Causes and consequences of child growth failure in low- and middle-income countries

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Abstract
Child growth failure is associated with a higher risk of illness and mortality,1 which contributed to the United Nations Sustainable Development Goal 2.2 to end malnutrition by 2030. Current prenatal and postnatal interventions, such as nutritional supplementation, have been insufficient to eliminate growth failure in low resource settings — motivating a search for key age windows and population subgroups in which to focus future preventive efforts. Quantifying the effect of early growth failure on severe outcomes is important to assess burden and longer-term impacts on the child. Here we show through an analysis of 35 longitudinal cohorts (108,336 children) that maternal and child characteristics at birth accounted for the largest attributable differences in growth. Yet, postnatal growth failure was larger than differences at birth, and characteristics of the child’s household environment were additional determinants of growth failure after age 6 months. Children who experienced early ponderal or linear growth failure were at much higher risk of persistent growth failure and were 2.0 to 4.8 times more likely to die by age 24 months. High attributable risk from prenatal causes, and severe consequences for children who experienced early growth failure, support a focus on pre-conception and pregnancy as key opportunities for new preventive interventions. Our results suggest that broad improvements in wellbeing will be necessary to eliminate growth failure in low resource settings, but that screening based on weight could help identify children at highest risk of death before age 24 months.
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Introduction

Growth failure in the form of stunting, a marker of chronic malnutrition, and wasting, a marker of acute malnutrition, is common among young children in low-resource settings, and may contribute to child mortality and adult morbidity.1,2 Worldwide, 22% of children under age 5 years are stunted and 7% are wasted, with most of the burden occurring in low- and middle-income counties (LMIC).3 Current estimates attribute > 250,000 deaths annually to stunting and > 1 million deaths annually to wasting.2 Stunted or wasted children also experience worse cognitive development4–9 and adult economic outcomes.10

Despite widespread recognition of the importance of growth failure to global public health, preventive interventions in LMICs have had limited success.11–13 A range of nutritional interventions, targeting all stages of fetal and child development, including nutrition education, food and micronutrient supplementation during pregnancy, promotion of exclusive breastfeeding for 6 months and continued breastfeeding for 2 years, and food and micronutrient supplementation during weaning, have been found to have a beneficial effect on child growth.14–16 However, postnatal breastfeeding interventions and nutritional interventions delivered to children who have begun complementary feeding have only had small effects on population-level stunting and wasting burdens.14,16–18 Additionally, water, sanitation, and hygiene (WASH) interventions, which aim to reduce childhood infections that may heighten the risk of wasting and stunting in non-emergency settings19,20, have had no effect on child growth in several recent large randomized control trials.21–24 The small effect sizes of preventative interventions may reflect an incomplete understanding of the optimal way and time to intervene.25

Modest effects of interventions to prevent stunting and wasting in recent decades have spurred renewed interest in efforts to combine rich data sources26 with advances in statistical methodology27 to more deeply understand the key causes of child growth failure.11,22,23,28 Understanding the relationship between the causes and timing of growth failure is also crucial because children who falter early could be at higher risk for more severe growth failure later. In companion articles, we report that the highest rates of incident stunting and wasting occur by age 3 months.29,30 Behaviours associated with higher risk of stunting or wasting could be targeted by future interventions, and interventions could be optimized to encourage behaviour change before the age at which growth failure occurs. Characteristics associated with higher risk could also be used to identify children at risk of growth failure who might benefit most from preventative interventions.

Pooled longitudinal analyses

Here, we report a pooled analysis of 35 longitudinal cohorts in 15 low- and middle-income countries in South Asia, Sub-Saharan Africa, Latin America, and Eastern Europe, initiated between 1969 and 2014. Our objective was to estimate relationships between child, parental, and household characteristics and measures of child chronic and acute growth failure, including length-for-age and weight-for-length Z-scores, stunting, wasting, and length and weight velocities from birth to age 24 months. Details on the estimation of growth failure outcomes are included in companion articles.29,30 We also estimated associations between early growth failure and more severe growth failure or mortality by age 24.
months.

Cohorts were assembled as part of the Knowledge Integration (ki) initiative of the Bill & Melinda Gates Foundation which includes a database of millions of participants from studies on childbirth, growth and development. We selected longitudinal cohorts from the database that met five inclusion criteria: 1) conducted in low- or middle-income countries; 2) enrolled children between birth and age 24 months and measured their length and weight repeatedly over time; 3) did not restrict enrollment to acutely ill children; 4) enrolled at least 200 children; and 5) collected anthropometric status measurements at least every 3 months (Extended Data Fig 1). Inclusion criteria ensured we could rigorously evaluate the timing and onset of growth failure among children who were broadly representative of populations in low- and middle-income countries. Thirty-one cohorts from 15 countries met inclusion criteria, and 94,019 children and 645,869 total measurements were included in this analysis (Fig 1). Child mortality was rare and not reported in many of the ki datasets, so we relaxed inclusion criteria for studies used in the mortality analysis to include studies that measured children at least twice a year. Four additional cohorts met this inclusion criterion, and 14,317 children and 70,659 additional measurements were included in mortality analyses (108,336 total children, 716,573 total observations, Extended data table 1). Cohorts were distributed throughout South Asia, Africa, and Latin America, with a single European cohort from Belarus.

We calculated length-for-age Z-scores (LAZ), weight-for-age Z-scores (WAZ), and weight-for-length Z-scores (WLZ) using WHO 2006 growth standards. We dropped 1,332 (0.2%) unrealistic measurements of LAZ (> 6 or < –6 Z), 1,493 (0.2%) measurements of WAZ (> 6 or < –5 Z), and 1,834 (0.3%) measurements of WLZ (> 5 or < –5 Z), consistent with WHO recommendations. We defined stunting as LAZ < –2, severe stunting as LAZ < –3, underweight as WAZ < –2, severe underweight as WAZ < –3, wasting as WLZ < –2, severe wasting as WLZ < –3, concurrent stunting and wasting as LAZ < –2 and WLZ < –2, and persistent wasting as > 50% measurements of WLZ < –2 during an age period with at least 4 measurements (e.g., birth to 24 months).

**Rank ordered causes of growth failure**

We selected exposures of interest based on important predictors of stunting and wasting from prior literature that were measured in multiple cohorts and could be harmonized across cohorts for pooled analyses (Fig 1, Extended data table 2). All reported estimates were adjusted for all other measured exposures that we assumed were not on the causal pathway between the exposure of interest and the outcome. For example, the association between maternal height and stunting was not adjusted for a child’s birthweight because low maternal height could increase stunting risk through lower child birthweight. Parameters were estimated using targeted maximum likelihood estimation, a doubly-robust, semiparametric method that allows for valid inference while adjusting for potential confounders using ensemble machine learning (details in Methods). We estimated cohort-specific parameters, adjusting for measured covariates within each cohort, and then pooled estimates across cohorts using random effects models (Extended data Fig 1). When estimating relative risks, Z-score differences, and attributable risk parameters, we chose the reference as the mode of the level of lowest risk across cohorts. We also estimated the effects of optimal dynamic treatment interventions, where no a-priori reference level of low risk was specified, and each child’s individual low-risk level of exposure was
estimated from covariates. Timing of exposures varied, from parental and household characteristics present before birth, to fetal or at-birth exposures, and postnatal exposures including breastfeeding and diarrheal disease. We estimated only associations for growth failure occurring after exposure measurements to ensure time-ordering of exposures and outcomes.

