Longitudinal growth in early childhood and vulnerability to infection and mortality

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Abstract

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Despite substantial improvements in child survival in the last 30 years, an estimated 5 million children still died before their 5th birthday worldwide in 2019.[1,2] At the current trajectory of decline, the world will not meet Sustainable Development Goals for infant and child mortality.[2,3] About 80% of under-5 deaths were due to birth, nutrition, or infectious disease-related causes.[1] However, there are gaps in our understanding of how infectious diseases and other factors in pregnancy, birth, and infancy can affect vulnerability to future infections, survival, and healthy development of infants and children.[4–9] Longitudinal analyses of height and weight in children can strengthen our understanding of the magnitude of infections on vulnerability and improve resiliency in child development.[10]

Childhood infectious disease vulnerability is likely a positive feedback loop. A child that is born premature might face obstacles in catching up to reference growth standards simply due to starting in a smaller place.[11,12] Further, underweight and short stature are both associated with a greater risk of mortality due to infectious diseases.[13,14] Infectious diseases broadly, and some pathogens specifically, are also associated with linear growth faltering.[15–17] In this mechanism, vulnerability might reinforce

itself through higher risk of infection, leading to greater vulnerability to future- and potentially more severe- infections. Being malnourished is most impactful in the first year of life, leading to increased risk of mortality from infectious causes and suppressing linear growth and cognitive development at a crucial period.[18]

There are several key terms that will be used throughout this dissertation. Childhood growth failure (CGF) metrics typically include height-for-age, weight-for-age, and weight-for-height z-scores (HAZ, WAZ, WHZ, respectively). These metrics are constructed from global growth reference standards. Given an individual child's height and weight, each can be calculated based on the distance between those values and the growth reference median based on age and sex. Representing height and weight as z-scores is very useful because it removes some of the complexity of modeling non-linear growth trajectories and because it enables instantaneous comparison of a child's growth with a reference. Children that are mildly (-1 to -2 z-scores), moderately (-2 to -3 z-scores), or severely (< -3 z-scores) below the global reference have worse health and developmental outcomes than children who are not. Stunting describes children with low HAZ, underweight describes children with low WAZ, and wasting describes children with low WHZ. Each has potentially important interpretations. For example, stunting is often considered a proxy indicator for chronically poor growth, associated with environmental and socio-demographic barriers to healthy development, and may predispose children to poor cognitive and educational attainment.[9,19–21] In contrast, WHZ is most frequently used to identify children with severe acute malnutrition, a devastating condition that requires urgent medical care and therapeutic intervention to prevent deaths directly due to malnutrition like organ failure.[18]

This dissertation sought to systematically review and apply statistical approaches to measuring longitudinal childhood growth and vulnerability to all-cause and infectious disease-specific incidence and mortality. It is structured in four distinct chapters, representing three specific aims. A short

summary of each chapter follows. Each is structured as an academic journal article and includes tables, figures, and references specific to each chapter. This document concludes with an overall reflection and proposes next steps related to this work.

The first chapter of this dissertation, *Statistical methods for repeated measurements of childhood growth, a systematic review and analysis*, describes how the academic literature has used specific methodologies and approaches to quantify longitudinal childhood growth. Specifically, we sought to identify statistical models for accounting for repeated measurements of height, weight, head circumference, and mid-upper arm circumference among children. We identified 12,355 articles in PubMed that matched our search criteria. Of these, 2,640 were included in a full text review and 1,301 publications had repeated measurements of childhood growth and an informative description of the statistical methods used to growth on its own or how growth was associated with other outcomes such as cognitive development or mortality. Most studies (59.6%) used statistical methodologies that explicitly accounted for correlation among measurements within individual children, largely multilevel or hierarchical models, generalized estimating equations, or latent class models. Analyses of longitudinal outcomes like growth and infections should account for variation within and between individuals to appropriately make the most reliable statistical models.[10] Statistical models that account for dependence in repeated observations are critical to producing valid inference because not accounting for this violates assumptions of independent and identically distributed observations in linear and generalized linear regression. There has been an increase in the number of studies that analyzed repeated measurements of childhood growth published since 2010 including wider geographical representation of the studies that collected those data. This interest in longitudinal childhood growth is exciting and research must use appropriate methods to analyze the data because it makes the results more reliable and valid and better strengthens our understanding of why growth varies between children. This review and synthesis provided a quantitative review of these methods, how they differ

between studies, and provided advice for how to consider repeated measures of childhood growth in future analyses.

The second chapter of this dissertation, *Effects of childhood growth failure on cause-specific infectious disease incidence and mortality: a Burden of Proof study,* estimated a continuous risk curve for low height-for-age, weight-for-height, and weight-for-height z-scores (HAZ, WAZ, and WHZ, respectively) for diarrhea, lower respiratory infections, malaria, and measles incidence and mortality. Previous efforts to quantify the risk of these infectious disease outcomes were based on categorical definitions of childhood growth failure (CGF) and were limited to fatal outcomes.[13] In this chapter, we describe how, for the first time, a continuous risk curve for each of the three CGF indicators was produced using a flexible, hierarchical, Bayesian meta-regression tool. We applied the Global Burden of Disease study (GBD) Burden of Proof criteria to our models and show that, with high confidence, low HAZ, WAZ, and WHZ are significant risk factors for mortality due to diarrhea, lower respiratory infections, and measles. Further, our analysis indicates novel associations between childhood growth metrics and the risk of malaria mortality and the risk of infectious disease incidence for each of the distinct infectious diseases. The results from this work are part of the GBD 2021 estimates of the burden of childhood growth failure for 195 countries, 5 age groups, and by sex from 1990-2021.

These updated burden estimates are described in the third chapter, *Quantifying the fatal and non-fatal burden of disease attributable to childhood growth failure: An analysis from the Global Burden of Disease study 2021.* We found that the burden of CGF is not equally distributed geographically, with substantial health loss attributable to infectious disease incidence and mortality concentrated in sub-Saharan Africa and South Asia. We show that, despite reductions in the prevalence of CGF in many locations, the percent attributable burden hasn't declined as fast as the attributable burden rate, suggesting that reducing CGF is essential to accelerate declines in under-5 child mortality. Reducing its

burden may be necessary but insufficient for countries to meet Sustainable Development Goals for under-5 mortality, demonstrating that interventions to reduce mortality due to other causes, especially neonatal causes of death, are also required to meet international goals for child survival. The two papers of this aim will both be submitted for peer review and publication in an academic journal and the second will be shared with the GBD Collaborator Network, a group of thousands of experts in disease burden and epidemiology, for critical feedback prior to being submitted for peer review. This chapter is based on final results from GBD 2021 as of November 2023. These papers advance our understanding of the consequences and stakes of childhood growth failure by quantifying infectious disease risk based on metrics of CGF and by quantifying the overall burden of disease and the magnitude of health loss associated with CGF on a global level.

The fourth and final chapter of this dissertation, *Longitudinal trajectories of early childhood vulnerability: a pooled analysis of cohort studies of growth and mortality,* uses a dataset of 58 studies to quantify vulnerability to all-cause mortality. Using vulnerability as a framework to describe the complex, interdimensional factors contributing to population- or individual-level risk of poor health and developmental outcomes. Recently, vulnerability has been used to segment newborns into birth phenotypes, or categorical groups based on their gestational age and birthweight.[12] These phenotypes are strongly associated with the probability of neonatal mortality. A separate analysis used a standardized, pooled dataset of prospective cohort studies from low-and middle-income countries to produce robust, longitudinal estimates of the incidence and recovery of stunting and wasting.[11,22] Our analysis uses this same pooled dataset and adds 18 other studies, standardized across growth metrics, maternal characteristics, birth outcomes, and sociodemographic indicators to quantify vulnerability in the first two years of life. We defined vulnerability as the risk of all-cause mortality and used a survival analysis to jointly estimate the impact of continuous values of HAZ and WHZ on that risk. This non-linear, compounded risk can be calculated for any child given their age, sex, weight, and height. We then

used a multidimensional model to estimate latent class trajectories in HAZ and WHZ to quantify how children grow in these metrics simultaneously. Membership in each trajectory cluster describes a child's magnitude and trend in vulnerability over time as they age from birth to 2 years. The analysis showed that children born to poorly nourished mothers and mothers with lower education were more likely to have lower starting and deteriorating vulnerability than their peers. This novel analysis used a very large, pooled dataset of tens of thousands of children and hundreds of thousands of anthropometric observations to produce robust quantitative estimates of vulnerability, transforming a useful framework into a practical and actionable way to identify children that are most likely to suffer from mortality and to intervene upon them to prevent it. This paper will be finalized and submitted to peer review and publication in an academic journal.

Altogether, this dissertation has advanced our understanding of how childhood growth failure affects the risk of disease burden among children younger than 5. It surveyed the landscape of statistical methods to assess repeated measurements of growth and applied lessons from that review to building appropriate and robust statistical models to quantifying outcomes of CGF. It has quantified risks of cause-specific infectious disease incidence and mortality and generated estimates of the burden of disease caused by CGF at the global level. Finally, repeated growth measurements were used to generate trajectories in childhood vulnerability and describe which children are most likely to have positive and negative slopes in their vulnerability as they age. Reducing early childhood vulnerability associated with childhood growth failure ultimately requires multi-sectoral policies, strategies, and interventions.[23] This dissertation has reiterated how urgent those efforts are and created a framework for identifying the children most vulnerable. Thanks for reading!

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Table of Contents

Chapter 1: Statistical methods for repeated measurements of childhood growth: a systematic review and analysis

Abstract

Growth failure is one of the leading risk factors for poor health and developmental outcomes in young children. Research studies that follow children longitudinally for changes in growth often use statistical models to quantify associations between growth and environmental, clinical, or epidemiological factors to understand when children are growing successfully. This study is a systematic review of publications that quantify childhood growth and an analysis of the statistical methodology used in those publications with an emphasis on studies that accounted for repeated measurements of growth within unique children. We identified **12,355** articles in PubMed that met our search criteria including **2,640** that were included following title/abstract screen. The final collection consisted of **1,301** publications with repeated measurements of childhood growth of which **59.6%** used statistical methods designed to account for correlation in measurements. Most of these studies used multilevel (hierarchical) models but generalized estimating equations and latent class models were also popular methodologies. Studies that constructed growth curves often used the lambda/mu/sigma (LMS) method used by global reference growth curve models. Using appropriate statistical methods might make findings about variation in growth between children more reliable and valid. This review provides a quantitative look into statistical methods for analyzing childhood growth, discusses how they vary, and gives advice for how future analyses should consider repeated measurements of growth.

Background

Childhood growth failure, specifically inadequate growth in height and weight, is one of the leading risk factors for mortality in children younger than 5 years old.[1] Slow growth may also predispose children to lower levels of cognitive development and educational attainment.[3] Inversely, there is evidence that accelerated childhood growth, specifically in weight, is associated with obesity in adolescence and adulthood, higher blood pressure, and greater risk of other chronic diseases.[4,5] Quantifying factors and conditions that influence growth and development is necessary to understand when children are growing successfully or when children are faltering and to determine appropriate interventions.[6]

Incredibly, records on childhood growth dates back to the ancient Babylonian and Egyptian peoples.[7] Much later, in the mid-1700s, Count Philibert de Montbeillard plotted his son's height every six months from birth to 18 years, producing the first recorded height growth curve, and by the early 20th century, most European nations had published national growth tables.[7,8] The advancements in mathematics and statistics, including those made possible by advancements in computation, have contributed to a diverse set of analytic tools to study longitudinal growth.[6,8] Research on childhood growth varies in study design, primary outcomes, and sampling strategy; longitudinal studies frequently collect repeated anthropometric, specifically height/length, weight, and head and mid-upper arm circumference, measurements within individual children. It is critical for these analyses to have reliable and valid methods to perform statistical inference and test hypotheses regarding growth and development.

Statistical models for data collected repeatedly among a set of individuals, like growth in children, should account for correlation within individuals. Models that do not account for repeated observations among individuals assume that each observation is independent. However, observations of childhood growth are correlated because of dependence on prior observations or because of biological or demographic factors unique to each child. Failing to account for this dependence violates the assumption of independence in linear regression, and statistical inferences based on these models can be misleading or biased, potentially leading to incorrect conclusions. It is essential to account for repeated observations among individuals by using appropriate statistical models that incorporate the correlation structure, such as mixed-effects or generalized estimating equations, to obtain accurate estimates and make better-informed decisions based on study data.

Although there are several reviews meant to describe or compare statistical approaches to measure growth,[6,9,10] none have systematically quantified how the broad landscape of childhood growth research

uses various statistical methodology nor are there publications that discuss the appropriateness of statistical methodology based on study design. The purpose of this manuscript is to provide a systematic review and structured analysis of childhood growth studies; describe how and when statistical models have been utilized in this research; and to give recommendations about how to account for repeated or longitudinal measurements of childhood growth.

Methods

We searched PubMed for articles matching the search string below. We searched using *easyPubMed*, a package in the programming language R that queries the PubMed database through an application programming interface (API).

("child"[All Fields] OR "children"[All Fields] OR "childhood"[All Fields] OR "antenatal"[All Fields] OR "perinatal"[All Fields] OR "infant"[All Fields] OR "neonatal"[All Fields] OR "neonate"[All Fields] OR "neonates"[All Fields] OR "postnatal"[All Fields]) AND ("longitudinal"[All Fields] OR "cohort"[All Fields] OR "repeated"[All Fields] OR "time series"[All Fields] OR "time-series"[All Fields]) AND ("growth"[All Fields] OR "growth trajector*"[All Fields] OR "stunting"[Title/Abstract]) AND ("height"[All Fields] OR "stunting"[All Fields] OR "stunted"[All Fields] OR "wasted"[All Fields] OR "underweight"[All Fields] OR "weight"[All Fields] OR "height-for-age"[All Fields] OR "weight-for-age"[All Fields] OR "length-for-age"[All Fields] OR "length velocity"[All Fields]) NOT "systematic review"[Publication Type] NOT "meta-analysis"[Publication Type] NOT "protocol"[Title] AND "humans"[MeSH] NOT "fetal growth"[Title] NOT *retin*[Title/Abstract] NOT"chart review"[Title] NOT "narrative review"[Title] NOT "review of the literature[Title]

Publications were screened based on title and abstract. Exclusion criteria were:

1. Unavailable abstract
2. Publications that were not primary research including reviews, commentaries, and study protocols papers
3. The primary research outcome or predictors of primary research outcome was not related to childhood growth

Publications that passed the title/abstract screening were reviewed comprehensively for eligibility and statistical methodology. Characteristics of manuscripts that were recorded, where available and applicable, include study name, location and timing of the study, subject age range, number of subjects

and anthropometric measurements, primary and secondary outcomes, sub-populations, exposed populations and definition, study design, open access availability of publication, and analytic methodology utilized to analyze growth or that incorporated growth in the analysis of a separate primary outcome. There was no exclusion based on language. Where full text was available for articles published in languages other than English, we used Google Translate. The completed extraction sheet with these data is available in the **Supplementary Materials**.

The relevancy of each publication was determined during extraction. The relevancy of some publications was revisited after completion of the systematic review. The relevant publications met two main criteria:

1. Repeated growth measurements (2 or more) among a set of children were considered primary or secondary outcomes or were used as predictors for separate outcomes.
2. Information to ascertain study location, study population, primary analysis, and statistical methodology was available in the abstract or full text.

Publications were not considered relevant for this analysis if:

1. Repeated measurements of growth among a set of subjects were not a primary or secondary outcome and not used as predictors for separate primary outcome.
2. The study was cross-sectional in design, did not measure the same set of children multiple times, or measured growth at only one-time point.
3. Abstract provided insufficient information to ascertain eligibility and full text was unavailable.
4. Any exclusion criteria from title/abstract screen that inadvertently made it to this step.

We categorized statistical methods among relevant publications into those that accounted for dependence in repeated anthropometric measurements and those that did not. Specifically, hierarchical models, generalized estimating equations, and latent class models are frequently used methods that account for correlation within individuals. A full list of methods that account for this dependence is provided in the **Supplementary Material**.

The systematic review was conducted through June 1, 2023. Christopher Troeger conducted all aspects of the title & abstract screening, literature extraction, and analysis. Quantitative analysis was conducted in **R version 4.3.0** and code to write this publication and make figures is available in the **Supplementary Material**.

Results

Search results

We searched PubMed on June 9, 2023. There were 12,355 results from this search (**Figure 1**). The title and abstract review identified 2640 articles for review. These 2640 articles were each reviewed and relevant metadata about the analyses and studies were extracted, yielding 1548 publications with multiple measurements of childhood growth as outcomes or predictors. Of these, 247 had insufficient information in the main text, or in the abstract where full text was unavailable, to determine the analytic method or research question. This left 1301 studies included in this analysis. Height or length was a primary outcome in in 932 publications while weight (n = 841), head circumference (n = 116), and arm or mid-upper arm circumference (n = 25) were included less frequently. There were 84 studies that were explicitly testing interventions in a randomized controlled trial.

Summary of methods

We categorized publications into two primary groups:

1. Studies that were designed to capture anthropometric measurements at two different time points per child (n = 185 publications). The most common statistical methodologies used were Linear, ANOVA, and Logistic. These studies do not need statistical methodologies to account for repeated measures and so are not considered in the remainder of this analysis.
2. Publications from studies designed to capture anthropometric growth measurements at two or more time points per child, from here forward called repeated measures studies (n = 1116 publications). The repeated measures trials were further subdivided into those that *considered* and those that left repeated measures *ignored* in their analyses. About 59.6% of studies accounted for repeated measurements within children.

Among publications that collected repeated growth measurements, generalized linear mixed models (GLMM; also known as hierarchical, mixed-effects, multilevel, or random effects) models were the most frequently used methodology (n = 323; **Figure 2**). These analyses accounted for repeated measures by adding a random intercept and/or slope by individual child. Many were non-linear, adding splines or polynomials (n = 19) to make them more flexible in estimating growth curves. Variations on linear mixed-effects models like repeated measures analysis of variance (ANOVA; n = 30) and generalized additive mixed models (GAMM; n = 50) were less frequently used. The other commonly used

approaches were generalized estimating equations (GEE; n = 80) and latent class growth trajectory, growth mixture, and group-based trajectory models (n = 103).

Some analyses sought to compare growth curves within a study population against global reference growth curves. Many of these analyses used the *lambda, mu, sigma* model (LMS; n = 26), a special type of generalized additive model for location, scale, and shape. LMS models are used by the US Centers for Disease Control and Prevention (US CDC)[11] and the World Health Organization (WHO)[12] to construct smoothed growth percentile curves. Other analyses use the *super-imposition by translation and rotation* model (SITAR; n = 21), a random-effects cubic spline model where size, tempo (timing of changes in growth rate), and velocity (speed of growth) are estimated for each child.[13] SITAR was frequently used for comparing timing of peak velocity, age of puberty, and size at repeated ages.

The statistical methods most frequently used in studies that failed to account for repeated measures were Linear, ANOVA, and Logistic (**Figure 2**).

Publications collecting repeated measurements of childhood growth increased over time, especially since 2010 (**Figure 3**). There was a statistically significant increase in the fraction of publications that used statistical methods to account for repeated measurements from 41% in 2000-2005 to 65% in 2016-2021 (t-test; p-value <0.001).

Geographic distribution of studies & representation

Publications in this analysis included data from studies with a wide geographic distribution (**Figure 4**). The locations with the most studies were the United States (173), China (92), and the United Kingdom (71) but low- and middle-income countries were also well represented including Brazil (63), Bangladesh (40), and India (50). Primary data from some studies were frequently used in different publications including the Young Lives (India, Vietnam, Ethiopia, Peru)[14], Generation R (the Netherlands)[15], MAL-ED (Peru, Brazil, Tanzania, South Africa, Pakistan, Nepal, India, Bangladesh)[16], Pelotas (Brazil)[17,18], and Birth to 20 (South Africa)[19] cohort studies.

Discussion

The value and importance of these studies in epidemiological sense as motivation for why it is critical to get statistical analysis correct.

Publications investigating childhood growth have been increasing over time, potentially reflecting a growing emphasis on early life exposures as risk factors for childhood mortality and poor developmental

outcomes. Characteristics of childhood growth identified in these studies have helped to identify potential mechanisms or points of intervention and interventional studies are required to determine efficacy or effectiveness of such strategies and treatments.

Reflection on where analyses are inappropriate and appropriate and existing gaps.

There was a substantial increase in the number of longitudinal growth studies since the year 2000, possibly reflecting advancements in methods or research interest. In 2006, the World Health Organization published its child growth standard based on a multisite study intended to measure optimal infant and child growth.[12] These global references enabled the more widespread adoption and use of standardized z-scores to define healthy growth and identify childhood growth failure in the form of stunting, underweight, and wasting based on deviation from height and weight reference standards.

There were many publications identified in this study that collected baseline and endline anthropometric measurements and analyzed either the change in growth between those two time points or the growth status at endline, accounting for baseline characteristics. For example, some studies used logistic regression to estimate the odds of being stunted at the end of the study, accounting for stunting growth at the start. Other studies were randomized trials that investigated the impact of an intervention on growth comparing the experimental and control arms using t-tests. These analyses are valid because there is not a true component of repeated measurements. An attempt to account for withing-child correlation, using random intercepts for example, would effectively remove explanatory power from other variables in the model, absorbing that variation.

In contrast, despite a variety of statistical models able to account for repeated measurements within individuals, only about two-thirds of publications that had multiple growth measurements per child accounted for them directly in the statistical models. Failure to account for correlation between repeated measurements violates one of the primary assumptions of linear regression- that observations are independent and identically distributed. Not accounting for the dependence of the measurements within individual children may lead to biased estimates; specifically in estimated variance and uncertainty in point estimates of effect sizes or other statistical associations between predictors and growth.[20] The level of bias depends on the strength of the association. This source of bias might lead to spurious conclusions about effect sizes such as the impact of an intervention or the association between growth and biological or demographic factors. As most studies in this review were descriptive or causal epidemiology, appropriate methods are crucial for reliable statistical inference.

The most frequent method to account for repeated measurements was mixed-effect models, sometimes called hierarchical or multilevel models, which treats observations within individual children as a random variable.[20,21] Some studies defined variation in the overall level of growth between children using random intercepts only while others considered variation in intercept and slope between children. Hierarchical models are parametric and make well-defined Gaussian assumptions in the fixed and random effects.[22] Hierarchical random effects can be used in generalized link functions (Poisson, logistic) and in survival models (like mixed-effects Cox proportional hazards models).[22,23]. Another approach some studies used was multilevel generalized additive models, a family of models that account for within-child correlation using random effects but with much greater flexibility in the fixed effects, such as time or age, allowing for complex splines and non-parametric models to describe non-linear changes in growth.[24,25] In contrast to multilevel models, generalized estimating equations (GEE) provide much more flexibility to defining how observations within children are correlated including fixed correlation, exchangeable correlation, or time-dependent autoregressive correlation.[20,26,27] These statistical models are complex, especially those with splines or complex correlation matrices and have only recently become tractable with improvements in statistical computing and may not always be familiar to researchers without expertise in biotstatistics.[20,24]

Suggestion of baseline for repeated measures analyses.

Based on the present analysis, we propose a baseline for methods to analyze repeated growth measurements for children. Construction of growth curves are meant to compare growth within a specific population to a reference or other population should use either the LMS or SITAR methods. These models use random effects to account for within child variation in growth trajectories.

Analyses testing for association or inference between an exposure and childhood growth should first standardize to z-scores when available.[6] A set of useful statistical packages exists for this purpose on the WHO website. Researchers should then decide on appropriate model families (Poisson, logistic, linear, proportional hazards) depending on the scientific question.

Hierarchical linear models, generalized additive mixed models, and generalized estimating equations are all appropriate methods to account for repeated growth measurements and choosing between them might depend on the research question and intended interpretation, the number of children, the number of observations per child, the required flexibility in statistical fit, and the complexity of assumed or measured correlation within and between children.

For some statisticians, hierarchical models and GEE models are thought of in opposition.[27,28] Although a detailed comparison of hierarchical and GEE models is outside the scope of this paper (see Walls 2006[27] and Vagenas 2018[20] for nice discussions of similarities and contrasts), there are two primary differences. First, GEEs impose fewer assumptions on the data and allow the researcher the ability to specify a covariance structure between observations.[27,29] Second, GEE models estimate a marginal, population effect of a predictor while hierarchical models estimate an effect at the individual level (random effects are based on a normal distribution meant to represent the sample population).[20,27] While this distinction may not change the statistical interpretation of linear models, it could makes GEE an attractive option for binary or count data analyzed as logistic or Poisson models.[27,30] Ultimately, choosing between a hierarchical and GEE model may come down to the intended inference (the population-level or the individual-level) and in the specification of linear and non-linear fixed effects (e.g. polynomials and splines).

Conclusion

Statistically measuring childhood growth is difficult. There have been thousands of publications in the last 20 years studying how children grow and those publications have used a wide variety of different methods and approaches, sometimes appropriately matched with sampling design and research question and sometimes not. Using appropriate statistical methods makes epidemiological or clinical results more reliable and valid and strengthens the evidence base of why growth varies between children. This review has provided a quantitative look into these methods, discussed how and why they vary, and given advice for how future analyses should consider repeated measurements of growth.

Figures

Figure 1. PRISMA diagram of systematic review

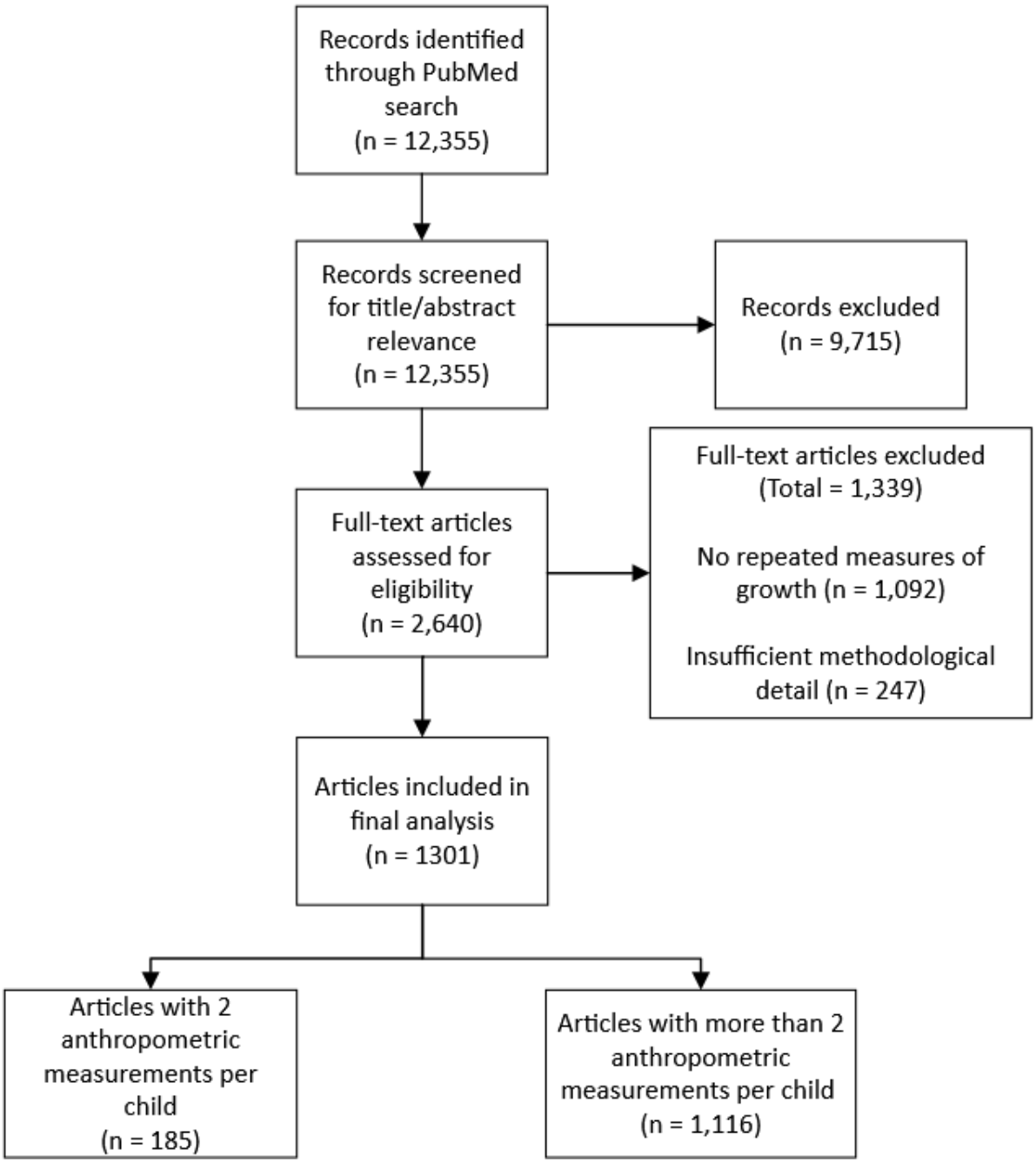


Figure 2. Summary of statistical methods for analyzing repeated measures of childhood growth from studies with more than two measurements per child.

