Early Life Experiences and Trajectories of Cognitive Development

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abstract

BACKGROUND: Multiple factors constrain the trajectories of child cognitive development, but the drivers that differentiate the trajectories are unknown. We examine how multiple early life experiences differentiate patterns of cognitive development over the first 5 years of life in low-and middle-income settings.

METHODS: Cognitive development of 835 children from the Etiology, Risk Factors, and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health and Development (MAL-ED) multisite observational cohort study was assessed at 6, 15, 24 (Bayley Scales of Infant and Toddler Development), and 60 months (Wechsler Preschool and Primary Scale of Intelligence). Markers of socioeconomic status, infection, illness, dietary intake and status, anthropometry, and maternal factors were also assessed. Trajectories of development were determined by latent class-mixed models, and factors associated with class membership were examined by discriminant analysis.

RESULTS: Five trajectory groups of cognitive development are described. The variables that best discriminated between trajectories included presence of stimulating and learning resources in the home, emotional or verbal responsivity of caregiver and the safety of the home environment (especially at 24 and 60 months), proportion of days (0–24 months) for which the child had diarrhea, acute lower respiratory infection, fever or vomiting, maternal reasoning ability, mean nutrient densities of zinc and phytate, and total energy from complementary foods (9–24 months).

CONCLUSIONS: A supporting and nurturing environment was the variable most strongly differentiating the most and least preferable trajectories of cognitive development. In addition, a higher quality diet promoted cognitive development while prolonged illness was indicative of less favorable patterns of development.

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Data (with the exception of the cognitive development variables) are available from https://clinepidb.org/ce/app/after registration and approval of proposed use.

Drs McCormick, Richard, and Seidman along with Profs Caulfield and Murray-Kolb designed and ran the analyses, then led the manuscript drafting; Prof Pendergast and Drs Maphula, Koshy, Roshan, Nahar, Shrestha, Haque, Oria, and Svensen, Mr Blacy, and Mrs Rasheed collected, curated, and processed cognitive data; Drs Rasmussen and Scharf contributed to the interpretation of results; and all authors contributed to the editing and approval of the manuscript.

WHAT'S KNOWN ON THIS SUBJECT: The Nurturing Care Framework highlights the importance of a stimulating and nurturing environment. Most studies of childhood cognitive development are characterized by cross-sectional analyses at key ages (e.g., school readiness or the first 1000 days) to identify drivers.

WHAT THIS STUDY ADDS: In our longitudinal approach from 6 to 60 months of age, we identified early life factors including a stimulating environment, maternal education, illness, and infant and young child feeding that differentiate patterns of cognitive development across low- and middle-income settings.

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Children living in poverty are disproportionately likely to have constrained development.[1] Multiple factors inhibit development including repeated infections and illness, low intake of a nutritious diet, and a less nurturing family environment. Particularly sensitive windows of development have been highlighted;[2] however, studies in which researchers examine characteristics of longitudinal patterns of infant development in low- and middle-income countries are needed. Such continued follow-up allows for better interpretation of infant assessments, which have low-to-moderate predictive power.[3]

Considerable attention has been devoted to the first 1000 days of life as a critical period in child development. However, more recent work has argued that the second 1000 days may be more influential in establishing a platform for cognitive development.[4] Along with others, we have previously shown that a supportive and stimulating home environment is positively associated with development at 5 years of life, whereas enteropathogen exposure from birth to 2 years, mediated by symptomatic illness, negatively impacted cognitive scores at 2 years but not at 5 years.[5,6] This supports the argument that fostering a stimulating and nurturing environment, as laid out in the Nurturing Care Framework,[7] is beneficial throughout the pre-school years. In contrast, reducing exposure to enteropathogens is likely to be beneficial in the short-term but may have a lesser impact on shaping the overall pattern of development.

In this study, we examine groups of trajectories of early cognitive development using 4 time points from 6 to 60 months of age in the Etiology, Risk Factors, and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health and Development (MAL-ED) cohort of children who were sampled intensely over the first 2 years of life. Building on our earlier work, which described the effects of variables on the mean of the study population, we now evaluate if there are distinct trajectories of cognitive development that can be differentially identified by early life factors. With this work, therefore, we leverage longitudinal observations of cognitive trajectories to characterize subpopulations who are most at risk and identify early life adversity factors on which to intervene.

METHODS

Study Design

The MAL-ED study was a multidisciplinary prospective community-based observational birth cohort study at 8 low- and middle-income sites[8]: Dhaka, Bangladesh; Fortaleza, Brazil; Vellore, India; Bhaktapur, Nepal; Loreto, Peru; Naushero Feroze, Pakistan; Venda, South Africa; and Haydom, Tanzania. Sites were selected because of historically high rates of malnutrition and diarrheal disease. Each site recruited $\geq$200 singleton children within the first 17 days of life who were managed until 24 months of age. Additional funding allowed follow-up at 5 years. Children were eligible for enrollment if they had no health problems at birth, weighed $>$1500 g, their mother was $>$16 years old, and the family planned to stay in the study area for $>$6 months. The study design has been published,[8] and brief details are provided below. Each site obtained institutional ethical approval and written consent from caregivers for the original and follow-up studies.

