission, HIV reactivity, previous known neurodisability, prematurity, meningitis, hemoglobin at discharge);

3. adjusted for both child and sociodemographic factors (parental education, PHQ score at follow-up, asset index, FCI play items, FCI interaction); and

4. adjusted for all child and sociodemographic factors while evaluating the interaction effect with stunting in children that showed recovery from wasting.

All models included a random intercept per participant, and hospital site was included as a fixed factor in adjusted models. Missing

covariates were imputed using standard procedures of Multiple Imputation by Chained Equations (R package; Supplemental Table 3); mixed model estimates were pooled across imputed data sets, thus accounting for added variability. Finally, generalized linear models were used to compare the adjusted MDAT DAZ score from the hospitalized children at day 180 to those from community participants. To improve interpretability, we calculated the group marginal means and assessed their differences on the basis of covariate adjusted models using the estimated marginal means package in R. Analyses were conducted using both R version 4.0.1 (The R Foundation for Statistical Computing Platform, 2020) and Stata (version 16).

Ethics Approval

This study protocol was reviewed and approved by the Oxford Tropical Research Ethics Committee, United Kingdom, and the research ethics committees of each institution where the study was conducted.

RESULTS

From November 2017 to January 2019, we recruited 645 hospitalized children (mean age 12.3 months, ± 5.5; 55% male): 262 (41%) with severe wasting, 134 (21%) with moderate wasting, and 249 (38%) who were not wasted. Thirty children (5%) died after discharge, 27 (4%) missed the follow-up neurodevelopment assessment, and 66 (10%) were lost to follow-up. A total of 459 (71%) children were assessed at both time points (Fig 1). Community children were also recruited ($n = 169$, mean age 12.8 months ± 5.6; 50% male). Children were recruited from Kampala ($n = 405$, 50%), Blantrye ($n = 339$, 41%), and Karachi ($n = 72$, 9%). The CHAIN neurodevelopment substudy enrolled 76% of children participating in the main CHAIN cohort at these sites within the same time span. Sociodemographic characteristics according to wasting status at admission are presented in Supplemental Table 4.

Wasting Recovery Trajectories

On the basis of model selection criteria, a 3 class solution was chosen for the MUACz wasting trajectories (Fig 2), which can be described as follows:

1. Group 1: high–stable; children ($n = 112$, 18.9%) in this group had a high mean MUACz both at discharge and 6 months' follow-up (0.1 [95% confidence interval [CI] 0.0–0.3]] and 0.2 [95% CI −0.0 to 0.3], respectively). This group mostly included initially nonwasted hospitalized children ($n = 108$, 96%), and $n = 29$ (26%) were stunted at follow-up;

2. Group 2: wasted–improved; these children ($n = 404$, 68.2%) demonstrated improved MUACz from −2.1 (95% CI −2.2 to −2.0) to −1.0 (95% CI −1.1 to −0.9). This group included severely wasted children ($n= 167$; 41%), moderately wasted children ($n = 115$, 29%), and also nonwasted children ($n = 122$, 30%); of these $n = 262$ (65%) children were stunted at follow-up;

3. Group 3: severely wasted–greatly improved; children ($n = 48$, 7.4%) in this group showed improved MUACz from −4.2 (95% CI −4.6 to −3.9) to −0.6 (95% CI −0.9 to −0.4). This group included severely wasted children ($n = 44$, 92%) with a few moderately wasted children ($n = 4$, 8%); 39 (81%) of these children were stunted at follow-up; and