Longer child birth length, higher maternal weight, earlier child birth order, higher maternal educations, and more rooms in the household were five of the top six population-level predictors of higher LAZ and WLZ at 24 months, as rank-ordered by population attributable difference, the estimated shift in population mean Z-score if the whole population had their exposure shifted from observed levels to the lowest-risk reference level (Fig 2a, 2b). The pooled, cross-validated $R^2$ for models that included these five key determinants, plus child sex and birthweight, was 0.29 for LAZ (N= 15 cohorts, 22,193 children) and 0.09 for WLZ (N=15 cohorts, 20,927 children). The dry season of the year was also an important predictor of higher WLZ, and taller mother’s height was an important predictor of higher LAZ. Mother’s height was a stronger predictor of both LAZ and WLZ than father’s height, which may reflect that maternal anthropometric status integrates across multiple distal and proximate causes, such as family socio-economic status (SES), fetal growth environment, and breastmilk quality. Maternal height and weight and child characteristics measured at birth were the strongest predictors of LAZ and WLZ at age 24 months; beyond those, key predictors of higher Z-scores included markers of better household socioeconomic status (e.g., number of rooms in the home, parental education, clean cooking fuel use, household wealth index) and having a cesarean birth, which may reflect healthcare access or larger fetal size. The findings underscore the importance of prenatal exposures for child growth outcomes, and at the population-level growth failure may be difficult to shift without broad improvements in standard of living. Exclusive or predominant breastfeeding before 6 months of age, which was not a major predictor of Z-scores at 24 months, was more strongly associated with higher WLZ than with higher LAZ at 6 months of age (Extended Data Figs 2,3,4).

Maternal anthropometric status can influence child Z-scores by affecting fetal growth and birth size. In a secondary analysis, we estimated the association between parental anthropometric status and child Z-scores controlling for child birth characteristics, which showed that the relationship of maternal anthropometric status to child Z-scores was only partially mediated by child birth characteristics (Extended data Fig 5). Maternal weight and BMI could directly affect postnatal health through breastmilk quality, or reflect family poverty, genetics, undernutrition, or food insecurity, or family lifestyle and diet.

The strongest predictors of stunting and wasting estimated through population attributable fractions closely matched those identified for child LAZ and WLZ at 24 months (Extended Data Fig 6), suggesting that information embedded in continuous and binary measures of child growth provide similar inference with respect to identifying public-health relevant causes. The magnitude of population attributable effects was relatively modest. For example, if all children were born to taller mothers (heights ≥155 cm) compared to the observed distribution of maternal height, one of the largest predictors of stunting, we estimate it would reduce the incidence of stunting by age 24 months by 19% (Extended Data Fig 6a). Patterns in associations across growth outcomes were broadly consistent, except for preterm birth, which had a stronger association with stunting outcomes than wasting outcomes, and rainy season, which had a stronger association with wasting outcomes than stunting.
outcomes (Extended Data Fig 2). Direction of associations did not vary across regions, but magnitude
did, notably with male sex less strongly associated with low LAZ in South Asia, and higher parental
education and larger household size more strongly associated with higher WLZ in South Asia (Extended
Data Figs 7,8).

Age-varying effects on growth failure

Maternal height and weight consistently arose as key predictors of population attributable
differences in child growth failure (Fig 2), so we sought to elucidate the longitudinal relationship
between maternal anthropometry and child growth. We estimated trajectories of mean LAZ and WLZ
stratified by maternal height, weight, and BMI. We found that maternal height strongly influenced at-
birth LAZ, but that LAZ progressed along similar trajectories through age 24 months regardless of
maternal height (Fig 3a), with similar though slightly less pronounced differences when stratified by
maternal weight (Fig 3b). By contrast, children born to taller mothers had similar WLZ at birth and WLZ
trajectories until age 3-6 months, when they diverged substantially (Fig 3a); WLZ trajectory differences
were even more pronounced when stratified by maternal weight (Fig 3b). Maternal BMI strongly
influenced WLZ, but not LAZ, at birth (Fig 3c). The findings illustrate how maternal status strongly
influences where child growth trajectories start, but that growth trajectories evolve in parallel, seeming
to respond similarly to postnatal insults independent of their starting point.

Children who were stunted by age 3 months exhibited a different longitudinal growth trajectory
from those who were stunted later. We hypothesized that causes of growth failure could differ by age
of growth failure onset. For key exposures identified in the population attributable effect analyses, we
conducted analyses stratified by age of onset and in many cases found age-varying effects (Fig 3d). For
example, most measures of socioeconomic status were associated with incident wasting or stunting only
after age 6 months, and higher birth order lowered growth failure risk under age 6 months, but
increased risk thereafter. Stronger relationships between key socio-demographic characteristics and
child wasting and stunting as children age likely reflects the accumulation of insults that result from a
child’s household conditions, particularly as children begin complementary feeding, exploring their
environment, and potentially face higher levels of food insecurity in homes with multiple children.

When viewed across multiple definitions of child growth failure, most causes had stronger associations
with severe stunting, severe wasting, or persistent wasting (> 50% of measurements < –2 WLZ), rarer
but more serious outcomes, than with incidence of any wasting or stunting (Fig 3e). Additionally, the
characteristics strongly associated with lower probability of recovering from a wasting episode in 90
days (birth size, small maternal stature, lower maternal education, later birth order, and male sex) were
also characteristics associated with higher risk of wasting prevalence and cumulative incidence
(Extended data fig 2). Age-specific risk factors were generally similar for different measures of linear
growth and wasting (Extended data fig 2).

Consequences of early growth failure

We documented high incidence rates of wasting and stunting from birth to age 6 months. Individual studies have suggested that early wasting could predispose children to later linear growth
We hypothesized that early wasting could contribute to subsequent linear growth restriction, and early growth failure could be consequential for persistent growth failure and mortality during the first 24 months of life. Among cohorts with monthly measurements, we examined age-stratified linear growth velocity by quartiles of WLZ at previous ages. We found a consistent, exposure-response relationship between higher mean WLZ and faster linear growth velocity in the following 3 months (Fig 4a), with a corresponding inverse relationship between WLZ and incident stunting at older ages (Extended data Fig 9). Persistent wasting from birth to 6 months (defined as > 50% of measurements wasted) was the wasting measure most strongly associated with incident stunting at older ages (Fig 4b).

We next examined the relationship between measures of growth failure in the first 6 months and serious growth-related outcomes: persistent wasting from 6-24 months and concurrent wasting and stunting at 18 months of age, both of which put children at high risk of mortality. Concurrent wasting and stunting was measured at 18 months because stunting prevalence peaked at 18 months and the largest number of children were measured at 18 months across cohorts. All measures of early growth failure were significantly associated with later, more serious growth failure, with measures of ponderal growth failure amongst the strongest predictors (Fig 4c).

Finally, we estimated the relative risk of mortality across measures of growth failure in the first 6 months within eight cohorts that reported mortality endpoints, including 2,510 child deaths by age 24 months (4.3% of children in the cohorts). Analyses used all-cause mortality occurring before children turned two years old (Extended data Fig 10). All measures of early growth failure were significantly associated with higher risk of death by age 24 months, and those most strongly associated with death were severely underweight before age 6 months (RR=4.8, 95% CI: 4.1, 5.6), concurrent wasting and stunting (RR=4.8, 95% CI: 3.9, 5.9), and persistent wasting under 6 months (RR=3.4, 95% CI: 3.0, 3.8) (Fig 4c).