Cognitive Development

A modified version of the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) was administered at 6, 15, and 24 months. Adaptations included changes to enhance cultural relevance following best practices[9]: redrawing pictures (or replacing photographs) to locally relevant equivalent images and dropping culturally inappropriate items to ensure that the test was appropriate in each population. Pooling data between sites was supported by detailed psychometric analysis (eg, exploratory and confirmatory factor analyses, multiple indicator multiple cause modeling), refining items to just those that were consistent and reliable across all sites.[10] In this article, the cognitive subscale is used.[11]

At 60 months, the Wechsler Preschool and Primary Scale of Intelligence, Third Edition (WPPSI-III) was used to assess cognitive function, again with culturally appropriate adaptations. Detailed psychometric analyses were conducted as before and yielded a fluid reasoning factor composed of items from the block design, matrix reasoning, and picture completion subscales that was consistent and reliable across all MAL-ED sites.[12]

For analyses, we required three assessments per child, including the WPPSI-III at 60 $\pm$ 2 months. Rigorous quality control and assurance meant eliminating data from the Tanzanian (issues with standardized administration) and Peruvian (WPPSI-III data unavailable) sites. Additionally, the psychometric analysis of the 24-month BSID-III showed that the Nepalese data were inconsistent with the data from other sites and could not be pooled (although valid within-site),[10] hence these data were also excluded because dropping the 24-month observation for all Nepalese children would introduce a systematic bias.

Determinants of Cognitive Trajectories

Our aim with these analyses was to identify factors from early life that distinguished membership in the cognitive trajectory groups. Candidate variables were drawn from an underlying conceptual model that

was used to identify factors influencing development at the 24- and 60-month assessments.[5,6] Briefly, 58 variables describing illness (personal prevalence of diarrhea, fever, vomiting, and acute lower respiratory infection [ALRI] between 0 and 24 months)[13] and enteropathogen exposure (average number of pathogens detected per monthly [first year] or quarterly [second year] nondiarrheal stool samples and additionally by category of pathogen),[14] complementary feeding intake (nutrient densities [per 1000 kcal] from monthly 24-hour recalls, 9–24 months),[15] nutrient status (mean plasma concentration of hemoglobin, zinc, retinol, ferritin, and transferrin receptor from 3 blood draws: 7, 15, 24 months), biomarkers of gut function (mean monthly or quarterly concentration in the first and second year respectively of myeloperoxidase, neopterin, and α-1-antitrypsin),[16] size at birth (weight-for-age *z* score at enrollment), weight gain velocity (from enrollment to 2 months old), socioeconomic status (a count of specified household assets, mean monthly household income, years of maternal education and whether the child had schooling),[17] and the Home Observation for Measurement of the Environment (HOME) Inventory[18] at 6, 24, and 60 months were subjected to psychometric analyses (see Supplemental Information for details).[19] At the 6- and 24-month assessments, 3 factors were identified that described the environmental safety of the home, child cleanliness, and the emotional and verbal responsivity of the caregiver. The 60-month HOME psychometric assessment resulted in a single factor characterizing the support for learning that was present in the household. Maternal reasoning was assessed using the Raven Progressive Matrices[20] when the child was between 6 and 8 months old, and a single factor was supported in psychometric analyses. Maternal depressive symptoms were evaluated at 1, 6, 15, 24, and 60 months by using the Self-Reporting Questionnaire-20[21]; a single factor was reported in the psychometric analyses,[22] but data from Brazil could not be pooled with the other sites for the 1- to 24-month time points, whereas all sites could be pooled at the 60-month time point. For these analyses, we chose to include the 60-month assessment because it was correlated (0.4–0.6) with the earlier time points and was useful across all sites.

Statistical Analysis

Cognitive assessments at each of the 4 ages were converted into *T* scores to eliminate differences in the scale of each assessment.

Groups of children with similar trajectories were identified using latent class-mixed models. Latent class models identify heterogeneous subgroups[23] rather than fit a mean curve to the population. Each group can therefore respond differently to the same suite of exposures and consequently follow a different path. Cognitive scores were modeled as a function of age, and these parameters were allowed to vary by trajectory group. A random intercept was included for the site of each child, which was considered a structural rather than explanatory factor. The optimum number of classes was determined statistically by using the Akaike information criterion. Trajectories were then reviewed visually, and those with few children that were similar (in shape and mean *T* score values) were combined to simplify the interpretation.

