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# Cumulative Febrile, Respiratory, and Gastrointestinal Illness among Infants in Rural Guatemala and Association with Neurodevelopmental and Growth Outcomes

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## Abstract

**Background:** Infectious disease exposures in early life are increasingly recognized as a risk factor for poor subsequent growth and neurodevelopment. We aimed to evaluate the association between cumulative illness with neurodevelopment and growth outcomes in a birth cohort of Guatemalan infants.

**Methods:** From June 2017 to July 2018, infants 0–3 months of age living in a resource-limited region of rural southwest Guatemala were enrolled and underwent weekly at-home surveillance for caregiver-reported cough, fever, and vomiting/diarrhea. They also underwent anthropometric assessments and neurodevelopmental testing with the Mullen Scales of Early Learning (MSEL) at enrollment, six months, and one year.

**Results:** Out of 499 enrolled infants, 430 (86.2%) completed all study procedures and were included in the analysis. At 12–15 months of age, 140 (32.6%) infants had stunting (length-for-age Z [LAZ] score <-2 SD) and 72 (16.7%) had microcephaly (occipital-frontal circumference [OFC] <-2 SD). In multivariable analysis, greater cumulative instances of reported cough illness (beta=-0.08/illness-week, p=0.06) and febrile illness (beta=-0.36/illness-week, p<0.001) were marginally or significantly associated with lower MSEL Early Learning Composite (ELC) Score at 12–15 months, respectively; there was no association with any illness (cough, fever, and/or vomiting/diarrhea; p=0.27) or with cumulative instances of diarrheal/vomiting illness alone (p=0.66). No association was shown between cumulative instances of illness and stunting or microcephaly at 12–15 months.

**Conclusions:** These findings highlight the negative cumulative consequences of frequent febrile and respiratory illness on neurodevelopment during infancy. Future studies should explore pathogen-specific illnesses, host response associated with these syndromic illnesses, and their association with neurodevelopment.



### Keywords

fever; cough; neurodevelopment; Guatemala; Mullen Scale of Early Learning (MSEL)


## INTRODUCTION

Among children under 5 years of age living in low- and lower middle–income countries (LMICs), an estimated 43% are at risk for not meeting their neurodevelopmental potential.[1,2] Neurodevelopmental problems likely result from the cumulative environmental exposures of living in poverty, including elevated risk of adverse birth outcomes, malnutrition, infectious and non-infectious disease-related inflammation, and psychosocial stressors, among others.[1]

These risk estimates of children are based largely on the global prevalence of stunting. Stunting, defined as <-2 SD below the mean in height/length-for-age, shares risk factors with neurodevelopmental delay, such as chronic malnutrition and enteric disease/dysfunction. Recent evidence suggests, however, that despite this overlap, the pathophysiology of each of these two outcomes (neurodevelopment and stunting) is likely unique and complicated by multiple clinical and environmental factors, and distinct inflammatory phenotypes.[3–7]

Recurrent enteric disease and dysfunction have been tied to both poor neurodevelopment and stunting.[1,8] However, the role and pathogenesis of other types of recurrent infectious diseases, such as febrile and respiratory illnesses, is less well understood. A longitudinal birth cohort study from Bangladesh found that recurrent febrile illness and cytokine profiles associated with both enteric and systemic inflammation were associated with neurodevelopmental delays among infants living in informal urban settlements (slums).[5–7,9] To our knowledge, this finding has not been replicated in other populations.

Similar to Bangladesh, Guatemalan children suffer from high rates of communicable illness and similar adverse environmental exposures, including the highest prevalence of stunting (49.8%) in the Americas and the sixth highest prevalence of stunting among children under five in the world.[10–14] We recently completed a longitudinal cohort study (DMID 16–0057) to evaluate the neurodevelopmental outcomes following postnatal Zika virus infection among infants living in rural, southwest Guatemala. The study, which included weekly syndromic illness data collection and extensive neurodevelopmental testing, providing an opportunity to conduct this secondary analysis exploring the association between caregiver-reported infectious illness symptoms with growth outcomes (i.e., stunting and microcephaly) and neurodevelopment in this community-based infant cohort.