Discussion

There were several limitations to this analysis. Measurement frequency and timing varied across cohorts, cohort locations were not geographically balanced, and Z-scores did not adjust for gestational age. Key exposures such as dietary diversity, nutrient consumption, micronutrient status, maternal and child morbidity indicators, pathogen-specific infections, and sub-clinical inflammation and intestinal dysfunction were measured in only a few cohorts, so were not included. The absence of these exposures in the analysis, some of which have been found to be important within individual contributed cohorts, means that results emphasize exposures that were more commonly collected, but likely excludes some additional causes of growth failure. Confounders were not measured in every cohort, so there could be residual confounding. Covariate adjustment had a minimal effect on most estimates (Extended Data Fig 11), and an unmeasured confounder would on average need to almost double the risk of both the exposure and the outcome to explain away observed significant associations (median E-value: 1.45, Extended Data Fig 12). Finally, included cohorts were highly monitored, so mortality rates were likely lower than in the general population, and without detailed medical histories, growth failure prior to death may have been a sequela of an underlying condition like malaria or a severe respiratory infection that caused death, rather than the cause itself.
Our large-scale assessment of principal causes and near-term consequences of child growth failure found that maternal, prenatal, and at-birth characteristics are the strongest predictors of growth failure in LMICs. Shifting several key population exposures to their observed low-risk level would modestly improve LAZ and WLZ in target populations and could be expected to prevent 20-30% of incident stunting and wasting and improve Z-scores by 0.2-0.4 Z in the study populations (Fig 2, Extended Data Fig 6). These results, along with the relative importance of prenatal and maternal exposures, accord with the limited success of numerous postnatal preventive interventions in recent decades.\textsuperscript{15,16,55–57} Prevention of early growth failure before age 6 months is additionally important and should be a high priority for global health programs because we observed that early life growth failure puts children at substantially higher risk of death by age 24 months. Our results suggest that targeting the next generation of interventions toward reproductive age and pregnant women could be a promising path forward to prevent growth failure amongst their children.\textsuperscript{58,59} The recent Women’s First trial found prenatal nutrition supplements improved children’s birth size, though there was no impact of giving supplements starting pre-conception compared to starting late in the first trimester.\textsuperscript{60} Emerging evidence suggests that interventions beyond nutrition, such as those that address maternal infection and inflammation, may further contribute to decreasing in utero growth failure.\textsuperscript{60–65} Nevertheless, a stronger focus on prenatal interventions should not distract from renewed efforts for postnatal prevention. Maternal anthropometric status strongly influenced birth size, but the parallel drop in postnatal Z-scores among children born to different maternal phenotypes was much larger than differences at birth, indicating that growth trajectories were not fully “programmed” at birth (Fig 3a-c). Wasting and stunting incidence was highest before age 6 months, but mean LAZ decreased until age 18 months,\textsuperscript{29} the dangerous concurrence of wasting and stunting peaked at age 18 months,\textsuperscript{30} and large, seasonally driven declines in WLZ were observed across all ages.\textsuperscript{30} Targeting postnatal interventions by season or by population subgroups defined by sex, socioeconomic status, maternal, and child birth characteristics identified herein should help focus preventive interventions to reduce the substantial, persistent burden of postnatal growth failure.

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Figure 1 | Cohort sample sizes and exposures measured. (a) Total number of children with a measured exposure, sorted from left to right by number of cohorts measuring the exposure. (b) Presence of exposure variables in the $ki$ data by within each included cohort. Cohorts are sorted by geographic region and sample size. (c) The number of observations of child anthropometry included in each cohort.
Figure 2 | Rank-ordered attributable differences between child, parental, and household characteristics and population attributable differences in anthropometry Z-scores.

(a) Exposures, ordered by pooled population attributable difference on child LAZ at 24 months. Inset figures plot the population attributable difference on the X-axis, and the optimal intervention attributable difference on the Y-axis, where the level the exposure is shifted to can vary by child. The optimal intervention attributable differences, which are not estimated with an a-priori specified low-risk reference level, were generally close to the static attributable differences, indicating that the chosen reference levels were the lowest risk strata in most or all cohorts. The largest outliers are marked: the crossed circle marks the single parent variable and the diamond marks the percent days with diarrhea under 6 months.

(b) Exposures, rank ordered by population attributable difference on child WLZ at 24 months. The crossed circle marks the father’s age variable and the diamond marks the child birth order variable.
Figure 3 | Effect of key exposures on the trajectories, timing, and severity of child growth failure

(a) Child length-for-age Z-score (LAZ) and weight-for-length Z-score (WLZ) trajectories, stratified by categories of maternal height (N=462,078 measurements, 71,286 children, 23 studies).

(b) Child LAZ and WLZ trajectories, stratified by categories of maternal weight (N=381,160 measurements, 63,551 children, 17 studies).

(c) Child LAZ and WLZ, stratified by categories of maternal BMI (N=373,382 measurements, 61,933 children, 17 studies).

(d) Associations between key exposures and wasting cumulative incidence, stratified by the age of the child during wasting incidence, show that many exposures strongly associated with wasting are only associated with wasting occurring after 6 months.

(e) Associations between key exposures and growth failure of different severities, showing that many exposures strongly associated with wasting and stunting have stronger associations with severe stunting and wasting or persistent wasting. Contrasts are between the highest and lowest risk exposure category of each exposure, which are printed in each panel title.
Figure 4 | Early life growth failure increases risk of more severe growth failure and mortality.

(a) Adjusted differences in linear growth velocity (in centimeters) across 3-month age bands, by quartile of weight-for-length z-score (WLZ) in the preceding three months. The reference group is children in the first quartile of WLZ in the previous age period. The panel with black points on the far right shows the pooled estimates, unstratified by child age. At all ages, children with higher mean WLZ over a three-month period had faster linear growth velocity in the next three-month period.

(b) Relative risk of stunting onset after age 6 months between children who experienced measures of early wasting compared to children who did not experience early wasting.

(c) Relative risk of short-term severe outcomes by measure of growth failure before age 6 months. Severe outcomes include: all-cause mortality (N included up to 8 cohorts, 2,418 deaths, and 57,903 children), persistent wasting from ages 6-24 months (N included up to 24 cohorts, 7,043 cases, and 76,347 children), and co-occurrent wasting and stunting at age 18 months (N included up to 21 cohorts, 1,635 cases, and 21,681 children).
Materials and Methods

1. Study designs and inclusion criteria

We included all longitudinal observational studies and randomized trials available through the ki project on April 1, 2018 that met five inclusion criteria: 1) conducted in low- or middle-income countries; 2) enrolled children between birth and age 24 months and measured their length and weight repeatedly over time; 3) did not restrict enrollment to acutely ill children; 4) enrolled at least 200 children; 5) collected anthropometry measurements at least quarterly. We included all children under 24 months of age, assuming months were 30.4167 days, and we considered a child’s first measure recorded by age 7 days as their anthropometry at birth. Four additional studies with high-quality mortality information that measured children at least every 6 months were included in the mortality analyses (The Burkina Faso Zinc trial, The Vitamin-A trial in India, and the iLiNS-DOSE and iLiNS-DYAD-M trials in Malawi).

2. Statistical analysis

Analyses were conducted in R version 3.6.2. All pooled, regional, and cohort-specific results, results for secondary outcomes, and sensitivity analyses are available online at (https://child-growth.github.io/causes).