Discriminant analysis was then used to identify variables that differentiate between the latent classes. Linear discriminant analysis with shrinkage and correlation-adjusted Student *t* (CAT) scores was used to account for correlation between independent variables.[24] Each variable was used individually to discriminate between trajectory groups and the agreement between the latent classes and those predicted by the discriminant analysis were compared with Cohen κ. Variables were then filtered using the univariate κ statistic, retaining those with $\kappa \geq 0.1$. Retained variables were entered into a multivariable discriminant analysis (both altogether and sequentially), and the sum of the squared CAT scores gives a summary of the relative importance for each variable.[25] Missing values for 0.5% of the exposure data were imputed (using predictive mean matching from multiple imputation chain equations and 10 imputations, see Supplemental Information). Analyses were performed in R 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Cognitive data were included from 835 children from 5 sites (Bangladesh, India, Pakistan, Brazil, and South Africa). The children represented 75% to 98% of those re-enrolled at 5 years. Descriptive child and family characteristics are provided in Table 1. There were considerable differences across sites in maternal education that ranged from a median of 11 years (Brazil and South Africa) to 2 years (Pakistan), mean monthly household income (US$349 in Brazil and US$72 in India), enrollment weight-for-age *z* score (0.04 in Brazil and −1.29 in Pakistan), duration of exclusive breastfeeding (110 days in Bangladesh but only 12.5 days in Pakistan), and proportion of the first 2 years of life when the mother reported symptoms of child illness (most respiratory) that was much higher in Pakistan (32%) than other sites (6% averaged across all other sites).

Trajectories

Six latent trajectory groups were found; however, 2 had visually similar profiles and few children in each (*n* =

TABLE 1 Selected Characteristics of the Analytic Population

Variable	Dhaka, Bangladesh	Fortaleza, Brazil	Vellore, India	Naushero Feroze, Pakistan	Venda, South Africa
Sex, *n* (%), male	89 (51.6)	36 (58.1)	111 (46.4)	93 (51.6)	81 (51.2)
First child, *n* (%)	72 (39.1)	27 (31.4)	68 (33.2)	42 (21.9)	60 (36.1)
Enrollment wt-for-age, *z* score, median (IQR)	−1.09 (−1.79 to −0.54)	0.04 (−0.57 to 0.68)	−1.02 (−1.75 to −0.48)	−1.29 (−1.94 to −0.68)	−0.24 (−0.9 to 0.33)
Exclusive breastfeeding, d, median (IQR)	110 (66 to 157)	78 (29 to 132)	81 (43 to 113)	12.5 (7 to 15)	26 (15 to 46)
Reported child illness,% d, 0–24 mo, median (IQR)	13 (9 to 18)	1 (0 to 2)	9 (6 to 13)	32 (22 to 48)	1 (1 to 2)
Number of household assets, 0–8, median (IQR)	3.3 (2.0 to 4.4)	7.3 (6.8 to 7.5)	3.5 (2.3 to 5.3)	2.5 (1.0 to 4.3)	7.3 (6.3 to 7.8)
Household monthly income, $, median (IQR)	116 (85.9 to 154)	349 (315 to 419)	71.7 (57.5 to 97.9)	143 (88.5 to 219)	232 (164 to 375)
Maternal education, y, median (IQR)	5 (2 to 7)	11 (8 to 12)	8 (4 to 9)	2 (0 to 5)	11 (9 to 12)

61 and 80); they both increased from 6 months, then declined from 24 to 60 months, and differed only in the mean 15-month BSID-III. Therefore, we combined these 2 groups, leaving 5 trajectories (Fig 1): children with consistently "high" scores throughout; children with "increasing" scores; children with intermediate scores that had an "early" decline or "late" decline; and children with consistently "low" scores. The sample size differed considerably between groups, with 2 groups (high and low) accounting for 61% (506 of 835) of the sample.

Differentiating Trajectory Groups

Discriminant analysis scores for the 58 variables are shown in the Supplemental Information and those with some discriminatory power ($\kappa \geq 0.1$) are shown in Fig 2. The cumulative κ statistic, indicating the accuracy of the discriminant analysis, plateaued at 8 variables: 3 aspects of the home environment (environmental safety, support for learning, and the caregiver's emotional and verbal responsivity), maternal reasoning ability, the proportion of days (0–24 months) for which the child had symptoms of illness, the mean nutrient densities of zinc and phytate, and the total energy from complementary foods (all from 9 to 24 months).

Additional variables had diminishing discriminating power. Notably, the next ranking variables also described the home environment from earlier times points, maternal characteristics (both education and depressive scores), and additional nutrient densities from non–breast milk foods. The mean subclinical pathogen detection rate was also relatively highly ranked. Factors such as child sex, anemia, weight-for-age at enrollment, and household assets and income were found to have little discriminatory power (Supplemental Fig 4).