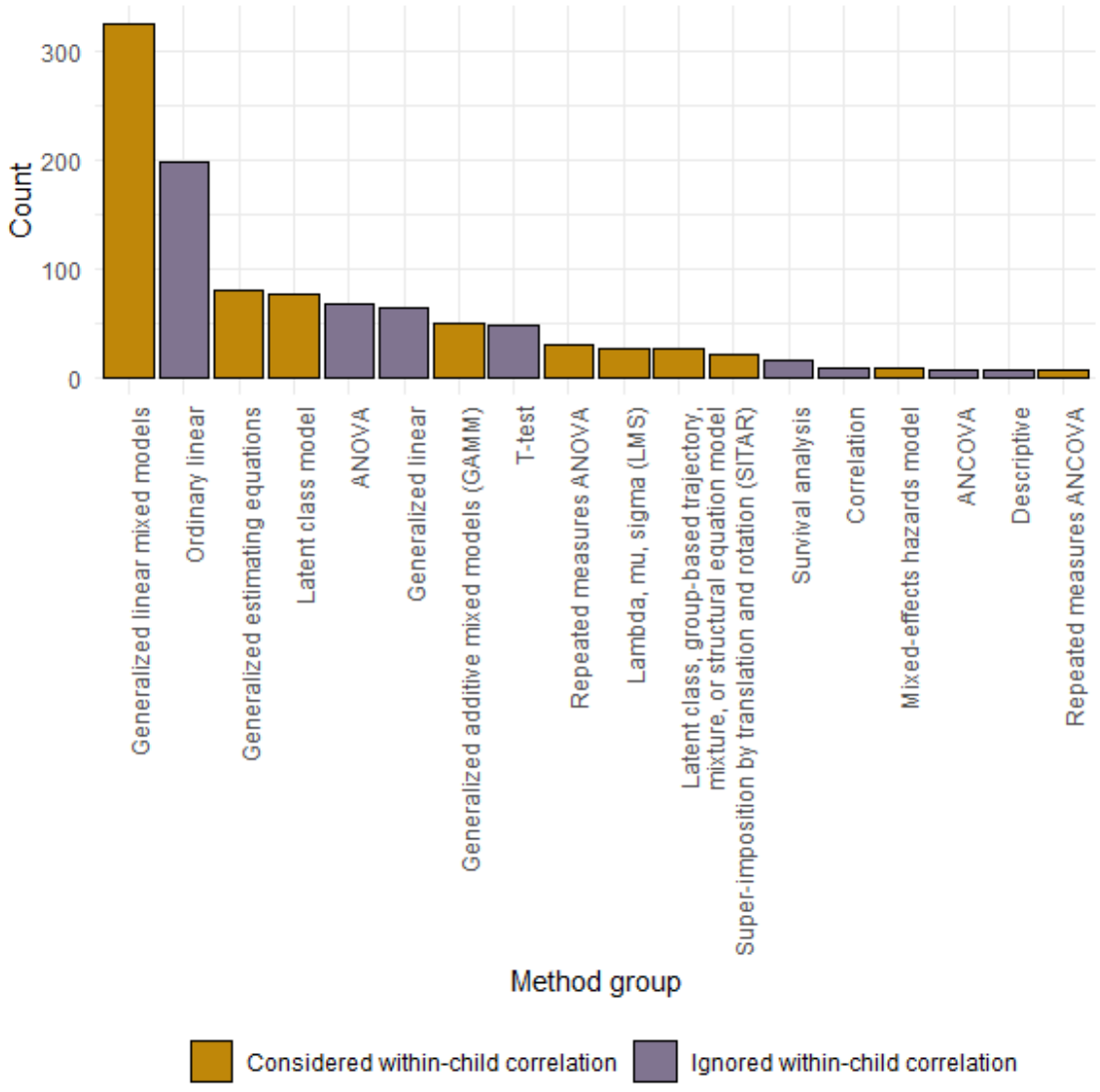


Figure 3. Distribution of studies with more than two observations per child that utilized statistical methods designed to account for repeated measures of childhood growth over time.

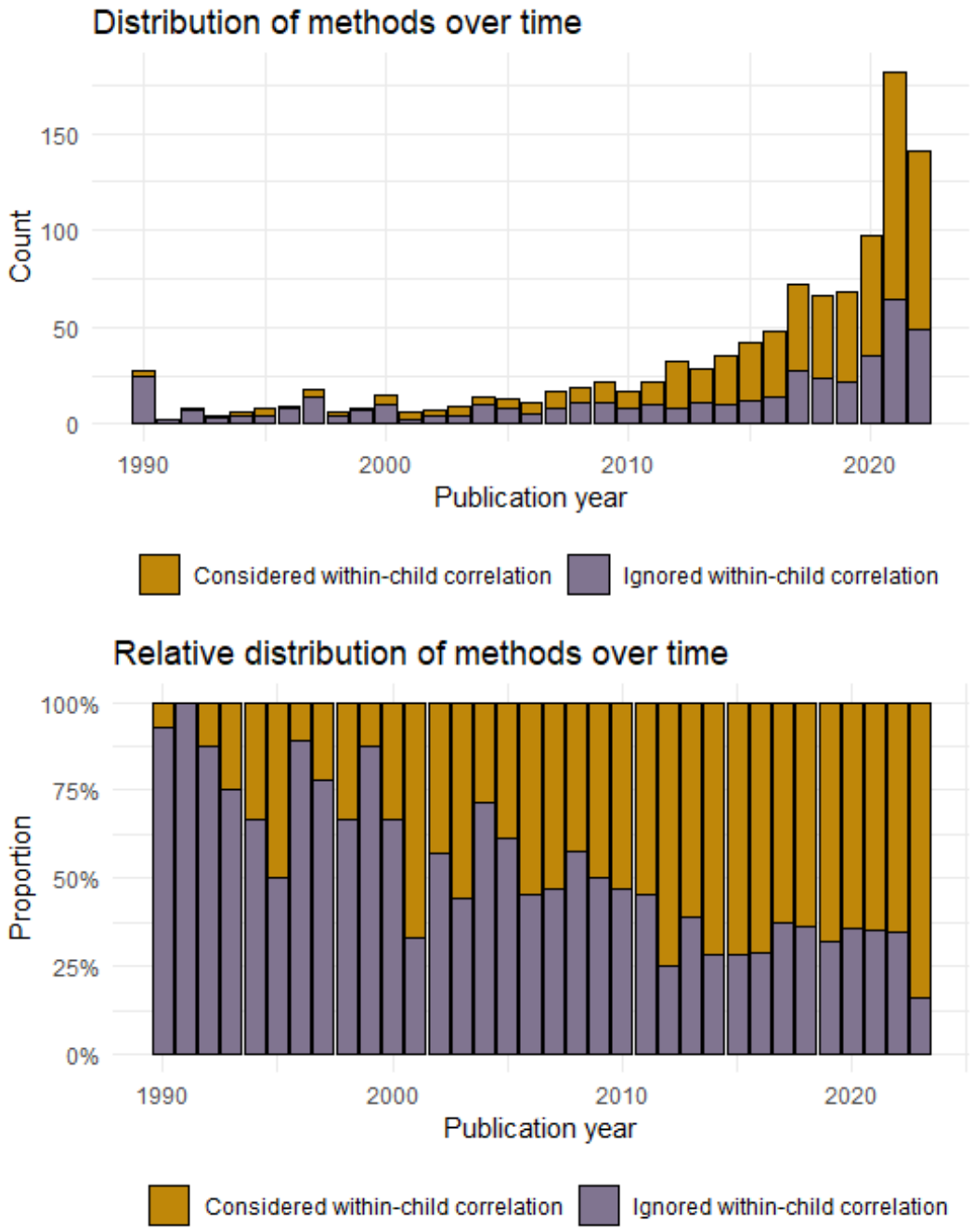
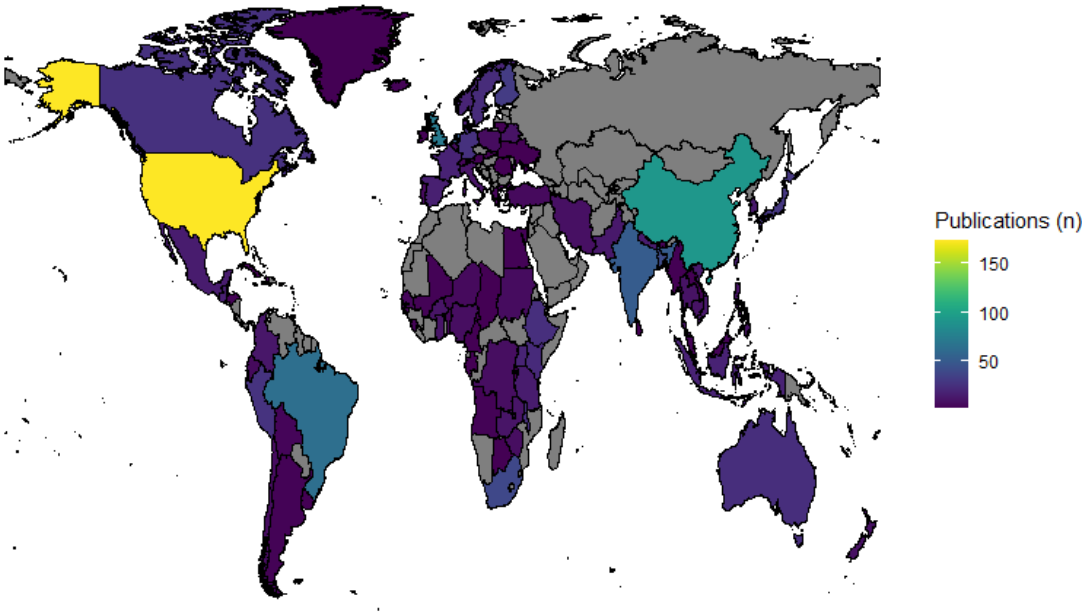


Figure 4. Geographic distribution of publications with two or more measurements of childhood growth



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Chapter 2: Effects of childhood growth failure on cause-specific infectious disease incidence and mortality: a Burden of Proof study

Abstract

Childhood growth failure (CGF) is one of the leading risk factors for under-5 childhood mortality. Using data from an existing database of longitudinal studies with anthropometric measurements of childhood growth and multiple measurements of cause-specific infectious disease incidence and mortality, we estimated a continuous relative risk distribution for infectious disease due to CGF. The indicators of CGF were height-for-age z-scores (HAZ), weight-for-age z-scores (WAZ), and weight-for-height z-scores (WHZ), three widely used metrics to describe childhood growth based on global reference standards. We evaluated different relative risk estimates with uncertainty for lower respiratory infections, diarrhea, malaria, and measles, separately, for both incidence and mortality. We further calculated a risk outcome score (ROS) and corresponding star rating (one to five). We found strong, significant relationships between CGF indicators and cause-specific infectious disease mortality for all causes including malaria. We also found statistically significant but marginal relationships between CGF indicators and some cause-specific infectious disease incidence. Our study emphasizes the importance of strengthening and developing strategies for preventing and treating CGF as part of a comprehensive approach to reducing under-5 mortality worldwide.

Introduction

Childhood growth failure is one of the most important risk factors for under-5 mortality.[1,2] Children suffer a substantial burden of disease from growth failure, especially in low- and middle-income countries where children tend to be born small and have a difficult time recovering their growth trajectories through infancy and early childhood.[3,4] Children who are smaller than their age peers are much more likely to die, and this risk is greater the more a child lags their peers.[5,6]

Traditionally, CGF has been defined by discrete categories from continuous distributions.[7] Several global reference growth curves were developed in the early 2000s to describe how children's height and weight *should* increase.[8] At each age and by sex, z-scores describe an individual child's distance from the median growth trajectory in terms of height-for-age (HAZ), weight-for-age (WAZ), and weight-for-height (WHZ). These z-scores exist in a continuous distribution such that 67.5% of children should exist between –1 and 1 z-scores. The further a measurement is from the median, the more extreme the growth difference. However, based in part on a desire to define prevalence of different CGF indicators and to set global goals for reductions in CGF, discrete categories were created to more easily describe children who are stunted (< -2 HAZ), underweight (< -2 WAZ), and wasted (< -2 WHZ). Sub-categories for mild (-1 to –2 z-scores), moderate (-2 to –3 z-scores), and severe (< -3 z-scores) were created to describe suboptimal growth in more detail.

In addition to the direct health loss associated with acute malnutrition, CGF increases a child's risk of infectious disease burden. The most comprehensive and widely cited analysis of the risk of CGF on infectious diseases comes from Olofin et al.[6] In a pooled analysis of cohort studies, the Authors found substantial and statistically significant increased risk of mortality due to lower respiratory infections, diarrhea, and measles for moderate and severe stunting, underweight, and wasting. The risk ratios were also higher for severe than for moderate or mild CGF. These results have been used in many estimates of the global burden of CGF.[1,9] However, to date, there have been no attempts to assess the continuous, opposed to discrete categorical, relationship between childhood growth and infectious disease incidence and mortality. This analysis uses data from 19 longitudinal cohort studies with repeated measurements of childhood growth and infectious disease incidence and mortality to quantify the risk associated with CGF using a robust modeling approach for the Global Burden of Disease study (GBD). The results from this study will be made available publicly for others to incorporate into their own research or analysis and have been used to inform the GBD 2021.

Methods

Description of cohorts

This is a pooled analysis of longitudinal studies with repeated measurements of childhood growth, infectious disease incidence, and cause-specific mortality from the Healthy Birth, Growth, and Development-Knowledge Integration (Ki) network.[10,11] This network is a Bill and Melinda Gates Foundation sponsored initiative to develop better understanding of and interventions for childhood growth faltering by working with researchers across 26 studies to create a knowledge base of pooled studies, standardized for various anthropometric, demographic, biological, and other variables.[4,10,12] We used all available studies from this dataset that were prospective studies with repeated measurements of height and weight for children under-5 years. We also included the summary results from the Olofin et al.[6] pooled analysis of cause-specific mortality risk due to CGF.

Data processing

Initial standardization of variables and definitions was performed by the Ki group. Further, we standardized the time between anthropometric measurements across studies and defined a 1-week period of recall for infectious disease incidence.

Data were shaped to ensure consistent use of variable names, extraction of birthweight from the first measurement in the first week of life, and differentiation between visit types (i.e., scheduled vs. unscheduled). The recall length for each reported morbidity event was extracted based upon study-specific variables. We calculated WHO Z-scores from raw anthropometric measurements, age, and sex using a custom version of the *igrowup* R package.

An algorithmic approach was applied to identify and flag unusual and implausible height observations in the individual-level data. Two examples of implausible observations are: a) a loss of height from the previous measurement (especially when the next measurement is ≥ the previous), b) measurement that is considerably greater than the previous and next observation. Additional details on this process can be found in the **Appendix [to be added when available].**

Data from the Pakistan site of the MAL-ED study were dropped from the dataset due to known issues with biased height measurements. Data from children in the Ilins-Dyad study were dropped after the first appearance of WHZ measurement < -2, because such children received nutrition supplementation. Observations for height, HAZ, WHZ, BMI, and BMIZ were assigned as NA in rows flagged as having unusual or implausible height observations (as identified above). BMI values that were considered suspicious (i.e., <5 and 40<) were dropped from the data set. GBD age group category was assigned to each observation based upon the child's age at the time: 1= 0-6d, 2= 7-27d, 3= 28d-5m, 4= 6m-11m, 5= 12m-23m, 6= 24m-4.99y (inclusive). Variables were also created for 1) age in months, and 2) to identify children from control group or cohort studies vs. intervention studies.

For each CGF indicator (HAZ, WAZ, WHZ), we defined discrete bins of 1 z-score width and summed the number of children, days of observation, and events (incidence, death for each infectious disease cause) by study and GBD age groups (early neonatal, late neonatal, 1 to 5 months, 6 to 11 months, 1 to 2 years, and 2 to 5 years).

Modeling continuous risk curves

We used a Bayesian meta-regression tool and risk factor assessment framework built for the Global Burden of Disease study and applied across risk factors to quantify a continuous risk curve for each CGF exposure category and outcome.[13,14] Each risk exposure indicator (HAZ, WAZ, WHZ) across the range -6 to 1 z-scores was paired separately with an outcome (incidence and mortality for each infectious disease) to create a **risk-outcome** pair. That is, we built two separate models for the incidence and mortality rates for four infectious disease outcomes, with each metric of growth failure as the risk factor (24 unique models). We used logit-transformed mortality rate and log-transformed incidence as the continuous independent variables in these models. Studies were included as random intercepts in the model and a flexible regularized spline fitting algorithm determined the shape of the curves.

We set Bayesian priors to define a monotonic relationship between risk exposures and outcomes and ran 50 model fits each with 5 knots with 3 interior knots randomly sampled within each model. Priors also defined the direction of the tails of the splines, forcing them to be linear in their last segment. We set a prior that the slope of the segment from 0 to 1 z-scores is flat because we assumed that the theoretical minimum risk value would be in that range of z-score values. The meta-regression model incorporates both within and between study uncertainty measured by standard errors and simulates

Bayesian uncertainty intervals including and excluding between study variation. A risk-outcome pair was given a scoring based on the magnitude and statistical strength of its association. If the 95% uncertainty interval excluding between study heterogeneity did not overlap with 1 (null relative risk), then that pair was included as a risk-outcome pair in the results.

We also calculated a burden of proof risk function (BPRF), described in detail elsewhere,[14] which is meant to capture the smallest level of excess risk (closest to the null) that is consistent with the data which is defined as the 5th percentile of the uncertainty incorporating between study heterogeneity. To compare the strength of the CGF risk curves to other risk–outcome pairs in the GBD, we also generated a risk-outcome score (ROS) from the average log (RR) of BPRF over the data-dense area of the observed exposure range, which we defined as the 15th–85th percentiles of the input data. Larger positive ROS indicates a higher average relative risk and stronger evidence for the relationship between exposure and outcome. We used a previously described star-rating system from one to five to assist in interpreting the ROS and to compare against other risk-outcome pairs in the GBD. Negative ROSs yield a one-star ranking and indicate risks for which the mean relationship is statistically significant as conventionally assessed (based on uncertainty estimates exclusive of between-study heterogeneity) but is not significant based on our conservative analysis of the available evidence, suggesting there may be no true association between risk exposure and health outcome. Positive ROS ranges were divided as follows: two stars represent at least a 0–15% risk increase based on average CGF exposure, three stars indicate >15–50% increase in risk, four stars >50–85% increase and five stars >85% increase. Translated into ROS values, the five-star-rating ranges are <0.0, 0.0–0.14, >0.14–0.41, >0.41–0.62 and >0.62.

Estimating the shape of the risk–outcome relationship [Details unavailable at time of submission but to be added]

Results

Pooled dataset

For cause-specific incidence, we included 60,436 children under five years of age, and over 286,000 anthropometric measurements from 19 studies. Ten of the studies included a nutritional intervention, one study was a clinical trial for rotavirus vaccine, one study was an educational intervention, and six were non-interventional. We also included the pooled analysis effect sizes from Olofin et al.[6] There were over 100,000 unique study-defined infectious disease episodes (95,950 diarrhea episodes, 12,947 acute lower respiratory infections, 4,896 malaria episodes, and 376 measles episodes). For cause-specific

mortality, we included 22,870 children and over 137,000 anthropometric measurements from 8 studies, representing 1123 cause-specific deaths, not including those in the pooled Olofin et al. study (320 due to diarrhea, 847 due to LRI, and 10 due to malaria). Including the pooled Olofin et al. study, there were 2437 total cause-specific deaths (691 due to diarrhea, 1034 due to acute lower respiratory infections, 80 due to measles, and 61 due to malaria). A summary of the studies used in this analysis is shown in **Table 1.**

We estimated that all CGF exposures increased the risk of LRI and diarrheal episodes (**Figure 1**). The risk of diarrhea was flat in log-space across the ranges of CGF indicators while there was a small increase in risk of LRI at more extreme values of CGF. We estimated that underweight was a significant risk for malaria incidence and that stunting and wasting were not. We found that stunting and wasting were significantly associated with measles incidence but underweight was not. The relative risk values were generally small for all CGF indicators and infectious diseases, only exceeding 2 at severe levels of CGF for LRI and measles, and otherwise between 1 and 2 for the significant risk-outcome pairs (**Table 2 & Figure 3**). The BPRF was equal to or less than 0 in log space (null association) for all the risk-outcome pairs. Therefore, the risk of cause-specific infectious disease incidence due to CGF is a one-star outcome for all the indicators and infectious disease outcomes (**Figure 5**). This leads to CGF as a risk factor for cause-specific infectious disease incidence being classified as one-star for all 12 pairs above (**Figure 5**).

We estimated that all CGF indicators were strongly associated with the risk of mortality due to LRI, diarrhea, and measles, with non-linear relationships in log-rate space (**Table 2 & Figure 2**). We found that stunting and underweight were significant risk factors for malaria mortality but that wasting was not. Only severe stunting (HAZ < -3) significantly increased the risk for malaria mortality. The relative risk of cause-specific mortality was generally highest for weight-for-height and lowest for height-for-age (**Figure 4**) except for LRI, where weight-for-height and height-for-age were similar and lower than for weight-for-age. The relative risk of mortality for severe CGF indicators was greater than 5 for LRI and diarrhea (except diarrhea and stunting), above 3 for measles, and between 1 and 3 for malaria. The BPRF was greater than 0 in log space (null association) for all the risk-outcome pairs except for malaria-specific mortality. The risk of diarrhea and measles mortality due to CGF indicators were between 3 and 5 stars, indicating that we are very confident in the strength of these risk-outcome associations. The risk of LRI mortality due to CGF indicators were either 4- or 5-star associations, making them comparable with some of the most certain risk-outcome pairs in the GBD (e.g., high systolic blood pressure and ischemic heart disease;[15] **Figure 5**).

There is generally close alignment with our estimates and the previous gold standard for CGF risk on infectious disease mortality, shown as points with error bars in **Figure 4.** Our estimates of the risk of LRI-specific mortality for stunting and underweight are notably greater than past estimates, especially for mild and moderate stunting and underweight with non-overlapping uncertainty intervals.

Discussion

These results represent the most comprehensive set of estimates for childhood growth failure as a risk factor for cause-specific infectious disease incidence and mortality among children younger than 5 years. We have shown, for the first time, continuous risk distributions for 24 risk-outcome pairs including the first estimates of the risk of CGF on infectious disease incidence. This analysis is more robust and comprehensive than previous work and improves existing estimates of growth failure as a risk factor for under-5 disease burden. We have completed these estimates as part of the Global Burden of Disease 2021 study and created the estimates in a modeling framework developed for that study to evaluate risk-outcome pairs in a structured and consistent manner.[14]

Interpretation and proposed mechanisms

Although the estimated relative risks for infectious disease incidence were modest, between 1 and 2 times higher than the reference group with z-scores 0 or greater, they were statistically significant for most of the CGF indicator-cause pairs. The CGF indicators are unique among risk factors for the GBD 2021 study in that we have identified different risks of incidence and mortality whereas for the other risk-outcome pairs in GBD 2021, the same values apply to both.[1] Combined with our findings on the risk of cause-specific mortality, this research further emphasizes the negative feedback loop between infectious diseases, childhood growth, and survival. Diarrhea and other enteric infections have been shown to decrease a child's growth, possibly through the deprivation of nutrients, intestinal inflammation and dysfunction,[16,17] and through dehydration[18,19] while some evidence suggests that episodes of pneumonia can also impair a child's linear growth.[20] There is not strong evidence that non-fatal episodes of malaria are associated with CGF, however.[21] Children who suffer from growth failure may be more susceptible to infection and severe outcomes because of immune system dysfunction, imbalances in biomarkers of immune activation like pro-inflammatory cytokines, poor endothelial mucosal barrier integrity, impaired innate immune reaction, lack of vitamins and protein for cellular processes, and altered metabolism and endocrine function.[22] Breaking free of this loop between

infectious diseases causing growth impairment and growth impairment making children more vulnerable to infection and death requires attention and interventions to help these children survive and thrive.[12,23]

Updates to previous work

This work updates the relative risk estimates used in the GBD that are used to quantify the burden of disease that is attributable to CGF. Previous iterations of the GBD (e.g. 2017, 2019) used the cause-specific mortality hazard ratios from Olofin et al. 2013 (shown in **Figure 4**) for both incidence and mortality.[1] This is the first instance in the GBD where there are different relative risks used for incidence and mortality. In addition to estimating the risk of cause-specific disease incidence for the first time, there are three main places where our estimates differ from those values. First, the relative risk of lower respiratory infection due to low HAZ and low WAZ are meaningfully higher than in Olofin et al. and in comparison to a separate systematic review and network meta-analysis.[6,24] Second, we have identified statistically significant relationships between low HAZ and low WAZ with malaria mortality which was not observed in the smaller sample size and discrete categorical analysis by Olofin et al.[6] Third, the relative risk of diarrhea incidence and mortality due to low WHZ is considerably lower than in the previous iterations of GBD. Considering these CGF indicators as risks for malaria mortality will be included for the first time in GBD 2021 based on these findings and may represent a gap in previous burden of malaria estimates.

Limitations

There are several limitations in this study. First, we were not able to include the primary data for the 10 studies used by Olofin and colleagues. However, we did include the overall effect sizes from that study and so that study's combined findings are part of our meta-regression. The disadvantage of including a pooled effect size is that our modeling methodology is built to fit estimates of between and within study variation and make final relative risk curve uncertainty including both those estimates. We have lost the ability to quantify the between study variation from the 10 studies included in the Olofin et al. analysis and that review gets a single value for study-level variation.

Second, there exist potential biases due to differences in the frequency of anthropometric measurements and variable illness recall period lengths from the studies included in our analysis. We have standardized the infectious disease self-reported recall periods to a duration of a week for each study and created a binary indicator for if an episode occurred in that period. We believe that unique

episodes are exceedingly unlikely to occur in a week period and this amount of time is well resolved to capture such episodes. Although self-reported disease incidence might be biased by severity, child age, and by recall period,[25–27] the use of one-week recall has been shown to be robust with minimal bias compared to longer recall periods, balanced against the loss of power in shortening recall to fewer days with generally good alignment with clinical examination.[27,28] Generally, definitions for self-reported LRI from caregivers are sensitive but not specific and could contribute to misclassification of LRI episodes from other true infections; a good example would be that malaria may also cause fever with cough and difficulty breathing which are symptoms frequently used to identify suspected acute LRI.[29] Other sources of error may exist in the underlying data but we believe that pooling across many studies and children helps to reduce systematic biases.

Third, nearly all the studies that reported a cause of death depended on verbal autopsy to determine the underlying cause. Verbal autopsy is generally moderately sensitive and specific in identifying infectious causes of death compared to more robust determinations of cause of death such as complete diagnostic autopsy but varies depending on the type of verbal autopsy used (physician-certified verbal autopsy, algorithm-assisted verbal autopsy, e.g.).[30–32] We believe that the inclusion of between study heterogeneity in our modeling helps to account for uncertainty in overall mortality rates but we do not directly quantify uncertainty in the specified cause of death. In our assessment, there is no reason to believe that there is systematic bias in determining cause of death by verbal autopsy depending on CGF status.

Fourth, metrics of CGF are necessarily correlated but our modeling approach treated each CGF indicator as an independent model.[4] This dependence is not reflected in the estimates of this study but is accounted for in the Global Burden of Disease study through a mediation analysis.[1] Finally, although this study used data from longitudinal studies, our model was essentially cross-sectional and did not account for individual trajectories or histories of CGF. A child who has been suffering from CGF for several months might have a different risk of infection or death than a child who has a newly incident case of CGF, for example, a nuance that is not measured in our analysis. Such an analysis would need to account for repeated measurements of growth and potentially repeated measures of infection.[33]

Conclusion

Our results strengthen the evidence that CGF is a critical risk factor for infectious disease burden in children younger than 5 years and show that illness from infections is more likely in children who suffer

from severe CGF especially. These estimates illustrate that poor growth status increases children's vulnerability to illness and reduces their chance of survival. There are likely additional negative acute and long-term consequences of CGF not captured in this study, but we have shown that the measured risk of infectious disease burden is non-linear and substantial. Increased efforts to prevent and treat childhood growth failure should be prioritized by the global health community to help children survive and thrive.