3. Outcome definitions

Anthropometry Z-scores were calculated using the 2006 WHO standards. We used the medians of triplicate measurements of heights and weights of children from pre-2006 cohorts to re-calculate Z-scores to the 2006 standard. We excluded extreme measurements of WLZ > 5 or < −5, WAZ > 5 or < −6, and LAZ > 6 or < −6, consistent with WHO growth standard recommendations. See Benjamin-Chung (2020) for details on cohort inclusion and assessment of anthropometry measurement quality. Children with length-for-age Z-scores (LAZ), weight-for-length Z-scores (WLZ), or weight-for-age Z-scores (WAZ) < −2 were classified as stunted, wasted, or underweight, respectively. Children with LAZ, WLZ, or WAZ < −3 were classified as severely stunted, severely wasted, or severely underweight, respectively. Children with ≥ 50% of WLZ measurements < −2 over a defined age range were classified as persistently wasted. Children were assumed to never recover from stunting episodes, but children were classified as recovered from wasting episodes (and at risk for a new episode of wasting) if their measured WLZ was ≥ −2 for at least 60 days (details in Mertens et. al (2020)). Child mortality was all-cause and was restricted to children who died after birth and before age 24 months.

4. Estimating relationships between child, parental, and household exposures and measures of growth failure

4.1 Exposure definitions

We selected the exposures of interest based on variables present in multiple cohorts that met our inclusion criteria, were found to be important predictors of stunting and wasting in
prior literature and could be harmonized across cohorts for pooled analyses. Extended data table 2 lists all exposures included in the analysis, as well as exposure categories used across cohorts, and the total number of children in each category. For parental education and asset-based household wealth, we categorized to levels relative to the distribution of educational attainment within each cohort. Continuous biological characteristics (gestational age, birth weight, birth height, parental weight, parental height, parental age) were classified based on a common distribution, pooling data across cohorts. Our rationale was that the meaning of socioeconomic variables is culturally context-dependent, whereas biological variables should have a more universal meaning.

4.2 Risk set definition

For exposures that occur or exist before birth, we considered the child at risk of incident outcomes at birth. Therefore, we classified children who were born stunted (or wasted) as incident episodes of stunting (or wasting) when estimating the relationship between household characteristics, paternal characteristics, and child characteristics like gestational age, sex, birth order, and birth location.

For postnatal exposures (e.g., breastfeeding practices, WASH characteristics, birth weight), we excluded episodes of stunting or wasting that occurred at birth. Children who were born wasted could enter the risk set for postnatal exposures if they recovered from wasting during the study period (see Mertens et al. 2020 for details). This restriction ensured that for postnatal exposures, the analysis only included postnatal, incident episodes. Children born or enrolled wasted were included in the risk set for the outcome of recovery from wasting within 90 days for all exposures (prenatal and postnatal).

4.3 Estimating differences in outcomes across categories of exposures

We estimated measures of association between exposures and growth failure outcomes by comparing outcomes across categories of exposures in four ways:

Mean difference of the comparison levels of the exposure on LAZ, WLZ at birth, 6 months, and 24 months. The Z-scores used were the measures taken closest to the age of interest and within one month of the age of interest, except for Z-scores at birth which only included a child’s first measure recorded by age 7 days.

Prevalence ratios (PR) between comparison levels of the exposure, compared to the reference level at birth, 6 months, and 24 months. Prevalence was estimated using anthropometry measurements closest to the age of interest and within one month of the age of interest, except for prevalence at birth which only included measures taken on the day of birth.

Cumulative incidence ratios (CIR) between comparison levels of the exposure, compared to the reference level, for the incident onset of outcomes between birth and 24 months, 6-24 months, and birth-6 months.

Mean Z-scores by continuous age, stratified by levels of exposures, from birth to 24 months were fit within individual cohorts using cubic splines with the bandwidth chosen to minimize the median Akaike information criterion across cohorts. We estimated splines separately for each
exposure category. We pooled spline curves across cohorts into a single prediction, offset by mean Z-scores at one year, using random effects models.  

4.4 Estimating population attributable parameters

We estimated three measures of the population-level effect of exposures on growth failure outcomes:

- **Population attributable difference** was defined as the change in population mean Z-score if the entire population’s exposure was set to an ideal reference level. For each exposure, we chose reference levels as the category with the highest mean LAZ or WLZ across cohorts.

- **Population attributable fraction (PAF)** was defined as the proportional reduction in cumulative incidence if the entire population’s exposure was set to an ideal low risk reference level. We estimated the PAF for the prevalence of stunting and wasting at birth, 6, and 24 months and cumulative incidence of stunting and wasting from birth to 24 months, 6-24 months, and from birth to 6 months. For each exposure, we chose the reference level as the category with the lowest risk of stunting or wasting.

- **Optimal individualized intervention impact** We employed a variable importance measure (VIM) methodology to estimate the impact of an optimal individualized intervention on an exposure. The optimal intervention on an exposure was determined through estimating individualized treatment regimes, which give an individual-specific rule for the lowest-risk level of exposure based on individuals’ measured covariates. The impact of the optimal individualized intervention is derived from the VIM, which is the predicted change in the population-mean outcome from the observed if every child’s exposure was shifted to their optimal level. This differs from the attributable difference and PAF parameters in that we did not specify the reference level, and the reference level could vary across participants. A companion article provides additional details Coyle et al. (2020).  

Attributable risk and difference parameters assume a causal relationship between exposure and outcome. For some exposures we considered attributable effects have a pragmatic interpretation — they represent a summary estimate of relative importance that combines the exposure’s strength of association and its in the population.

5. Estimating relationships between early life growth failure and severe outcomes including mortality by age 24 months.

We estimated unadjusted and adjusted relative risks of severe outcomes between children who experienced measures of early life growth failure and children who did not.

6.1 Outcomes

- **All-cause mortality** included all deaths among children ages 1-day to 24 months who had anthropometry measurements prior to death.

- **Concurrent wasting and stunting prevalence** at age 18 months was estimated using the anthropometry measurement taken closest to age 18 months, and within 17-19 months.
of age, and a child was considered concurrently stunted and wasted if they had both a LAZ <-2 and a WLZ <-2.

Persistent wasting was estimated from child measurements between 6 and 24 months of age, and a child was considered persistently wasted if ≥50% of measurements of WLZ were < -2.

6.2 Exposures

We estimated associations between the outcomes listed in 6.1 and the cumulative incidence of wasting, stunting, underweight, and concurrent wasting and stunting from birth to 6 months of age, and persistent wasting before 6 months of age. In the analysis of child mortality, we also estimated associations between mortality and the cumulative incidence of wasting, stunting, underweight, and concurrent wasting and stunting from birth to 24 months of age, and persistent wasting before 24 months of age.

6.3 Parameter of interest

We estimated cumulative incidence ratios, unadjusted and adjusting for all pre-birth exposures, as well as birth month, month of measurement, and treatment arm of randomized trials.

We were also interested in determining if low weight-for-length preceded slower linear growth velocity or the onset of stunting. We estimated the difference in linear growth over three-month periods across quartiles of mean WLZ in the prior three-month period and the relative risk of stunting cumulative incidence over three-month periods across quartiles of mean WLZ in the prior three-month period. We calculated linear growth velocity as the change in length in centimeters within 3-month age intervals, including measurements within a two-week window around each age in months to account for variation in the age of each length measurement.

6. Estimation approach

6.1 Estimation of cohort-specific effects

For each exposure, we used directed acyclic graphs (DAGs) to identify potential confounders from the broader set of exposures used in the analysis.9 We did not condition on characteristics that were assumed to be intermediate on the causal path between any exposure and the outcome.10

For missing covariate observations, we imputed missing measurements as the median (continuous variables) or mode (categorical variables) among all children within each cohort, and analyses included an indicator variable for missingness in the adjustment set. When calculating the median for imputation, we used children as independent units rather than measurements so that children with more frequent measurements were not over-represented.