## METHODS

We conducted a secondary analysis of a prospective cohort study of infants and young children at the University of Colorado-associated Center for Human Development (CHD) in the rural lowlands of southwest Guatemala. The site encompasses primarily rural communities with approximately 25,000 residents and is located approximately 30 km from the border of Chiapas, Mexico. These communities are monolingual Spanish-speaking. The population suffers from high rates of year-round food insecurity and child undernutrition, diarrheal disease, maternal depression, and maternal and child morbidity and mortality.[15–17] Community-based care programs are limited to those provided by the CHD.

From June 2017 to July 2018, 499 infants and their mothers were enrolled at 0–3 months of age into the parent study, which leveraged an existing maternal-child health program to identify a convenience sample of mothers/infants in the community. Per study design,[18] there were no exclusion criteria other than living outside the study catchment area and inappropriate age, though children who were acutely unwell at the time of study screening were referred for medical evaluation and enrollment deferred. Gestational age and intrauterine growth are typically unknown in this community, though the cohort[19] and community[20] have a high prevalence of microcephaly. ZIKV infection status was unknown at the time of enrollment. In summary the cohort is comprised of a representative sample of children from the community who were not acutely ill at the time of enrollment.

In this secondary analysis, we included enrolled subjects who had complete outcome data at 12–15 months. Enrollment included collection of baseline demographic, epidemiologic, clinical, anthropometric, and neurodevelopmental data. Mother and father's literacy (yes/no) and education were self-reported at enrollment, with education being reported on a 4-point scale (mother/father had completed no, primary, secondary, or university/postgraduate

education). Households were queried for food insecurity at enrollment using three questions asking if, in the preceding 4 weeks: 1) the household didn't have any food due to lack of resources, 2) if anyone went to bed hungry because there was not enough food, or 3) if anyone in the household went a whole day without eating because there was not enough food.[21,22] Anthropometric data were collected at enrollment and 3-month intervals on children, and at enrollment and final visit for mothers. Length-for-age z scores (LAZ) were calculated to determine stunting, defined as >2 standard deviations (SDs) below the mean on World Health Organization (WHO)-defined growth curves.[23] Head circumference was determined by taking the mean of two occipital-frontal circumference (OFC) measurements using the Seca 211 Head Circumference Measuring Tape (12–59 cm) following standard operating procedures, and microcephaly was defined as <2 standard deviations below the mean on WHO-defined growth curves.

Infants underwent neurodevelopmental testing by trained Guatemalan psychologists, supervised by bilingual US-based neuropsychologists. Neurodevelopmental testing included the Mullen Scales of Early Learning (MSEL) with rigorous procedures previously described.[24] The MSEL is comprised of five subscales: Gross and Fine Motor, Expressive and Receptive Language, and Visual Reception. The scores from four of the scales (excluding Gross Motor) are then summed to create the Early Learning Composite Score. The instrument underwent extensive validation and adaptation to the local population at the study site in Guatemala.[25,26] Guatemalan children are not represented in the US norming sample of the original, English-version of the MSEL. Therefore, raw scores adjusted for age were used in all analyses instead of standard scores, which is best practice for translated and adapted tests.[27] This also helped us to detect more subtle differences among this group of children with multiple shared neurodevelopmental risk factors.

Following enrollment, households were visited weekly by trained study nurses, and caregivers were asked to report presence/absence of each of the following symptoms in the week (last 7 days) preceding their surveillance visit: fever, cough, vomiting/diarrhea (≥3 loose stools/day), rash, conjunctivitis (non-purulent/hyperemic), arthralgia, myalgia, or peri-articular edema. The weekly household visits were continued for 12 months. Anthropometric data were collected, and medical examination and neurodevelopmental assessments (including the MSEL) were also conducted at 6–9 and 12–15 months of age on all children.