Tables and Figures

Figure 1. Log relative risk and burden of proof risk function estimates of cause-specific infectious disease incidence for stunting, underweight, and wasting.

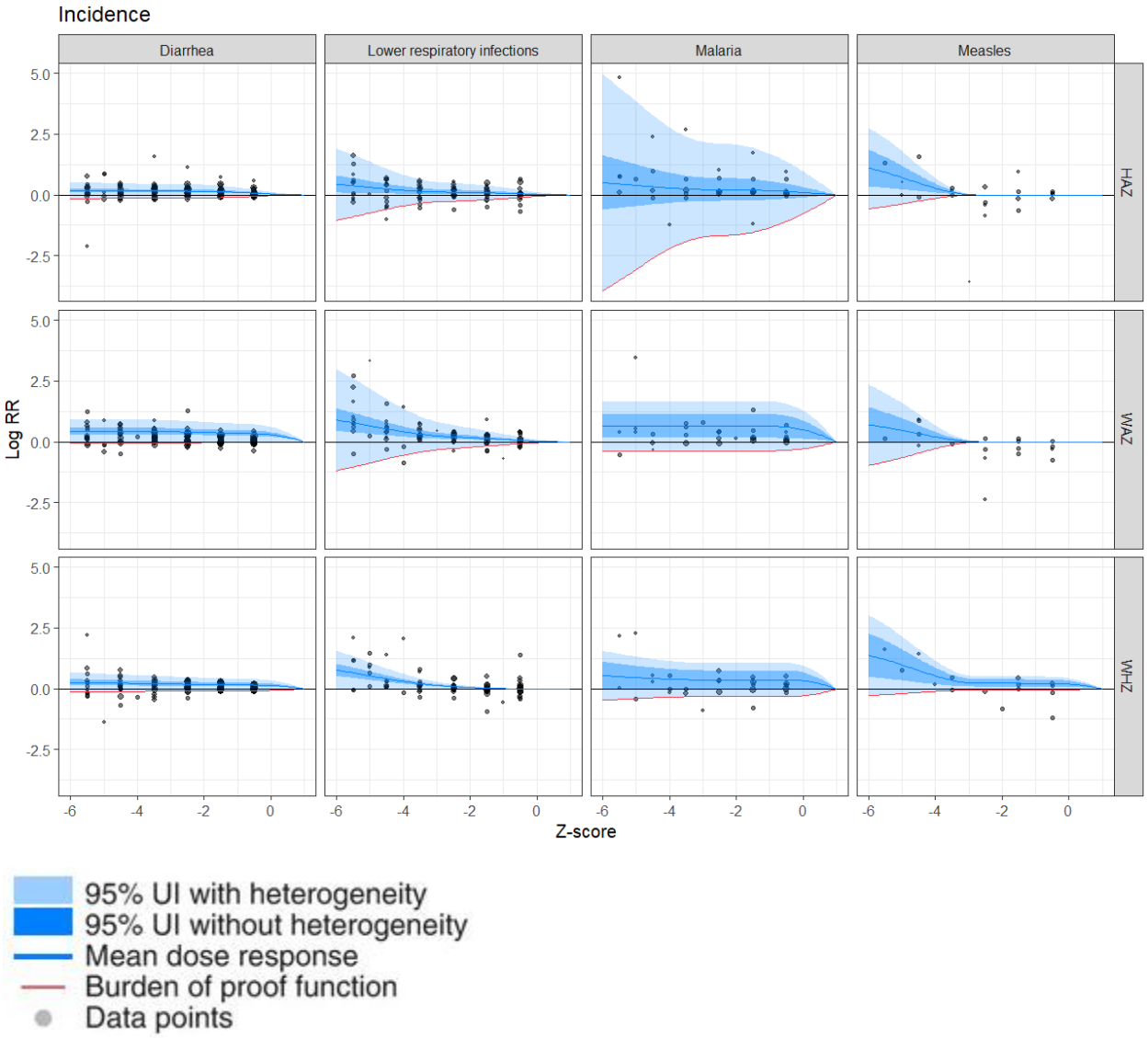

Figure 2. Log relative risk and burden of proof risk function estimates of cause-specific infectious disease mortality for stunting, underweight, and wasting.

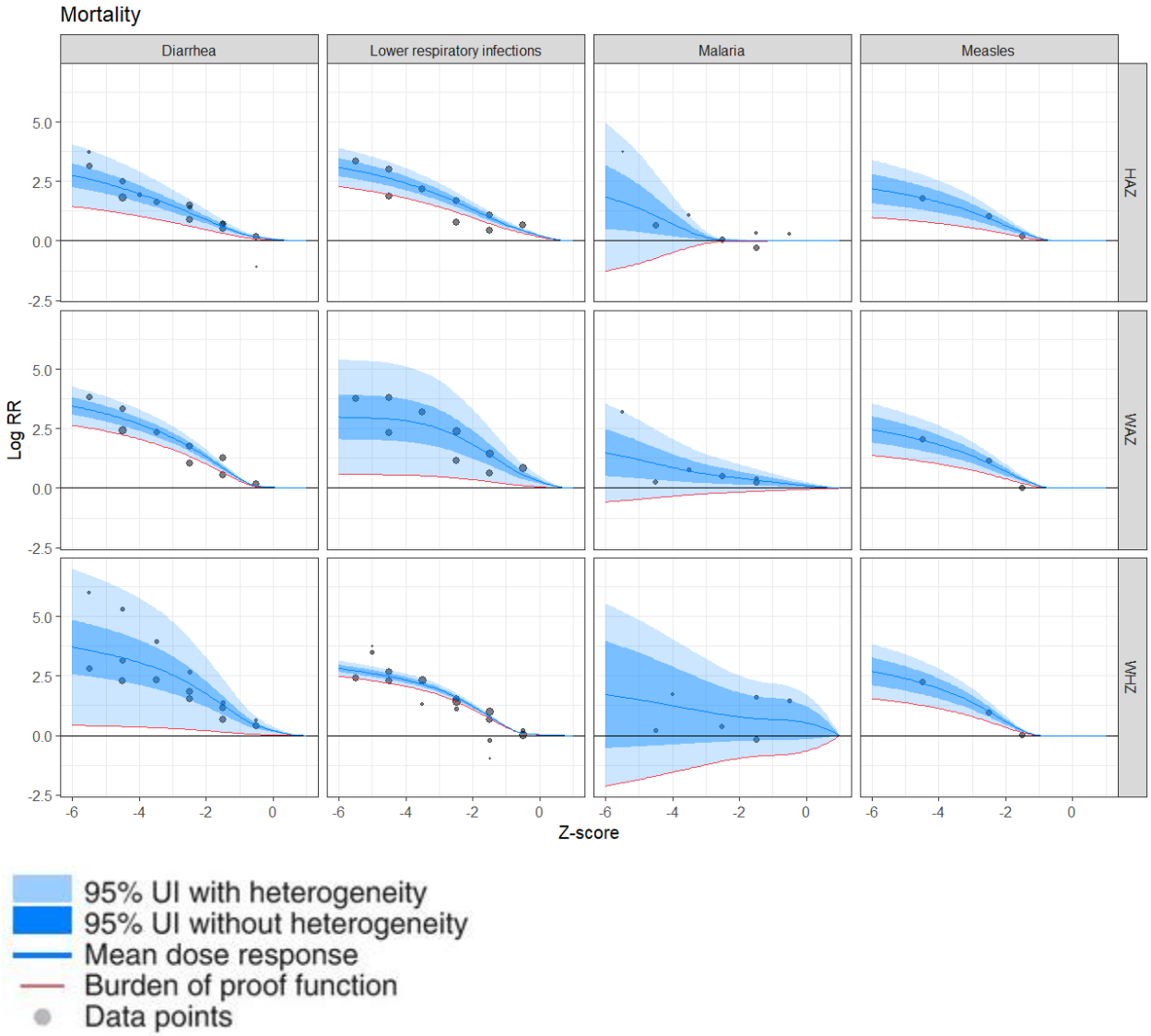

Figure 3. Relative risk estimates of cause-specific infectious disease incidence by CGF indicator.

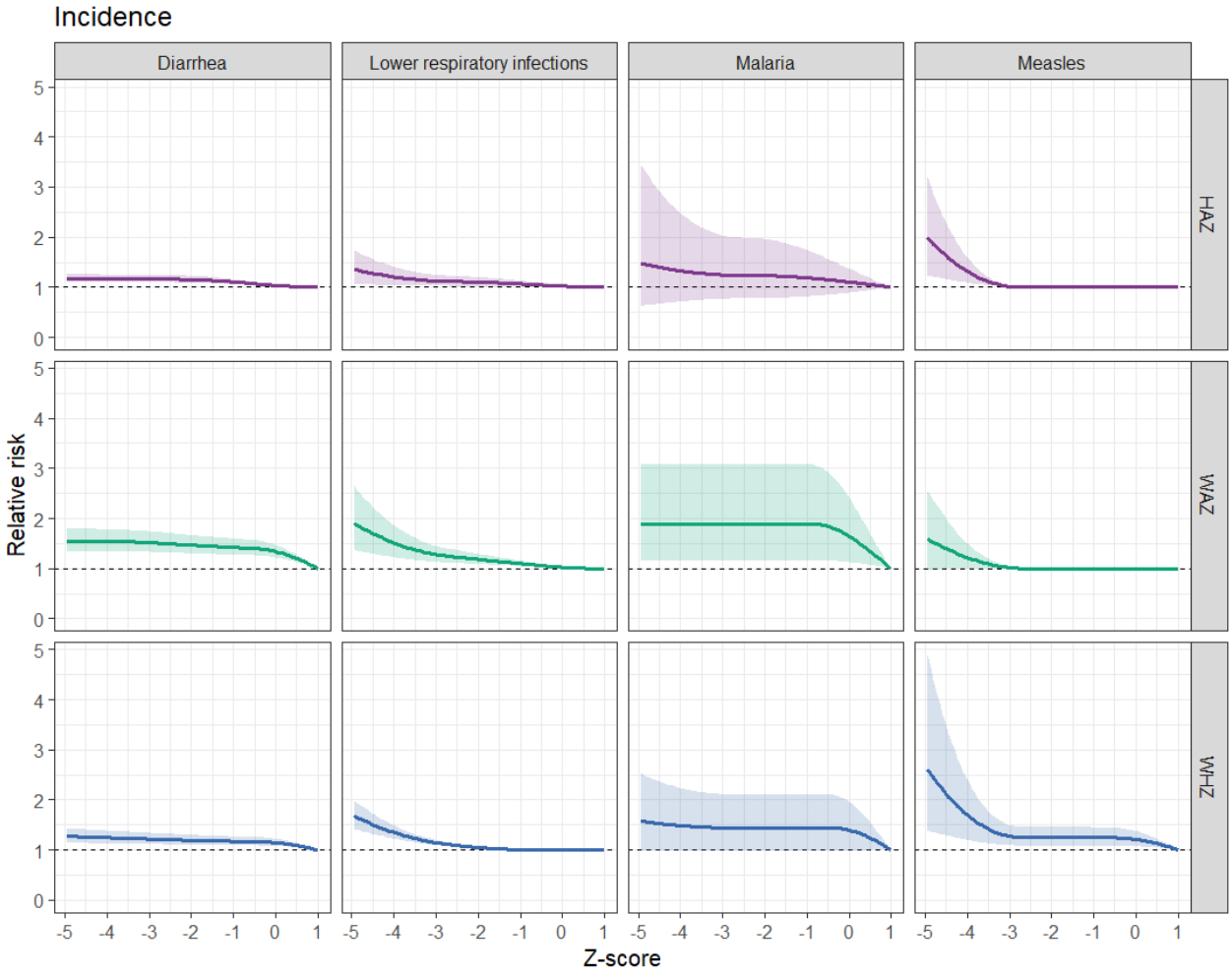

Figure 4. Relative risk of cause-specific infectious disease mortality by CGF indicator. Points and error bars represent mean and 95% confidence intervals around estimates by Olofin et al. 2013.[6]

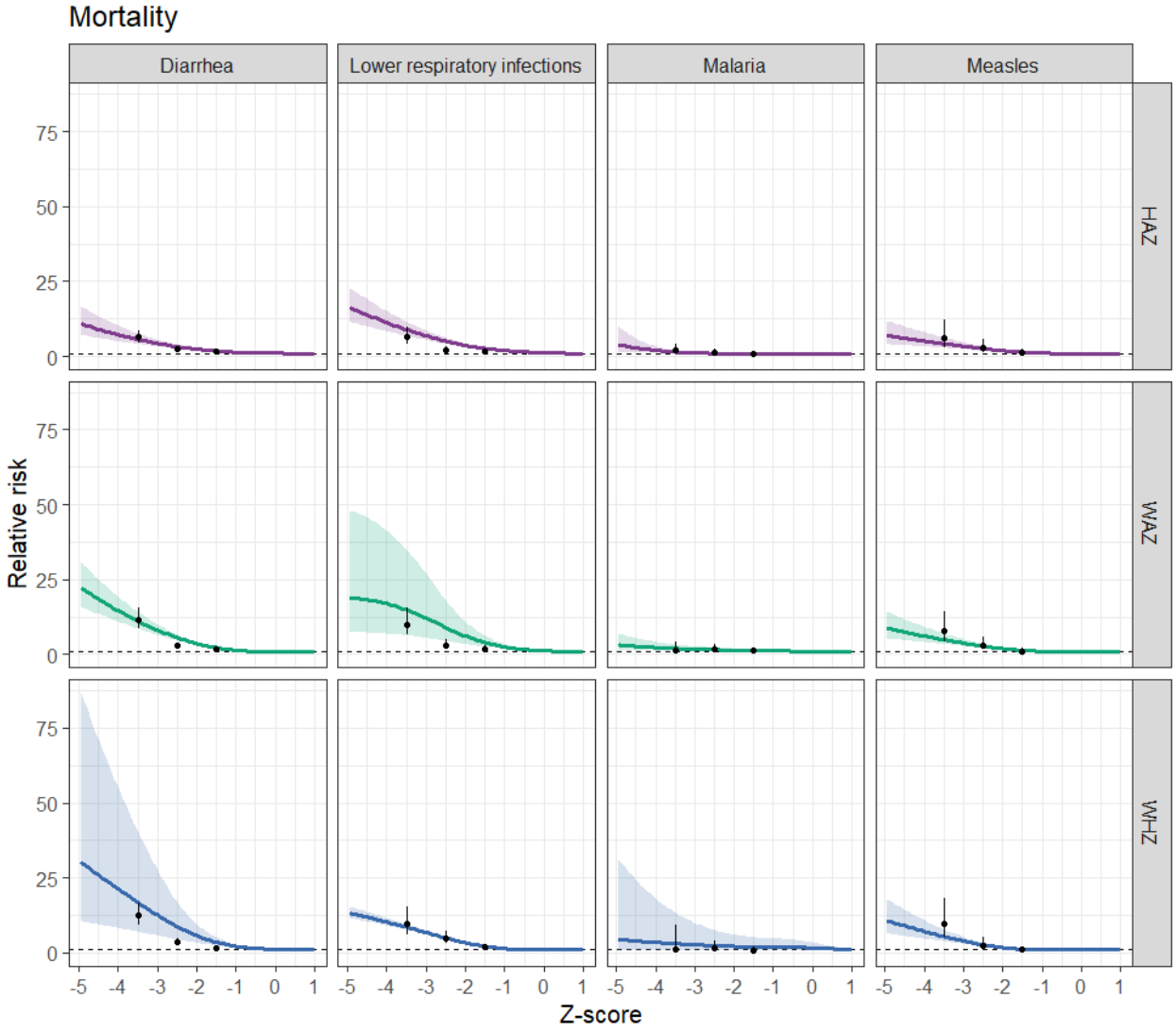

Figure 5. Burden of proof star ratings for cause-specific incidence and mortality for each stunting, underweight, and wasting.

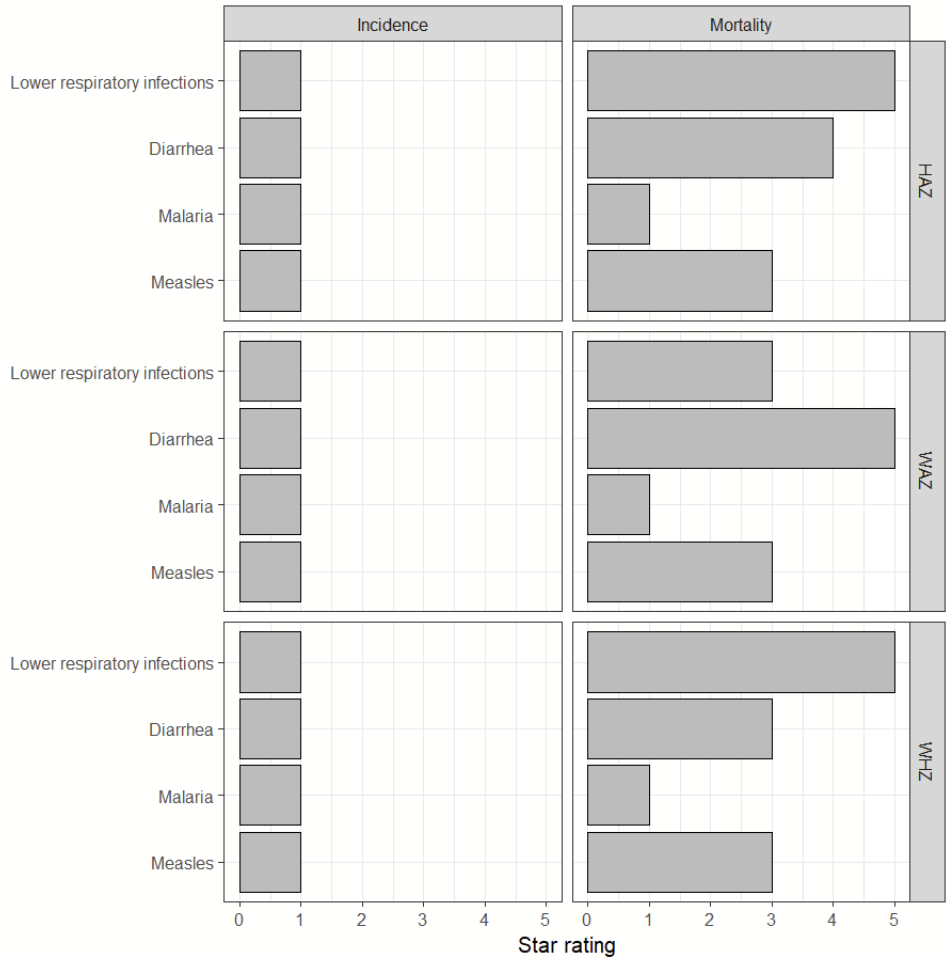

Table 1. Input data used in meta-regressions.

Study name	Study description	Country	Study year	Study population	Intervention	Children (n)	Deaths in study	Diarrhea deaths	LRI deaths	Measles deaths	Malaria deaths	Diarrhea episodes	ALRI episodes	Malaria episodes	Measles episodes
Associations of suboptimal growth with all-cause and cause-specific mortality in children under five years: a pooled analysis of ten prospective studies	Pooled analysis of prospective studies by Olofin et al.	Multiple					1314	371	187	80	51				
Bangladesh NIH Cryptosporidium Cohort Study	Natural history of Cryptosporidiosis in slum-dwelling children: association with severe malnutrition	BGD	2014-2021	Slum-dwelling newborns in Mirpur and Mirzapur	No intervention	758	0	0	0	0	0	5569	0	0	0
Child Malnutrition and Infection Network	7 longitudinal cohort studies of early childhood in low- and middle-income countries	BGD, BRA, GNB, PER	1985-1998	7 longitudinal infant cohorts	No intervention	3126	0	0	0	0	0	25615	0	0	0
CMC Vellore Birth Cohort 2002	Rotavirus seasonality and age effects in a birth cohort study in Vellore	IND	2002-2006	Birth cohort in urban Vellore	No intervention	373	0	0	0	0	0	10011	1539	0	3
DIVIDS-1 with 5 year Follow-up	Randomised Controlled Trial to Evaluate the Preventive Effect on Mortality	IND	2007-2016	Children who are not severely malnourished, anemic, or acutely	Nutritional	2100	16	1	6	0	0	2070	154	3	1

	and Serious Morbidity/ Hospitalisations of Daily Vitamin D Supplements in Small for Gestational Age Term Infants			or chronically ill, but are small for gestational age											
EPI Linked Vita A	Vitamin A supplementation	IND	1995-1995	Mother-Infant pairs	Nutritional	4000	108	40	21	0	0	2479	3942	0	255
Growth Monitoring Study, Nepal	Monthly monitoring of newborn infants in Dhanusha district through age 24 or 25 mo	NPL	2012-2014	Newborns in Dhanusha District	No intervention	699	8	0	0	0	0	2616	642	18	0
iLiNS-DOSE	Randomised controlled trial of growth effects of long-term complementary feeding of infants with different doses and formulations of high-energy, micronutrient fortified lipid-based nutrient supplements (LNS)	MWI	2009-2011	Rural children	Nutritional	1932	10	0	0	0	0	933	4	0	0
iLiNS-DYAD-M	Supplementing maternal and infant diet with high-energy,	MWI	2011-2015	Women with neonates	Nutritional	1246	0	0	0	0	0	62	18	0	0

	micronutrient fortified Lipid-based Nutrient Supplements (LNS)														
MAL-ED Study	Global study of enteropathy and its effects on anthropometry from birth through age 2 years	BGD, BRA, IND, NPL, PAK, PER, TZA, ZAF	2009-2017	Multinational birth cohort	No intervention	2145	20	0	0	0	0	10299	1277	65	0
Optimal Infant Feeding Practices	Cluster randomized trial of the promotion of optimal complementary feeding practices	IND	1999-2001	Infants in rural Haryana	Educational	1535	0	0	0	0	0	1072	153	0	0
PROBIT Study	Promotion of Breast Feeding Intervention al Trial	BLR	1996-1998	Children	Nutritional	17046	0	0	0	0	0	769	813	0	0
PROVIDE Study	Performance of Rotavirus and Oral Polio Vaccines in Developing Countries	BGD	2011-2017	Birth cohort	Vaccine	700	3	0	0	0	0	7040	0	0	0
Study of Biomarkers for Environmental Enteropathy	Monthly anthropometry since birth, daily symptoms, and biomarkers for environmental enteropathy	PAK	2012-2013	Community based cohort of children aged 6 and 9 mo in rural Matiari District	No intervention	380	4	0	0	0	0	7673	252	0	3

	in blood, urine, and stool														
Tanzania Child 2	Zinc and micronutrients	TZA	2000-2002	Infants born to HIV-negative women	Nutritional	2400	0	0	0	0	0	775	1439	872	31
Vit B12 Supp Trial	Vitamin B12 supplementation	IND	2010-2010	Children	Nutritional	1000	0	0	0	0	0	4478	1566	125	23
Zn Supp Trial in LBW	Zinc supplementation in children with low birth weight	IND	2005-2005	Hospital born children with low birth weight	Nutritional	2052	0	0	0	0	0	2979	927	0	2
Zn Trial in Burkina Faso	Effect of preventive and therapeutic zinc supplementation programs on nutritional status, growth, and morbidity among young children: a randomized, partially masked, community-based trial	BFA	2010-2011	Children who are not severely malnourished, anemic, or acutely or chronically ill	Nutritional	7641	0	0	0	0	0	7001	164	3481	0
ZVITAMBO	Placebo-Controlled Study of a Single Dose of Vitamin A to Prevent Vertical and Horizontal Transmission of HIV	ZWE	1997-2001	Lactating mothers and their children	Nutritional	14110	1123	279	820	0	10	4509	57	332	58

Table 2. Relative risk estimates for incidence and mortality for each CGF indicator and infectious disease outcome by selected z-scores. Full results are available in Supplementary Materials.

		Incidence			Mortality		
Cause	Z-score	Height-for-age	Weight-for-age	Weight-for-height	Height-for-age	Weight-for-age	Weight-for-height
Diarrhea	-6	1.2 (95% UI 1.11-1.29)	1.55 (95% UI 1.35-1.79)	1.3 (95% UI 1.15-1.47)	15.64 (95% UI 9.53-25.66)	31.43 (95% UI 21.89-45.12)	40.75 (95% UI 12.94-128.32)
	-5	1.18 (95% UI 1.1-1.27)	1.55 (95% UI 1.35-1.79)	1.27 (95% UI 1.14-1.43)	11.23 (95% UI 7.27-17.36)	22.85 (95% UI 16.46-31.72)	30.9 (95% UI 10.69-89.34)
	-4	1.17 (95% UI 1.09-1.25)	1.55 (95% UI 1.35-1.78)	1.25 (95% UI 1.12-1.38)	7.29 (95% UI 5.1-10.43)	14.83 (95% UI 11.18-19.68)	21.59 (95% UI 8.34-55.84)
	-3.5	1.16 (95% UI 1.09-1.24)	1.54 (95% UI 1.34-1.76)	1.23 (95% UI 1.12-1.36)	5.71 (95% UI 4.17-7.82)	11.4 (95% UI 8.83-14.71)	17.17 (95% UI 7.12-41.37)
	-3	1.16 (95% UI 1.09-1.24)	1.52 (95% UI 1.33-1.74)	1.22 (95% UI 1.11-1.34)	4.39 (95% UI 3.37-5.74)	8.41 (95% UI 6.73-10.52)	12.94 (95% UI 5.86-28.59)
	-2.5	1.16 (95% UI 1.09-1.24)	1.49 (95% UI 1.31-1.7)	1.21 (95% UI 1.1-1.32)	3.2 (95% UI 2.59-3.94)	5.54 (95% UI 4.63-6.64)	8.51 (95% UI 4.39-16.51)
	-2	1.15 (95% UI 1.08-1.22)	1.47 (95% UI 1.3-1.66)	1.19 (95% UI 1.1-1.3)	2.39 (95% UI 2.04-2.8)	3.62 (95% UI 3.17-4.15)	5.55 (95% UI 3.26-9.42)
	-1.5	1.13 (95% UI 1.07-1.19)	1.44 (95% UI 1.28-1.63)	1.18 (95% UI 1.09-1.28)	1.79 (95% UI 1.61-1.99)	2.28 (95% UI 2.09-2.49)	3.47 (95% UI 2.36-5.1)
	-1	1.11 (95% UI 1.06-1.16)	1.42 (95% UI 1.27-1.59)	1.17 (95% UI 1.09-1.26)	1.39 (95% UI 1.31-1.47)	1.46 (95% UI 1.4-1.52)	2.16 (95% UI 1.7-2.75)
	-0.5	1.07 (95% UI 1.04-1.1)	1.4 (95% UI 1.26-1.56)	1.17 (95% UI 1.08-1.25)	1.17 (95% UI 1.14-1.2)	1.1 (95% UI 1.09-1.11)	1.5 (95% UI 1.33-1.71)
	0	1.04 (95% UI 1.02-1.05)	1.34 (95% UI 1.22-1.47)	1.15 (95% UI 1.07-1.22)	1.08 (95% UI 1.06-1.09)	1.04 (95% UI 1.03-1.04)	1.22 (95% UI 1.15-1.29)
	0.5	1.01 (95% UI 1.01-1.02)	1.2 (95% UI 1.13-1.28)	1.09 (95% UI 1.05-1.14)	1.02 (95% UI 1.02-1.02)	1.01 (95% UI 1.01-1.01)	1.05 (95% UI 1.04-1.07)
	1	1 (95% UI 1-1)	1 (95% UI 1-1)	1 (95% UI 1-1)	1 (95% UI 1-1)	1 (95% UI 1-1)	1 (95% UI 1-1)