To flexibly adjust for potential confounders and reduce the risk of model misspecification, we estimated adjusted PRs, CIRs, and mean differences using targeted maximum likelihood estimation (TMLE), a two-stage estimation strategy that incorporates state-of-the-art machine learning algorithms.
The super learner is an ensemble machine learning method that uses cross-validation to select a weighted combination of predictions from a library of algorithms. We included in the library simple means, generalized linear models, LASSO penalized regressions, generalized additive models, and gradient boosting machines. The super learner was fit to maximize the 10-fold cross-validated area under the receiver operator curve (AUC) for binomial outcomes, and minimize the 10-fold cross-validated mean-squared error (MSE) for continuous outcomes. That is, the super learner was fit using 9/10 of the data, while the AUC/MSE was calculated on the remaining 1/10 of the data. Each fold of the data was held out in turn and the cross-validated performance measure was calculated as the average of the performance measures across the ten folds.

This approach is practically appealing and robust in finite samples, since this cross-validation procedure utilizes unseen sample data to measure the estimator’s performance. Also, the super learner is asymptotically optimal in the sense that it is guaranteed to outperform the best possible algorithm included in the library as sample size grows. The initial estimator obtained via super learner is subsequently updated to yield an efficient double-robust semi-parametric substitution estimator of the parameter of interest. To estimate the $R^2$ of models including multiple exposures, we fit super learner models, without the targeted learning step, and within each cohort measuring the exposures. We then pooled cohort-specific $R^2$ estimates using fixed effects models.

Unadjusted PRs and CIRs between the reference level of each exposure and comparison levels were estimated using logistic regressions. Unadjusted mean differences for continuous outcomes were estimated using linear regressions.

We estimated influence curve-based, clustered standard errors to account for repeated measures in the analyses of recovery from wasting or progression to severe wasting. We assumed that the children were the independent units of analysis unless the original study had a clustered design, in which case the unit of independence in the original study were used as the unit of clustering. We used clusters as the unit of independence for the ilInS-Zinc, Jivita-3, Jivita-4, Probit, and SAS Complementary Feeding trials. We estimated 95% confidence intervals for incidence using the normal approximation.

Data sparsity

We did not estimate relative risks between a higher level of exposure and the reference group if there were 5 or fewer cases in either stratum. In such cases, we still estimated relative risks between other exposure strata and the reference strata if those strata were not sparse.

7. Pooling parameters

We pooled adjusted estimates from individual cohorts using random effects models, fit using restricted maximum likelihood estimation. The pooling methods are detailed in Benjamin-Chung (2020). All parameters were pooled directly using the cohort-specific estimates of the same parameter, except for population attributable fractions. Pooled PAFs were calculated from random-effects pooled population attributable risks (PARs), and pooled outcome prevalence in the population using the following formulas.
For PAFs of exposures on the cumulative incidence of wasting and stunting, the pooled cumulative incidence was substituted for the outcome prevalence in the above equations. We used this method instead of direct pooling of PAFs because, unlike PAFs, PARs are unbounded with symmetrical confidence intervals.

8. Figure-specific method details

Figure 2.
(a) Exposures, rank ordered by population attributable difference on child LAZ at 24 months. The population attributable difference is the expected difference in population mean Z-score if all children had the reference level of the exposure rather than the observed distribution. Inset figures plot the pooled population attributable difference on the X-axis, and the pooled optimal intervention attributable difference on the Y-axis, where the level the exposure is shifted to can vary by child, on the y-axis.
(b) Exposures, rank ordered by population attributable difference on child WLZ at 24 months. The population attributable difference is the expected difference in population mean Z-score if all children had the reference level of the exposure rather than the observed distribution.

In both panels, reference levels are printed next to the name of the exposure. Estimates are adjusted for all other measured exposures not on the causal pathway.

Figure 3.
(a-c) Mean trajectories estimated using cubic splines in individual studies and then curves were pooled using random effects. Curves estimated from all anthropometry measurements of children taken from birth to 24 months of age within studies that measured the measure of maternal anthropometry.
(d) The cumulative incidence of stunting or severe stunting from 6-24 months is among children who had not become stunted by 6 months, while the cumulative incidence of wasting or severe wasting from 6-24 months is among children who were not wasted at 6 months or who recovered from a wasting episode after 6 months. Persistent wasting from 6-24 months is among all children with at least 4 measurements between 6 months and 24 months. Children born stunted, and wasting episodes starting at birth, are excluded from the analysis of gestational age.

Figure 4.
(a) Linear growth velocity was calculated as the change in length in centimeters from the start of an age period to the end of an age period, using the closest anthropometry measurements within 14 days of the start and end of the age period.
(b) The three wasting measures were defined as: child experienced any measure of wasting (WLZ < –2) under 6 months, child was enrolled into the study wasted, and child was persistently wasted under 6 months (≥50% of measurements of WLZ < –2, and at least 4 measurements prior to age 6 months).
Estimates compare risk among children with each measure of growth failure before age 6 months with risk among children who did not experience the specific measure of growth failure.

9. Sensitivity analyses

We compared estimates pooled using random effects models, which are more conservative in the presence of heterogeneity across studies, with estimates pooled using fixed effects, and we compared adjusted estimates with estimates unadjusted for potential confounders. We estimated associations between growth failure and mortality at different ages, after dropping the trials measuring children less frequently than quarterly, and we plotted Kaplan Meier curves of child mortality, stratified by measures of early growth failure. We also conducted a sensitivity analysis on methods of pooling splines of child growth trajectories, stratified by maternal anthropometry. We re-estimated the attributable differences of exposures on WLZ and LAZ at 24 months, dropping the PROBIT trial, the only European study. Results from secondary outcomes and sensitivity analyses are viewable online at https://child-growth.github.io/causes.

Data and code availability

The data that support the findings of this study are available from the Bill and Melinda Gates Foundation Knowledge Integration project upon reasonable request. Replication scripts for this analysis are available here: https://github.com/child-growth/ki-longitudinal-growth.

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Competing interest declaration

Thea Norman is an employee of the Bill & Melinda Gates Foundation (BMGF). Kenneth H Brown and Parul Christian are former employees of BMGF. Jeremy Coyle, Vishak Subramoney, Ryan Hafen, and Jonas Häggström work as research contractors funded by the BMGF.

Additional information

Supplementary Information is available for this paper at https://child-growth.github.io/causes.
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Extended Data Figure 1 | Example forest plot of cohort-specific and pooled parameter estimates

Cohort-specific estimates of the cumulative incidence ratio of stunting are plotted on each row, comparing the risk of any stunting from birth to 24 months among boys compared to a reference level of girls. Below the solid horizontal line are region-specific pooled measures of association, pooled using random-effects models. Below the dashed line are overall pooled measures of association, comparing pooling using random or fixed effects models. The primary results reported throughout the manuscript are overall (not region stratified) estimates pooled using random effects models.
Extended Data Figure 2 | Heatmap of significance and direction across exposure-outcome combinations.

The heatmap shows the significance and direction of estimates through the cell colors, separated across primary outcomes by child age. Red and orange cells are harmful exposures, while blue and green cells are protective exposures. The
outcomes are labeled at the top of the columns, with each set of three columns the
set of three ages analyzed for that outcome. Each row is a level of an exposure
variable, with reference levels excluded. Rows are sorted top to bottom by
increasing average p-value. Grey cells denote comparisons that were not estimated
or could not be estimated because of data sparsity in the exposure-outcome
combination. All point estimates and confidence intervals for exposure-outcome
pairs with P-values plotted in this figure are viewable online at (https://child-
growth.github.io/causes).

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Extended Data Figure 3 | Age-stratified population attributable differences in length-for-age Z-scores.