Descriptive statistics were used to characterize the study population. Univariate and multivariable linear and generalized linear regression models were used to test associations between cumulative instances (weeks in which symptoms were reported) of each syndromic illness of interest (fever, cough, vomiting/diarrhea, or any of the three illnesses) in infancy (exposures), and 12–15-month MSEL Early Learning Composite (ELC) score (continuous outcome), MSEL subscale scores (continuous outcome), stunting (dichotomous outcome), and microcephaly at 12–15 months (dichotomous outcome). Beta estimates are presented for continuous outcomes, and relative risks (RR) are presented for dichotomous outcomes. After identification of potentially relevant confounders via review of the literature, we conducted a bivariate analysis, adjusted for age at MSEL collection, of the following individual variables for association with MSEL scores, stunting, and microcephaly: sex,

maternal height, maternal/paternal literacy, maternal/paternal education, housing material (proxy for socioeconomic status), food insecurity, community (dichotomized into 'high risk for infectious illness' vs. 'not high risk for infectious illness'), and breastfeeding status at study completion. Communities at "high risk for infectious illness" were defined as communities that had significantly greater reporting of instances of syndromic illness ($p<0.05$, Mann Whitney U Test) than the overall mean.

We then selected all variables with a p-value <0.20 in the univariate analysis to be included in the multivariate analysis. In the case of stunting and microcephaly, any variable with a p-value <0.20 for either of these anthropometric outcomes was included in the multivariate analyses for both outcomes. We assessed collinearity of the education variables (maternal/paternal literacy and education) using Spearman correlation coefficients and chose maternal education as the most relevant variable to include in the multivariable analyses. As enrollment occurred after birth, and gestational age and birth weight are rarely documented in this community (and so retrospective caregiver-report is the only available data), those potential confounders were not considered for these multivariable models. Multivariable models of MSEL outcomes were not adjusted for stunting, which is a separate 12–15-month outcome that shares complex and incompletely overlapping causal pathways with neurodevelopment.[28–33]

All descriptive analyses and regression modeling were conducted using SAS version 9.4 (SAS Institute, Cary, NC) and maps were created in ArcGIS Pro (Esri, Redlands, CA). Global Positioning System (GPS) coordinates of households were used to map cumulative syndromic illness by geolocation. Instances (weekly reports) of illness for fever, cough, vomiting/diarrhea, and any illness were averaged by community to visualize the spatial distribution of disease burden. The averages for each community were compared to the average of all other communities using the Mann Whitney U Test ($p<0.05$), to identify communities with significantly greater disease burden ('high risk for infectious illness').

The study protocol was reviewed and approved by the Institutional Review Board at Baylor College of Medicine, the Colorado Multiple Institutional Review, the National Ethics Committee of the Guatemalan Ministry of Public Health and the local Community Advisory Board in Trifinio, Guatemala.

## RESULTS

Of 499 enrolled infants in the parent study, 430 (86.2%) completed the 12-month study and were included in this analysis. The analysis cohort had a mean enrollment age of 1.45 months; 223 (51.9%) were male, 392 (91.4%) had mothers who self-reported functional literacy skills, and 323 (75.5%) were breastfeeding at study completion (Table 1). Over the 12 months of observation, infants had caregiver-reported illness for a median of 16 weeks (IQR 10–22 weeks). Cough was reported most frequently (median=11 weeks, IQR 7–17 weeks), followed by diarrhea/vomiting (5 weeks, IQR=3–8 weeks), and fever (3 weeks, IQR=1–5 weeks). Male infants had a somewhat higher incidence of febrile illness than females (17.3 vs 15.9 weeks, $p=0.07$). There were no instances of PCR-confirmed ZIKV infection in any infant during the course of the study.

## Neurodevelopment

In univariate regression models to identify potential confounders of our primary outcome, higher MSEL ELC Score at 12–15 months was significantly associated with the following variables: maternal height (β=0.23, CI=0.13 – 0.33, p<0.001), maternal literacy (β=3.97 CI=1.90 – 6.05, p<0.001), maternal education (β=2.03, CI=1.22 – 2.85, p<0.001), child not breastfeeding at 12–15 months (β=-1.63, CI=-1.63 - -0.28, p=0.02), paternal education (β=0.89, CI=-0.001 – 1.79, p=0.05), and living in a community at high risk for infectious illness (β=-2.44, CI=-3.65 – -1.23, p=<0.0001) (Table 2).