The 17 factors with univariate discriminatory power (Fig 2) were "fairly accurate" (Cohen κ, 0.34; 95% confidence interval, 0.29–0.39) (Table 2) in determining membership in the 5 trajectories from the latent class-mixed model. Their individual contribution to overall classification accuracy is shown in Fig 2. The 2 largest trajectory groups were most accurately classified (>60% correct in the case of both high and low), and the smaller clusters were less accurate (39%–47% correct). The distributions of each of these factors is compared in Table 3.

Radar plots contrast the profiles of the 8 most-discriminatory factors influencing membership in each group (Fig 3). Stimulating and nurturing aspects of the home environment and maternal reasoning ability were strongly positively associated with the consistently high or increasing trajectories and strongly negatively correlated with the early and low groups. The late group had positive correlations with earlier (24 month) descriptions of a safe environment and maternal reasoning ability but a null correlation with the later (60 month) assessment of support for learning.

Aspects of complementary feeding also influenced membership across trajectories. Greater energy intake was positively associated with the high group and negatively associated with the late and low groups. The combination of zinc and phytate densities is informative for differentiating the various groups. Higher zinc density and lower phytate density are associated with the increasing group, but the reverse is true for the early group. Greater zinc and phytate densities are associated with the late group but are negatively associated with the low group.

As shown, illness prevalence was strongly positively associated with membership in the low group and more weakly with membership in the early group. In contrast, greater time spent ill was negatively associated with the high, increasing, and late groups.

DISCUSSION

We describe 5 clusters depicting differing trajectories of development in resource-limited settings. A harmonized protocol with rigorous quality control and extensive psychometric analyses to support pooling of cognitive development

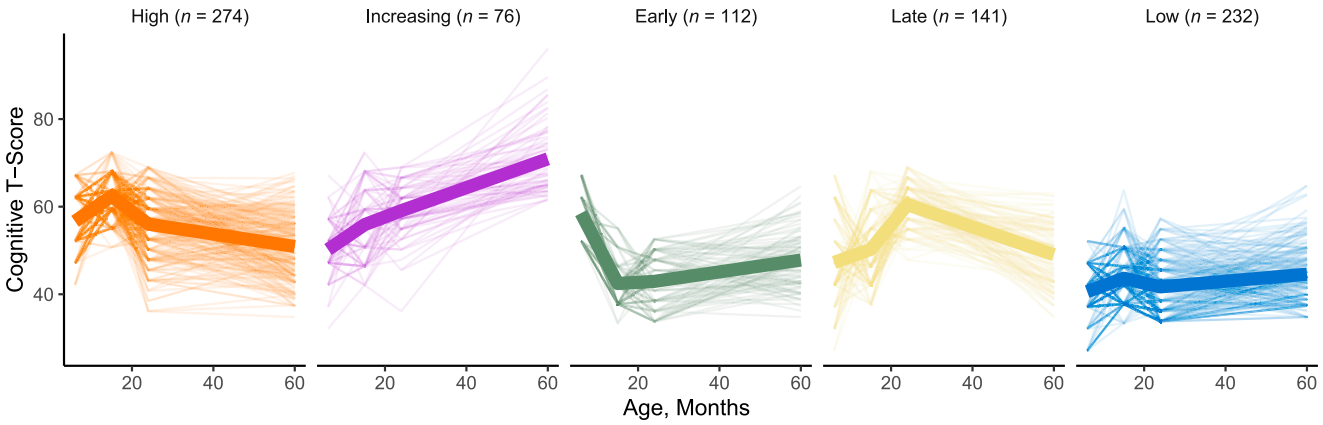

FIGURE 1

Profiles of the five latent classes; the bold line shows the mean of each trajectory group. Six classes were identified statistically, but two sparse and similar groups were combined into the late group. The number of children in each class is shown above each plot.

assessments across settings permitted this novel analysis. Because of the rich multidisciplinary focus in the study, we were able to evaluate a wide range of influences on child development over time. This study represents a unique opportunity to consider the developmental paths of pre-school aged children and the role of early environmental factors influencing those paths.

The contrasts between life experiences of children in the positive trajectories of the high and increasing groups and children in the low group, a concerning pattern of development, are most striking. The