4. Lastly, a small but clinically relevant group (Group 4), was identified: severely wasted–not improved ($n = 28$, 4%), comprising
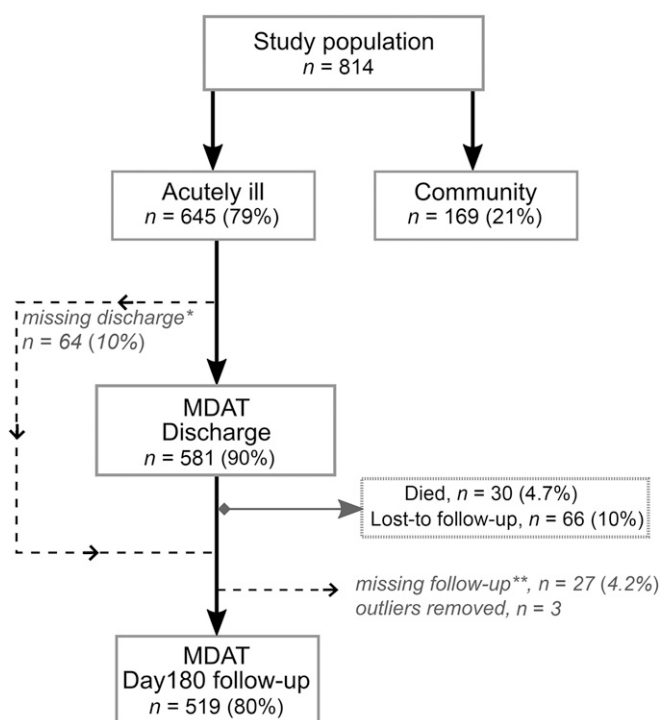

FIGURE 1
Study flow diagram. Number of participants with missed time points are indicated for discharge (*) and follow-up (**).
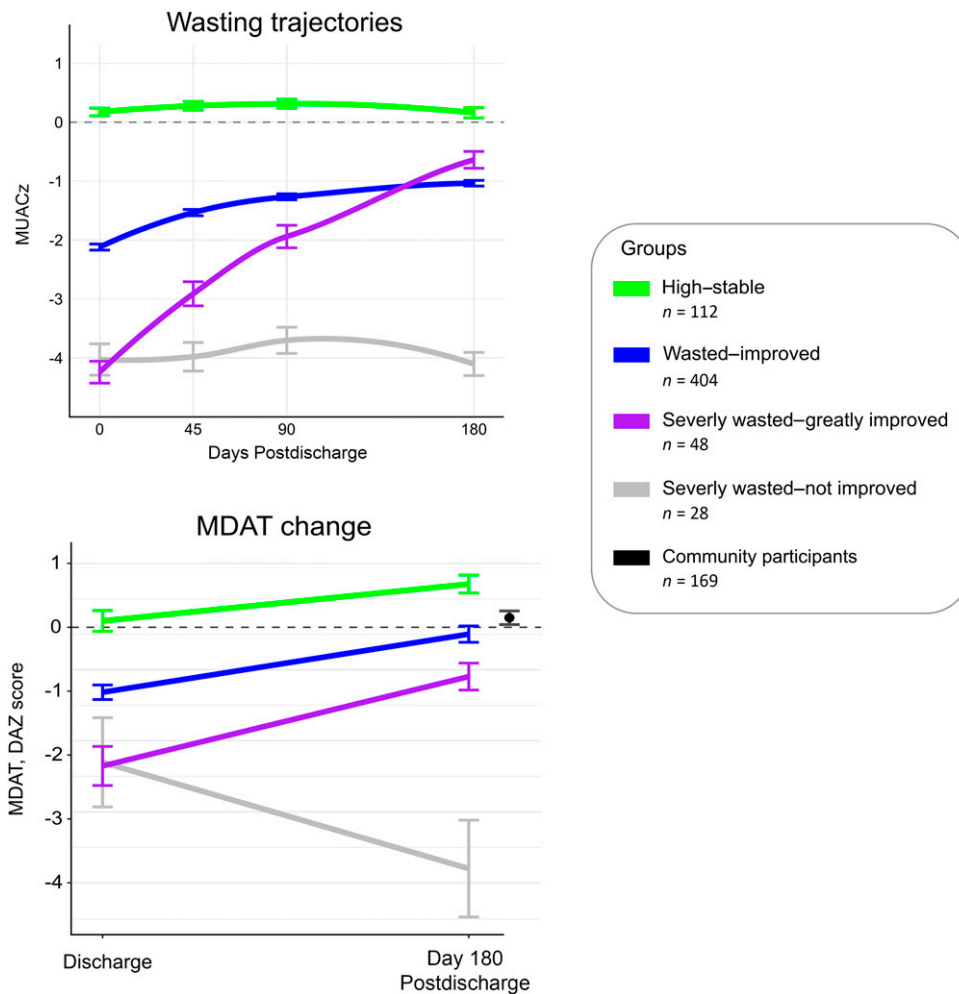
FIGURE 2
Wasting (MUACz) and development (MDAT DAZ) trajectories.