After adjusting for variables identified on univariate analysis with p<0.2, the cumulative number of instances with reported cough (beta estimate=-0.08 per illness-week, CI=-0.16 – 0.003, p=0.06) or fever (beta estimate=-0.36 per illness-week, CI=-0.56 - -0.16, p<0.001) had a non-significant trend or were significantly associated with decreased 12–15-month MSEL ELC score (Table 3); there was no association with any illness (cough, fever, or vomiting/diarrhea combined: p = 0.27) or diarrhea/vomiting (p=0.60). Instances of fever were significantly associated or trended towards significance with all ELC subdomain scores at 12–15 months (p=0.055 to 0.002; Table 3). Gross motor subdomain MSEL score at 12–15 months, which is not part of the ELC score, was also significantly associated with cough (beta estimate =-0.05, CI=-0.09 - -0.02, p=0.005), fever (beta estimate =-0.19, CI=-0.28 - -0.11, p<0.001), and total illness weeks (beta estimate =-0.04, CI=-0.07 - -0.005, p=0.02), but not diarrhea/vomiting (p=0.73).

Cumulative syndromic illness was distributed broadly across the study catchment area (see Figures Supplemental Digital Content 1 and 2). However, there were several communities that demonstrated a significantly greater number of instances of illness than the overall mean (p<0.05). Living in a community at high risk for infectious illness was associated with neurodevelopmental outcome but was not associated with the stunting or microcephaly outcomes; thus this ‘high risk for infectious illness’ community variable was included in the multivariable models of neurodevelopmental outcomes, but not the multivariable models of stunting or microcephaly outcomes (Table 3).

**Stunting—**Stunting was common, with 140 (32.6%) infants demonstrating a LAZ <-2 SD at 12–15 months. In univariate analysis, male sex (RR=2.03, CI=1.50 – 2.74, p<0.001), wood/aluminum housing material (RR=1.39, CI=1.04 – 1.86, p=0.02), lower maternal height (RR per -1 cm=0.97, CI=0.96 – 0.98, p<0.001), and lower maternal education (RR=0.82, CI=0.67 – 0.997, p=0.046) were significantly associated with stunting at 12–15 months (see table, Supplemental Digital Content 1). After adjusting for gender, house material, maternal height at end of study, and maternal education, there was no association between caregiver-reported instances of cough, fever, or vomiting/diarrhea and stunting at 12–15 months (Table 3).

## Microcephaly

Microcephaly was also common, with 72 (16.7%) of infants demonstrating microcephaly (OFC <-2SD) at 12–15 months. Microcephaly was significantly associated with male sex (RR=1.64, CI=1.06 – 2.56, p=0.03) and marginally associated with maternal height at the

end of the study (RR=0.97, CI=0.94 - -1.002, p=0.06) on univariate analysis (see table, Supplemental Digital Content 1). After adjusting for sex, house material, maternal height at end of study, and maternal education, there was no association between caregiver-reported cough, fever, or vomiting/diarrheal instances of illness and microcephaly at 12–15 months (Table 3).

## DISCUSSION

We found that cumulative instances of febrile illness in the first year of life were significantly associated with worse neurodevelopmental outcome, and cough trended towards significance. Cumulative instance of syndromic illness did not have an association with stunting or microcephaly. Though some studies have identified harmful effects of cumulative illness in early childhood, including within Guatemala,[11] few have evaluated neurodevelopment in a community-based longitudinal cohort using rigorous procedures with a measure adapted and found to have sufficient validity, then implemented by trained personnel in the assessment of neurodevelopmental outcomes.