Lower respiratory infection	-6	1.54 (95% UI 1.08-2.21)	2.45 (95% UI 1.55-3.89)	2.15 (95% UI 1.68-2.77)	21.93 (95% UI 14.99-32.08)	19.78 (95% UI 7.7-50.81)	16.63 (95% UI 14.27-19.38)
	-5	1.37 (95% UI 1.06-1.77)	1.94 (95% UI 1.38-2.73)	1.71 (95% UI 1.44-2.04)	16.61 (95% UI 11.75-23.47)	19 (95% UI 7.49-48.21)	13.52 (95% UI 11.74-15.58)
	-4	1.21 (95% UI 1.04-1.42)	1.52 (95% UI 1.23-1.89)	1.36 (95% UI 1.23-1.51)	11.39 (95% UI 8.44-15.37)	17.03 (95% UI 6.95-41.72)	10.36 (95% UI 9.12-11.76)
	-3.5	1.16 (95% UI 1.03-1.31)	1.38 (95% UI 1.17-1.63)	1.24 (95% UI 1.16-1.33)	9.07 (95% UI 6.91-11.9)	15.07 (95% UI 6.39-35.54)	8.68 (95% UI 7.72-9.77)
	-3	1.13 (95% UI 1.02-1.24)	1.29 (95% UI 1.13-1.46)	1.15 (95% UI 1.1-1.21)	7.01 (95% UI 5.52-8.91)	12.47 (95% UI 5.61-27.68)	6.94 (95% UI 6.24-7.71)
	-2.5	1.11 (95% UI 1.02-1.22)	1.23 (95% UI 1.1-1.36)	1.09 (95% UI 1.06-1.12)	5.02 (95% UI 4.11-6.12)	8.85 (95% UI 4.44-17.65)	4.88 (95% UI 4.47-5.31)
	-2	1.1 (95% UI 1.02-1.19)	1.18 (95% UI 1.09-1.29)	1.05 (95% UI 1.03-1.07)	3.65 (95% UI 3.11-4.28)	6.12 (95% UI 3.45-10.85)	3.32 (95% UI 3.11-3.54)
	-1.5	1.09 (95% UI 1.02-1.16)	1.14 (95% UI 1.07-1.22)	1.02 (95% UI 1.02-1.03)	2.63 (95% UI 2.34-2.97)	4.02 (95% UI 2.59-6.24)	2.17 (95% UI 2.08-2.27)
	-1	1.07 (95% UI 1.01-1.13)	1.1 (95% UI 1.05-1.15)	1.01 (95% UI 1-1.01)	1.96 (95% UI 1.8-2.12)	2.56 (95% UI 1.9-3.44)	1.43 (95% UI 1.4-1.46)
	-0.5	1.04 (95% UI 1.01-1.08)	1.06 (95% UI 1.03-1.09)	1 (95% UI 1-1)	1.54 (95% UI 1.46-1.62)	1.73 (95% UI 1.46-2.06)	1.1 (95% UI 1.09-1.1)
	0	1.02 (95% UI 1-1.04)	1.03 (95% UI 1.01-1.04)	1 (95% UI 1-1)	1.24 (95% UI 1.21-1.28)	1.32 (95% UI 1.21-1.45)	1.04 (95% UI 1.04-1.04)
	0.5	1.01 (95% UI 1-1.01)	1.01 (95% UI 1-1.01)	1 (95% UI 1-1)	1.07 (95% UI 1.06-1.07)	1.08 (95% UI 1.05-1.11)	1.01 (95% UI 1.01-1.01)
	1	1 (95% UI 1-1)	1 (95% UI 1-1)	1 (95% UI 1-1)	1 (95% UI 1-1)	1 (95% UI 1-1)	1 (95% UI 1-1)
Malaria	-6	1.65 (95% UI 0.54-5.03)	1.89 (95% UI 1.16-3.07)	1.72 (95% UI 0.98-3.01)	6.3 (95% UI 1.64-24.27)	4.43 (95% UI 1.65-11.92)	5.58 (95% UI 0.59-53.22)
	-5	1.48 (95% UI 0.62-3.53)	1.89 (95% UI 1.16-3.07)	1.59 (95% UI 0.98-2.56)	3.95 (95% UI 1.44-10.81)	3.32 (95% UI 1.5-7.39)	4.51 (95% UI 0.63-32.56)

	-4	1.33 (95% UI 0.71-2.49)	1.89 (95% UI 1.16-3.07)	1.49 (95% UI 0.99-2.24)	2.07 (95% UI 1.22-3.53)	2.4 (95% UI 1.34-4.31)	3.53 (95% UI 0.67-18.49)
	-3.5	1.28 (95% UI 0.74-2.2)	1.89 (95% UI 1.16-3.07)	1.46 (95% UI 0.99-2.16)	1.51 (95% UI 1.12-2.05)	2.08 (95% UI 1.28-3.38)	3.11 (95% UI 0.7-13.78)
	-3	1.25 (95% UI 0.76-2.04)	1.89 (95% UI 1.16-3.07)	1.44 (95% UI 0.99-2.11)	1.18 (95% UI 1.05-1.33)	1.84 (95% UI 1.23-2.75)	2.74 (95% UI 0.73-10.28)
	-2.5	1.24 (95% UI 0.77-1.98)	1.89 (95% UI 1.16-3.07)	1.44 (95% UI 0.99-2.1)	1.04 (95% UI 1.01-1.06)	1.65 (95% UI 1.18-2.31)	2.39 (95% UI 0.76-7.5)
	-2	1.23 (95% UI 0.78-1.95)	1.89 (95% UI 1.16-3.07)	1.44 (95% UI 0.99-2.1)	1.02 (95% UI 1.01-1.03)	1.52 (95% UI 1.15-2)	2.17 (95% UI 0.79-6.01)
	-1.5	1.22 (95% UI 0.79-1.87)	1.89 (95% UI 1.16-3.07)	1.44 (95% UI 0.99-2.1)	1.01 (95% UI 1-1.01)	1.4 (95% UI 1.12-1.75)	2.03 (95% UI 0.8-5.15)
	-1	1.19 (95% UI 0.81-1.74)	1.89 (95% UI 1.16-3.07)	1.44 (95% UI 0.99-2.1)	1 (95% UI 1-1)	1.29 (95% UI 1.09-1.53)	1.96 (95% UI 0.81-4.75)
	-0.5	1.15 (95% UI 0.85-1.56)	1.84 (95% UI 1.16-2.92)	1.44 (95% UI 0.99-2.1)	1 (95% UI 1-1)	1.2 (95% UI 1.06-1.35)	1.89 (95% UI 0.82-4.37)
	0	1.1 (95% UI 0.89-1.37)	1.65 (95% UI 1.13-2.4)	1.39 (95% UI 0.99-1.96)	1 (95% UI 1-1)	1.11 (95% UI 1.04-1.2)	1.7 (95% UI 0.85-3.4)
	0.5	1.05 (95% UI 0.94-1.18)	1.35 (95% UI 1.07-1.69)	1.24 (95% UI 0.99-1.54)	1 (95% UI 1-1)	1.05 (95% UI 1.02-1.08)	1.39 (95% UI 0.9-2.15)
	1	1 (95% UI 1-1)	1 (95% UI 1-1)	1 (95% UI 1-1)	1 (95% UI 1-1)	1 (95% UI 1-1)	1 (95% UI 1-1)
Measles	-6	3 (95% UI 1.4-6.42)	2.02 (95% UI 0.97-4.19)	3.98 (95% UI 1.61-9.85)	8.92 (95% UI 4.82-16.52)	11.77 (95% UI 6.75-20.52)	14.78 (95% UI 8.23-26.55)
	-5	2.05 (95% UI 1.25-3.38)	1.61 (95% UI 0.98-2.65)	2.7 (95% UI 1.41-5.18)	7.03 (95% UI 4.06-12.16)	8.94 (95% UI 5.45-14.65)	10.96 (95% UI 6.51-18.44)
	-4	1.33 (95% UI 1.09-1.62)	1.23 (95% UI 0.99-1.53)	1.71 (95% UI 1.2-2.44)	5.17 (95% UI 3.26-8.22)	6.27 (95% UI 4.15-9.5)	7.27 (95% UI 4.72-11.18)
	-3.5	1.13 (95% UI 1.04-1.22)	1.1 (95% UI 1-1.22)	1.43 (95% UI 1.13-1.81)	4.29 (95% UI 2.85-6.46)	5.06 (95% UI 3.51-7.3)	5.6 (95% UI 3.85-8.14)

	-3	1.02 (95% UI 1.01-1.03)	1.02 (95% UI 1-1.05)	1.28 (95% UI 1.09-1.51)	3.44 (95% UI 2.43-4.86)	3.93 (95% UI 2.89-5.35)	4.09 (95% UI 3.01-5.55)
	-2.5	1 (95% UI 1-1)	1 (95% UI 1-1)	1.26 (95% UI 1.08-1.47)	2.51 (95% UI 1.94-3.26)	2.76 (95% UI 2.2-3.48)	2.63 (95% UI 2.13-3.25)
	-2	1 (95% UI 1-1)	1 (95% UI 1-1)	1.26 (95% UI 1.08-1.46)	1.87 (95% UI 1.57-2.23)	1.98 (95% UI 1.69-2.3)	1.75 (95% UI 1.55-1.98)
	-1.5	1 (95% UI 1-1)	1 (95% UI 1-1)	1.26 (95% UI 1.08-1.46)	1.4 (95% UI 1.28-1.54)	1.43 (95% UI 1.32-1.54)	1.21 (95% UI 1.16-1.27)
	-1	1 (95% UI 1-1)	1 (95% UI 1-1)	1.25 (95% UI 1.08-1.45)	1.12 (95% UI 1.08-1.16)	1.11 (95% UI 1.08-1.13)	1 (95% UI 1-1.01)
	-0.5	1 (95% UI 1-1)	1 (95% UI 1-1)	1.24 (95% UI 1.08-1.44)	1.01 (95% UI 1.01-1.01)	1 (95% UI 1-1)	1 (95% UI 1-1)
	0	1 (95% UI 1-1)	1 (95% UI 1-1)	1.21 (95% UI 1.07-1.38)	1 (95% UI 1-1)	1 (95% UI 1-1)	1 (95% UI 1-1)
	0.5	1 (95% UI 1-1)	1 (95% UI 1-1)	1.13 (95% UI 1.04-1.23)	1 (95% UI 1-1)	1 (95% UI 1-1)	1 (95% UI 1-1)
	1	1 (95% UI 1-1)	1 (95% UI 1-1)	1 (95% UI 1-1)	1 (95% UI 1-1)	1 (95% UI 1-1)	1 (95% UI 1-1)

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Chapter 3: Quantifying the fatal and non-fatal burden of disease attributable to childhood growth failure: An analysis from the Global Burden of Disease study 2021

GBD 2021 Childhood Growth Failure Collaborators

Abstract

Childhood growth failure is among the most impactful risk factors for mortality among children under 5 years worldwide. Poor height and weight gain arises from a variety of biological and sociodemographic factors and makes children more vulnerable to infectious disease burden. The Global Burden of Disease study produces iterative estimates of childhood growth failure prevalence, the risk of infectious disease due to childhood growth failure, and the disease burden attributable to it. Each of these steps has unique methods. The population-level continuous distributions of height-for-age z-scores, weight-for-age z-scores, and weight-for-height z-scores were estimated using data from surveys, literature, and individual-level study data. The risk of incidence and mortality due to diarrhea, lower respiratory infections, malaria, and measles was estimated in a meta-regression framework from longitudinal cohort data. Finally, fatal outcomes associated with those diseases were estimated using vital registration, verbal autopsy, and case fatality data while non-fatal outcomes were estimated using surveys, healthcare utilization, and case reporting data. The exposure prevalence and relative risk estimates were from continuous distributions allowing for direct assessment of the attributable fractions within populations. All estimates were age-, sex-, geography- and year-specific. We estimated that among children younger than 5 years in 2021, 773,600 (95% UI 390,500-1,099,500) deaths, or 15.9% of all deaths (95% UI 8.3-21.6%), were attributable to childhood growth failure. Compared to stunting and wasting, child underweight was responsible for the most disease burden, responsible for 10.9% (95% UI 3.7-16%) of deaths among children under-5. Most deaths due to childhood growth failure were due to lower respiratory infections (298,000 deaths, 95% UI 213,000-379,000). While it is necessary to reduce the overall under-5 mortality ratio, eliminating childhood growth failure will be insufficient for many countries that are projected to miss the Sustainable Development Goal target for under-5 mortality. Our results emphasize the urgent need for policies, strategies, and interventions to improve childhood growth and to reduce its burden of disease.

Introduction

Childhood growth failure, characterized by poor linear height and weight gain, prevents children from developing, thriving, and surviving. It represents a complex interplay of nutritional, maternal, developmental, socio-economic, environmental, and healthcare factors.[1] Children who suffer from growth failure have a greater infectious disease burden, including risk of mortality, than those who do not.[2–5] For those children with growth failure that don't die, lifelong consequences include cognitive and metabolic impairment, potentially leading to poor educational performance and lost opportunity.[1,6] Therefore, quantifying its prevalence and avertable disease burden on a global scale is of critical importance for devising targeted interventions and policies aimed at alleviating its burden and to generate advocacy for funding prevention and treatment.

In recent decades, significant strides have been made in reducing childhood mortality and improving overall child growth and health,[7,8] despite an expected setback caused by disruptions in healthcare services and treatment of acute malnutrition due to the COVID-19 pandemic.[9,10] However, many countries are not on track to meet Sustainable Development Goals for child mortality and prevalence of childhood growth failure and there is substantial overlap in the countries that suffer from child mortality and from growth failure.[7,8,11,12] In 2019, more than half of all under-5 deaths globally were attributable to malnutrition, including child growth failure and low birthweight.[13] This is because growth failure is a leading risk factor for the leading infectious causes of death among children under-5 years.[3,14]

Existing estimates of childhood growth failure focus primarily on the prevalence stunting, underweight, and wasting defined by the proportion of children below 2-zscores from the median age- and sex-specific global growth standards.[4,11,15,16] Children who are 2 or more z-scores below the median are considered stunted (height-for-age), underweight (weight-for-age), or wasted (weight-for-height).[17] Measuring the prevalence of these indicators is convenient for comparing populations between geographies and over time and for creating and monitoring progress towards global goals.[18] However, focusing exclusively on prevalence estimates may obscure meaningful changes in population distributions and does not connect childhood growth failure with disease burden and mortality.[19]

This novel analysis extends on previous estimates for the prevalence of childhood growth failure by quantifying infectious disease specific attributable fractions from previously estimated continuous distributions of growth indicators and newly estimated continuous relative risks for incidence and

mortality due to diarrhea, lower respiratory infections, measles, and malaria.[4,14,15,19] This study, based on the Global Burden of Disease study 2021 (GBD), has three objectives. First, we present comprehensive estimates of deaths attributable to childhood growth failure at the global, regional, and national level including changes over time. Second, we describe updated cause-specific risks of incidence and mortality due to each childhood growth failure indicator and the associated attributable burden. Finally, we report on how alleviating childhood growth failure accelerates trajectories in under-5 mortality and its impact on reaching Sustainable Development Goal 3.2.1 for under-5 mortality.[20] In doing so, this study seeks to highlight populations most in need of interventions to reduce the burden of childhood growth failure and to accelerate declines in under-5 mortality. The resulting estimates of the disease burden attributable to childhood growth failure are available for 204 countries and territories, 5 age groups under-5 years, by sex, and from 1990-2021. This manuscript was produced as part of the GBD Collaborator Network and in accordance with the GBD protocol.

Methods

There are four main methodological steps we used to estimate the burden of CGF. To estimate the attributable fractions for each stunting, underweight, and wasting for diarrhea, lower respiratory infections, malaria, and measles, we produced estimates of exposure and estimates of the risk of disease given varying levels of exposure. Finally, we multiplied those attributable fractions by cause-specific cases, deaths, and disability-adjusted life-years to produce our results for CGF burden. Each step will be described briefly here with specific references for further information.

Step 1: Estimate the population-level distributions of height-for-age, weight-for-age, and weight-for-height.

A detailed description of the methods to estimate continuous distributions for each of the CGF indicators is provided in Fitzgerald et al. 2022.[19] We included data from various sources such as population-representative surveys, administrative data, and published scientific literature. More than 1700 sources were used in this model. A Spatio-Temporal Gaussian Process Regression (ST-GPR) model, a methodology used across many models in the GBD, was used to make predictions of the mean and prevalence of moderate (<-2 z-scores) and severe (<-3 zscores) growth failure of HAZ, WAZ, and WHZ by age, sex, year, and location. This model is first a linear mixed-effects regression that included maternal care and immunization, health care access and quality index, prevalence of severe anemia, the socio-

demographic index, age- and sex-specific unsafe sanitation summary exposure value, and all age energy (kilocalories per person per day) as covariates.

Separately, we fit an ensemble model of distribution families to describe each CGF z-score distribution from individual-level data. Ten distributions were fit simultaneously (normal, log-normal, log-logistic, exponential, gamma, mirrored gamma, inverse gamma, Gumbel, mirrored Gumbel, and Weibull). We derived weights for each distribution based on minimized error in predicting CGF prevalence of <-1 z-score, <-2 z-scores, and <-3 z-scores. Finally, we synthesized the results from these steps to estimate continuous HAZ, WAZ, and WHZ curves to estimate a weighted probability density function based on the ensemble distributions and ST-GPR mean and standard deviation values.

Step 2: Estimate the relative risk of cause-specific incidence and mortality at varying levels of CGF indicators. [Methods are slightly incomplete]

For GBD 2021, we created new estimates of the relative risk of cause-specific incidence and mortality for continuous distributions of CGF exposure. Previous estimates of CGF burden in the GBD study used categorical exposures (-3, -2, -1 z-scores) matched with relative risks of cause-specific disease burden at each of those levels of exposure.[2] A longer description of the methods is available elsewhere[14] and we have summarized the methods here.

For cause-specific mortality, we included 22,870 children and over 137,000 anthropometric measurements from 8 studies, representing 1028 cause-specific deaths (283 due to diarrhea, 737 due to acute lower respiratory infections, and 9 from malaria). We also included hazard ratios for cause-specific mortality from a pooled analysis by Olofin et al. (2013) in our meta-regression.[3] For cause-specific incidence, we included 60,436 children and over 286,000 anthropometric measurements from 19 studies, representing over 100,000 unique study-defined infectious disease episodes (95,950 diarrhea episodes, 12,947 acute lower respiratory infections, 4,896 malaria episodes, and 376 measles episodes). These data were from longitudinal studies that reported multiple measurements of height and weight over time. We collapsed these observations into bins of z-scores for each CGF indicator and by age and study while summing the number of child-days, infectious disease episodes based on a standardized one-week recall, and cause-specific deaths within each bin.

We used a Bayesian meta-regression tool and risk factor assessment framework built for the Global Burden of Disease study and used across risk factors to quantify a continuous risk curve for each CGF exposure category and outcome.[21,22] Each risk exposure indicator (HAZ, WAZ, WHZ) across the range -6 to 1 z-scores was paired with each outcome (incidence and mortality for each infectious disease) to create a risk-outcome pair. In other words, we built separate models for the incidence and mortality rates for each infectious disease outcome, and for each metric of growth failure (24 models). We used logit-transformed mortality ratio and log-transformed incidence as the continuous independent variables in our models. Age was included as a fixed effect in the model. Studies were included as random intercepts in the model and a flexible regularized spline fitting algorithm determined the shape of the curves. The meta-regression model incorporates both within and between study uncertainty measured by standard errors and simulates Bayesian uncertainty intervals including and excluding between study variation.

Because of the high degree of correlation between stunting, underweight, and wasting, we needed to adjust our relative risk values. We did so by simulating a joint distribution of the three indicators using extracted data from Demographic and Health Surveys. Based on an analysis done by McDonald and colleagues,[5] we fit an interaction term between the three indicators and calculated adjusted relative risks by minimizing the error between the crude relative risks from our meta-regression and the expected relative risk derived from the joint estimate with the interaction term.

Step 3: Calculate a cause-, age-, sex-, location-specific attributable fraction and multiply by cause burden. [Methods are slightly incomplete]

Given two continuous distributions, we were able to produce estimates of the attributable fraction of disease incidence and mortality. The attributable fraction represents the proportion of disease burden that was caused by a given risk factor, or said differently, the proportion of disease burden that wouldn't exist in the absence of the risk factor.

First, we estimated the prevalence-weighted relative risk for each category of CGF (mild, moderate, severe; stunting, underweight, wasting).

$$RR_{i,m,c,j} = \sum_{j-1}^{j} \frac{RR_{i,m,c}(x)P_i(x)dx}{P_i(x)dx}$$

The attributable fraction is defined as:

$$PAF_{i,m,c} = \frac{\sum_{j=1}^{n} RR_{i,m,c,j} * P_{i,j} - 1}{\sum_{j=1}^{n} RR_{i,m,c,j} * P_{i,j}}$$

For CGF indicator *i* (HAZ, WAZ, WHZ), CGF category *j* (-1 to -2, -2 to -3, < -3), disease outcome *m* (incidence, death), and cause *c* (diarrhea, lower respiratory infections, malaria, measles). An attributable fraction for CGF overall was estimated with a multiplicative aggregation of the individual indicator attributable fractions:

$$PAF_{m,c} = 1 - \prod_{i=1}^{n} (1 - PAF_{i,m,c})$$

Cause-specific incidence and mortality modeling

A full description of the modeling methods for the incidence and mortality of diarrhea, lower respiratory infections, malaria, and measles is outside the scope of this paper. Please refer to prior GBD publications, especially the Supplementary Information from the paper cited here [cause-specific descriptions start on page 58 of the PDF].[23]

In short, mortality due to diarrhea, LRI, and measles was modeled using a Bayesian ensemble hierarchical tool called the Cause of Death Ensemble Model (CODEm).[23,24] Measles used CODEm for settings with vital registration systems and used a separate incidence and case-fatality based model for other settings.[23] Malaria mortality was modeled using spatially defined incidence and case fatality estimates.[23,25] Input data include vital registration, verbal autopsy, administrative records, and surveys. Covariates inform the models, and the final set of ensemble models are selected based on out of sample predictive validity. Non-fatal incidence of diarrhea and lower respiratory infections was modeled in a meta-regression tool using data from population-representative surveys, clinical data, administrative data, and scientific literature.[23] This meta-regression tool includes a compartmental component that enforces consistency between disease incidence and mortality making it an internally consistent estimate with mortality. Malaria incidence was based on estimates from the Malaria Atlas Project and is based on administrative, routine surveillance, and other geolocated and community-representative observations of infection prevalence for *Plasmodium falciparum.*[25] Measles incidence was estimated in a

mixed-effects regression model using Joint Reporting Form case notifications and five-year rolling lagged routine measles vaccination rates.[23]

Cause-specific cases and deaths were multiplied by the PAF values to produce our final estimates of the disease burden attributable to each CGF indicator. All steps in the estimation process include 1000 iterations of each age-, sex-, geography-, and year-specific values. This uncertainty is carried through the entire process to maintain the variation in the estimates.

We used existing forecasts of the under-5 mortality ratio (U5MR) from Goalkeepers 2023 for projected country-level values between 2021 and 2030.[26] We calculated the annualized rate of change for the attributable fraction of childhood growth failure from 2010-2021 and used this to project that value in 2030 to estimate the attributable U5MR for that year.

Code and input data are available on the Institute for Health Metrics and Evaluation GHDx website. This study complies with the GATHER requirements for burden estimation and reporting.

Results

Global results

Globally, childhood growth failure (CGF) was the second leading risk factor for disease burden among children younger than 5 years (under-5) following low birthweight and short gestation and the leading risk factor among infants 28-364 days. It was responsible for 17% (95% UI 10.1-23%) of deaths among children under 5 years old representing 773,600 (95% UI 390,500-1,099,500) deaths (**Figure 1, Table 1**). It was also responsible for 153,898,900 (95% UI 95,320,100-193,906,800) disability-adjusted life-years (DALYs) among children under-5, representing 15.9% (95% UI 8.3-21.6%) of attributable DALYs in this age group. The attributable burden of CGF has decreased by 2.6% per year since 2000, when it was responsible for 29.0% (95% UI 20.3-33.9%) of deaths burden among children under-5 (**Figure 1**). However, the attributable burden of CGF among causes of death for which it is a risk factor has decreased less rapidly since 2000 when it was 68.5% (95% UI 42.4-86.5%) to 58.9% (95% UI 29.7-83.7%) in 2021 (1.4% decrease per year). Among the different indicators of CGF, child underweight was responsible for the most disease burden, responsible for 10.9% (95% UI 3.7-16%) deaths, followed by child wasting (8.1% (95% UI 4.3-10.6%)) and child stunting (6.7% (95% UI 4.6-9.4%)) (**Figure 1, Table 1)**.

Although CGF was responsible for more deaths at the global level among boys [415,200 (95% UI 206,700-587,900)] than girls [358,400 (95% UI 182,200-509,500)], it was responsible for a smaller fraction of all deaths among boys [16.2% (95% UI 8.6-22%)] compared to girls [17% (95% UI 8.9-23.4%)].

The highest attributable burden of child growth failure occurred in countries in sub-Saharan Africa [20.6% (95% UI 8.9-29.6%) of under-5 deaths] and in South Asia [12.6% (95% UI 9.5-15.1%)] where it was responsible for 690,100 (95% UI 329,400-1,006,200) deaths in those regions combined. The largest number of deaths among children under-5 attributable to child growth failure occurred in Nigeria (186,700 (95% UI 74,400-271,800)), India (99,800 (95% UI 69,700-130,500)), and Pakistan (40,200 (95% UI 26,900-56,900)). The highest attributable fraction for under-5 deaths due to child growth failure was in Chad (32.5% (95% UI 19.6-43.2%)), Somalia (28.4% (95% UI 17.2-38%)), and South Sudan (26.6% (95% UI 14.5-35.6%)).

Cause specific results.

Childhood growth failure was attributable for 298,000 (95% UI 213,000-379,000) deaths due to lower respiratory infections (59.3% of LRI deaths (95% UI 45.6-67.6%)), followed by diarrheal diseases (259,300 (95% UI 155,900-358,200); 76.1% of diarrhea deaths (95% UI 50.6-88.2%)), malaria (109,700 (95% UI -74,800-353,500); 26.1% of malaria deaths (95% UI -18.7-70.2%)), and measles (32,000 (95% UI 15,700-52,600); 26.1% of measles deaths (95% UI -18.7-70.2%)) (**Figures 2 & 3, Table 2)**. Infectious disease incidence was also attributable to childhood growth failure including 23.7% (95% UI -17.9-55%) of diarrheal episodes, 13.6% (95% UI -34.2-51.1%) of LRI episodes, 27.6% (95% UI -25.7-70.3%) of malaria episodes, and 11% (95% UI -4.7-29.7%) of measles episodes (**Figure 3)**. Deaths in the neonatal period were not attributed to CGF.

Attributable mortality and global malnutrition and mortality goals.

The under-5 deaths per 1000 live births attributable to CGF is greatest in the Sahelian region of Africa, including South Sudan (33.1, 95% UI 17.6-47.9), Chad (35.1, 95% UI 19.9-48.2), Niger (22.8, 95% UI 6.2-36.9), Nigeria (22.4, 95% UI 8.9-32.6), and Mali (19.3, 95% UI 10-28.6) (**Figure 4**). Other countries that had high U5MR in their regions included Bolivia (2.9, 95% UI 1.9-3.9), Haiti (12.9, 95% UI 7.9-18), Tajikistan (8.0, 95% UI 5.1-11.1), Pakistan (6.5, 95% UI 4.4-9.2), Afghanistan (7.7, 95% UI 5.4-10.3), and Papua New Guinea (12.2, 95% UI 8.1-16.7).

Reducing childhood growth failure may be necessary but insufficient for many countries to close the gap between the forecasted under-5 mortality ratio and the Sustainable Development Goal of 25 per 1000 live births. Sub-Saharan Africa is not on track to meet the SDG target for U5MR, even in the absence of all CGF attributable mortality. There are 64 countries that are above the SDG target for under-5 mortality in 2021. These countries represent 741,300 deaths due to CGF, or 94.2% of all CGF attributable deaths. In the absence of CGF, 3 would be below the SDG target for under-5 mortality (Azerbaijan, Bolivia, and Turkmenistan) (**Figure 5A**). At the continued annualized rate of decrease in the attributable fraction of CGF, in 2030 there will be 55 countries that fail to meet the SDG target but in the absence of CGF, 7 additional countries would meet the SDG target including India (**Figure 5B**).

Discussion

Summary of findings.

Childhood growth failure was the second leading risk factor for under-5 mortality globally, responsible for nearly a million deaths due to diarrhea, lower respiratory infections, malaria, and measles in 2021. It accounted for more than 5 deaths per 1000 live births among children under-5 across nearly all sub-Saharan Africa and parts of South Asia due both to its high prevalence in those geographies and due to the high burden of infectious diseases as a cause of death. The burden of childhood growth failure has decreased since 2000 and has been important in reducing childhood mortality.[27,28] Still, despite its substantial residual burden, ameliorating CGF is insufficient to meet SDG targets for under-5 child mortality in many countries. Multifaceted strategies to address the intersectional contribution of environmental, socio-economic, biological, and behavioral factors that affect childhood growth are needed.