children who met criteria for severe wasting at follow-up (Supplemental Fig 5). The mean MUAC z-score in this group was −4.0 (95% CI −4.6 to −3.5) at discharge and −4.1 (95% CI −4.5 to −3.7) at day 180; 27 (96%) of these children were stunted.

For further analysis, the high–stable group was chosen as the reference group. Sociodemographic characteristics according to wasting trajectory group are presented in Supplemental Table 5. Results obtained from the recovery patterns of WLZ mirrored those obtained for MUACz (ie, 3-class solution with similar patterns per group); thus, these data and analysis are presented as Supplemental Table 6 and Supplemental Fig 6).

Children Convalescing From Acute Illness With Improved Wasting Trajectories Show Neurodevelopmental Recovery at 6-Month Follow-Up

Mean developmental scores at discharge and follow-up grouped by wasting recovery trajectory are presented in Table 1. Similar to their MUACz recovery pattern, children in the wasted–improved and severely wasted–greatly improved groups showed marked improvements in their neurodevelopmental outcome scores at follow-up (Table 1 and Fig 2). While adjusting for child and sociodemographic factors, MDAT DAZ scores at follow-up increased compared with hospital discharge by 0.68 z-score (95% CI 1.0–0.4, $P < .0001$) in the wasted–improved group, and by 1.49 z-score (95% CI 2.4–0.6, $P < .0001$) in the severely wasted–greatly improved group. In contrast, the MDAT DAZ scores decreased by −1.8 z-score (95% CI −0.6 to −3.0, $P < .001$) among children in the severely wasted–not improved group.

TABLE 1 Mean Developmental Scores in Children With Specific Wasting Recovery Trajectories at Discharge and Follow-Up

MUACz Groups									Community
	High–Stable		Wasted–Improved		Severely Wasted–Greatly Improved		Severely Wasted–Not Improved		
	Discharge	Follow-Up	Discharge	Follow-Up	Discharge	Follow-Up	Discharge	Follow-Up	
DAZ score	0.1 (1.6)	0.7 (1.4)	−1.0 (2.2)	−0.1(2.4)	−2.2 (2.1)	−0.8 (1.4)	−2.1 (3.4)	−3.8 (4.0)	0.2 (1.4)
Domain scores									
Gross motor	0.2 (1.6)	0.8 (1.4)	−1.0 (1.8)	0.2 (1.8)	−2.1 (1.7)	−0.5 (1.6)	−2.5 (1.8)	−3.1 (2.0)	0.3 (1.7)
Fine motor	0.1 (1.7)	0.2 (1.6)	−0.9 (1.8)	−0.2 (1.6)	−1.8 (1.8)	−0.4 (1.3)	−1.7 (2.3)	−2.7 (2.3)	0.0 (1.4)
Language	0.1 (1.2)	0.1 (1.3)	−0.4 (1.3)	−0.4 (1.3)	−1.1 (1.0)	−0.3 (1.0)	−0.8 (1.8)	−1.5 (1.8)	0.1 (1.3)
Social	0.2 (1.3)	0.5 (1.3)	−0.2 (1.3)	0.2 (1.4)	−0.7 (1.2)	−0.1 (1.0)	−0.4 (1.7)	−1.3 (1.9)	0.4 (1.6)

Unadjusted MDAT mean (SD) scores are presented.

The 4 individual developmental domains showed similar patterns consistent with the overall MDAT scores, with marked delays at discharge but with strong improvement by 6 months' follow-up; this effect was most notable in the domains of gross and fine motor skills (Table 1, Fig 3).