Though several factors were associated with lower 12–15-month MSEL score, such as sex, maternal height, breastfeeding, housing type and maternal education, after adjusting for these variables, caregiver-reported instances of fever remained significantly associated with low MSEL, with a decreased MSEL ELC raw score of 0.36 per instance of reported illness (fever was also significantly associated with lower scores for all subdomains individually). In the original, US-normed version of the MSEL, a raw score decrease of 1 point represents an approximate 3-point decrease in the ELC standard score.[24] Therefore, the median 3 (IQR 1–5) instances of febrile illness in the cohort would correspond to approximately a 3-point decrease in the ELC. While this is certainly significant, the clinical implications of this point decrease may not be readily apparent. However, that this finding is significant in only the first-year life is important to consider. If one considers the cumulative impact over time, this may mean that a child experiencing the median number of febrile illnesses each year in a 3-year period could have a resulting decrease in ELC of around a standard deviation if the effect is consistent. For a child experiencing the highest number of febrile illnesses in our sample (5) in a single year, the impact of a single year of illness is about half a standard deviation in ELC score decrease, meaning the child's ELC may be a standard deviation lower in only a 2-year timeframe. Moreover, decades of research have demonstrated that children living in poverty are exposed to many developmental risk factors simultaneously, and no single risk factor wholly explains the neurodevelopmental performance gap that exists between children growing up in poverty and those that are not. Therefore, while further studies are needed over a longer time period to further characterize these outcomes, these findings contributes to the body of literature working to identify all potential influences on neurodevelopment and adverse outcomes, highlighting that recurrent illness (especially febrile illness) may play an important and underrecognized role amongst the many factors impacting neurodevelopment. This finding is also consistent with data from a Bangladeshi birth cohort, which found associations between febrile illness and systemic/enteric inflammatory cytokine profiles and decreased neurodevelopmental performance.[5–7,9] Reported instances of cough did not achieve significance but also trended towards worse neurodevelopmental outcome.

Our findings provide additional insight into the complex pathways driving the neurodevelopment of young children in low resource settings. Accumulating evidence suggests that nutritional deficiency is only one of many contributors to poor neurodevelopmental outcome.[4,8,34,35] Importantly, as was the case with several variables, we did not find an association between cumulative instances of illness and either stunting or microcephaly, supporting the hypothesis that cumulative febrile/respiratory illnesses may not negatively impact neurodevelopment through stunting or its biological consequences, at least in the short term. Accumulating data from multinational cohorts suggest that neurodevelopment may have a related, but distinct causal pathway from stunting.[9,30–33,36,37] Indeed, the aforementioned Bangladeshi cohort found that birth anthropometry and maternal weight were better predictors of growth, while clinical (fever) and biological markers of inflammation were more strongly associated with neurodevelopment.[5–7,9] Though not completely analogous to recurrent infections, mounting evidence suggests that human immunodeficiency virus (HIV)-infected, or even HIV-exposed, uninfected infants and children demonstrate neurodevelopment delays likely attributable to inflammation and immune dysregulation.[38,39] Putting our data into this context, we hypothesize that recurrent infections in our cohort may negatively impact neurodevelopment in the first year of life, possibly through systemic inflammation, and not necessarily through stunting and its biological consequences. Another possibility is that recurrent illnesses may be associated with changes in behavior or environment, such as decreased energy and exploration/stimulation, that results in lower neurodevelopment over time. Further studies may provide greater insight on causality.

Interestingly, we did not find an association between diarrheal illness and stunting or neurodevelopment in our cohort. It is possible that within our population, the impact of diarrhea on growth would become more apparent in the second year of life. A smaller study in the Guatemalan highlands found that indigenous children (mean age 2.6 years) with >1 caregiver-reported illness (all-cause) per month did have increased risk of stunting, though they did not measure neurodevelopment.[40] Other potential explanations are that pathogens in this community differ and/or that background rates of diarrhea are high enough in this community[41] that our case definition (caregiver report of ≥3 loose stools/24 hours) did not adequately differentiate children with and without illness, or what is considered abnormal. Additionally, the type of inflammation and inflammatory pathways in diarrheal illness may be different than respiratory diseases, or they may be pathogen-specific to organisms less prevalent in this community.

Relying on caregiver report of illness was an overall limitation of the study, and our approach did not attempt to differentiate separate illnesses when children reported symptoms during sequential weeks, as this was likely to be inaccurate given the burden of overlapping childhood illnesses in this community. Weekly in-person visits reduced the risk of recall bias. In addition, we found that breastfeeding at 12–15 months was associated with lower MSEL ECL at 12–15 months in both univariate and multivariable analyses and a non-significant increased risk of stunting. This is inconsistent with previously reported research on the protective factors associated with breastfeeding and is difficult to interpret without additional data on breastfeeding and other feeding practices. One potential explanation is that infants still breastfeeding at 12–15 months may have had greater food insecurity and/or