What the results suggest should be done.

On average, children in low- and middle-income settings tend to grow slower than the WHO global reference standard, moving further away from the global mean as they age up to 5 years. In part this appears to be because they are born small and children born low birthweight or of short gestational age are more likely to suffer from growth failure as they age.[29,30] In a pooled analysis of 19 studies and about 60,000 infants, the cumulative incidence, including at birth, of stunting was 25% in the first three months of life.[31,32] Recovery from stunting is rare and most stunted children do not recover towards the global mean for length/height and those that do gain a small amount on their peers.[32] Wasting incidence also peaked in the first three months of life.[31] Recovery from wasting is more common than

from stunting. About 65% of infants recovered from wasting within 60 days in the first 3 months of life and about 50% of infants wasted in older ages recovered in 60 days.[31] Wasting and stunting reinforce each other meaning that stunting increased the risk of future wasting and vice-versa with a relationship that got stronger as children aged.[31] This suggests that changes in lifestyle or interventions have a larger impact in younger compared to older children and for wasting compared to stunting. Other reviews support the importance of intervening in pre-conception, pregnancy or the neonatal period to prevent the burden of CGF.[29,33–35]

There are several potential mechanisms that explain how suboptimal growth increases the risk of infectious disease burden including altered microbiome, chronic inflammation, immune system dysregulation, changes in endothelial barrier function, and others.[36] A review of the literature concluded that while improvements in nutrition can reverse susceptibility to infection, this effect is not well characterized.[1] Reversing acute malnutrition might help make children more resilient to infection.

Unfortunately, no single intervention is likely to improve childhood growth for all children.[1] Recent reviews of effective interventions for maternal and childhood malnutrition describes interventions according to direct and indirect relationships at the health sector or other macro-level sectors with undernutrition and provide a useful framework to think about interventions at different points in the life cycle.[35,37] Although societal and indirect interventions, like family planning and reproductive health services or poverty alleviation and women's empowerment strategies, might have important effects on childhood growth failure, several reviews have focused on the more proximal interventions that affect child environment and biology. [35,38] Proximal and effective interventions with strong evidence of impact are described **Table 3**.

Updates in methods, impact on estimates, comparison with other estimates of CGF.

Our study includes meaningful updates to previously reported estimates of CGF burden in the Global Burden of Disease study 2019. We used continuous estimates of height and weight by age, sex, geography, and year instead of modeled estimates of the prevalence of CGF indicators. This approach reflects the continuous definition of CGF indicators. We also used continuous estimates of the relative risks of incidence and mortality due to infectious causes for each CGF indicator by age group. Together, these advancements have produced estimates of higher specificity and better reflections of the true, underlying relationship between population-level exposures and risk factors. Still, there remain some important gaps in quantifying the burden of growth failure. First, our approach does not account for

longitudinal changes in growth status. It is likely that a cross-sectional measurement of growth does not accurately represent an individual child's risk of disease, especially given the importance of birth and early life exposures.[32] Second, we used an adjustment after modeling our relative risk curves to account for the correlation between different growth failure indicators. Children who have low height-for-age are more likely to have low weight-for-age, for example.[31] Future work to simultaneously quantify such correlation in a single statistical model might have an important impact on risk estimates.

Compared to previous iterations of the GBD, the overall CGF burden in this study was comparable to GBD 2019 for all children under-5 (SI Figure XX) but the burden by indicators was substantially different. Deaths attributable to stunting increased by about 2 times (XX%), deaths attributable to underweight increased by about 2-3 times (XX%), and deaths attributable to wasting decreased by about one-third (XX%; SI Figure XX). SI Figure XX shows that the attributable fraction differences appear to be largely driven by updates to the relative risks of infectious disease mortality [Sentences should be updated with the finalized version of the GBD 2021 results]. Prior estimates of the relative risk of diarrhea mortality given severe underweight (< -3) was about 100 after a mediation analysis, meaning that in previous iterations of the GBD nearly all diarrhea deaths among those children were attributable to severe underweight.[2] The risk of mortality due to underweight and stunting was meaningfully higher in this study for diarrhea and LRI compared to GBD 2019, while the risk of mortality due to wasting for LRI was much lower than in GBD 2019. In addition, underweight was considered a risk factor for malaria incidence and mortality for the first time.

This work updates the relative risk estimates used in the GBD that are used to quantify the burden of disease that is attributable to CGF.[14] Previous iterations of the GBD (e.g. 2017, 2019) used the cause-specific mortality hazard ratios from Olofin et al. 2013 for both incidence and mortality.[2] In addition to estimating the risk of cause-specific disease incidence for the first time, there are two main places where our estimates differ from those values. First, the relative risk of lower respiratory infection due to low HAZ and low WAZ are meaningfully higher than in Olofin et al. and in comparison to a separate systematic review and network meta-analysis.[3,14,39] Second, we have identified statistically significant relationships between low HAZ and low WAZ and malaria mortality which was not observed in the smaller sample size and discrete categorical analysis by Olofin et al.[3] Considering these CGF indicators as risks for malaria mortality will be included for the first time in GBD 2021 based on these findings and may represent a gap in previous burden of malaria estimates.

The current results are more closely aligned with estimates from a different group, the Maternal and Child Nutrition Study Group[4] which used CGF indicator prevalence estimated by the United Nations[40] and the Nutrition Impact Model Study[41] and cause-specific relative risks from a pooled analysis of ten longitudinal studies[3] to produce CGF attributable deaths for children under-5 in 2011 (**Table 4**). While the attributable fraction for stunting is lower in our study, the fraction for underweight is between MCNS estimates and our estimate is marginally higher for child wasting. A comprehensive comparison between estimates is difficult considering it depends on exposure prevalence, risk of cause-specific death, and in the total number of under-5 and cause-specific deaths. Still, results from different groups with different methods appear to converge around 10-20% of deaths in children under-5 being attributable to CGF.

Limitations

There are several limitations to this analysis. First, our estimates depend on numerous sources of data for childhood growth, infectious disease incidence, and infectious disease mortality, each with various potential gaps and biases which we attempt to resolve using expert opinion and sophisticated statistical models. One common data gap for each of the inputs into this study is that the burden of CGF is highest in some of the poorest areas of the world that lack robust vital registration and disease surveillance systems. We attempt to account for uncertainty throughout our modeling process by including measured error when possible and producing estimates incorporating uncertainty in each step. We have strived to report our findings both as the mean from the posterior distributions as well as the 5th and 95th percentiles of those distributions. Capturing and reporting uncertainty is critical in burden of disease modeling, including this one. Second, there are many remaining, unanswered questions about the impact of the COVID-19 pandemic and associated disruptions in maternal and child health services on child nutrition and mortality.[9,10] We have included modeled impacts on cause-specific child mortality[42] but strong evidence of changes in vaccine coverage[43] or birth size and gestational age, two confounding risks for infectious disease mortality in children, may change our understanding of the current and forecasted burden of CGF. Third, although we believe that our analysis strengthens previous burden estimates by using estimated continuous distributions for CGF prevalence and for the risk of infections due to CGF, our approach is cross-sectional in time and may not reflect the longitudinal nature of childhood growth. A child who has been suffering from CGF for several months might have a different risk of infection or death than a child who has a newly incident case of CGF, for example, a

nuance that is not measured in our analysis. Such an analysis would need to account for repeated measurements of growth and potentially repeated measures of infection.[44]

Conclusion

The global burden of disease attributable to childhood growth failure is substantial and concentrated in South Asia and central Africa. Children suffering from growth failure are at increased risk of mortality and incidence of infectious diseases. Although the burden of childhood growth failure has decreased in the last 20 years, more must be done to prevent children from being born small or preterm and to prevent children from faltering as they age. All children deserve an opportunity to have a healthy and productive life, but too many are being denied that chance because of poor growth.

Tables and Figures

Table 1. Burden of childhood growth failure at the global and super-regional level among children under-5 years old in 2021.

Location	Population children under 5	Live births	Deaths among children under 5	Child growth failure attributable deaths (95% UI)	Child stunting attributable deaths (95% UI)	Child underweight attributable deaths (95% UI)	Child wasting attributable deaths (95% UI)
Global	658,171,700	129,279,100	4,725,100	773,600 (390,500-1,099,500)	311,100 (203,000- 430,200)	509,200 (172,000- 750,300)	379,400 (196,600- 524,900)
Central Europe, Eastern Europe, and Central Asia	25,701,600	4,890,800	58,200	6,300 (4,300- 8,600)	2,300 (1,400- 3,200)	3,500 (600- 6,500)	2,700 (2,000- 3,500)
High-income	54,274,500	10,396,100	47,300	500 (300- 800)	100 (100- 200)	300 (100- 600)	200 (200- 300)
Latin America and Caribbean	47,322,000	9,350,700	156,800	14,400 (9,400- 20,100)	4,500 (2,900- 6,700)	9,100 (4,600- 13,600)	7,300 (4,000- 10,900)
North Africa and Middle East	61,137,100	12,126,100	250,600	24,300 (16,600- 31,600)	9,600 (6,900- 12,800)	15,500 (7,600- 22,300)	12,000 (6,900- 16,500)
South Asia	158,593,800	32,043,400	1,186,100	149,300 (107,400- 193,800)	62,000 (42,400- 86,400)	105,000 (38,900- 148,600)	85,500 (56,000- 110,900)
Southeast Asia, East Asia, and Oceania	138,292,600	22,770,900	345,900	37,800 (25,100- 49,400)	14,900 (10,200- 20,800)	23,400 (8,300- 35,500)	18,900 (11,200- 25,600)
Sub-Saharan Africa	172,850,100	37,701,100	2,680,200	540,800 (222,000- 812,500)	217,700 (116,300- 344,900)	352,500 (110,600- 534,100)	252,600 (114,600- 384,300)

Table 2. Cause-specific deaths attributable to childhood growth failure at the global and super-regional levels among children under 5 years in 2021.

Location	Cause name	Cause-specific deaths	Child growth failure (95% UI)	Child stunting (95% UI)	Child underweight (95% UI)	Child wasting (95% UI)
Global	Diarrheal diseases	340,700	259,300 (155,900-358,200)	89,500 (53,900-131,300)	129,500 (80,100-196,300)	178,700 (-9,400-327,200)
	LRI	502,200	298,000 (213,000-379,000)	154,900 (104,900-206,800)	208,000 (8,100-350,800)	113,900 (70,800-162,100)
	Malaria	422,300	109,700 (-74,800-353,500)	50,700 (-24,800-229,400)	80,100 (-48,100-250,200)	0 (0-0)
	Measles	48,100	32,000 (15,700-52,600)	16,000 (6,600-26,500)	17,100 (7,700-28,700)	12,100 (4,500-25,100)
Central Europe, Eastern Europe, and Central Asia	Diarrheal diseases	2,000	1,300 (600-1,900)	300 (200-500)	500 (200-800)	1,000 (0-1,800)
	LRI	11,000	5,000 (3,600-6,800)	2,000 (1,100-2,800)	3,000 (100-6,200)	1,700 (1,000-2,500)
	Malaria	NaN	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)
	Measles	0	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)
High-income	Diarrheal diseases	400	100 (0-200)	0 (0-0)	0 (0-0)	100 (0-200)
	LRI	900	300 (200-500)	100 (100-200)	200 (0-500)	100 (0-100)
	Malaria	0	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)
	Measles	0	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)
Latin America and Caribbean	Diarrheal diseases	8,200	5,000 (2,800-7,300)	1,500 (900-2,300)	2,000 (1,100-3,300)	3,100 (-100-6,600)
	LRI	12,200	6,600 (4,100-9,400)	3,000 (1,700-4,500)	4,300 (100-8,800)	1,500 (800-2,200)
	Malaria	200	0 (0-100)	0 (0-100)	0 (0-100)	0 (0-0)
	Measles	0	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)
North Africa and Middle East	Diarrheal diseases	11,500	7,900 (4,500-12,500)	2,500 (1,500-4,400)	3,900 (2,300-7,100)	5,200 (-200-10,600)

Location	Cause name	Cause-specific deaths	Child growth failure (95% UI)	Child stunting (95% UI)	Child underweight (95% UI)	Child wasting (95% UI)
	LRI	20,300	11,500 (8,100-14,900)	5,600 (3,500-7,800)	7,800 (300-13,900)	4,100 (2,500-5,900)
	Malaria	1,700	500 (-400-1,700)	200 (-100-1,000)	400 (-300-1,300)	0 (0-0)
	Measles	3,600	2,500 (1,300-4,200)	1,300 (600-2,200)	1,500 (700-2,600)	700 (300-1,600)
South Asia	Diarrheal diseases	56,200	43,700 (25,000-64,700)	15,700 (8,300-25,700)	25,000 (12,900-41,600)	31,100 (-1,800-57,200)
	LRI	154,300	90,200 (67,800-113,300)	44,600 (27,900-61,800)	65,600 (2,900-106,000)	42,000 (27,100-60,400)
	Malaria	6,500	2,100 (-1,600-11,200)	1,000 (-600-5,700)	1,600 (-1,100-8,400)	0 (0-0)
	Measles	1,700	1,200 (600-2,200)	700 (300-1,200)	700 (300-1,300)	500 (200-1,000)
Southeast Asia, East Asia, and Oceania	Diarrheal diseases	16,300	11,800 (6,400-16,500)	4,000 (2,500-5,800)	5,300 (3,200-8,200)	8,200 (-400-15,500)
	LRI	41,700	23,100 (16,200-30,200)	10,800 (6,700-15,100)	15,300 (500-27,700)	8,100 (5,000-11,700)
	Malaria	400	100 (-100-400)	100 (0-300)	100 (-100-300)	0 (0-0)
	Measles	400	200 (100-400)	100 (100-200)	100 (100-200)	100 (0-200)
Sub-Saharan Africa	Diarrheal diseases	246,300	189,500 (108,800-285,600)	65,400 (38,500-100,100)	92,900 (54,300-144,600)	130,100 (-6,800-252,700)
	LRI	262,300	161,300 (108,000-215,800)	88,900 (58,400-121,600)	111,700 (4,200-192,700)	56,500 (31,600-84,500)
	Malaria	413,200	106,900 (-72,900-340,600)	49,400 (-24,200-224,700)	78,000 (-47,600-240,300)	0 (0-0)
	Measles	42,400	28,000 (13,100-46,700)	13,900 (5,700-23,500)	14,700 (6,300-25,500)	10,800 (3,900-22,800)

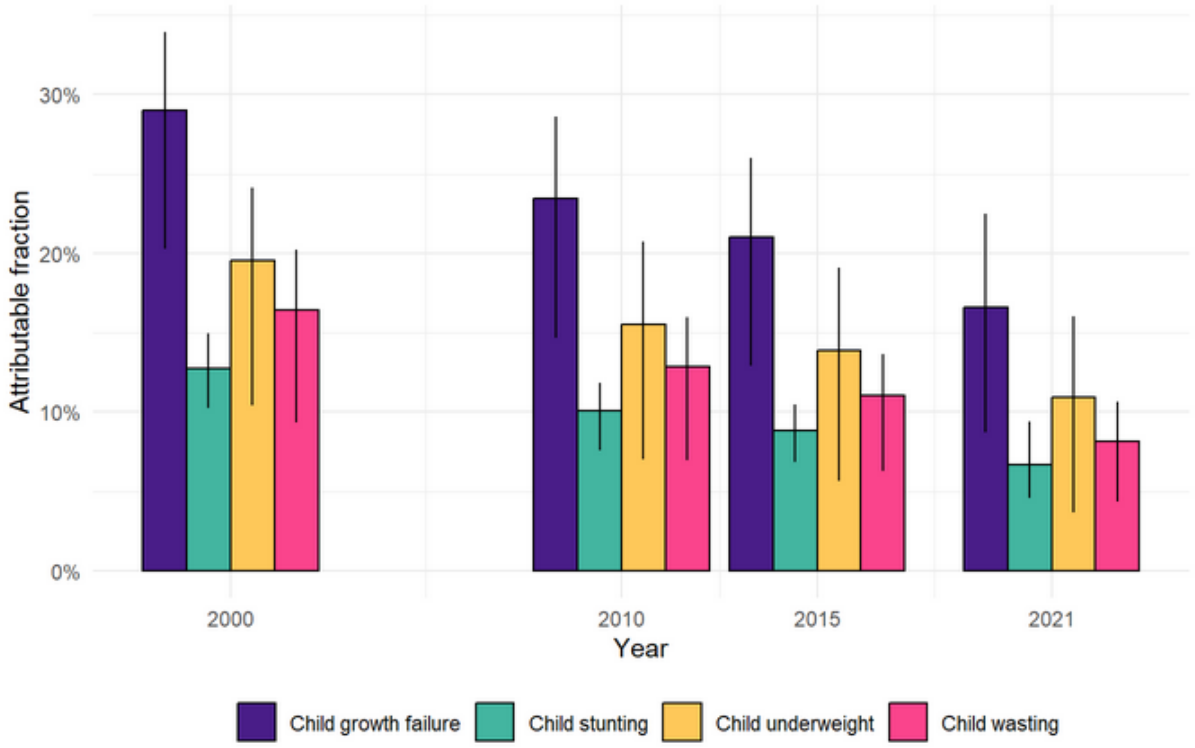
Table 3. Interventions and strategies to reduce the burden of childhood growth failure.

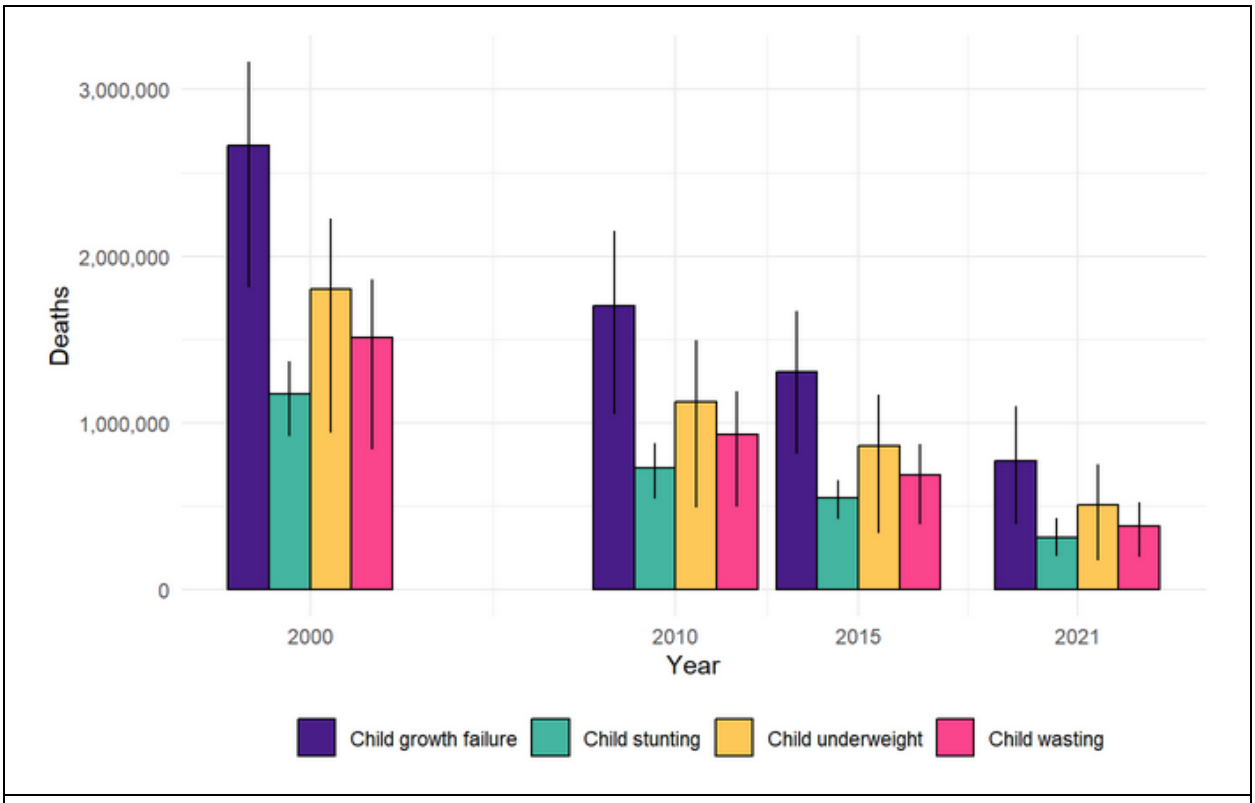
Socio-economic factors	During Pregnancy	Postpartum and infancy	Acute malnutrition treatment
Gender equality and programs to give women economic and educational opportunities and social autonomy Expanded access to educational opportunities for adolescent girls and prevention of adolescent pregnancy[45] Family planning and reproductive health services give women greater decision making over number and timing of children. Birth spacing may result in 10-50% reduction in stunting prevalence[46] Poverty alleviation programs including conditional cash transfers can improve linear growth and decrease stunting prevalence by 10%[38,47] Prevention of infectious disease episodes, like diarrhea and enteric infections (reduction in childhood growth failure burden of 39%[48]) and malaria (Insecticide treated bed nets reduce low birthweight by up to 23%.[49] Malaria chemoprevention reduces moderate/severe anemia by 40% and 27% reduction in low birthweight)[50]	Supplementation of single and multiple micronutrients to mothers may reduce the prevalence of small-for-gestational age (SGA) and stunting at birth.[51] Multiple micronutrient supplementation can reduce low birthweight by 15%, and babies born SGA by 7%.[52] Iron supplementation in pregnancy to prevent or treat maternal anemia can reduce the risk of low birthweight by 12%.[52] Balanced energy protein supplementation in pregnancy reduces risk of low birthweight and SGA.[53]	Kangaroo mother care, especially for preterm and small for gestational age, can increase weight gain by 40% in the first two weeks of life.[35] Prompt initiation of exclusive breastfeeding is important to optimize macronutrient intake for infants and can protect against infections.[54] Complementary feeding practices improves WAZ, HAZ, and reduces stunting prevalence.[55] Small-quantity lipid-based nutrient supplementation during complementary feeding reduces severe and moderate stunting, moderate wasting, and moderate underweight.[56] Supplementary feeding programs reduce wasting prevalence and reduce risk of infant mortality.[55] Maternal mental health support[57]	Facility- and community-based strategies to manage severe acute malnutrition (including ready-to-use therapeutic food, supplementary food, antibiotics, and vitamin A) can result in recovery rates of up to 83%.[58] Ready to use therapeutic food (RUTF) is extremely effective in treating uncomplicated severe acute malnutrition with recovery proportions of around 90%.[59]

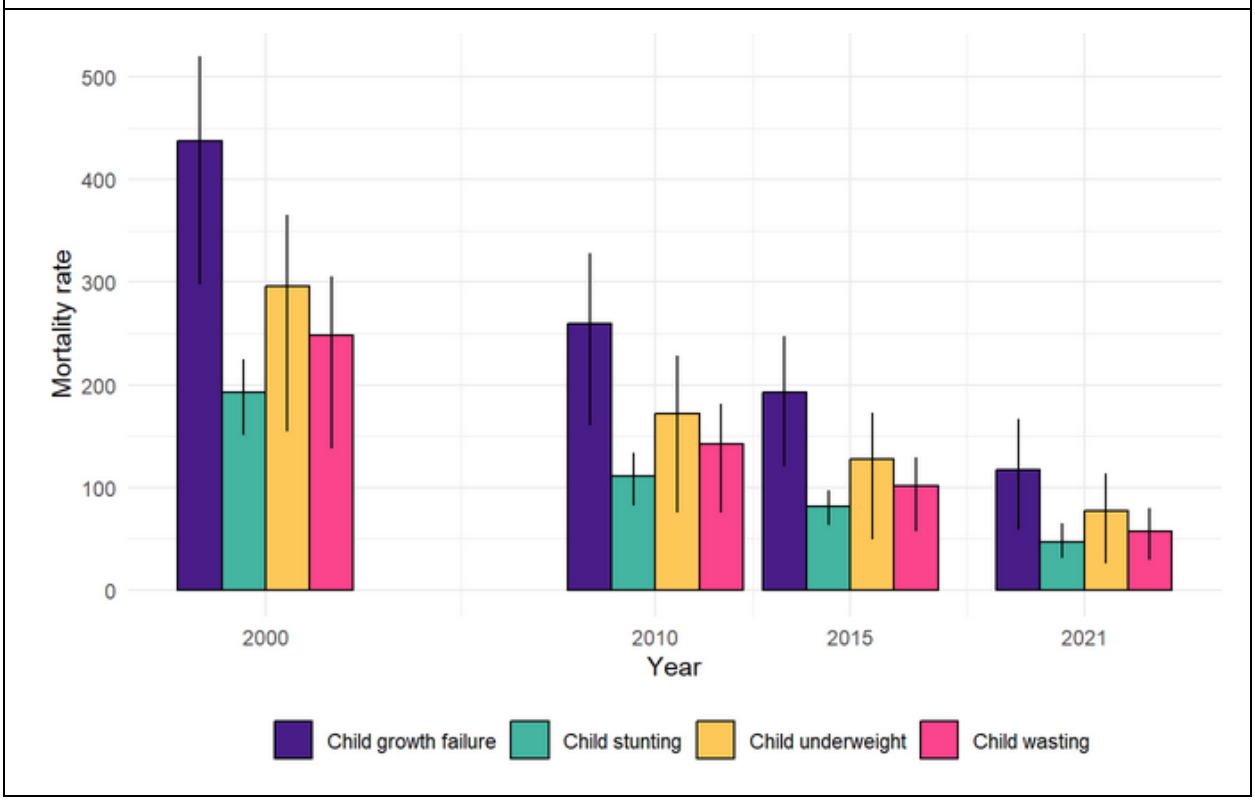
Table 4. Comparison of all-cause population attributable fractions for stunting, underweight, and wasting deaths among children younger than 5 years between current and previous iterations of the Global Burden of Disease study[2] and with the Maternal and Child Nutrition Study Group[4] estimates published in 2013.

CGF indicator	GBD 2021	GBD 2019	MCNS: United Nations prevalence	MCNS: Nutrition Impact Model Study prevalence
Child stunting	10.1%	4.4%	14.7%	17.0%
Child underweight	15.5%	6.5%	14.4%	17.0%
Child wasting	12.8%	20.1%	12.6%	11.5%

Figure 1. The attributable burden for childhood growth failure is shown at the global level for children under 5 years. Separate bars show the attributable burden for stutning, underweight, and wasting separately. A) The fraction of all deaths that can be attributed to CGF. B) The number of deaths that can be attributed to CGF. C) The number of deaths per 100,000 attributable to CGF. D) The fraction of infectious diseases deaths for which CGF is a risk factor that can be attributed to CGF.




3,000,000
2,000,000
1,000,000
0
Deaths
2000
2010
2015
2021
Year
Child growth failure
Child stunting
Child underweight
Child wasting


500
400
300
200
100
0
Mortality rate
2000
2010
2015
2021
Year
Child growth failure
Child stunting
Child underweight
Child wasting

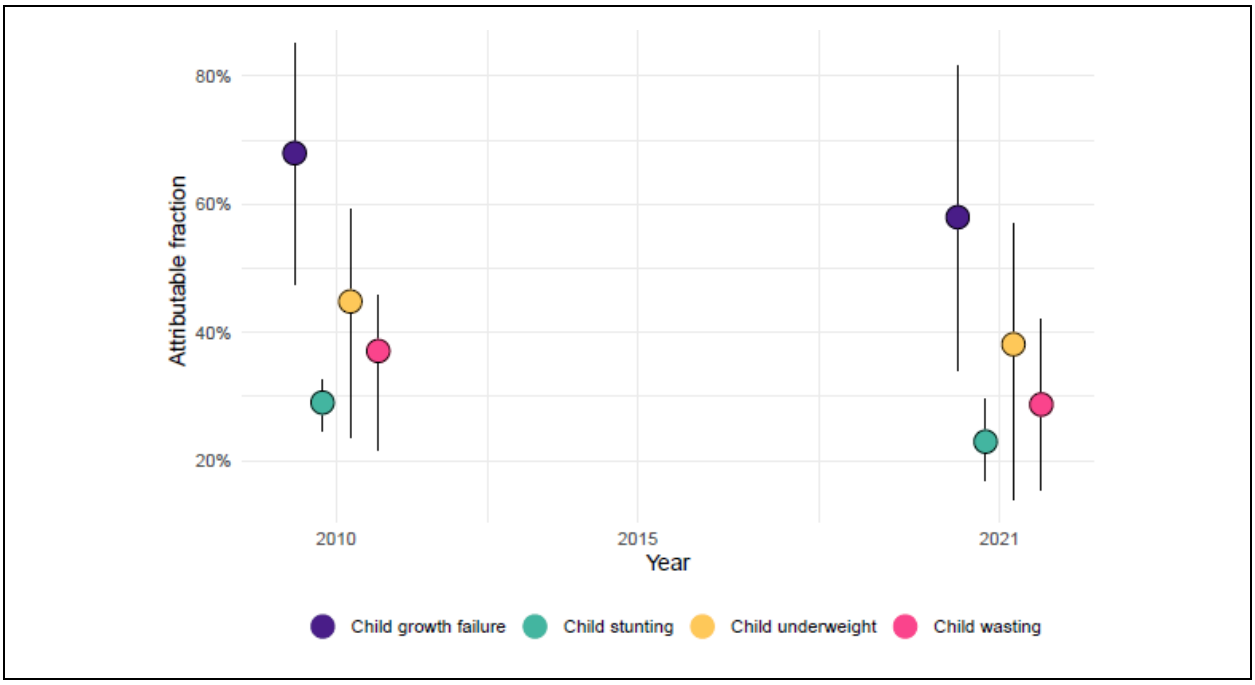

80%
60%
40%
20%
Attributable fraction
2010
2015
2021
Year
Child growth failure
Child stunting
Child underweight
Child wasting

Figure 2. The number of deaths due to infectious diseases attributable to childhood growth failure globally by age group in 2021. A) Age-group specific deaths, B) Cumulative deaths.