Exposures, rank ordered by population attributable difference on child LAZ at 24 months, stratified by the age of the child at the time of anthropometry measurement.
The population attributable difference is the expected difference in population mean Z-score if all children had the reference level of the exposure rather than the observed distribution. For all plots, reference levels are printed next to the name of the exposure. Estimates are adjusted for all other measured exposures not on the causal pathway.
Extended Data Figure 4 | Age-stratified population attributable differences in weight-for-length Z-scores.

Exposures, rank ordered by population attributable difference on child WLZ at 24 months, stratified by the age of the child at the time of anthropometry measurement. The population attributable difference is the expected difference in population mean Z-

Attributable difference - WLZ, stratified by age
score if all children had the reference level of the exposure rather than the observed
distribution. For all plots, reference levels are printed next to the name of the exposure.
Estimates are adjusted for all other measured exposures not on the causal pathway.
Extended Data Figure 5 | Mediation by birth characteristics of associations between parental anthropometry and child Z-scores at 24 months.

The plot panels show the mediating effect of adjusting for child birth anthropometry and at-birth characteristics on the estimated Z-score differences between levels of parental anthropometry. There is little to partial mediation of the association between parental anthropometry and child LAZ and WLZ at 24 months by at-birth characteristics, implying that the causal pathway between parental stature and child growth failure operates through both affecting birth size as well as other pathways. Primary estimates were adjusted for all other measured exposures not on the causal pathway, while the mediation analysis estimates are adjusted for the same set of measured exposures, plus birth weight, birth length, gestational age at birth, birth order, vaginal birth vs. C-section, and home vs. hospital delivery. Only estimates from cohorts measuring at least 4 of the 6 at-birth characteristics are used to estimate the pooled Z-score differences.
Extended Data Figure 6 | Rank-ordered associations between child, parental, and household characteristics and population attributable fractions of stunting and wasting.

(a) Exposures, rank ordered by population attributable difference on the cumulative incidence of child stunting between birth and 24 months. The population attributable fraction is the estimated proportion of the observed outcome in the whole population attributable to the exposure. For postnatal and at-birth exposures, including birth characteristics, breastfeeding practice, food security, and diarrheal disease, the cumulative incidence of stunting from 6-24 months is used.

(b) Exposures, rank ordered by population attributable difference on the cumulative incidence of child wasting between birth and 24 months. The population
attributable fraction is the estimated proportion of the observed outcome in the whole population attributable to the exposure. For postnatal and at-birth exposures, including birth characteristics, breastfeeding practice, food security, and diarrheal disease, the cumulative incidence of wasting from 6-24 months is used.

For all plots, reference levels are printed next to the name of the exposure. Estimates are adjusted for all other measured exposures not on the causal pathway.
Extended Data Figure 7 | Regionally-stratified population attributable differences in length-for-age Z-scores.

Exposures, rank ordered by population attributable difference on child LAZ at 24 months, stratified by region. The population attributable difference is the expected
difference in population mean Z-score if all children had the reference level of the exposure rather than the observed distribution. For all plots, reference levels are printed next to the name of the exposure. Estimates were adjusted for all other measured exposures not on the causal pathway. The confidence intervals extend beyond the scale for diarrhea under 24 months in Africa and for safe water source in Latin America.
Extended Data Figure 8 | Regionally-stratified population attributable differences in weight-for-length Z-scores.

Exposures, rank ordered by population attributable difference on child WLZ at 24 months, stratified by region. The population attributable difference is the expected difference in population mean Z-score if all children had the reference level of the exposure.

Attributable difference - WLZ, stratified by region

24 months, Africa

24 months, Latin America

24 months, South Asia
exposure rather than the observed distribution. For all plots, reference levels are printed next to the name of the exposure. Estimates were adjusted for all other measured exposures not on the causal pathway.
Extended Data Figure 9 | Risks of subsequent linear-growth faltering across categories of prior WLZ.

Relative risk of stunting onset within 3-month age bands, comparing cohort-specific quartiles on mean WLZ in the prior 3-month age to the reference level of the first quartile. Children are assumed to not recover from stunting, so only the first measure of LAZ < −2 is used to define stunting onset.

Extended Data Figure 10 | Age at death and preceding anthropometry measurements among recorded deaths within the included ki cohorts

Each row is a child, with the furthest right grey dots marking the age at death, and the colored points mark anthropometry measurements prior to death. Children are sorted to show the cumulative distribution of mortality by age 24 months (marked on the right Y-axis), illustrating that more than half of child deaths occurred before 6 months. The figure is based on 2,247 recorded child deaths in children under the age of 2 years from 8 cohorts. Deaths were not plotted for 206 children with missing ages of death.
Extended Data Figure 11 | Difference between adjusted and unadjusted Z-score effects by number of selected adjustment variables.

Points mark the difference in estimates unadjusted and adjusted estimates of the difference in average Z-scores between exposed and unexposed children across 31 cohorts, 33 exposures and length-for-age and weight-for-length Z-score outcomes included in the analysis. Different cohorts measured different sets of exposures, and a different number of adjustment covariates were chosen for each cohort-specific estimate based on outcome sparsity, so cohort-specific estimates adjust for different covariates and numbers of covariates. The plot shows no systematic bias between unadjusted and adjusted estimates based on number of covariates chosen. The blue line shows the average difference between adjusted estimates from unadjusted estimates, fitted using a cubic spline.
Extended Data Figure 12 | Assessing sensitivity of estimates to unmeasured confounding using E-values

An E-value is the minimum strength of association in terms of relative risk that an unmeasured confounder would need to have with both the exposure and the outcome to explain away an estimated exposure–outcome association. Orange points mark the E-values for the pooled estimates of relative risk for each exposure. Grey points are cohort-specific E-values for each exposure-outcome relationship. Non-significant pooled estimates have points plotted at 1.0. Orange points are median E-values among statistically significant estimates for each exposure.
### Extended data table 1