lower socioeconomic status and therefore decreased neurodevelopment. Another hypothesis is that delayed neurodevelopment may lead to continued breastfeeding (reverse causality), and therefore breastfeeding was continued due to delayed neurodevelopment. Other study limitations include our lack of pathogen-specific testing (the number of children with ZIKV exposure were too small to include in multivariable models) and self-reporting of some exposures (literacy, syndromic illness). While food insecurity was only collected at a single timepoint, food production in the community is generally not seasonal, and the prevalence of food insecurity reported in our cohort was similar to a 2016 survey (unpublished) and an ongoing study[42] of agricultural workers within the same community. Finally, we did not look at trajectories in growth outcomes (only absolute measures), and these should be included in future studies.

We did find some geographic heterogeneity in cumulative disease burden, with the three northeastern most communities showing the greatest burden. These findings suggest there may be some associated environmental risk factors (i.e., poverty, shared watershed, population density) that warrant further investigation.

In conclusion, cumulative, caregiver-reported febrile illness in a birth cohort of infants in rural Guatemala was associated with decreased neurodevelopmental outcomes at 12–15 months of age and respiratory illness was marginally associated with worse neurodevelopmental outcome. There was no association with syndromic illness and stunting or microcephaly. Further studies should evaluate for pathogen-specific illness and explore biomarkers of enteric and systemic inflammation, which may provide additional insight into the causal pathway between illness, inflammation, and neurodevelopmental outcome with longitudinal follow up beyond the first year of life.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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**Table 1:**

Subject characteristics of infants who completed study follow-up in rural Southwest Guatemala, 2017–19 (n=430).

| Variable | Mean (SD) |
|---|---|
| Age at enrollment, months | 1.45 (0.73) |
| Age at last study visit (MSEL measured), months | 13.11 (0.84) |
| Maternal height at end of study (cm) | 149.85 (9.20) |
| MSEL Early Learning Composite score | 56.28 (6.72) |
| | **Median (IQR)** |
| # illness instances in first year of life | 16 (10–22) |
| # cough illness instances in first year of life | 11 (7–17) |
| # fever illness instances in first year of life | 3 (1–5) |
| # diarrhea/vomiting illness instances in first year of life | 5 (3–8) |
| | **N (%)** |
| Male sex | 223 (51.9) |
| Ethnicity | |
| Ladino/Mestizo | 106 (24.7) |
| Indigenous | 12 (2.8) |
| Don’t know / not reported | 312 (72.6) |
| Maternal literacy | 392 (91.4) |
| Maternal education | |
| None | 27 (6.3) |
| Primary school | 242 (56.3) |
| Secondary school | 128 (29.8) |
| University/postgraduate | 30 (7.0) |
| Paternal literacy | 340 (93.9) |
| Paternal education | |
| None | 19 (4.4) |
| Primary school | 188 (43.7) |
| Secondary school | 126 (29.3) |
| University/postgraduate | 26 (6.1) |
| Housing material | |
| Cement | 334 (77.7) |
| Wood/Aluminum/other | 96 (22.3) |
| Caregiver-reported food insecurity | 54 (12.6) |
| Child breastfed at 12–15 months | 323 (75.5) |
| Child stunted at 12–15 months | 140 (32.6) |
| Child lives in community at high risk for infectious illness (N = 419) | 145 (34.6) |

**Table 2:**

Bivariate association between demographic and clinical variables and MSEL Early Learning Composite (ELC) Score at 12–15 months