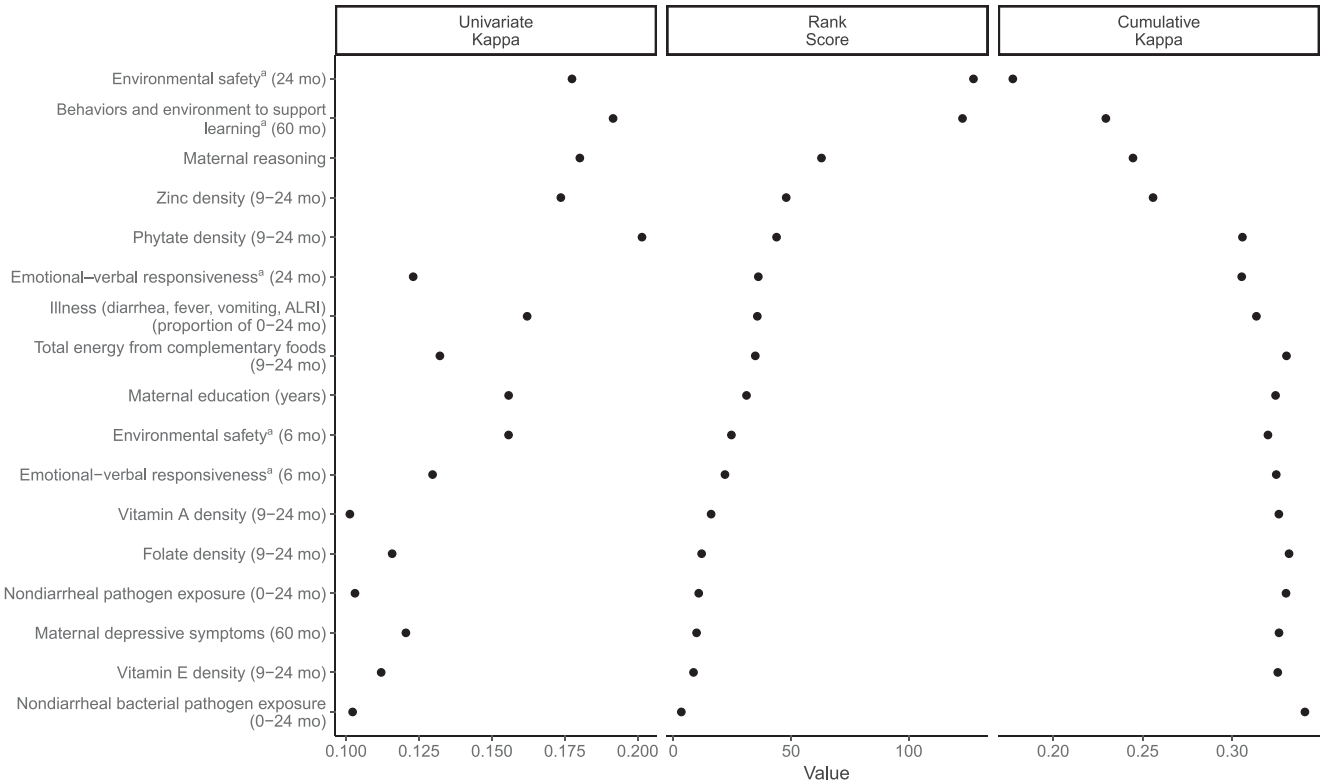

FIGURE 2

Left: the κ agreement between univariate linear discriminant analysis and the latent class model, only showing variables with κ ≥ 0.1. Middle: the multivariable sum of the CAT gives a rank score of the contribution of each variable to the overall discriminant analysis. Right: the cumulative (included from top to bottom) contribution of each variable to the κ agreement of the multivariable discriminant analysis model. [a] Factors derived from HOME Inventory.

TABLE 2 Matrix of Classification Errors by the Latent Class Model and Discriminant Analysis Based on the 17 Variables Shown in Fig 2

Discriminant Analysis	Latent Class-Mixed Model				
	High	Increasing	Early	Late	Low
High	198	34	28	65	33
Increasing	18	24	0	13	10
Early	4	1	11	7	6
Late	19	5	16	27	10
Low	35	12	57	29	173

Values give the number of children in each trajectory group.

most discriminating factors were aspects of the home environment with higher nurturing associated with the high and increasing groups and less nurturing associated with the low group. Our assessment of the home environment captured the opportunities, constraints, and demands afforded to these children within the context of their home environments. Although there are societal differences in parenting behavior, there is strong evidence that provision of certain experiences to children within their home context is universally related to child adaptive functioning and development. These experiences include (1) warmth and responsiveness, (2) discipline and control, and (3) stimulation and teaching.[26–28] Indeed, accumulating evidence reveals that parental participation in cognitively stimulating activities like reading, provision of child-appropriate learning materials, and sensitive and responsive interactions between caregiver and child are significant contributors to optimal child development.[29–31] The MAL-ED

TABLE 3 Mean (Interquartile Range) of the Observed Data From the 17 Variables That Most Discriminated Between Trajectory Groups, Shown in Order of Most to Least Discriminatory