| Region, Study ID | Country | Study Years | Design | Children Enrolled* | Anthropometry measurement ages (months) | Total measurements* | Primary References |
|------------------|---------|-------------|--------|-------------------|----------------------------------------|-------------------|-------------------|
| South Asia       | Pakistan| 2013-2015   | Prospective cohort | 380 | Birth, 1, 2, ..., 18 | 8918 | Iqbal et al 2018 | Nature Scientific Reports |
|                  | Pakistan| 2011-2014   | Prospective cohort | 284 | Birth, 1, 2, ..., 17 | 3177 | Ali et al 2016 | Journal of Medical Virology |
| Growth Monitoring Study | Nepal | 2012-ongoing | Prospective cohort | 698 | Birth, 1, 2, ..., 24 | 13487 | Not yet published |
| MAL-ED           | Nepal   | 2010-2014   | Prospective cohort | 240 | Birth, 1, 2, ..., 24 | 5936 | Shrestha et al 2014 | Clin Infect Dis |
| CMC Birth Cohort, Vellore | India | 2002-2006   | Prospective cohort | 373 | Birth, 0.5, 1, 1.5, ..., 24 | 9131 | Gladstone et al 2011 | NEJM |
| MAL-ED           | India   | 2010-2012   | Prospective cohort | 251 | Birth, 1, 2, ..., 24 | 5947 | John et al 2014 | Clin Infect Dis |
| Vellore Crypto Study | India | 2008-2011   | Prospective cohort | 410 | Birth, 1, 2, ..., 24 | 9825 | Kattula et al 2014 | BMJ Open |
| CMIN             | Bangladesh | 1993-1996  | Prospective Cohort | 280 | Birth, 3, 6, ..., 24 | 5399 | Pathela et al 2007 | Acta Paediatrica |
| MAL-ED           | Bangladesh | 2010-2014  | Prospective cohort | 265 | Birth, 1, 2, ..., 24 | 5816 | Ahmed et al 2014 | Clin Infect Dis |
| PROVIDE RCT      | Bangladesh | 2011-2014  | Individually RCT | 700 | Birth, 6, 10, 12, 14, 17, 18, 24, 39, 40, 52, 53 (weeks) | 12165 | Kirkpatrick et al 2015 | Am J Trop Med Hyg |
| Food Suppl RCT   | India    | 1995-1996   | Individually RCT | 418 | Baseline, 6, 9, 12 | 2242 | Bhandari et al 2001 | J Nutr |
| Optimal Infant Feeding | India | 1999-2001  | Cluster RCT | 1535 | Birth, 3, 6, ..., 18 | 9539 | Bhandari et al 2004 | J Nutr |
| New Delhi Birth Cohort | India | 1969-2002  | Prospective cohort | 7452 | Birth, 3, 6, 9, 12, 18, 24 | 32463 | Bhardwaj et al 2005 | NEJM |
| NIH Birth Cohort | Bangladesh | 2008-2009  | Prospective cohort | 629 | Birth, 3, 6, ..., 12 | 6216 | Korpe et al 2016 | PLOS NTD |
| JViT4-3 Trial    | Bangladesh | 2012-2014  | Cluster RCT | 5444 | 6, 9, 12, 14, 18 | 36167 | Christian et al 2015 | IJE |
| JViT3 Trial      | Bangladesh | 2008-2012  | Cluster RCT | 27342 | Birth, 1, 3, 6, 12, 24 | 109535 | West et al 2014 | JAMA |
| NIH Cryptosporidium Study | Bangladesh | 2014-2017 | Prospective cohort | 758 | Birth, 3, 6, ..., 24 | 9774 | Steiner et al 2018 | Clin Infect Dis |
| The Cebu Longitudinal Health and Nutrition Survey | Philippines | 1983-2005 | Prospective cohort | 3073 | Birth, 2, 4, ..., 24 | 32636 | Adair 2007 | Am J Hum Biol |

### Africa

| Region, Study ID | Country   | Study Years | Design | Children Enrolled* | Anthropometry measurement ages (months) | Total measurements* | Primary References |
|------------------|-----------|-------------|--------|-------------------|----------------------------------------|-------------------|-------------------|
| MAL-ED           | Tanzania  | 2009-2014   | Prospective cohort | 262 | Birth, 1, 2, ..., 24 | 5857 | Mduma et al 2014 | Clin Infect Dis |
| Tanzania Child 2 | Tanzania  | 2007-2011   | Individually RCT | 2400 | 1, 2, ..., 20 | 32198 | Locks et al 2016 | Clin Nutr |
| MAL-ED           | South Africa | 2009-2014 | Prospective cohort | 314 | Birth, 1, 2, ..., 24 | 6478 | Bessong et al 2014 | Clin Infect Dis |
| MRC Keneba       | Gambia    | 1987-1997   | Cohort | 2931 | Birth, 1, 2, ..., 24 | 40952 | Schoenbuchner et al 2019 | AJCN |
| Study                          | Country         | Period            | Type               | Sample Size | Measurements | Authors and Publication Details |
|-------------------------------|-----------------|-------------------|--------------------|-------------|--------------|---------------------------------|
| ZVITAMBO Trial                | Zimbabwe        | 1997 - 2001       | Individual RCT     | 14104       | Birth, 6 wks, 3, 6, 9, 12      | Malaba et al. 2005 Am J Clin Nutr |
| Lungwena Child Nutrition RCT  | Malawi          | 2011 - 2014       | Individual RCT     | 840         | Birth, 1-6 wk, 6, 12 18       | Mangani et al. 2015, Mat Child Nutr |
| iLiNS-Zinc Study              | Burkina Faso    | 2010 - 2012       | Cluster RCT        | 3266        | 9, 12, 15, 18                  | Hess et al. 2015 Plos One |
| Latin America                 |                 |                   |                    |             |                           |                                  |
| MAL-ED                        | Peru            | 2009 - 2014       | Prospective cohort | 303         | Birth, 1, 2, ..., 24          | Yori et al. 2014 Clin Infect Dis |
| CONTENT                       | Peru            | 2007 - 2011       | Prospective cohort | 215         | Birth, 1, 2, ..., 24          | Jaganath et al. 2014 Helicobacter |
| Bovine Serum RCT              | Guatemala       | 1997 - 1998       | Individual RCT     | 315         | Baseline, 1, 2, ..., 8        | Begin et al. 2008, EJCN |
| MAL-ED                        | Brazil          | 2010 - 2014       | Prospective cohort | 233         | Birth, 1, 2, ..., 24          | Lima et al. 2014 Clin Infect Dis |
| INCAP Nutrition Supplementation Trial Longitudinal Study | Guatemala       | 1969 - 1977       | Cluster RCT        | 1406        | Birth, 3, 6, ..., 24          | Habicht et al. 1995 J Nutr |
| Europe                        |                 |                   |                    |             |                           |                                  |
| PROBIT Study                  | Belarus         | 1996 - 1997       | Cluster RCT        | 16898       | 1, 2, 3, 6, 9, 12             | Kramer et al. 2001 JAMA |
| Mortality analysis only       | Burkina Faso    | 2010 - 2011       | Cluster RCT        | 7167        | 6, 10, 14, 17, 22             | Becquey et al. 2016 J Nutr |
| Vitamin A Trial               | India           | 1995 - 1996       | Cluster RCT        | 3983        | 1, 3, 6, 9, 12                | WHO CHD Vitamin A Group 1998 Lancet |
| iLiNS-DOSE                    | Malawi          | 2009 - 2011       | Individual RCT     | 1932        | 6, 9, 12, 18                  | Malata et al. 2015 J Nutr |
| iLiNS-DYAD-M                  | Malawi          | 2011 - 2015       | Individual RCT     | 1235        | 1, 6, 12, 18                  | Ashorn et al. 2015 J. Nutr |

*Children enrolled is for children with measurements under 2 years of age. Total measurements are number of measurements of anthropometry on children under 2 years of age.
## Extended data table 2

All exposures included in the analysis, as well as the categories the exposures were classified into across all cohorts, categorization rules, and the total number of children and percent of children in each category. We selected the exposures of interest based on variables present in multiple cohorts that met our inclusion criteria, were found to be important determinants of stunting and wasting in prior literature, and could be harmonized across cohorts for pooled analyses.