| Variable | Beta estimate, per instance (95% Confidence Interval) | p-value |
|---|---|---|
| # illness instances in first year of life | −0.08 (−0.16 – −0.01) | 0.03 |
| # cough illness instances in first year of life | −0.12 (−0.20 – −0.04) | 0.005 |
| # fever illness instances in first year of life | −0.40 (−0.61 – −0.20) | <0.001 |
| # diarrhea/vomiting illness instances in first year of life | −0.05 (−0.17 – 0.07) | 0.41 |
| Male sex | −1.06 (−2.24 – −0.13) | 0.08 |
| Maternal height (per cm) at end of study | 0.23 (0.13–0.33) | <0.001 |
| Maternal literacy * | 3.97 (1.90 – 6.05) | <0.001 |
| Maternal education * | 2.03 (1.22 – 2.85) | <0.001 |
| Paternal literacy * | 1.05 (−1.59 – 3.69) | 0.44 |
| Paternal education * | 0.89 (−0.001 – 1.79) | 0.050 |
| Housing made of wood/aluminum * | −2.13 (−3.54 – −0.72) | 0.003 |
| Food insecurity * | −1.49 (−3.27 – 0.30) | 0.10 |
| Child breastfed at 12–15 months * | −1.63 (−2.98 – −0.28) | 0.02 |
| Child lives in community at high risk for infectious illness * | −2.44 (−3.65 – −1.23) | <0.001 |

* indicates presence of variable (yes/no)

**Table 3:**

Multivariable association* between cumulative illness in the first year of life, MSEL scores at 12–15 months, and presence of microcephaly or stunting at 12–15 months.

| | # Total Illness Instances | | # Cough Instances | | # Fever Instances | | # Diarrhea/Vomiting Instances | |
|---|---|---|---|---|---|---|---|---|
| | **Beta estimate (95% Confidence Interval)** | **p-value** | **Beta estimate (95% Confidence Interval)** | **p-value** | **Beta estimate (95% Confidence Interval)** | **p-value** | **Beta estimate (95% Confidence Interval)** | **p-value** |
| Early Learning Composite* | −0.04 (−0.11 – 0.03) | 0.27 | −0.08 (−0.16– 0.003) | 0.06 | −0.36 (−0.56 – −0.16) | 0.0004 | −0.03 (−09– 0.15) | 0.66 |
| Gross Motor* | −0.04 (−0.07 – −0.005) | 0.02 | −0.05 (−0.09 – −0.02) | 0.005 | −0.19 (−0.28 – −0.11) | <0.0001 | −0.009 (−0.47 – 0.06) | 0.73 |
| Fine Motor* | −0.01 (−0.04 – 0.02) | 0.42 | −0.02 (−0.05 – 0.01) | 0.20 | −0.03 (−0.05 – 0.0006) | 0.055 | 0.001 (−0.04 – 0.04) | 0.93 |
| Visual Receptive* | −0.01 (−0.04 – 0.01) | 0.30 | −0.03 (−0.06 – −0.002) | 0.03 | −0.07 (−0.14 – −0.005) | 0.03 | 0.02 (−0.02 – 0.06) | 0.42 |
| Expressive Language* | −0.008 (−0.05 – 0.03) | 0.65 | −0.02 (−0.06 – 0.02) | 0.31 | −0.11 (−0.20 – −0.01) | 0.03 | 0.02 (−0.03 – 0.08) | 0.44 |
| Receptive Language* | −0.009 (−0.03 – 0.009) | 0.33 | −0.01 (−0.03 – 0.008) | 0.24 | −0.08 (−0.13 – −0.03) | 0.002 | −0.01 (−0.05 – 0.02) | 0.37 |
| | **RR (95% CI)** | **p-value** | **RR (95% CI)** | **p-value** | **RR (95% CI)** | **p-value** | **RR (95% CI)** | **p-value** |
| Stunting**,† | 1.00 (0.98–1.01) | 0.84 | 1.00 (0.98–1.02) | 0.79 | 0.8 (0.94–1.03) | 0.39 | 1.00 (0.98–1.02) | 0.95 |
| Microcephaly** | 0.99 (0.96–1.01) | 0.35 | 0.99 (0.96 – 1.02) | 0.66 | 0.95 (0.87–1.03) | 0.20 | 0.97 (0.93–1.02) | 0.29 |

Abbreviations: MSEL=Mullen Stages of Early Learning, SE=standard error, RR=relative risk

*adjusted for age at last visit, sex, maternal height at end of study, breastfeeding at last visit, housing material, maternal education, food insecurity, and living in a community at high risk for infectious illness. Beta estimate reflects change in MSEL score per additional instance (week reported) of illness.

**adjusted for sex, maternal height at end of study, housing material, and maternal education; binary outcome (yes/no)

†Stunting defined as length-for-age <2 -SD on WHO growth curves[20].