Trajectory Group	Time, mo	Units	High	Increasing	Early	Late	Low
Environmental safety*	24	*z* score	0.4 (0.7 to 0.7)[a]	0.4 (−0.1 to 0.7)[a]	−0.3 (−1 to 0.7)[b]	0.4 (−0.1 to 0.7)[a]	−0.7 (−2 to −0.1)[b]
Behaviors and environment to support learning*	60	*z* score	0.40 (0.01 to 0.82)[a]	0.28 (−0.1 to 0.71)[a]	−0.15 (−0.6 to 0.21)[b]	0.11 (−0.2 to 0.21)[c]	−0.18 (−0.4 to 0.21)[b]
Maternal reasoning	6–8	Score (0–45)	31 (24 to 40)[a]	32 (26 to 41)[a]	25 (12 to 36)[b]	28 (18 to 38)[a,b]	19 (8 to 28)[c]
Zinc density	9–24	sqrt, g per 1000 kcal	2.2 (1.9 to 2.5)[a]	2.3 (1.9 to 2.9)[a]	2.1 (1.8 to 2.5)[b,d]	2.2 (1.9 to 2.6)[a,d]	1.9 (1.7 to 1.9)[c]
Phytate density	9–24	sqrt, g per 1000 kcal	24 (18 to 26)[a]	19 (17 to 22)[b]	23 (16 to 34)[c]	24 (17 to 34)[a,c]	18 (15 to 19)[d]
Illness**	0–24	% d	9.3 (1.9 to 12)[a]	8.5 (1.7 to 13)[a]	17 (1.2 to 27)[b]	9 (1.2 to 13)[a]	25 (9.2 to 37)[c]
Total energy from complementary foods	9–24	kcal/d	790 (600 to 970)[a]	720 (540 to 890)[a,c]	700 (490 to 880)[a]	650 (380 to 880)[b,c]	580 (360 to 770)[b]
Emotional–verbal responsiveness*	24	*z* score	0.3 (0.3 to 0.8)[a]	0.1 (−0.1 to 0.8)[b,c]	−0.3 (−0.6 to 0.3)[b,e]	0.2 (−0.1 to 0.8)[a,c]	−0.4 (−1 to 0.3)[d,e]
Maternal education	—	y	7.6 (5 to 11)[a,c]	8.7 (6 to 12)[a]	6.2 (0.75 to 10)[c]	7.4 (5 to 10)[a,c]	4.1 (0 to 8)[b]
Environmental safety	6	*z* score	0.3 (0.6 to 0.6)[a]	0.2 (−0.5 to 0.6)[a,b]	−0.1 (−0.5 to 0.6)[b,c]	0.2 (−0.5 to 0.6)[a,c]	−0.5 (−2 to 0.6)[b]
Emotional–verbal responsiveness*	6	*z* score	0.4 (−0.1 to 1)[a]	−0.1 (−0.9 to 1)[b,c]	0 (−0.9 to 1)[b,c]	0.1 (−0.5 to 1)[b]	−0.4 (−1 to 0.2)[c]
Vitamin A density	9–24	sqrt, g per 1000 kcal)	18 (14 to 20)[a]	20 (14 to 29)[b]	17 (13 to 20)[a,d]	17 (12 to 21)[b,d]	15 (11 to 17)[c]
Folate density	9–24	sqrt, g per 1000 kcal	12 (10 to 14)[a,b]	12 (10 to 13)[a]	13 (9.5 to 16)[b]	13 (9.9 to 16)[b]	11 (9.5 to 11)[c]
Nondiarrheal pathogen exposure	0–24	Count	1.1 (0.69 to 1.3)[a]	1.1 (0.82 to 1.3)[a]	1.2 (0.81 to 1.6)[a,b]	1 (0.73 to 1.3)[a]	1.4 (1 to 1.7)[b]
Vitamin E density	9–24	sqrt, g per 1000 kcal	1.6 (1.3 to 1.9)[a]	1.6 (1.3 to 1.8)[a]	1.6 (1.2 to 2)[a]	1.6 (1.3 to 2)[a]	1.4 (1.2 to 1.6)[b]
Maternal depressive symptoms	60	Count, 0–18	2.7 (1 to 4)[a]	3.4 (1 to 5)[a,c]	4.4 (1 to 7)[b,c,d]	3.7 (1 to 5)[a,d]	5 (2 to 7)[b,c]
Nondiarrheal bacterial pathogen exposure	0–24	Count	0.79 (0.54 to 1)[a]	0.83 (0.59 to 1)[a]	0.85 (0.6 to 1.1)[a,b]	0.78 (0.5 to 1)[a]	0.98 (0.75 to 1.2)[b]

Values within a row with different superscript letters are significantly different ($P \leq .05$ with Bonferroni correction tested using Kolmogorov–Smirnov tests). sqrt, square root; —, not applicable.

* HOME *z* score with higher scores indicating a more stimulating and responsive environment.