| Exposure variable          | N children under 24 months with both measured exposure and length | Exposure levels [N (%)] First listed level is reference | Categorization rules                        |
|----------------------------|------------------------------------------------------------------|--------------------------------------------------------|---------------------------------------------|
| Sex                        | 93756                                                             | Female: 45638 (48.7%) Male: 48118 (51.3%)             |                                             |
| Gestational age at birth   | 53500                                                             | Full or late term: 27079 (50.6%) Early term: 18377 (34.3%) Preterm: 8044 (15%) | <260 days is preterm, [260-274) days is early term, >= 274 is full term |
| Birthweight (kg)           | 80162                                                             | Normal or high birthweight: 63631 (79.4%) Low birthweight: 16531 (20.6%) |                                             |
| Birth length (cm)          | 75832                                                             | >=50 cm: 26909 (35.5%) (48-50) cm: 19308 (25.5%) <48 cm: 29615 (39.1%) |                                             |
| Birth order                | 58044                                                             | Firstborn: 20041 (34.5%) Secondborn: 17125 (29.5%) Thirdborn or later: 20878 (36%) |                                             |
| Delivery location          | 17158                                                             | Hospital or clinic: 9123 (53.2%) Home: 8035 (46.8%) |                                             |
| Delivery method            | 66826                                                             | C-section: 5684 (8.5%) Vaginal birth: 61142 (91.5%) |                                             |
| Maternal weight            | 63917                                                             | >=58 kg: 20534 (32.1%) (52-58) kg: 9868 (15.4%) <52 kg: 33515 (52.4%) |                                             |
| Maternal height            | 71666                                                             | >=155 cm: 35237 (49.2%) (151-155) cm: 12996 (18.1%) <151 cm: 23433 (32.7%) |                                             |
| Maternal body mass index (BMI) | 62281                                                                 | Normal weight: 49423 (79.4%) Underweight: 12858 (20.6%) | WHO categories (<18.5 BMI is underweight) Excludes mothers whose only weight measurement was taken during pregnancy. |
| Mother’s age               | 85002                                                             | [20-30]: 50917 (59.9%) <20: 19310 (22.7%) >=30: 14775 (17.4%) |                                             |
| Maternal education         | 84912                                                             | High: 26564 (31.3%) Medium: 30319 (35.7%) Low: 28029 (33%) | Classified by splitting distribution of numbers of years of educations into thirds within each cohort, or grouping ordered categories of educational attainment into three levels. |
| Paternal height            | 16268                                                             | >=167 cm: 13569 (83.4%) |                                             |
| Description                                      | Value            | Description                                                                 |
|-------------------------------------------------|------------------|----------------------------------------------------------------------------|
| [162-167] cm                                   | 1713 (10.5%)     | >162 cm: 986 (6.1%)                                                        |
| Paternal age                                    | 23328            | >=38: 1873 (8%)                                                            |
|                                                |                  | [32-38]: 3912 (16.8%)                                                      |
|                                                |                  | <32: 17543 (75.2%)                                                         |
| Paternal education                              | 75358            | High: 15623 (20.7%)                                                        |
|                                                |                  | Medium: 32968 (43.7%)                                                      |
|                                                |                  | Low: 26767 (35.5%)                                                        |
| Paternal education                              |                  | Classified by splitting distribution of numbers of years of educations into |
|                                                |                  | thirds within each cohort, or grouping ordered categories of educational   |
|                                                |                  | attainment into three levels.                                             |
| Caregiver marital status                        | 50468            | Married/partnered: 48223 (95.6%)                                           |
|                                                |                  | Single/widow/partner overseas: 2245 (4.4%)                                 |
| Asset based household wealth index              | 44263            | Wealth Q4: 13671 (26.4%)                                                   |
|                                                |                  | Wealth Q1: 10844 (24.5%)                                                   |
|                                                |                  | Wealth Q2: 10496 (23.7%)                                                   |
|                                                |                  | Wealth Q3: 11252 (25.4%)                                                   |
| Asset based household wealth index              |                  | First principal component of a principal components analysis of all        |
|                                                |                  | recorded assets owned by the household (examples: cell phone, bicycle, car.)|
| Household food security                          | 25848            | Food Secure: 13082 (50.6%)                                                 |
|                                                |                  | Mildly Food Insecure: 8632 (33.4%)                                         |
|                                                |                  | Food Insecure: 4134 (16%)                                                  |
| Household food security                          |                  | Combination of three food security scales:                                 |
|                                                |                  | 1. The Household Hunger Scale (HHS)34                                      |
|                                                |                  | 2. Food Access Survey Tool (FAST)35                                        |
|                                                |                  | 3. USAID Household Food Insecurity Access Scale (HFIAS), with middle 2     |
|                                                |                  | categories classified as mildly food insecure.36                         |
|                                                |                  | And one survey question from the NIH Bangladesh birth cohort and NIH       |
|                                                |                  | Bangladesh Cryptosporidium cohort:                                         |
|                                                |                  | "In terms of household food availability, how do you classify your         |
|                                                |                  | household?"                                                                  |
|                                                |                  | 1. Deficit in whole year                                                    |
|                                                |                  | 2. Sometimes deficit                                                        |
|                                                |                  | 3. Neither deficit nor surplus                                               |
|                                                |                  | 4. Surplus                                                                   |
|                                                |                  | Where the middle two categories were classified as mildly food insecure.    |
| Improved floor                                  | 37686            | Yes: 6477 (17.2%)                                                           |
|                                                |                  | No: 31209 (82.8%)                                                           |
| Improved sanitation                             | 44216            | Yes: 27350 (61.9%)                                                          |
|                                                |                  | No: 16866 (38.1%)                                                           |
| Improved water source                           | 36980            | Yes: 35392 (95.7%)                                                          |
|                                                |                  | No: 1588 (4.3%)                                                             |
| Clean cooking fuel usage                        | 2678             | Yes: 1338 (50%)                                                             |
|                                                |                  | No: 1340 (50%)                                                              |
| Number of children <5 in the                    | 35453            | One: 21653 (61.1%)                                                          |
| household | Two or more: 13800 (38.9%) |
|-----------|---------------------------|
| Number of individuals in the household | 3732 | 3 or less: 692 (18.5%)<br>4-5: 1609 (43.1%)<br>6-7: 887 (23.8%)<br>8+: 544 (14.6%) |
| Number of rooms in household | 42851 | Four or more: 2819 (6.6%)<br>Three: 4155 (9.7%)<br>Two: 11351 (26.5%)<br>One: 24526 (57.2%) |
| Rain season | 7462 | Opposite max rain: 1579 (21.1%)<br>Pre max rain: 1884 (25.3%)<br>Max rain: 2170 (29.1%)<br>Post max rain: 1829 (24.5%) |

Rainfall data was extracted from the University of East Anglia Climate Research Unit CRU TS dataset (version 3.23, 23 October 2015) and averaged by month over the duration of cohorts. The three-month period opposite the three months of maximum rainfall was used as the reference level (e.g., if June-August was the period of maximum rainfall, the reference level is child mean WLZ during January-March). Due to the time-varying nature of this exposure, N's are reported for children with length measures at 24 months and measures of rain season.

| Breastfed hour after birth | 50188 | Yes: 12483 (24.9%)<br>No: 37705 (75.1%) |
|---------------------------|-------|----------------------------------|
| Exclusive or predominant breastfeeding in the first 6 months of life | 26948 | Yes: 18471 (68.5%)<br>No: 8477 (31.5%) |

Exclusive breastfeeding: mother reported only feeding child breastmilk on all dietary surveys
Predominant breastfeeding: mother reported only feeding child breastmilk, other liquids, or medicines on all dietary surveys

| Cumulative percent of days with diarrhea under 6 months | 4812 | [0%, 2%]: 2668 (55.4%)<br>&gt;2%: 2144 (44.6%) |
|-------------------------------------------------------|------|----------------------------------|
| Cumulative percent of days with diarrhea under 24 months | 13430 | [0%, 2%]: 6536 (48.7%)<br>&gt;2%: 6894 (51.3%) |

Percent days defined as proportion of disease surveillance days a child had diarrhea during. Diarrhea defined by 3 or more loose stools, or bloody stool, in a 24 hour period. Only included studies with at least 100 disease surveillance measurements during age range.

| Enrolled or born stunted | 96217 | No: 79110 (82.2%)<br>Yes: 17107 (17.8%) |
|--------------------------|-------|----------------------------------|
| Enrolled or born wasted | 8664189263 | No: 73722 (85.1%) |
Yes: 12919 (14.9%) No: 76610 (85.8%)

|                          | Yes: 12653 (14.2%) | No: 74617 (85.6%) |
|--------------------------|--------------------|-------------------|
| Any wasting under 6 months | 10328              | 7849 (76%)        |
| Persistently wasting under 6 months | 9631               | 9176 (95.3%)      |

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