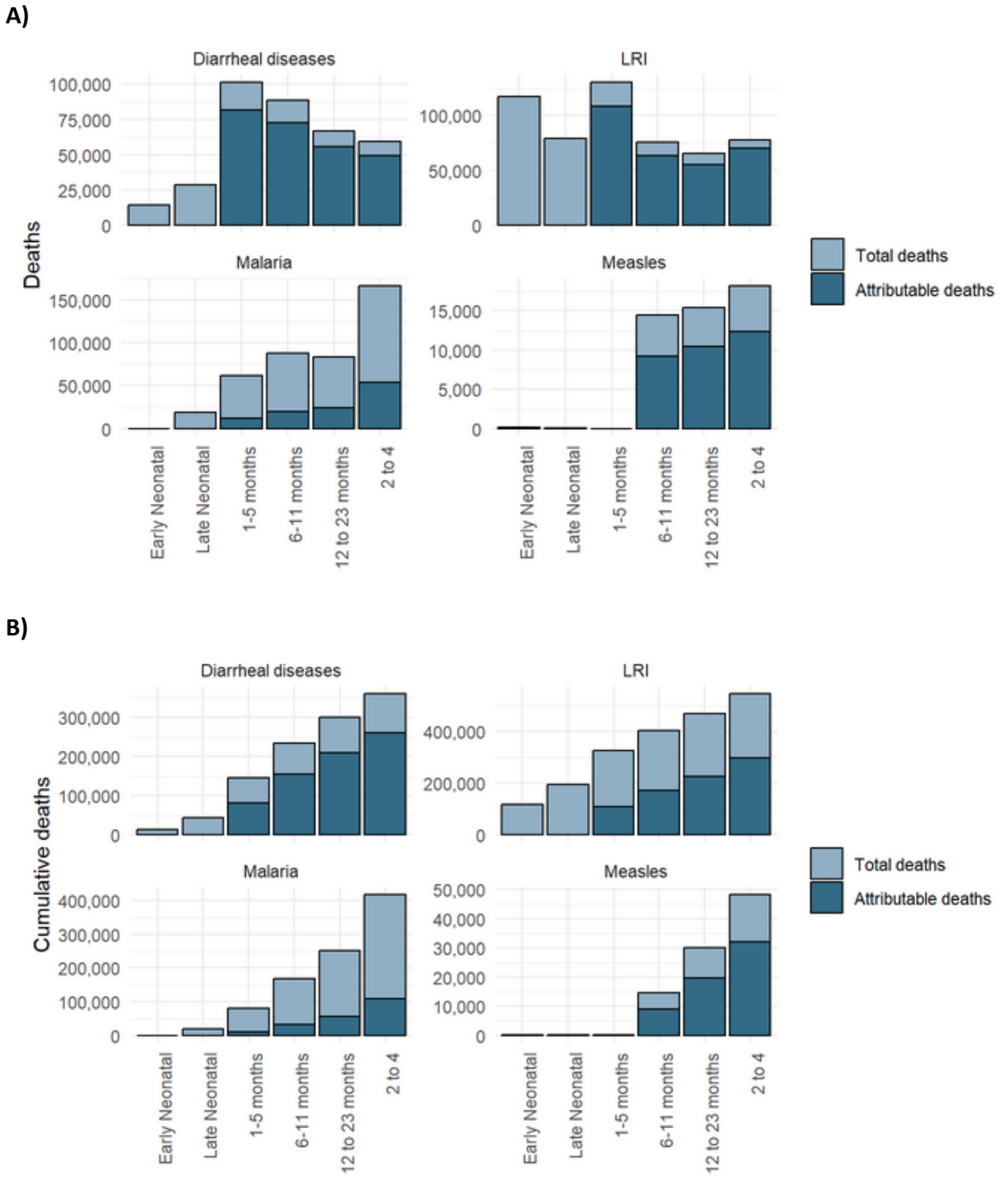


Figure 3. The percentage of deaths and years lived with disability among children under 5 years attributable to childhood growth failure, globally, in 2021.

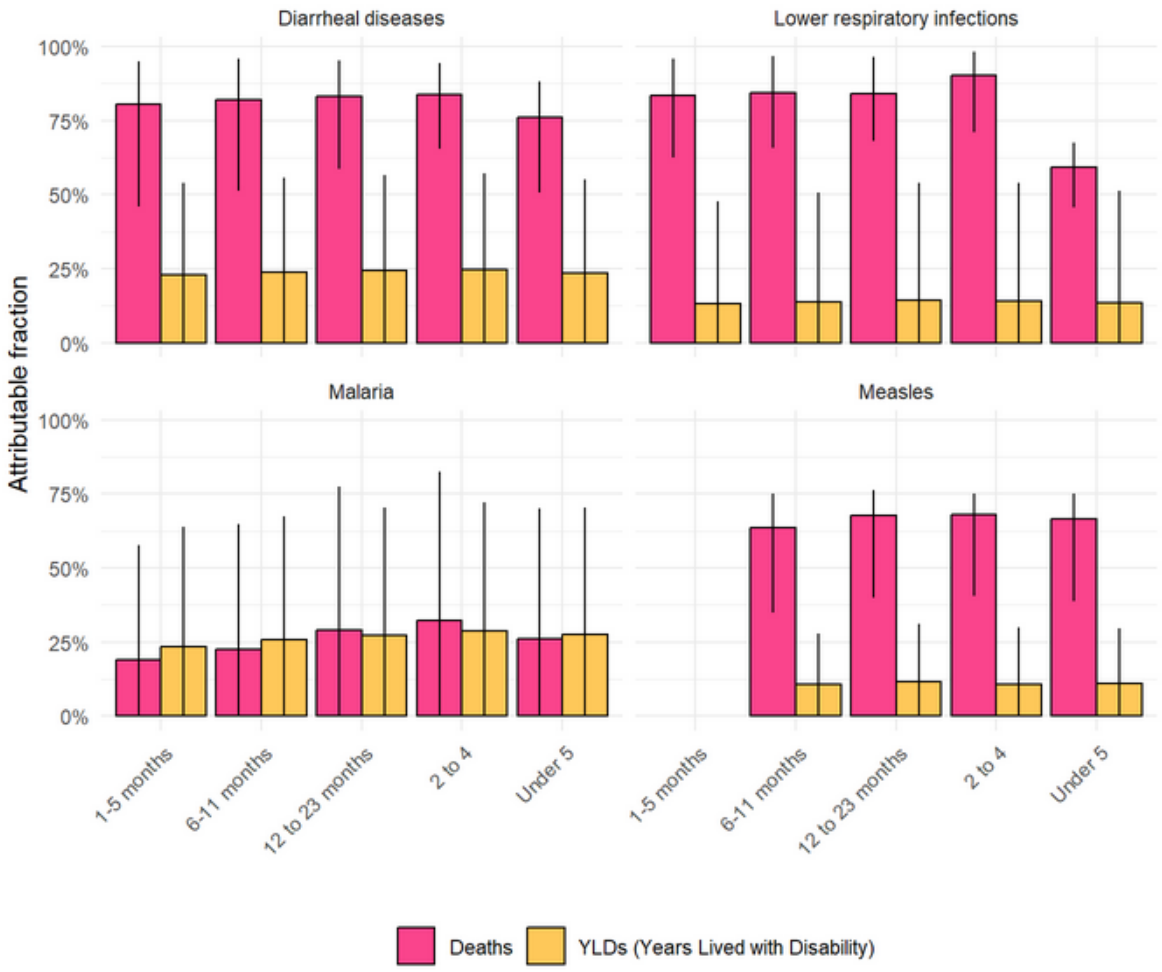


Figure 4. Childhood growth failure deaths among children under-5 per 1000 live births in 2021.

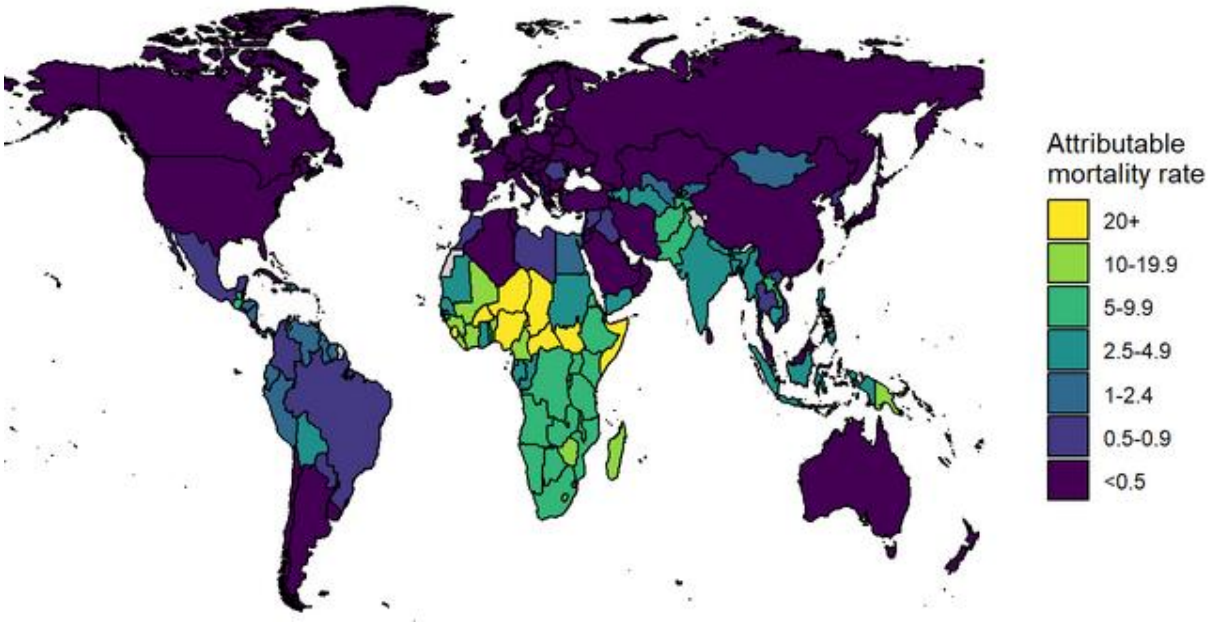
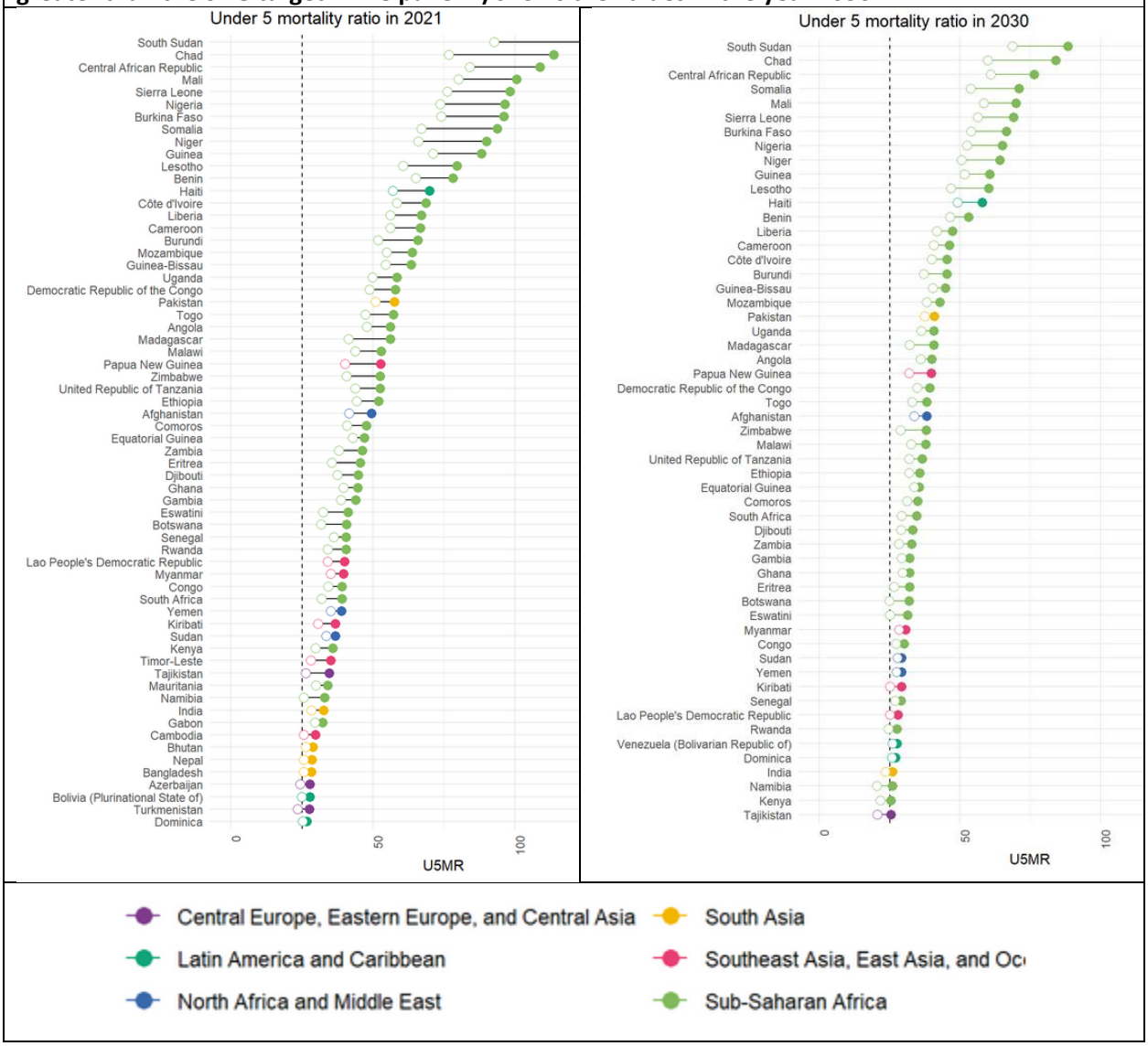


Figure 5. The under-5 mortality ratio (deaths per 1000 live births) is shown for countries that exceeded the Sustainable Development Goal for child survival (25 deaths per 1000 live births) solid dots. Open circles show the under-5 mortality ratio in the absence of childhood growth failure. Panel A) shows values in the year 2021 for countries where the projected under-5 mortality ratio is greater than the SDG target while panel B) shows the values in the year 2030.



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Chapter 4: Longitudinal trajectories of early childhood vulnerability: a pooled analysis of cohort studies of growth and mortality

Abstract

In the last year, about 5 million children died before their fifth birthday. Many of those deaths occurred among children in low- and middle-income countries (LMICs) that suffered from growth failure. Identifying the children that are most vulnerable to mortality is critical to designing and implementing strategies to improve their health and wellbeing. We used a pooled dataset representing 58 studies from 31 LMICs with repeated measurements of childhood length/height and weight to construct vulnerability trajectories from birth to 2 years. First, we fit a multidimensional latent class growth model to assign growth trajectories in height-for-age and weight-for-height z-scores (HAZ, WHZ) to each child. We then estimated the relative risk of all-cause mortality in a survival model using repeated measurements of HAZ and WHZ among children younger than 2 years. We combined these estimates into a vulnerability trajectory for each child that represented their risk of mortality as they aged. We evaluated the association between demographic, socio-economic, and biological factors with vulnerability cluster membership to identify children most susceptible to overall and increasing vulnerability. The risk of all-cause mortality increases non-linearly with more negative values of HAZ and WHZ and the relative risk was between 1.4 and 7 for most children in this study, compared to children with HAZ and WHZ of 0. We identified six clusters with different trajectories in HAZ and WHZ and in vulnerability. Boys, children born with shorter gestational age, and children born to mothers with low education were all at increased risk of being in highly vulnerable trajectories. These results illustrate the potential of quantifying vulnerability and categorizing children into different clusters based on their longitudinal vulnerability.

Introduction

The likelihood of a child dying before their fifth birthday is a fundamental measure of socio-demographic development and human capital.[1] The Sustainable Development Goals (SDGs) used neonatal and under-5 mortality as two primary metrics of population health because they are functions of a variety of factors associated with health like health system access and affordability, water & sanitation infrastructure, and reliable or dependable economic conditions.[1] In the last 35 years, under-5 mortality has declined precipitously, a major achievement.[2,3] Still, approximately 5 million children died before they reached 5 years and the risk is especially high in the neonatal period and in infancy and globally, we are not on track to reach the SDG targets for these indicators.[3,4]

Global trends obscure important geographical and within-population differences in the risk of under-5 mortality.[5] Better quantifying individual and group variation in risk is critical to understand which children are most at risk and to develop strategies to intervene. A growing body of literature has considered a child's size at birth and sequential measurements of their length or height and their weight to describe their vulnerability.[6–8] Vulnerability in this context typically means the risk of dying. Children who are born preterm or low birthweight are much more likely to die than their peers, especially in the first month of life, largely due to birth complications and susceptibility to infectious diseases.[6,9,10]

Poor linear growth is also detrimental beyond the neonatal period. Childhood growth failure (CGF), defined as suboptimal growth in height, weight, and weight-for-height, is one of the leading risk factors for under-5 mortality.[11,12] Global reference curves, describing how children should grow, are used to create distributions of growth by age and sex.[13,14] From these distributions, z-scores representing standard deviations in height-for-age (HAZ), weight-for-age (WAZ), and weight-for-height (WHZ) are constructed. These metrics are useful because given a child's height and weight, child-specific growth metrics are straightforward to calculate, and these metrics are associated with poor health.[15,16] Like children who are born small, children suffering from growth failure are more likely than their peers to get enteric, respiratory, and other infections and to die from those infections.[16] The amount of growth failure matters a great deal because there is a non-linear association between CGF and cause-specific infectious disease mortality.[16]

Until recently, analyses that estimate CGF prevalence and disease burden have been categorical in defining growth failure, cross-sectional in time, and treated height and weight as independent in prevalence and associated outcomes.[11,15,17–21] Treating CGF as discrete, categorical indicators by defining

stunting, underweight, and wasting as values less than -2 z-scores is helpful for estimating population prevalence and defining varying risks at different levels of CGF exposure.[18,21] Yet doing so in statistical models drops substantial information by transforming a continuous variable into an ordered categorical one.[22,23] Further, a child's weight and height are highly dependent and separating them when estimating prevalence or the risk of health outcomes is missing important information on this covariance.[24,25] Lastly, treating growth as a cross-sectional metric for health and vulnerability reduces a complex longitudinal history for each child into a single measurement and is an incomplete reflection of their trajectory in growth.[24,26,27]

This analysis seeks to address these limitations in the assessment of early childhood growth and susceptibility to poor health outcomes by using a pooled dataset of longitudinal cohort studies to define trajectories of childhood vulnerability to all-cause mortality in children under-2 years old. It then tests the association between health and demographic characteristics to identify children most likely to follow different trajectories in vulnerability. The resulting novel definition of childhood vulnerability may be a powerful tool to describe and identify children and populations of children that might most benefit from specific and targeted interventions to support survival and healthy development.

Methods

We constructed a standardized, pooled dataset of longitudinal studies that included multiple anthropometric measurements of children's length/height and weight from low- and middle-income countries. Of the 56 studies in the final analytic dataset, 38 were from the Healthy Birth, Growth, and Development Knowledge Integration (HBGDki) data repository.[28,29] This repository was constructed with an explicit purpose of facilitating research and building evidence around health birth and growth in low- and middle-income countries. A major advantage of using these data was that the HBGDki network included pre-standardized datasets covering not just growth metrics but birth characteristics (gestational age, birth weight, birth order and parity), maternal and paternal characteristics (age, education years, height, weight, body mass index), and other socio-demographic information (assets, household size, number of children, household income). A longer description of data standardization for HBGDki is available elsewhere.[7,24,26] Further, we identified 10 studies with multiple anthropometric growth measurements from published literature that provided their data on an open data platform or directly with published materials while the remaining 8 studies were from a separate pooled dataset from the Institute for Health Metrics and Evaluation.[16] We used demographic and birth data from those

studies, where available, standardized using the same definitions as the HBGDki data. There were 33 interventional studies that were included in this analysis, primarily macro- and micro-nutrient interventions (n = 22) or antibiotic use in clinical or mass distribution settings (n = 3). Children from interventional studies were defined as either treatment or control. Geographical distribution of studies providing data in this analysis is presented in **Supplementary Figure 1.**

We defined vulnerability as the relative risk of all-cause mortality among children 0-2 years of age. To describe and identify trajectories of this vulnerability, we used height-for-age z-scores (HAZ) and weight-for-height z-scores (WHZ) as our exposure. We used this pooled dataset for three distinct analyses to quantify early childhood vulnerability. Each is described below.

Joint estimation of height- and weight-for-age as a risk factor for all-cause mortality

We identified all studies in the dataset that reported at least one death among children 0-2 years. We excluded deaths that occurred in the first day of life for this analysis because we wanted to avoid perinatal deaths due to birth complications which would not conceptually be associated with growth. We used a frailty Cox proportional hazards model to fit the risk of mortality associated with joint HAZ and WHZ values with nested random intercepts by children within each study to account for study-specific variation in risk and repeated measurements within each child.[30] We tested different polynomial degrees for the relationship between the growth metrics and mortality and models without nested study-specific random effects and evaluated with model fit statistics, primarily through analysis of variance and AIC (**Supplementary Table 1**). Children began contributing person-time at the age when they had their first anthropometric observation and the time in days between anthropometric measurements was their exposure time. Children who had their last valid survival observation before 2 years old were censored in the model. The Cox proportional hazards model included fixed effects for categorical age group (based on age at the start of person-time range), child sex, and a binary indicator for if they were in a treatment arm from interventional studies. We included children in treatment arms because they represented a substantial fraction of all deaths in the dataset and dropping them would limit statistical power (699 deaths, 43% of deaths). We conducted a sensitivity analysis of limiting the Cox proportional hazards model to only children in non-treatment arm of interventional studies or those in observational studies (**Supplementary Figure 4**). We also included mid-upper arm circumference for age z-score (MUAZ) as a predictor of mortality hazard in a separate model shown in the **Supplementary results**.

We defined a theoretical minimum risk exposure level, or the value of HAZ and WHZ where the risk of mortality is lowest, as 0. The estimated risk at that joint combination of HAZ and WHZ was considered the reference risk and relative risks were computed dividing risk at each joint value of HAZ and WHZ by that reference value. The result of this analysis is continuous relative risk estimates for each combination of HAZ and WHZ among children under 2 years old.

Multidimensional latent class trajectory model

We built a multidimensional latent class trajectory model using all children from our pooled dataset that were not in a treatment arm of an interventional study and that had more than one anthropometric measurement before 2 years. Latent class trajectories in both HAZ and WHZ were fitted simultaneously using random intercepts by child to account for repeated measurements.[31,32] Trajectories were fitted with varying flexibility in cubic b-splines using generalized additive models (GAMs).[33] The starting number of latent clusters was allowed to vary between 2 and 6. We limited the possible number of clusters to 6 to assist in the practical interpretation of the results. The different models were compared using fit statistics such as the Bayesian Information Criterion and log-likelihood, and the best performing model combination of the number of clusters and knots was selected.[31] Lastly, we iteratively ran this model using different starting values in the likelihood optimization function to identify the model with the lowest log-likelihood value.[31] Each child was assigned to the cluster with the highest probability that they belonged in that cluster.

To create a vulnerability score, we matched each anthropometric measurement to the sex-specific relative risk of all-cause mortality for its joint HAZ and WHZ values. Vulnerability trajectories for each cluster were refit separately using the same GAM specifications used in the latent class model to visualize the trajectories in vulnerability that define each cluster.

Predicting vulnerability trajectory clusters

The last step was to quantify factors that predicted vulnerability cluster membership. We considered a diverse set of predictors including maternal characteristics, birth characteristics, breastfeeding and food behaviors, and other socio-demographic indicators that were available across multiple studies in the dataset. The analysis sought to quantify factors that predicted more vulnerable clusters early in life to identify children most likely to have poorer trajectories so that targeted interventions may reach them. Multinomial logistic regression models including a random intercept by study-site were used, and marginal predicted probabilities were estimated using the *ggeffects* package.[34]

All analyses were completed in the statistical programming language R version 4.3.0 using the packages *coxme* (mixed-effects Cox proportional hazards),[35] *flexmix* (flexible growth mixture models),[32] *and mclogit* (multinomial logistic regression with random effects).[36]

Results

All-cause mortality risk

There were 30 studies that had at least one death from our analytic dataset, including 63,742 children contributing 187,858 anthropometric measurements and 1,640 deaths. The best performing Cox proportional hazards model based on AIC was a cubic polynomial function on HAZ and WHZ. Both low HAZ and low WHZ were statistically significantly associated with an increased risk of all-cause mortality among children younger than 2 years (**Figure 1**). Small arm circumference was also associated with mortality risk, but the sample size was much smaller for this indicator and since it was not used in the trajectory modeling, results are shown in **Supplementary Figure 5.** There was a sharp increase in the relative risk as children become more stunted and/or more wasted and the relative risks compounded as children become stunted and wasted simultaneously (**Figure 1**). A child that is on the cusp of being stunted (HAZ -2) but not wasted (WHZ 0) has a relative risk of 2.1 (95% CI 1.88-2.35). However, if that child is also on the cusp of being wasted (WHZ -2 & HAZ -2), that risk increases to 4.97 (95% CI 4.24-5.77). A child that is severely wasted (WHZ -4) but not stunted (HAZ 0), has a higher relative risk than a child that is severely stunted (HAZ -4) but not wasted (WHZ 0) (RR 6.7, 95% CI 5.72-7.84 | RR 4.92, 95% CI 4.16-5.72, respectively), but both combinations are uncommon (**Figure 1**). It is much more common for children to have mild stunting and no or mild wasting. Nearly 50% of observations in this dataset had relative risk estimates greater than 2 and 3.2% of observations had relative risk estimates greater than 10. About 63% of children had at least one observation with a relative risk greater than 2 and 6.7% had one greater than 10.

Defining vulnerability trajectories

There were 89,199 children with 2 or more anthropometric measurements in the first two years of life that were used in this part of the analysis from 49 studies, representing 395,345 HAZ and WHZ observations. The best performing multidimensional latent class growth trajectory model was one with six clusters and 5 knots in the GAM b-splines that included a dummy variable for studies in South Asia. Statistical prediction of cluster membership was generally robust (**Supplementary materials**).

Fitted trajectories in HAZ, WHZ, and relative risk of all-cause mortality in the first two years of life varied substantially between clusters both in the level and trend of those trajectories (**Figures 2-3, Table 3**). The fitted trajectories by each cluster indicate that most children in this dataset grew more stunted over the first two years of life, meaning that their heights increasingly negatively deviated from reference growth curves **(Figure 2A)**. Only one cluster had a fitted trajectory in HAZ that did not decrease by a substantial amount (dark green, **Figure 2A**). Although the fitted trajectories in HAZ were similar between the clusters, the magnitude varied considerably. The shortest children, on average, were most likely to be assigned to the red cluster (**Figure 2A**). Cluster membership depended on magnitude in HAZ but also in WHZ trajectory. For example, while two clusters, yellow and purple, had similar fitted HAZ over the first two years of life, they had deviating trajectories in WHZ, especially in the first six months of life (**Figure 2B)**. Two clusters, blue and dark green, had substantial recovery in WHZ in the first 6 months of life. No clusters had declines in WHZ in the first 6 months of life, but two had rapid deterioration in WHZ between 6 months and 1 year (red and yellow; **Figure 2B**).