Wasting Recovery Trajectory and Stunting are Associated With Neurodevelopmental Outcomes

While adjusting for child and sociodemographic factors, there was no difference in the magnitude of change in MDAT scores from baseline to follow-up for the wasted–improved group as compared with the high–stable group. The children in the severely wasted–greatly improved group showed the greatest positive change in MDAT DAZ scores (Fig 2; Table 2; M_3) compared with the high–stable group. We found that stunting influenced the recovery patterns of MDAT DAZ scores (Fig 4). We identified a significant third-order interaction (improved wasting trajectory × time × stunting; Table 2; M_4; Supplemental Table 7). This interaction showed that there was a difference in the magnitude of change in MDAT scores in children who are stunted versus nonstunted children in both wasted–improved groups, when compared with the difference in magnitude of change in MDAT scores of stunted versus nonstunted children in the high–stable group. Nonstunted children in the wasted–improved group had higher MDAT scores compared with their stunted counterparts at discharge (adjusted marginal mean difference (0.98 95% CI 0.2–1.7, $P < .01$), but this no longer differed at follow-up (adjusted marginal mean difference 0.60, 95% CI −0.1 to 1.3, $P = .24$) (Fig 4, panel A and B). Without reaching statistical significance, similar patterns were obtained when examining separately each developmental domain (Fig 3 and Supplemental Table 8).

Children Convalescing From Acute Illness With Wasting Recovery Reach Community Neurodevelopment Levels by 6 Months Follow-Up

At 6 months' follow-up, the MDAT DAZ scores measured in the hospitalized children who had stable or improved wasting trajectories
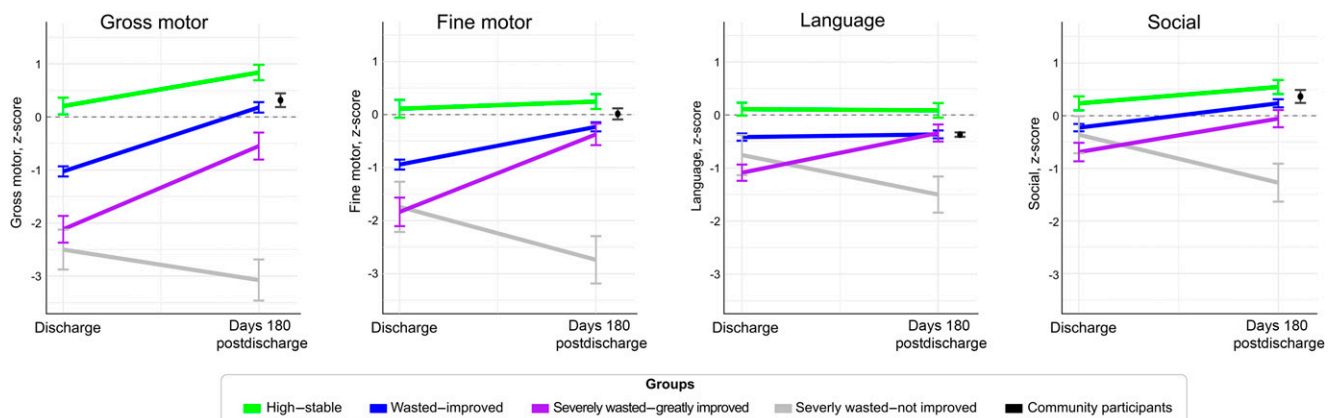

FIGURE 3
Individual neurodevelopment domain trajectories. Unadjusted MDAT mean (SD) scores are presented.