** Illness defined as the percent of days between 0 and 24 mo with reported diarrhea, fever, vomiting, or ALRI.

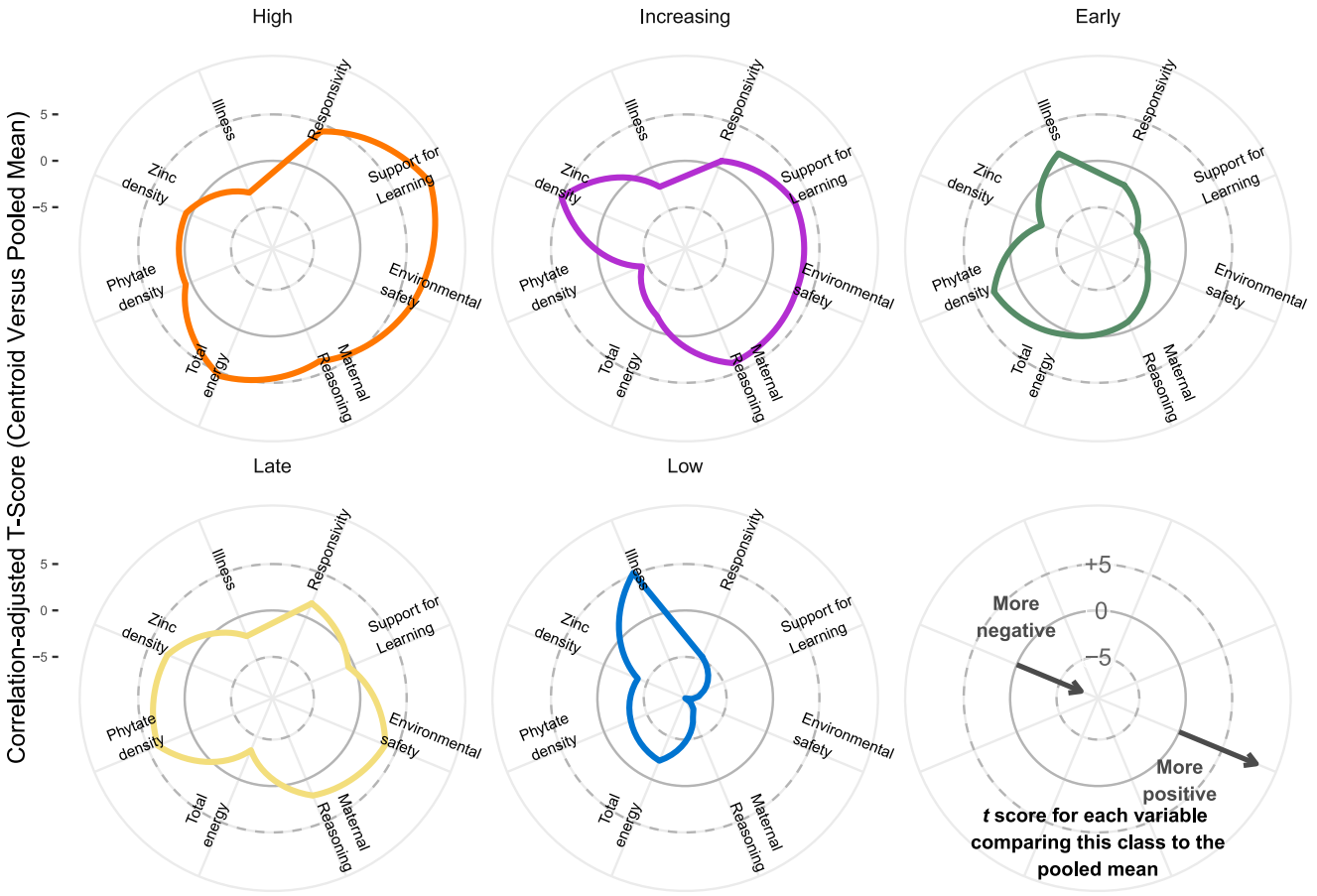

FIGURE 3

Profiles for each trajectory group showing the CAT comparing each group to the pooled mean for the top 8 discriminating variables. Scores that are closer to the center indicate a negative association between a given variable and the probability of belonging to a class; scores that are further to the outer ring have a positive association with the probability of belonging to a class. The solid circle indicates a *t* score of zero, hence no association between the variable and a trajectory class.

children live in settings characterized by poverty, and yet those living in a more stimulating and responsive home environment were more likely to be in groups with higher scoring trajectories. Greater maternal reasoning ability may also lead to a more responsive or nurturing environment; here, it is independently associated with cognitive trajectories in the same pattern as aspects of the nurturing home environment. As evidenced in the recent study by Zhu et al,[32] the factors identified in our study as influencing early life trajectories can also differentiate functioning in midchildhood and adolescence.