Clusters varied in their fitted vulnerability (**Figure 3**). The most vulnerable cluster (red) was the one with the lowest average fitted HAZ at birth and they grew substantially more vulnerable as they aged with declining trajectories in both HAZ and WHZ (**Figure 2**). Compared to children with HAZ and WHZ values of 0, this cluster had a fitted relative risk of all-cause mortality of about 4 at birth, increasing to 7 by 18 months (**Figure 3**). The fitted relative risk for the lowest vulnerability cluster was just above 1 at birth with a mostly flat trajectory to two years. The fitted relative risk for the remaining clusters was around 2 at birth, but these clusters had different trajectories as children aged. The cluster with WHZ recovery had decreasing vulnerability through the first two years of life while the cluster that maintained but did not substantially improve WHZ, light green, stayed relatively flat in vulnerability (**Figure 3**). The remaining two clusters, purple and yellow, had parallel trajectories up to 6 months but the yellow cluster increased more than the purple from 6 to 12 months, probably corresponding to a declining WHZ trajectory in this period (**Figures 2 & 3**).

The fraction of cluster membership among all children varied from 11.3% in the most vulnerable cluster to 23.2% in cluster 4 (**Figure 4**). If the children were spread equally between the clusters, each would have about 16.7% of all children. The fraction of children assigned to the most vulnerable cluster was larger in Africa (13.2%) than in South Asia (9.4%) (**Figure 4**).

Predicting vulnerability trajectory membership

There were 70,855 unique children with valid HAZ and WHZ values for this part of the analysis from 43 studies. The reference category for the multinomial logistic models was the blue cluster with the lowest overall fitted vulnerability.

Child sex is associated with cluster membership. Girls are more likely than boys to be in the clusters with the lowest fitted vulnerability trajectory and much less likely than boys to be in the most vulnerable cluster (**Figure 5A**). The probability that children belong to clusters with better trajectories in vulnerability (blue, dark green, and light green) increases with gestational age and birthweight and correspondingly the probability that children belong to more vulnerable clusters (purple, yellow, red) decrease. At 2500 grams at birth, there was a 70% probability that a child belongs to one of the three most vulnerable clusters, and at 2000 grams at birth, that probability was 85% (**Figure 5B**). The probability that children with birth length greater than 55 centimeters belonged to the dark green group was more than 75%, but less than 1% of newborns are this long at birth. This cluster had rapid recovery in WHZ, perhaps indicating that long newborns fill out in weight after birth (**Figure 5**).

Maternal characteristics were also associated with the probability of cluster membership (**Figure 6**). The probability that children belong to one of the clusters with the lowest fitted vulnerability increases with each additional year of maternal education. Greater maternal weight and height were both positively associated with the probability of belonging to a cluster with low fitted vulnerability. Maternal mid-upper arm circumference was also positively associated with low vulnerability trajectory membership, but the sample size was much smaller than for height or weight (**Figure 6D**). Maternal age was not associated with cluster membership (not shown).

Discussion

Overall summary

This large, pooled analysis of 58 cohort studies of children under 2 years defined vulnerability as longitudinal growth in height-for-age and weight-for-height z-scores. It quantified longitudinal childhood risk of all-cause mortality and identified different trajectories of vulnerability based on this risk and their determinants. We have considered multiple metrics of childhood growth, height & weight, simultaneously in estimating joint-relative risk of all-cause mortality and in growth patterns. The results from this work are instructive in quantifying childhood vulnerability to all-cause mortality based on

growth, segmenting children into groups based on their vulnerability trajectories, and provide insights into understanding likely trajectories in vulnerability based on maternal, demographic, and birth characteristics.

Biological plausibility

Stratifying newborns and infants into vulnerability categories and assessing longitudinal changes in childhood growth is becoming more common, particularly with analyses of pooled data.[6,7,9,24,26] Pooled datasets of childhood growth and outcomes, like the HBGDki,[29] enable more robust statistical analyses because combining multiple studies provides larger samples sizes, better temporal coverage of growth measurements, and can capture more rare events like mortality and cause-specific mortality that might be limited in number in single cohort studies. Recent publications have shown that children who are born premature, small for gestational age, and low birthweight are at much greater risk of neonatal mortality than children born healthy.[6,8,9] Those risks are perhaps compounded longitudinally as children age because it is rare for children to recover from being small in the neonatal period, especially for recovery from low height-for-age.[26]

Children who suffer from growth failure are at greater risk of infectious disease episodes, potentially making healthy growth more difficult and setting them back further in their growth relative to their peers.[16,40] Growth failure also makes children more likely to die from infectious diseases, including diarrhea, lower respiratory infections, measles, and malaria, possibly due to immune system dysfunction, impaired mucosal barrier integrity, or systemic inflammation.[16,41] Growth failure and inadequate caloric and micronutrient deficiency also has detrimental effects on cardiovascular, hepatic, renal, enteric, and brain function, possibly leading to higher risk of mortality due to non-infectious causes but certainly preventing healthy development of these systems.[41]

Practical applicability and implications for identifying vulnerable children.

We found that the risk of all-cause mortality is non-linear with low HAZ and low WHZ, suggesting that, while suffering from growth failure in one dimension may make a child more susceptible to mortality, suffering from both is substantially worse, particularly at extreme values. Most children in the LMICs represented by this pooled cohort dataset (88%) have mild to moderate stunting (HAZ between -3 and 0) and mild wasting (WHZ between -2 and 0).

The most vulnerable children in this analysis tend to be the ones born the smallest. Low weight and length at birth are highly predictive of belonging to the most vulnerable trajectory. Growth faltering

probably begins during fetal development and not only are these children at high risk of mortality in their first few months of life but that risk increases as they age up to 1 year.[8] Further, we have shown that maternal nutritional status is associated with cluster membership with smaller mothers more likely to have children in the highest vulnerability trajectories. Interventions to address fetal development and women's health including multiple micronutrient supplementation, oral or intravenous iron for anemia, and balanced energy protein supplementation are all likely to have impacts on the prevalence of extremely vulnerable newborns.[42–45]

Three clusters had increasing vulnerability trajectories in the first 6 months of life. Identifying these children should be a high priority given the much higher overall mortality rate in that period compared to older infancy and childhood. In addition to the children born small and preterm, children born to mothers with little or no education are much more likely to experience increasing vulnerability in this period. For each additional year of maternal education, children were about 80% less likely to be in trajectories that had increasing vulnerability in the first six months than trajectories with flat or decreasing vulnerability. Maternal education is associated with more ANC visits, higher rates of health seeking, total fertility, and overall maternal and child mortality.[46–48] Although maternal education might also be a confounder between vulnerability and other factors like urbanicity or overall availability of healthcare,[48] we did not find a meaningful difference when controlling for household income. Using maternal education to identify children at highest risk of WHZ loss could be used to target preventative interventions like probiotics that help to prime infants' enteric systems to absorb more nutrients from breastmilk.[49,50]

Recovery from low HAZ is rare.[26] This analysis supports previous findings that most children will experience decreasing HAZ values in their first two years of life.[8,26] Although all clusters experienced declining HAZ, the decline was much less pronounced in one cluster. Children were more likely to belong to this cluster if they were born term and/or large in length than clusters with greater declines in HAZ in the first two years of life. Although we did not find that maternal age predicted cluster membership, maternal age might be associated with more living children and higher parity. Another study found that infants born later in birth order had lower length-for-age than those born earlier,[7] but in this analysis there wasn't a statistically significantly different odds of belonging to clusters with greater declines in HAZ. Other studies have suggested that young maternal age is associated with early childhood stunting, so there may be some other mechanism. [51,52] Children who have lower HAZ in early childhood have worse prospects for educational and economic attainment.[8,21,53]

Severe acute malnutrition, frequently defined by WHZ status, needs immediate medical attention.[41,54] The WHO recommends that children who have WHZ <-3 receive a course of treatment to recover from the most immediate negative outcomes like death due to malnutrition.[41] This analysis suggests that the most critical period of declines in WHZ occurs at 6 to 12 months, largely consistent with other research based on the HBGDki dataset.[24] Fitted WHZ trajectories in this analysis tended to have an inflection in trend at six months when WHZ stopped increasing or started decreasing. A possible mechanism is increased pathogen exposure during introduction of complementary foods after the recommended period of exclusive breastfeeding or due to an infant being exposed to more of their environment as they become increasingly mobile through crawling.[37] We did not identify any factors that predicted membership in the trajectories that did not experience WHZ loss at 6 months. It is unlikely that exclusive breastfeeding in the first six months of life explains why some children have WHZ recovery or maintenance, however.[38,39] Beyond being born small or preterm, boys and children born to mothers with low body mass index and mid-upper arm circumference are at higher risk of rapid deterioration in WHZ making them more vulnerable to suffering from SAM and all-cause mortality. Identifying those children most likely to deteriorate into SAM could lead to community-based prevention and treatment using ready-to-use therapeutic foods (RUTF).[41] Preventing infants from being hospitalized for SAM could reduce strain on health systems and out-of-pocket costs to families.[55,56] Antibiotics are also recommended for children with SAM and have been shown to reduce the risk of all-cause mortality when used in mass distribution, prophylactic programs.[41,57] Similarly, identifying children at risk of SAM could be used to target prophylactic antibiotic treatment without giving it to entire communities, perhaps reducing the risk of resistance from overuse in populations that might not benefit from them.

Limitations

There are a few important limitations to this analysis. We included children in treatment arms from interventional studies in our estimates of the risk of all-cause mortality due to HAZ and WHZ because they represented a substantial fraction of all deaths in the dataset (43%) and attempted to account for varying risk of mortality with a fixed effect for being in an intervention and a random effect by study. This choice to include those children may bias our estimates despite the effort to limit that because children receiving interventions are very likely to have a different longitudinal experience in their growth and health outcomes. The interventions in these studies were largely intended to affect childhood macro- and micronutrient intake (22 studies) including the Zvitambo study of a single dose of vitamin A to prevent vertical transmission of HIV (899 study deaths).[58] We decided that including these deaths in

our analysis was critical to a sufficient sample size and, like in the case of Zvitambo, we determined that the intervention was unlikely to substantially affect the relationship between growth and mortality risk. It is possible to derive many different latent class trajectory models from researcher-defined settings including prior number of clusters, model structure, and parameters. Identifying a reliable and valid model should incorporate several considerations including statistical ones and biological plausibility.[59]

Fitting multidimensional latent class trajectory models on tens of thousands of individuals is computationally intensive, particularly for GAM models, which was a barrier to extensive model decision testing (2-6 hours per model). However, we tested model specifications more generally with GLM polynomial regression models and implemented structured tests of the influence of prior cluster number selection and different starting points in the maximum likelihood optimization algorithm. These repeated model fitting tests depend on information criterion (AIC, BIC) or log-likelihood statistics which may be relied on too heavily when determining that a particular latent class trajectory model represents real heterogeneity in the sample population.[60]

Our analyses of factors that predict vulnerability cluster membership were based on data that varied between studies. Definitions to assess gestational age, the timing of measuring birthweight, the ways that studies described maternal educational attainment (categorical or continuous), even the way that children's lengths or heights were measured all varied across the studies. Substantial effort by the HBGDki project went into standardizing the datasets to make these kinds of analyses possible, but there were still records with implausible or non-standard values. We attempted to account for unmeasured variation by using random effects for both individuals and studies, assuming that statistical variation could be quantified, in part, by grouping variance by study. A similar potential limitation is related to biological or generational height deficits among women in South Asia.[26] On average, children in this dataset from countries in South Asia were born smaller than their peers from other countries. It is difficult to untangle the meaningful intergenerational link between small mothers and small newborns and the possibility that global growth references do not accurately represent growth of children in South Asia and how these factors might affect the vulnerability of those infants.[8] We included a fixed effect for South Asian countries in the latent class trajectory model to attempt to account for this fact.

Conclusion

We have used a pooled analysis of repeated measurements of childhood height and weight-for-height to construct distinct trajectories in growth and vulnerability to mortality. These novel results provide a

quantitative framework for considering early childhood vulnerability and insights into identifying the children most at risk of poor outcomes. Targeting these children could make existing interventions more effective and help reduce early childhood mortality.

Tables and Figures

Table 1. Summary information of studies used in this analysis.

Study name	Short description	Study population	Intervention	Years	Country	Children	Anthropometric measurements	Child-days	Deaths
Bangladesh NIH Cryptosporidium Cohort Study	Natural history of Cryptosporidiosis in slum-dwelling children: association with severe malnutrition	Slum-dwelling newborns in Mirpur and Mirzapur	No intervention	2014-2021	BGD	742	6,782	443,229	-
Birth cohort in Gabon	Birth weight, growth, nutritional status and mortality of infants from Lambaréné and Fougamou in Gabon in their first year of life	Infants recruited in Fougamou in Gabon from a birth cohort of a malaria in pregnancy clinical trial	No intervention	2009-2012	GAB	344	912	108,377	-
Birth cohort study in Burkina Faso	Anthropometry at birth and at age of routine vaccination to predict mortality in the first year of life: A birth cohort study in Burkina Faso	Birth cohort recruited at four health facilities within Bansalogho District	No intervention	2004-2005	BFA	1,076	12,104	360,210	81
Caplow	Journey through baby birth and newborn survival	Pregnant mothers and infants in the first month of life in Rehri Goth community	No intervention	2020-	PAK	3,572	7,144	84,453	14
Child Malnutrition and Infection Network	7 longitudinal cohort studies of early childhood in low- and middle-income countries	7 longitudinal infant cohorts	No intervention	1985-1998	BGD, BRA, GNB, PER	1,950	19,781	895,839	-
Childhood Acute Illness and Nutrition	Childhood Acute Illness and Nutrition Hospitalization Cohort Study	Children, 2-23 months of age, admitted to the hospital for reasons other than trauma, poisoning or surgery, but without an underlying condition	No intervention	2016-2019	BGD, KEN, MWI, PAK, UGA	1,323	4,891	161,439	41
CMC Vellore Birth Cohort 2002	Rotavirus seasonality and age effects in a birth cohort study in Vellore	Birth cohort in urban Vellore	No intervention	2002-2006	IND	371	6,453	223,174	-
DIVIDS	Randomised Controlled Trial to Evaluate the Preventive Effect on Mortality and Serious Morbidity/ Hospitalisations of Daily Vitamin D Supplements in Small for Gestational Age Term Infants	Children who are not severely malnourished, anemic, or acutely or chronically ill, but are small for gestational age	Nutritional	2007-2016	IND	1,263	4,416	116,298	8
EPI Linked Vita A	Vitamin A supplementation	Mother-Infant pairs	Nutritional	1995-1995	IND	3,615	13,570	1,085,180	71
Fetal and Neonatal survival	Pregnancy rate and outcomes in rural eastern Ethiopia- Fetal and Neonatal survival	All married/widowed/divorced women of reproductive age	No intervention	2009-2010	ETH	828	3,453	17,881	24
GEMS1	Global Enteric Multicenter Study Moderate-to-Severe diarrhea	Children presenting to study hospital with moderate to severe diarrhea and age/sex matched-controls	No intervention	2006-2009	GMB, MLI, MOZ, KEN, IND, BGD, PAK	14,037	28,074	918,052	180
GEMS1A	Global Enteric Multicenter Study Less-Severe diarrhea	Children presenting to study hospital with less severe diarrhea and age/sex matched-controls	No intervention	2006-2009	GMB, MLI, MOZ, KEN, IND, BGD, PAK	8,833	17,666	597,038	-

Study name	Short description	Study population	Intervention	Years	Country	Children	Anthropometric measurements	Child-days	Deaths
Growth Monitoring Study, Nepal	Monthly monitoring of newborn infants in Dhanusha district through age 24 or 25 mo	Newborns in Dhanusha District	No intervention	2012-2014	NPL	576	6,484	324,268	5
Guatemala birth cohort	Prevalence and Predictors of Malnutrition among Guatemalan Children at 2 Years of Age	Birth cohort of children born in San Lucas Toliman	No intervention	2008-2013	GTA	1,255	9,215	542,848	-
GWG ARG	Multi-central study on weight gain and guidelines of Food selection during gestation and its impact on the Newborn	pregnant women over 19 years of age, without concomitant pathologies, with singleton pregnancies and parity of 0 to 5, non-smokers or with a habit of no more than 5 cigarettes a day	No intervention	2005-—	ARG	1090	63	260	-
iLiNS-DOSE	Randomised controlled trial of growth effects of long-term complementary feeding of infants with different doses and formulations of high-energy, micronutrient fortified lipid-based nutrient supplements (LNS)	Rural children	Nutritional	2009-2011	MWI	1,653	4,842	660,303	54
iLiNS-DYAD-Ghana	Efficacy of small-quantity lipid-based nutrient supplements (SQ-LNS) consumed by women during pregnancy and the first 6 months postpartum, and by their infants from age 6 to 18 months	Healthy newborns	Nutritional	2009-2014	GHA	1,153	5,218	578,509	-
iLiNS-DYAD-Malawi	Supplementing maternal and infant diet with high-energy, micronutrient fortified Lipid-based Nutrient Supplements (LNS)	Women with neonates	Nutritional	2011-2015	MWI	1,147	4,056	601,536	36
INCAP GTA	Institute of Nutrition of Central America and Panama: nutrition supplementation longitudinal next generation study	Offspring of child participants of a village-level nutrition intervention randomized trial	No intervention	1996-2007	GTM	734	6,321	276,928	-
Influence of EBF on adolescent and adult mother's postpartum weight loss and infant growth.	Effects of breastfeeding on weight loss and recovery of pregestational weight in adolescent and adult mothers in Mexico.	Adolescent and adult pregnant women and their children	No intervention	2005-2010	MEX	82	620	26,870	-
Influence of Leptin concentration in serum on adolescent and adult mother's postpartum weight	Influence of Leptin concentration in serum on adolescent and adult mother's postpartum weight loss and infant growth.	Adolescent and adult pregnant women and their children	No intervention	2009-2016	MEX	168	672	15,120	-

Study name	Short description	Study population	Intervention	Years	Country	Children	Anthropometric measurements	Child-days	Deaths
loss and infant growth.									
Leptin GWG	To evaluate the effect of leptin and other selected variables on gestational weight gain (GWG) according to pre-gestational body mass index (BMI).	pregnant women with 20–40 years of age between 5 and 13 weeks of gestation	No intervention	2009-2011	BRA	296	216	13,507	-
Low birthweight infant feeding exploration study (LIFE)	Low birthweight infant feeding exploration study (LIFE)	Low birthweight infants recruited at hospitals	No intervention	2019-2022	TZA, MWI, IND	1,075	8,247	188,048	-
Lungwena Child Nutrition Intervention Study 5	A single-centre, randomised, single-blind, parallel group clinical trial in rural Malawi, testing the growth promoting effect of long-term complementary feeding of infants with a high-energy, micronutrient fortified spread	Rural infants aged 6 mo, without severe stunting (HAZ < -2.8), in Mangochi district	Nutritional	2008-2014	MWI	798	4,246	360,312	-
Malaria Prevention PNG	Intermittent preventive treatment with azithromycin-containing regimens for the prevention of malarial infections and anaemia and the control of sexually transmitted infections in pregnant women in Papua New Guinea	Pregnancy women in 14-26 week of gestation with Age between 16 years to 49 years.	Pharmaceutical	2009-2013	PNG	2793	79	2,028	5
Malawi-Egg	An Evaluation of Eggs During Complementary Feeding in Rural Malawi	Children aged 6–9 months.	Nutritional	2018-2021	MWI	600	1,776	106,665	-
MAL-ED Study	Global study of enteropathy and its effects on anthropometry from birth through age 2 years	Multinational birth cohort	No intervention	2009-2017	BGD, BRA, IND, NPL, PAK, PER, TZA, ZAF	1,697	38,948	1,135,733	-
Mama Sweet potato Action for Security and Health in Africa (Mama SASHA) project	Cohort study of the impact of an integrated agriculture, nutrition and health intervention on the Vitamin A and health status of mothers and their infants from pregnancy through 9 months postpartum	Pregnant women from the 8 facilities in mid pregnancy (10-24 weeks)	Nutritional	2012-2014	KEN	362	724	50,469	-
MORDOR	Cluster randomized trial of mass azithromycin distribution	Cluster-randomized trial among 30 rural communities in the Boboye and Loga departments in Niger	Pharmaceutical	2014-2020	NGR	979	2,086	331,632	38
MothersGift	Designs of two randomized, community-based trials to assess the impact of influenza immunization during pregnancy on respiratory illness among pregnant women and their	Married women between 15 and 40 years of age who were identified as pregnant with gestational age between 17 and 34 weeks.	Pharmaceutical	2011-2014	NPL	2,114	4,228	378,406	20

Study name	Short description	Study population	Intervention	Years	Country	Children	Anthropometric measurements	Child-days	Deaths
	infants and reproductive outcomes in rural Nepal								
MyHealth	The relationship between wasting and stunting in Cambodian children: Secondary analysis of longitudinal data of children below 24 months of age followed up until the age of 59 months	Open cohort study from six districts in Cambodia enrolling all women who were pregnant or lactating	No intervention	2016-2018	KHM	4,473	14,192	1,404,763	-
NIH Birth Cohort Study	Children at birth in Mirpur neighborhood, Dhaka	Birth cohort	No intervention	2008-2015	BGD	591	6,145	327,460	-
Optimal Infant Feeding Practices	Cluster randomized trial of the promotion of optimal complementary feeding practices	Infants in rural Haryana	Educational	1999-2001	IND	1,457	9,287	719,577	31
Pith Moromo 2: Cohort	Pith Moromo 2: Cohort to Study Health Consequences of Food and Nutrition Insecurity During Pregnancy and Lactation	A cohort of 371 pregnant HIV-infected and -uninfected women (ratio 1:1) were recruited from 7 rural and urban clinics in Nyanza, Kenya. Participants were followed from =30 weeks pregnancy until 9 months postpartum.	No intervention	2014-2017	KEN	263	1,378	132,864	5
Prenatal LNS	Prenatal Lipid-Based Nutrient Supplements Affect Maternal Anthropometric Indicators Only in Certain Subgroups of Rural Bangladeshi Women.	Pregnant women at <=20 wk gestation.	Nutritional	2011-2015	BGD	3,005	6,010	6,385	52
Prenatal Nutrition and Psychosocial Health Outcomes (PreNAPS)	To determine the differential impacts of food insecurity on gest. weight gain and prenatal depression, and b) to elucidate the mechanisms underlying the relationship between food insecurity and weight gain and/depression among HIV infected and HIV uninfected pregnant women in Gulu, Northern Uganda.	Pregnant women with gest. Age from 10 weeks to 26 weeks.	No intervention	2013-2014	UGA	203	566	19,245	-
PROBIT Study	Promotion of Breast Feeding Interventional Trial	Children	Nutritional	1996-1998	BLR	21	44	5,691	-
PROVIDE	Performance of Rotavirus and Oral Polio Vaccines in Developing Countries	Birth cohort	Vaccine	2011-2017	BGD	657	9,156	387,547	4
RETAPP Pneumonia	A double blind community-based randomized trial of amoxicillin versus placebo for fast breathing pneumonia in children aged 2-59 months in Karachi, Pakistan (RETAPP)	Children with cough or fast breathing for <14 days, but no danger signs for pneumonia	Pharmaceutical	2014-2018	PAK	4,002	19,866	58,985	6
SAS-FoodSuppl	Randomized Food Supplementation Trial Ages 4-12 Months	Infants, age 4 months, from an urban slum in Delhi	Nutritional	1995-1996	IND	402	2,197	160,023	4

Study name	Short description	Study population	Intervention	Years	Country	Children	Anthropometric measurements	Child-days	Deaths
Study of Biomarkers for Environmental Enteropathy	Monthly anthropometry since birth, daily symptoms, and biomarkers for environmental enteropathy in blood, urine, and stool	Community based cohort of children aged 6 and 9 mo in rural Matiari District	No intervention	2012-2013	PAK	379	8,382	242,995	3
Tanzania Child 2 Study	Zinc and micronutrients	Infants born to HIV-negative women	Nutritional	2000-2002	TZA	2,317	28,934	869,841	-
UZ-MatNutri	Effect of multi-micronutrient supplementation on gestational length and birth size: a randomized, placebo-controlled, double-blind effectiveness trial in Zimbabwe	Women between 22 and 36 wk of gestation	Nutritional	1996-1997	ZWE	623	1,447	40,040	8
Vietnam maternal food supplementation	Effect of maternal prenatal food supplementation, gestational weight gain, and breast-feeding on infant growth during the first 24 months of life in rural Vietnam	Women recruited when they registered to marry from 29 communes of Cam Khe district	Nutritional	2011-2015	VNM	236	2,210	154,479	-
Vit B12 Supp Trial	Vit B12 Supp Trial	Children	Nutritional	2010-2010	IND	554	1,108	100,447	-
VITAL Pregnancy	VITAL Pregnancy	Pregnant Women	No intervention	2014-2018	PAK	945	6,371	164,604	11
WASH Benefits Bangladesh Trial	Cluster-randomised controlled trials of individual and combined water, sanitation, hygiene, and nutritional interventions	Rural children	WASH; Nutritional	2012-2015	BGD	3,252	6,504	1,326,515	-
WASH Benefits Kenya Trial	Cluster-randomised controlled trials of individual and combined water, sanitation, hygiene, and nutritional interventions	Rural pregnant women and infants up to age 3 mo	WASH; Nutritional	2013-2015	KEN	2,244	4,488	819,130	-
WomenFirst	Preconception Women First Trial	Women 16-35 y of age; parity 0-5; expectation to have first or additional pregnancy within next 2 y and without intent to utilize contraception; became pregnant no sooner than 3 months from randomization	Nutritional	2014-2017	COD, GTM, IND, PAK	2,668	685	7,559	8
XJU-RuralChina	Impact of micronutrient supplementation during pregnancy on birth weight, duration of gestation, and perinatal mortality in rural western China: double blind cluster randomised controlled trial	Pregnant women with <28 weeks gestation	Nutritional	2002-2006	CHN	21	42	15,168	23
Zinc Mortality Prevention	Zinc supplementation and infant mortality	Children aged 1-23 mo	Nutritional	2000-2000	IND	1	2	364	6

Study name	Short description	Study population	Intervention	Years	Country	Children	Anthropometric measurements	Child-days	Deaths
Zn Supp for Diarrheal Pneumonia	Zinc supplementation in diarrheal pneumonia	Children in a New Delhi slum	Nutritional	1995-1995	IND	1,499	2,998	178,979	-
Zn Supp IND	Zinc supplementation in children with low birth weight	Hospital born children with low birth weight	Nutritional	2005-2005	IND	1,895	7,499	511,987	-
Zvitambo	Placebo-Controlled Study of a Single Dose of Vitamin A to Prevent Vertical and Horizontal Transmission of HIV	Lactating mothers and their children	Nutritional	1997-2001	ZWE	11,814	53,456	3,686,823	899

Table 2. Relative risk estimates for joint height-for-age and weight-for-height z-scores. Numbers indicate mean relative risk estimates and 95% confidence intervals. Color represents the density of observations in each HAZ and WHZ bin. Yellow indicates that many children fell in each range of growth metrics.