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TABLE 2 Mixed-Effect Models Testing the Association Between Children With Different MUACz Recovery Trajectories and Development scores (MDAT-DAZ) at Discharge and Follow-Up

	M₁: Unadjusted[a]	M₂: Adjusted for Child Factors[b]	M₃: Adjusted for Child[a,b] and Sociodemographic[c] Factors	M₄: Adjusted for Child[b] and Sociodemographic[c] Factors With Stunting Interaction
Time point, discharge	Ref.	Ref.	Ref.	Ref.
Time point, follow-up	0.36 (−0.03 to 0.76)	0.39 (−0.01 to 0.78)	0.35 (−0.04 to 0.74)	0.47 (0.02–0.93)*
Group 1: high–stable	Ref.	Ref.	Ref.	Ref.
Group 2: wasted–improved	−0.96 (−1.46 to −0.46)***	−0.8 (−1.29 to −0.31)**	−0.68 (−1.14 to −0.22)**	−0.04 (−0.63 to 0.55)
Group 3: severely wasted–greatly improved	−2.33 (−3.10 to −1.56)***	−2.12 (−2.89 to −1.35)***	−1.74 (−2.48 to −1.00)***	−0.55 (−2.03 to 0.94)
Group 4: severely wasted–not improved	−2.02 (−3.00 to −1.04)***	−1.90 (−2.86 to −0.93)***	−1.82 (−2.73 to −0.92)***	—
Stunted	—	—	—	0.16 (−0.69 to 1.01)
2-way interactions: group × time point, group × stunted, and time point × stunted				
High–stable × time point	Ref.	Ref.	Ref.	Ref.
Wasted–improved × time point	0.34 (−0.10 to 0.79)	0.23 (−1.11 to 0.79)	0.33 (−0.11 to 0.78)	−0.05 (−0.65 to 0.54)
Severely wasted–greatly improved × time point	1.10 (0.40–1.80)**	1.08 (−0.38 to 1.78)**	1.14 (0.45–1.83)**	−0.27 (−1.72 to 1.19)
Not improved × time point	−2.19 (−3.06 to −1.32)***	−2.14 (−3.01 to −1.27)***	−2.11 (−2.97 to −1.25)***	—
High–stable × stunted	—	—	—	Ref.
Wasted–improved × stunted	—	—	—	−1.14 (−2.09 to −0.19)
Severely wasted–greatly improved × stunted	—	—	—	−1.70 (−3.43 to 0.04)
Follow-up × stunted	—	—	—	−0.64 (−1.5 to 0.22)
3-way interaction: group × time point × stunted				
Wasted–improved x time point × stunted	—	—	—	1.01 (0.04–1.99)*
Severely wasted–greatly improved × time point × stunted	—	—	—	2.19 (0.45–3.93)*

Stunted was measured at follow-up and defined as LAZ < −2 SD. Estimates and 95% CIs presented are pooled across imputed data sets, which account for variability linked to imputation procedures of missing covariates. Supplemental Table 3 indicates missing and imputed values. Significance threshold: *$P < .05$, **$P < .01$, ***$P < .001$.
Ref., reference category. —, not applicable.
[a] All models were adjusted for hospital site.
[b] Child factors: sex, age, HIV status, neurodisability, prematurity, meningitis, hemoglobin at discharge.
[c] Sociodemographic factors: maternal mental health, parental education, asset index, FCI play items, FCI interaction.

after discharge caught up to community levels (high–stable, 0.48; 95% CI −0.1 to 1.0; wasted–improved, 0.2; 95% CI −0.2 to 0.6; severely wasted–greatly improved, 0.1; 95% CI −0.6 to 0.89 compared with community children) after adjusting for child, sociodemographic factors, and stunting (Supplemental Table 9). The children in the severely wasted–not improved group continued to have significantly lower MDAT DAZ scores than the community participants (full adjusted analysis −3.08 (95% CI −4.0 to −2.2, $P < .001$; Supplemental Table 9).