Higher socioeconomic status is a frequently reported driver of cognitive development.[33] However, in these analyses, aspects of wealth (household income or assets) did not differentiate trajectories despite the fact that both were associated with cognitive development at specific ages.[5,6] We posit that our consideration of multiple aspects of the home environment, more closely associated with behavior and engagement over time, displaced influences associated with wealth.[34,35]

Other key factors differentiating these contrasting groups related to child health and variation in infant feeding practices. The group with consistently low scores was characterized by high rates of illness in the first 2 years of life, higher rates of enteropathogen detection, and lower intakes from complementary foods in terms of energy and densities of zinc and phytate. Chronic illness during childhood is negatively associated with cognitive development and consequently delays school readiness.[36] In our study, we examined the prevalence of symptoms of illness in early life that were related to cognition in our earlier analyses at 24[5] but not 60 months.[6] Infants were excluded from the study if they weighed <1500 g or had serious health problems at birth, which ought to have excluded the most vulnerable children who might be more prone to illnesses; however, despite this, children in the low group had ≥1 illness symptom for an

average 25% of their first 2 years of life. The most common symptoms were respiratory.[13] Combined, the negative roles of illness, infection, and poor infant feeding practices in settings with less promotion of development suggest an identifiable subgroup of vulnerable infants who are at risk for constrained cognitive development.

Higher mean energy from non–breast milk foods was positively associated with the high group, and greater zinc and lower phytate densities were associated with the increasing group. The zinc and phytate densities also influenced membership in the early and late groups. Our earlier analyses found that diets richer in B vitamins were positively associated with cognitive scores at 24 months[5] and that greater intakes of nutrients consistent with animal source foods were positively associated with cognitive scores at 60 months.[6] Analyses at 24 months were determined by specific hypotheses regarding dietary factors, hemoglobin, and cognitive development, whereas those at 5 years broadly considered dietary exposures, as we have done here. In this data set, the zinc density of the diet is associated with iron, folate, and protein densities, and a lower phytate density is associated with a more bioavailable trace mineral diet or a diet with more animal food sources. In this way, our current findings are consistent with our earlier findings.

There were unexpected findings from this analysis, the most notable of which was the relatively weak discriminatory power of maternal depressive symptoms, which is a known correlate with child development, especially through mother–child interactions.[37] In this study, we included maternal depressive symptoms at 60 months in an effort to capture underlying (not postpartum) depression, although considerable development has already occurred. As noted earlier, we chose the latter time point because of its psychometric properties and correlations with earlier assessments. The high univariate association but lower multivariate association between maternal depressive symptoms and the trajectory groups suggests that maternal depression covaries with other aspects of the nurturing environment, which were captured by other included variables. Anemia and micronutrient deficiencies,[38] and gut inflammation[39] in the first 2 years of life, were weakly associated with trajectory groups. If data were available on micronutrient deficiencies or gut inflammation after 24 months, it is possible that we may have found an association. This temporal resolution (high in the first 2 years but low thereafter) is a limitation of the study, as was the loss of children to follow-up after the original study had ended. Additionally, the rigorous requirements for inclusion meant that we necessarily excluded some children and some sites from analyses. As children get older, the importance of their microenvironment diminishes as the mesoenvironment becomes increasingly influential.[40] Although the original study design did not capture this expanding web, the breadth of domains that were measured is unique, and with these results, we identify early drivers of cognitive development across markedly different populations using common (and validated) methods.

Even with the breadth of variables collected, the classification agreement between the discriminant analysis and latent classes was at best "fair" (including all variables), and only then for the more populous trajectory groups. The sparser groups (notably the early and late groups) were poorly cross-classified, and some 16% (12 of 76) from the increasing group were assigned to the low group. Figure 1 reveals considerable variability and overlap between groups. It is likely that additional or combined factors were missing from these analyses, but the variables that did emerge to either constrain or support cognitive development fit within the existing evidence of a pattern of vulnerability and the potential of a nurturing environment to make a positive difference. Importantly, these results suggest that positive impacts can be made in the postnatal period, for example, teaching optimal caregiver behaviors through educational sessions and learning opportunities with children including semistructured play and access to materials.[41–44] With our analyses, we point to patterns that may help identify subpopulations of children who would benefit the most from interventions and also indicate aspects of the environment on which to intervene.

CONCLUSIONS

Despite their impoverished environments, some children had preferable trajectories of cognitive development through age 60 months. Such patterns were characterized by fewer illnesses, a more nutrient dense diet from complementary foods, having a mother with greater reasoning ability, and, crucially, living in a home with a more nurturing and stimulating environment over the pre-school period. Although we cannot provide causal evidence, with our findings, we support the need for strengthening comprehensive services to improve child health, nutrition, and the responsivity of the home environment to support cognitive development[45] and suggest that specific early life characteristics can identify a group of children at high risk who would benefit from additional inputs to support their development through the pre-school period.

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ABBREVIATIONS

ALRI: acute lower respiratory infection
BSID-III: Bayley Scales of Infant and Toddler Development, Third Edition
CAT: correlation-adjusted Student *t*
HOME: Home Observation for Measurement of the Environment
MAL-ED: The Etiology Risk Factors and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health and Development
WPPSI-III: Wechsler Preschool and Primary Scale of Intelligence, Third Edition

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