DISCUSSION

In a cohort of hospitalized young children in LMICs, both the trajectory of wasting recovery and stunting were significantly associated with neurodevelopmental outcomes. Children who recovered from wasting also demonstrated neurodevelopmental recovery at 6 months' follow-up. A small group ($n = 28$, 4%) without wasting recovery similarly had no neurodevelopmental recovery at follow-up. Children in the groups with an improved wasting trajectory had lower MDAT scores at discharge than the children who were not wasted. The children who recovered

from severe wasting also showed the steepest recovery in neurodevelopment scores and this recovery was more notable in children who were both wasted and stunted. This suggests that young children who are stunted and show recovery from wasting have the capability to improve in neurodevelopmental outcomes after hospital admission. Furthermore, neurodevelopmental outcomes in children who recovered from wasting no longer differed from those of community children after adjusting for stunting and other factors important for early child development. These findings
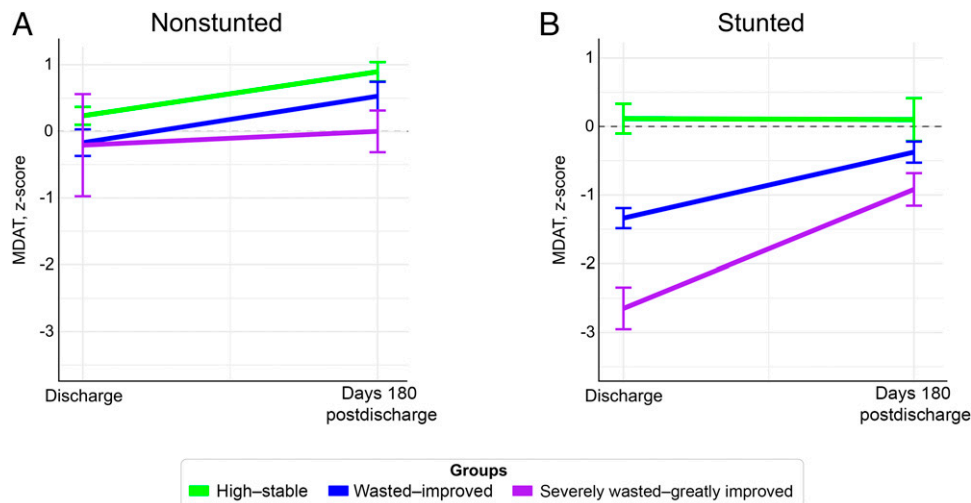
FIGURE 4
Development (MDAT DAZ) trajectory according to stunting. Unadjusted MDAT mean (SD) scores are presented.

indicate that the association between wasting and neurodevelopment might be reversible given enough time and nutritional recovery.

Children in LMICs often present with multiple anthropometric deficits, and few studies have examined how these deficits influence child development. Wasting and stunting are correlated; children who are stunted have a higher risk of becoming wasted and children with wasting have a higher risk of becoming stunted.[28] In our study, almost all children who did not recover from wasting were also stunted, and these children had significantly worse developmental scores than community participants. Other groups have demonstrated a strong interaction between wasting and stunting on mortality.[29,30] Shared sociodemographic risk factors and/ or common pathophysiological mechanisms could be responsible for the increased risk of poor neurodevelopmental outcomes and mortality in children with persistent wasting and stunting.[29]

Our findings are critical to the development of guidelines and policy in LMICs. Currently, the WHO recommends providing psychosocial stimulation in "guidelines for the inpatient treatment of severely malnourished children."[31] Although this is likely beneficial for all hospitalized children with wasting, in resource-scarce settings, children with both wasting and stunting should be prioritized for developmental interventions. Further research on etiology and prevention of children who suffer from both wasting and stunting is urgently needed to inform novel treatment strategies.[26]

In this analysis, we examined longitudinal continuous MUAC z-scores instead of the categorical classification of severe and moderate wasting because for individual children, undernutrition exists on a dynamic continuum. This explains why some children who did not qualify as wasted at discharge on the basis of the WHO threshold but showed improvement in the MUACz at follow-up were grouped by the LCMM in the wasted–improved trajectory group.

Children with wasting often have recurrent episodes of wasting and, by using wasting trajectories, we were also able to capture this. This study has several additional strengths: we employed a large sample size from a multicountry setting and used standardized measurements across countries. Furthermore, we adjusted for multiple child and sociodemographic confounders important for child development. The use of a culturally validated developmental tool tailored for children in LMICs to assess developmental outcomes, as well as standardized training of research assistants, provided a robust framework.

It is important to acknowledge the limitations of our study. The Malawian MDAT norms used to calculate the DAZ score were also used for children in Uganda and Pakistan. Other limitations were not all children included in the main CHAIN study being included in the neurodevelopmental substudy because trained research assistants were not always available to assess neurodevelopment and loss to

follow-up. It is essential to note that the children included were recovering from acute illness and these results may not be generalizable to children with wasting in the community. Our study cannot provide any details about the exact time frame of neurodevelopment recovery within the 6 months' follow-up postdischarge. Importantly, the community children recruited into our study were not specifically chosen as a developmental reference group. Therefore, this study cannot conclude that hospitalized children have achieved optimal developmental outcomes. Finally, this study examined associations without causal relationships, and it is important to realize that many biological and socioeconomic factors are important in child development, and developmental outcomes can improve without seeing changes in growth.

In conclusion, in children convalescing from acute illness, neurodevelopment recovery mirrored wasting recovery and stunting influenced this relationship. The association between acute illness and wasting on neurodevelopment appears reversible given nutritional recovery.

ABBREVIATIONS

CHAIN: Childhood Acute Illness & Nutrition
CI: confidence interval
DAZ: development-for-age z-score
FCI: Family Care Indicator
LAZ: length-for-age z-score
LCMM: latent class mixed model
LMIC: low- and middle-income countries
MDAT: Malawi Developmental Assessment Tool
MUAC: mid–upper arm circumference
MUACz: mid–upper arm circumference for age z-score
PHQ: Patient Health Questionnaire
WHO: World Health Organization
WLZ: weight-for-length z-score

REFERENCES

1. Black MM, Walker SP, Fernald LCH, et al. Lancet Early Childhood Development Series Steering Committee. Early childhood development coming of age: science through the life course. *Lancet.* 2017;389(10064):77–90

2. Sustainable Development Goals Knowledge Platform. Available at: https://sustainabledevelopment. un.org/. Accessed February 22, 2019

3. Krebs NF, Lozoff B, Georgieff MK. Neurodevelopment: the impact of nutrition and inflammation during infancy in low-resource settings. *Pediatrics.* 2017;139(Suppl 1): S50–S58

4. Suchdev PS, Boivin MJ, Forsyth BW, Georgieff MK, Guerrant RL, Nelson CA III. Assessment of neurodevelopment,

nutrition, and inflammation from fetal life to adolescence in low-resource settings. *Pediatrics.* 2017;139(Suppl 1):S23–S37

5. WHO/UNICEF. *WHO Child Growth Standards and the Identification of Severe Acute Malnutrition in Infants and Children.* WHO: Geneva; 2009

6. Sudfeld CR, McCoy DC, Danaei G, et al. Linear growth and child development in low- and middle-income countries: a meta-analysis. *Pediatrics.* 2015; 135(5):e1266–e1275

7. van den Heuvel M, Voskuijl W, Chidzalo K, et al. Developmental and behavioural problems in children with severe acute malnutrition in Malawi: a cross-sectional study. *J Glob Health.* 2017;7(2):020416

8. Grantham-McGregor S, Powell C, Walker S, Chang S, Fletcher P. The long-term follow-up of severely malnourished children who participated in an intervention program. *Child Dev.* 1994;65(2 Spec No):428–439

9. Lelijveld N, Jalloh AA, Kampondeni SD, et al. Brain MRI and cognitive function seven years after surviving an episode of severe acute malnutrition in a cohort of Malawian children. *Public Health Nutr.* 2019;22(8):1406–1414

10. Jiang NM, Tofail F, Ma JZ, et al. Early life inflammation and neurodevelopmental outcome in Bangladeshi infants growing up in adversity. *Am J Trop Med Hyg.* 2017;97(3):974–979

11. McCormick BJJ, Caulfield LE, Richard SA, et al. MAL-ED NETWORK INVESTIGATORS. Early life experiences and trajectories of cognitive development. *Pediatrics.* 2020;146(3):e20193660

12. Berkley JA, Walson JL, Diallo AH, et al. Childhood Acute Illness and Nutrition Network. Childhood Acute Illness and Nutrition (CHAIN) Network: a protocol for a multisite prospective cohort study to identify modifiable risk factors for mortality among acutely ill children in Africa and Asia. *BMJ Open.* 2019;9(5):e028454

13. Diallo AH, Sayeem Bin Shahid ASM, Khan AF, et al. Childhood Acute Illness and Nutrition (CHAIN) Network. Childhood mortality during and after acute illness in Africa and south Asia: a prospective cohort study. *Lancet Glob Health.* 2022;10(5):e673–e684

14. Guidelines WHO. *Updates on the Management of Severe Acute Malnutrition in Infants and Children.* WHO: Geneva; 2013

15. UNICEF Supply Division. Ready-to-Use Therapeutic Food: Market Outlook UNICEF Supply Division. 2021

16. Gladstone M, Lancaster GA, Umar E, et al. The Malawi Developmental Assessment Tool (MDAT): the creation, validation, and reliability of a tool to assess child development in rural African settings. *PLoS Med.* 2010; 7(5):e1000273

17. Olsen MF, luel-Brockdorff AS, Yaméogo CW, et al. Early development in children with moderate acute malnutrition: a cross-sectional study in Burkina Faso. *Matern Child Nutr.* 2020; 16(2):e12928

18. De Onis M. WHO Multicentre Growth Reference Study Group. Reliability of anthropometric measurements in the WHO Multicentre Growth Reference Study. *Acta Paediatr Suppl.* 2006;450:38–46

19. Sania A, Sudfeld CR, Danaei G, et al. Early life risk factors of motor, cognitive and language development: a pooled analysis of studies from low/middle-income countries. *BMJ Open.* 2019;9(10):e026449

20. The Demographic and Health Surveys Program. Available at: https://dhsprogram.com/. Accessed February 22, 2019

21. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med.* 2001;16(9):606–613

22. Gallis JA, Maselko J, O'Donnell K, et al. Criterion-related validity and reliability of the Urdu version of the patient health questionnaire in a sample of community-based pregnant women in Pakistan. *PeerJ.* 2018;6(7):e5185

23. Udedi M, Muula AS, Stewart RC, Pence BW. The validity of the patient health Questionnaire-9 to screen for depression in patients with type-2 diabetes mellitus in non-communicable diseases clinics in Malawi. *BMC Psychiatry.* 2019;19(1):81

24. Kariger P, Frongillo EA, Engle P, Britto PM, Sywulka SM, Menon P. Indicators of family care for development for use in multicountry surveys. *J Health Popul Nutr.* 2012;30(4):472–486

25. Lennon H, Kelly S, Sperrin M, et al. Framework to construct and interpret latent class trajectory modelling. *BMJ Open.* 2018;8(7):e020683

26. Li X, Keown-Stoneman CDG, Lebovic G, et al. TARGet Kids! Collaboration. The association between body mass index trajectories and cardiometabolic risk in young children. *Pediatr Obes.* 2020; 15(8):e12633

27. Munthali RJ, Kagura J, Lombard Z, Norris SA. Childhood adiposity trajectories are associated with late adolescent blood pressure: birth to twenty cohort. *BMC Public Health.* 2016;16(1):665

28. Garenne M, Myatt M, Khara T, Dolan C, Briend A. Concurrent wasting and stunting among under-five children in Niakhar, Senegal. *Matern Child Nutr.* 2019;15(2):e12736

29. Myatt M, Khara T, Schoenbuchner S, et al. Children who are both wasted and stunted are also underweight and have a high risk of death: a descriptive epidemiology of multiple anthropometric deficits using data from 51 countries. *Arch Public Health.* 2018;76(28):28

30. McDonald CM, Olofin I, Flaxman S, et al. Nutrition Impact Model Study. The effect of multiple anthropometric deficits on child mortality: meta-analysis of individual data in 10 prospective studies from developing countries. *Am J Clin Nutr.* 2013;97(4):896–901

31. Ashworth A, Schofield C. Guidelines for the Inpatient Treatment of Severely Malnourished Children. Published online 2005.