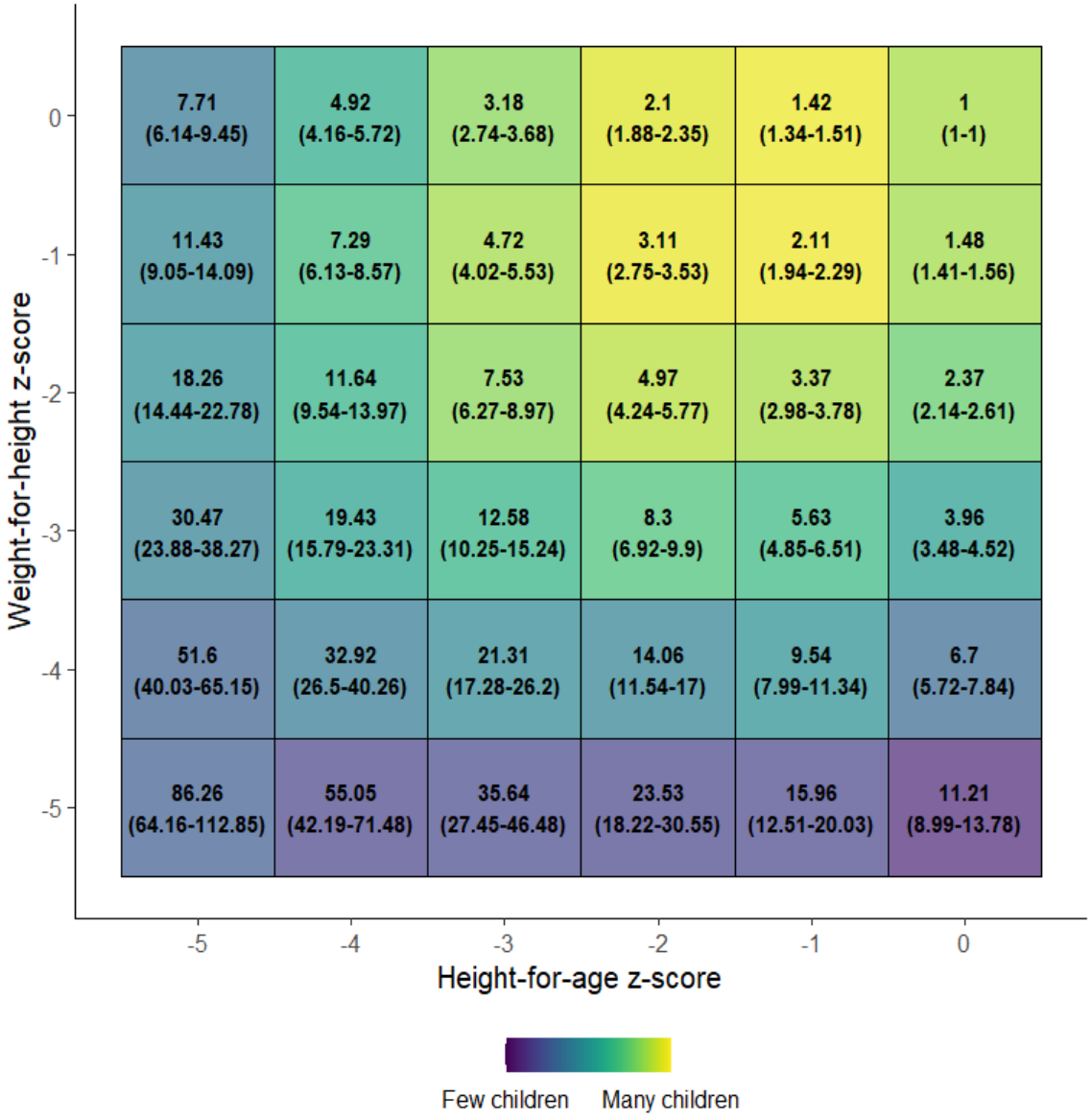


Table 3. Qualitative description of latent class growth trajectory clusters.

Cluster	Level HAZ	Trend HAZ	Level WHZ	Trend WHZ	Level Vulnerability	Trend Vulnerability
Delayed HAZ loss & fast WHZ recovery	Second tallest overall level	Moderate decrease 6 to 18 months and flat 18 to 24 months	Highest starting and overall level	Rapid increase in first 6 months and then mostly flat	Lowest overall	Mostly flat with small increase 6 to 18 months
HAZ maintenance & ongoing WHZ recovery	Tallest level overall	Maintenance or small decrease in HAZ birth to 24 months	Lowest starting level	Rapid increase in first 6 months and increases again 12 to 18 months	Second lowest overall	Decreasing birth to 6 months and 12 to 18 months
Ongoing HAZ loss & WHZ maintenance	Medium starting level	Moderate decrease from 6 to 24 months	Second lowest starting level	Nearly flat through 2 years	Third lowest overall	Flat or small increase
Ongoing HAZ loss & halted WHZ loss	Short starting level	Consistent decrease through 2 years	Moderately high starting level	Slight decrease from 6 to 12 months then flat or recovers	Third highest overall	Moderate at birth and modest increase from 6 to 12 months
Ongoing HAZ loss & fast WHZ loss	Short starting level	Consistent decrease through 2 years	Moderately high starting level	Rapid decline from 6 to 12 months	Second highest overall	High at birth and increase from 6 to 12 months
Delayed HAZ loss & fast WHZ loss	Shortest starting level	Moderate decrease from 6 to 18 months	Moderately high starting level	Rapid decline from 6 to 12 months with small rebound to 2 years	Highest overall	Highest at birth and large increase to 18 months

Figure 1. Risk curves for all-cause mortality by height-for-age and weight-for-height z-scores. Panel A shows the values in relative risk space and Panel B shows the values in log relative risk space. Uncertainty is the 95% confidence interval.

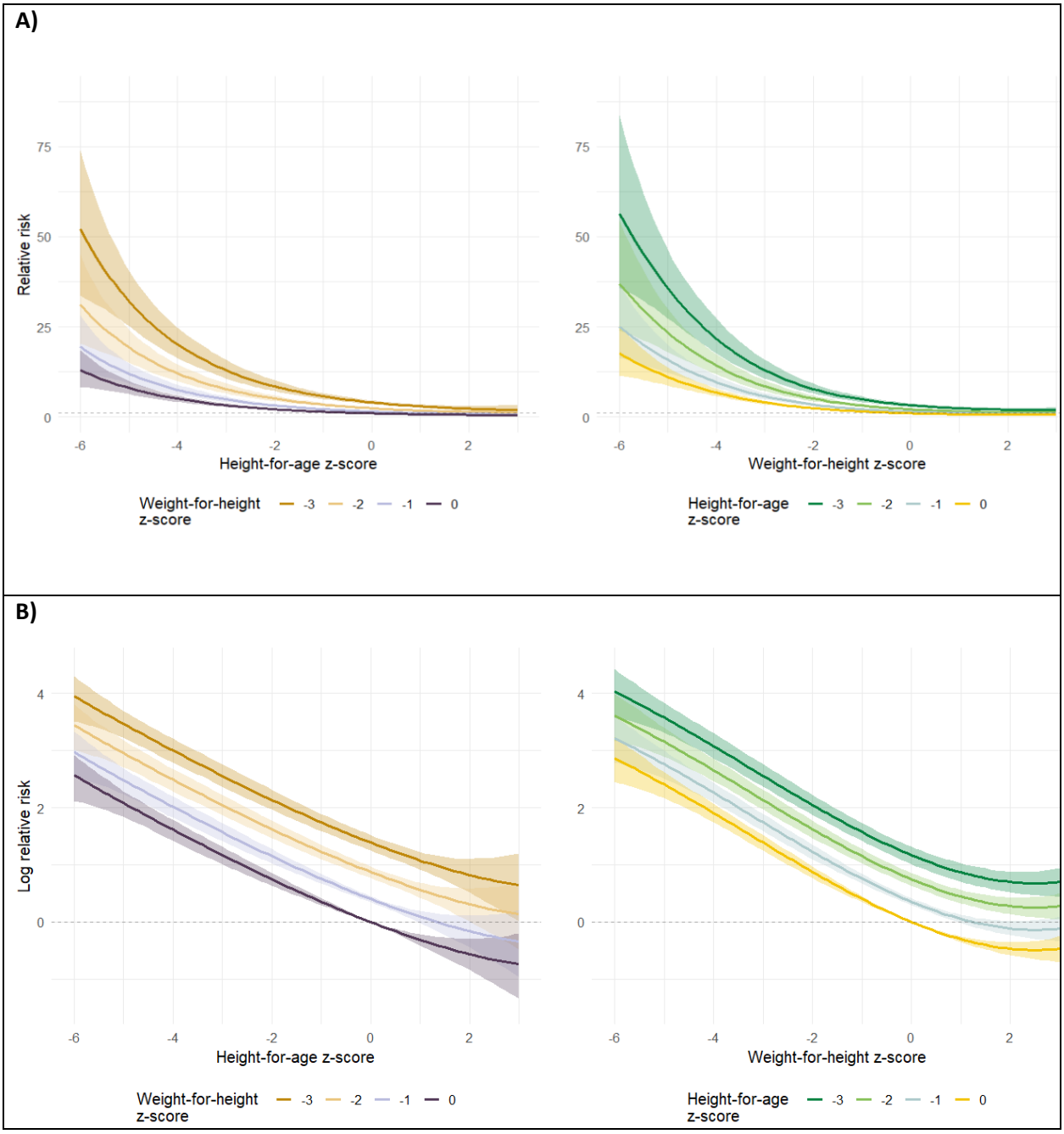


Figure 2. Latent class vulnerability trajectories from birth to 2 years. Uncertainty shown is the 95% confidence interval from the standard error of the mean. Panel A shows the trajectories for height-for-age z-scores and Panel B shows the trajectories for weight-for-height z-scores.

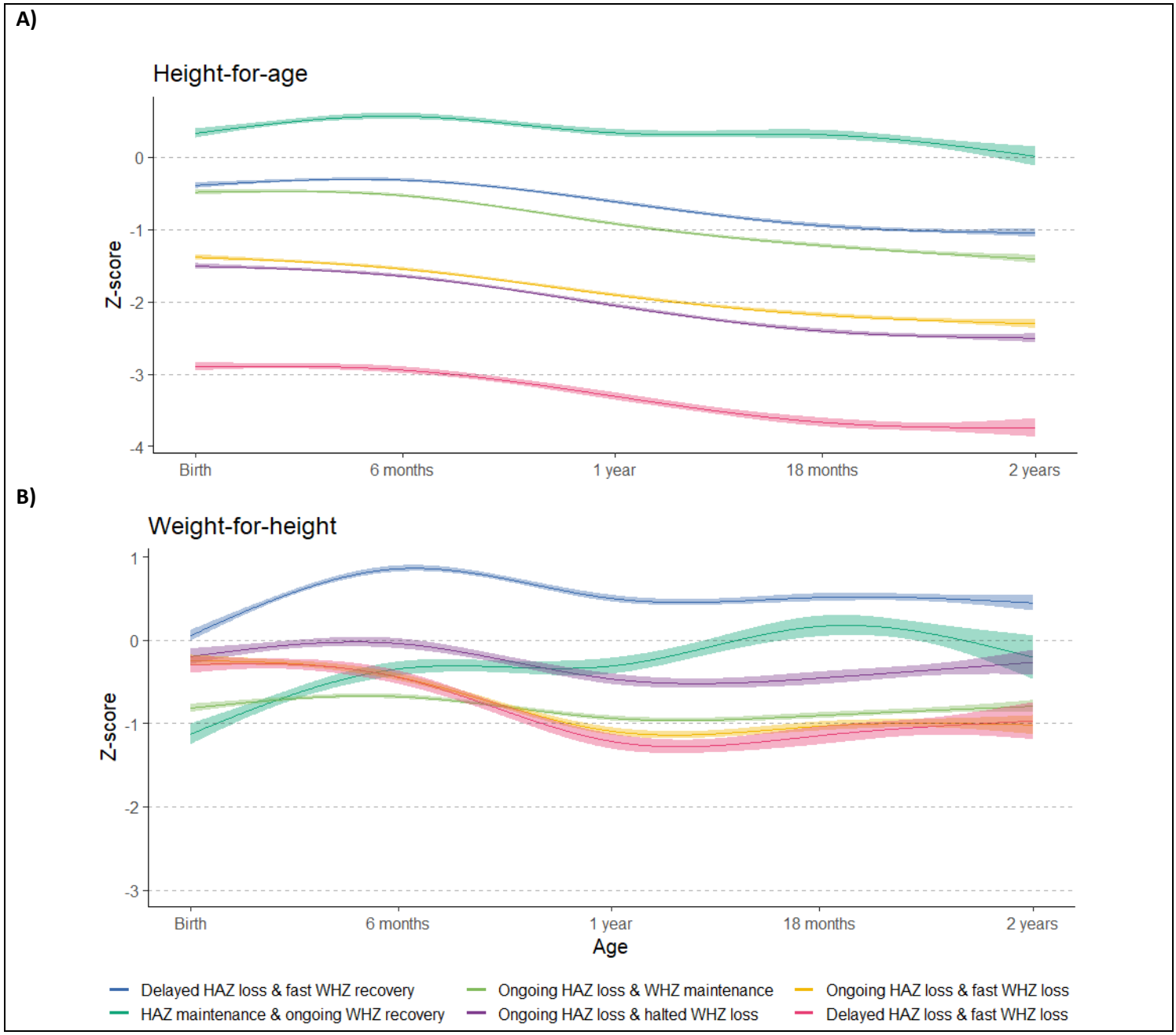


Figure 3. Fitted vulnerability trajectories by cluster membership. Uncertainty shown is the 95% confidence interval from the standard error of the mean.

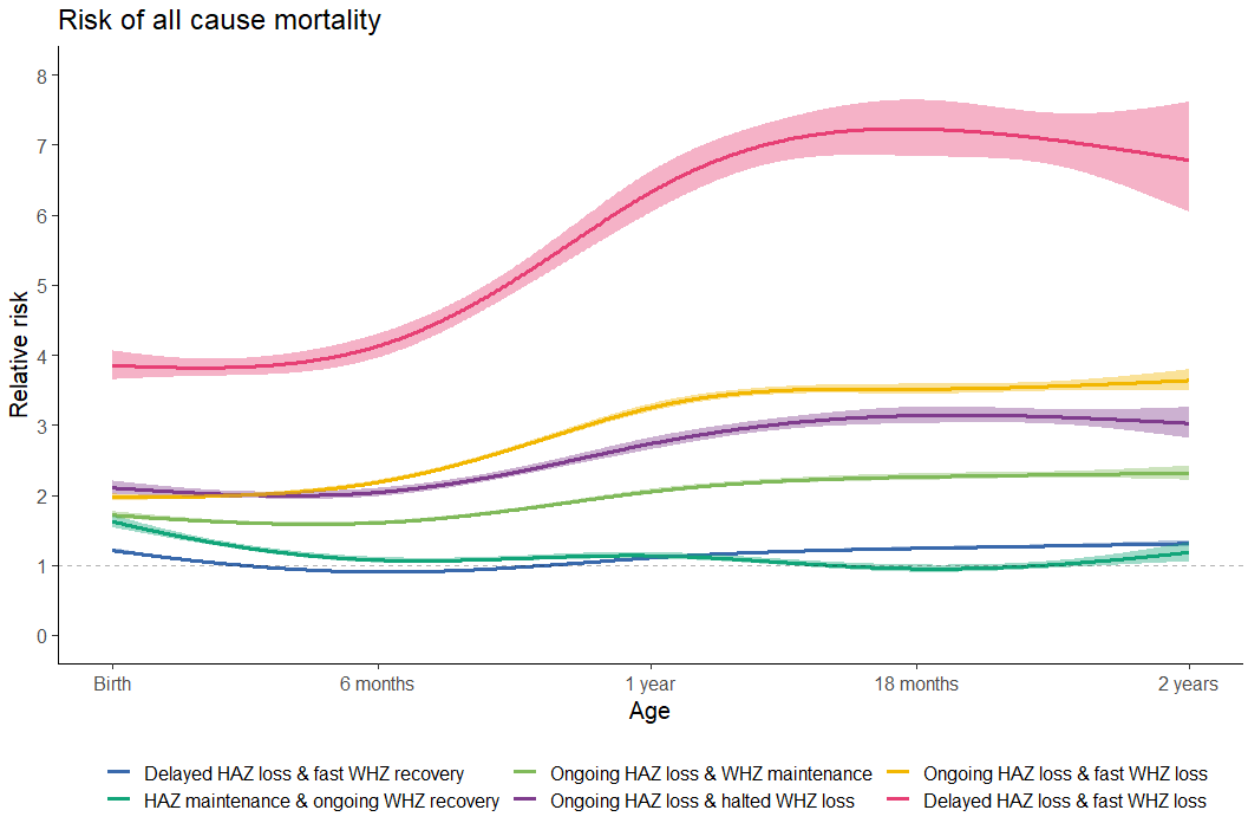


Figure 4. Distribution of cluster membership among 64,581 children.

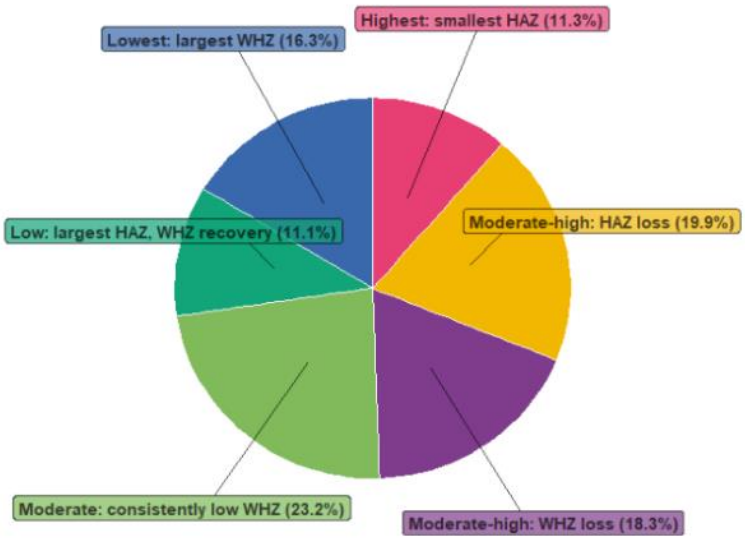
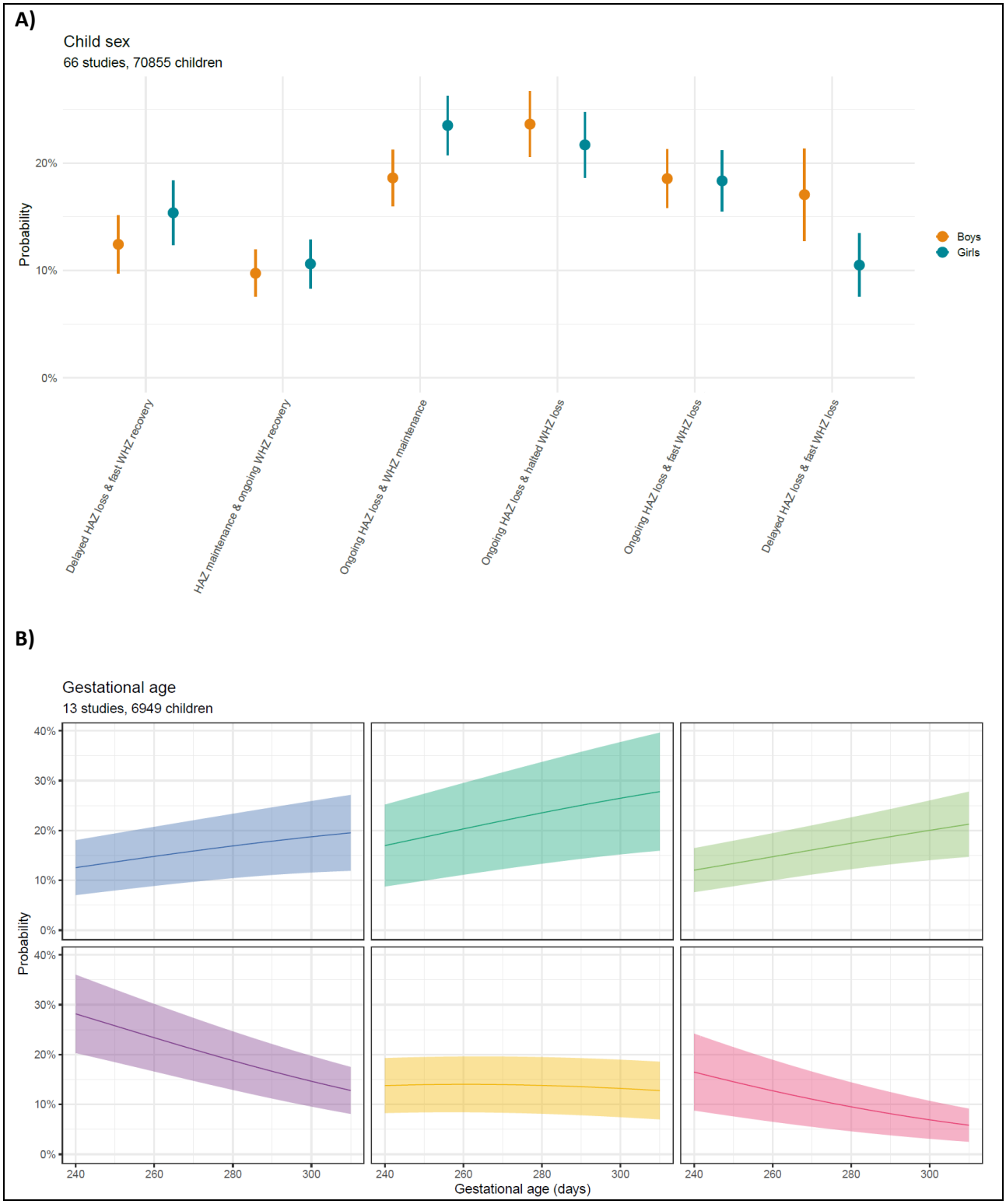


Figure 5. Probability of cluster membership based on child characteristics. Panels A-D show the predicted probabilities for different factors.



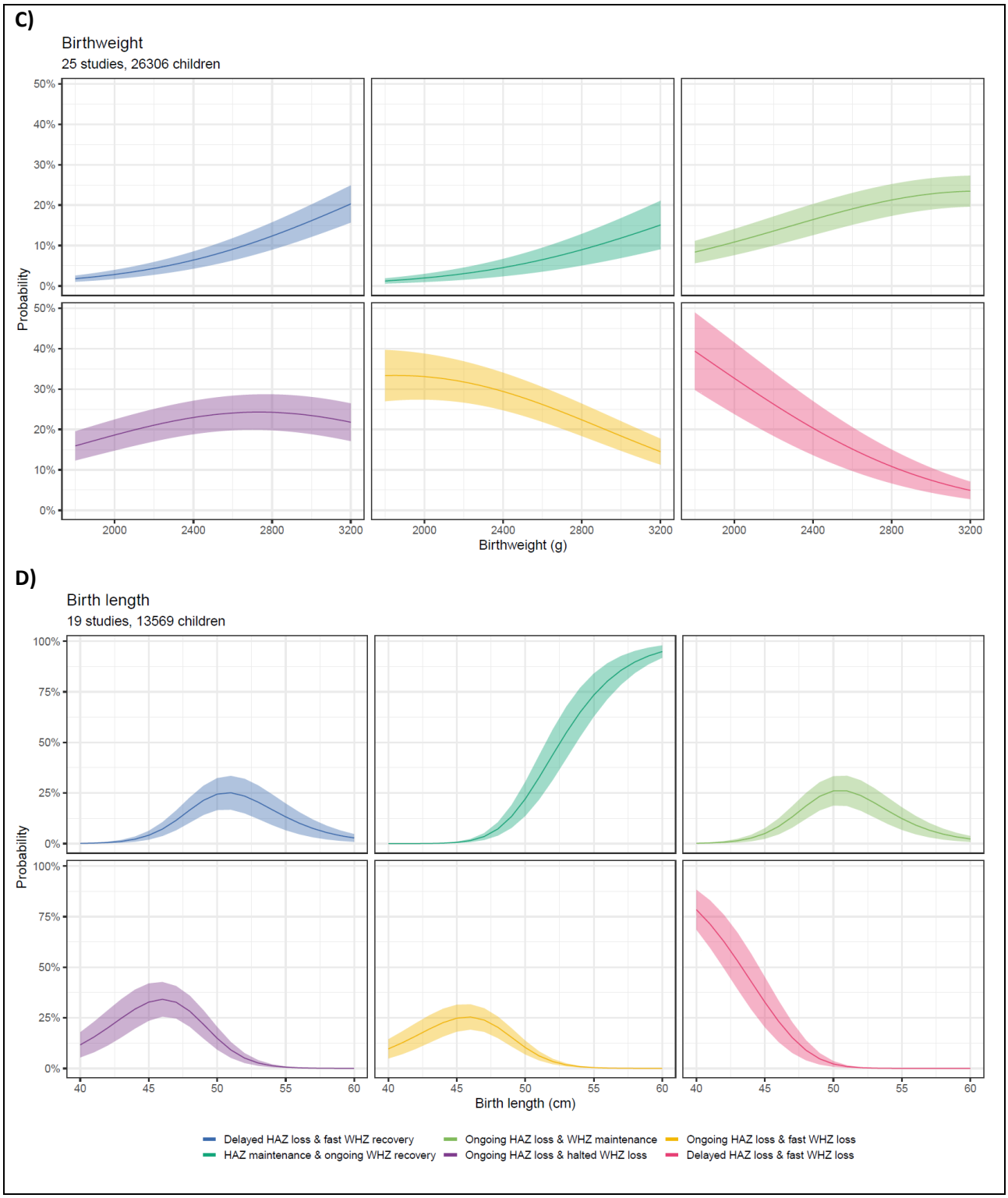
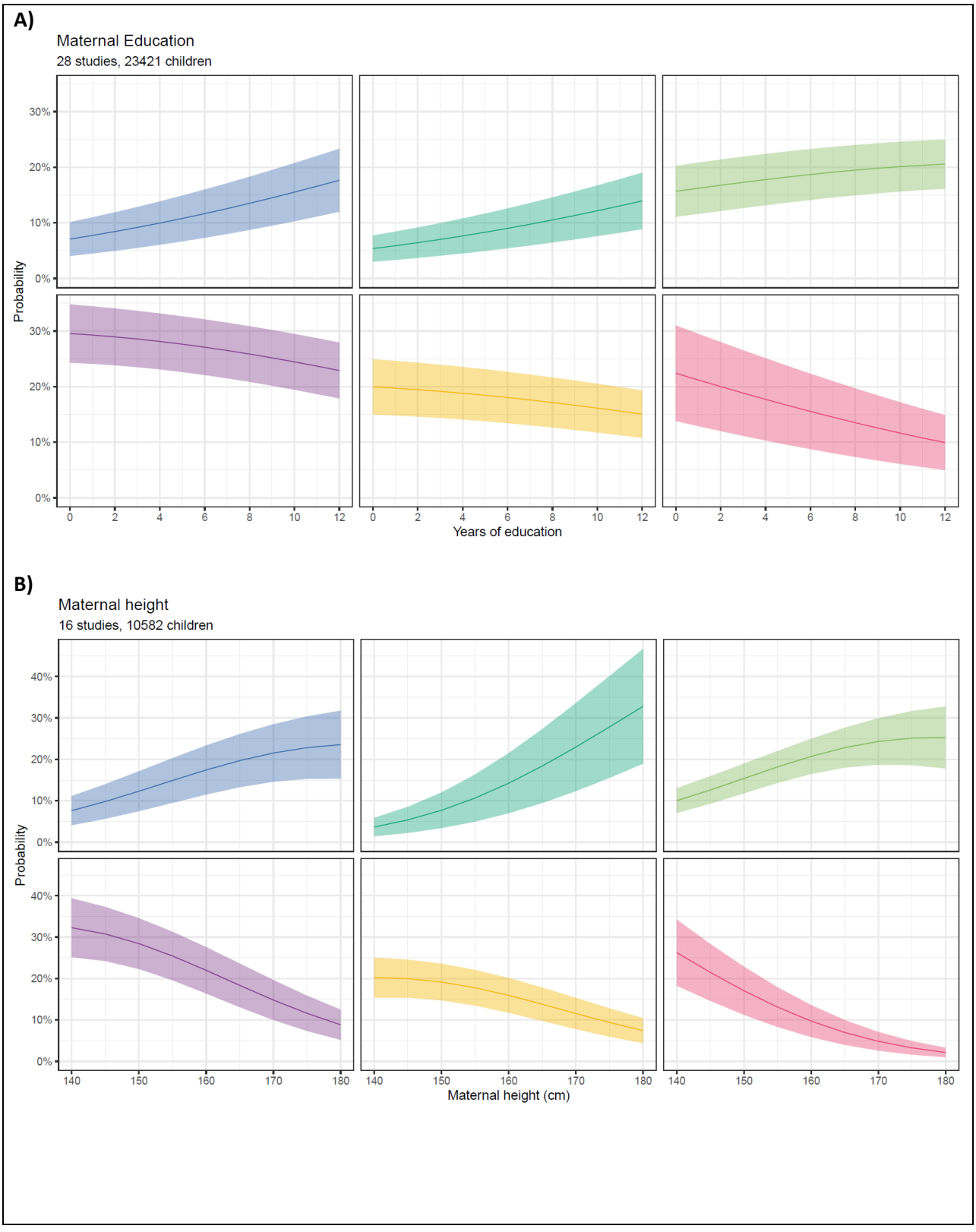
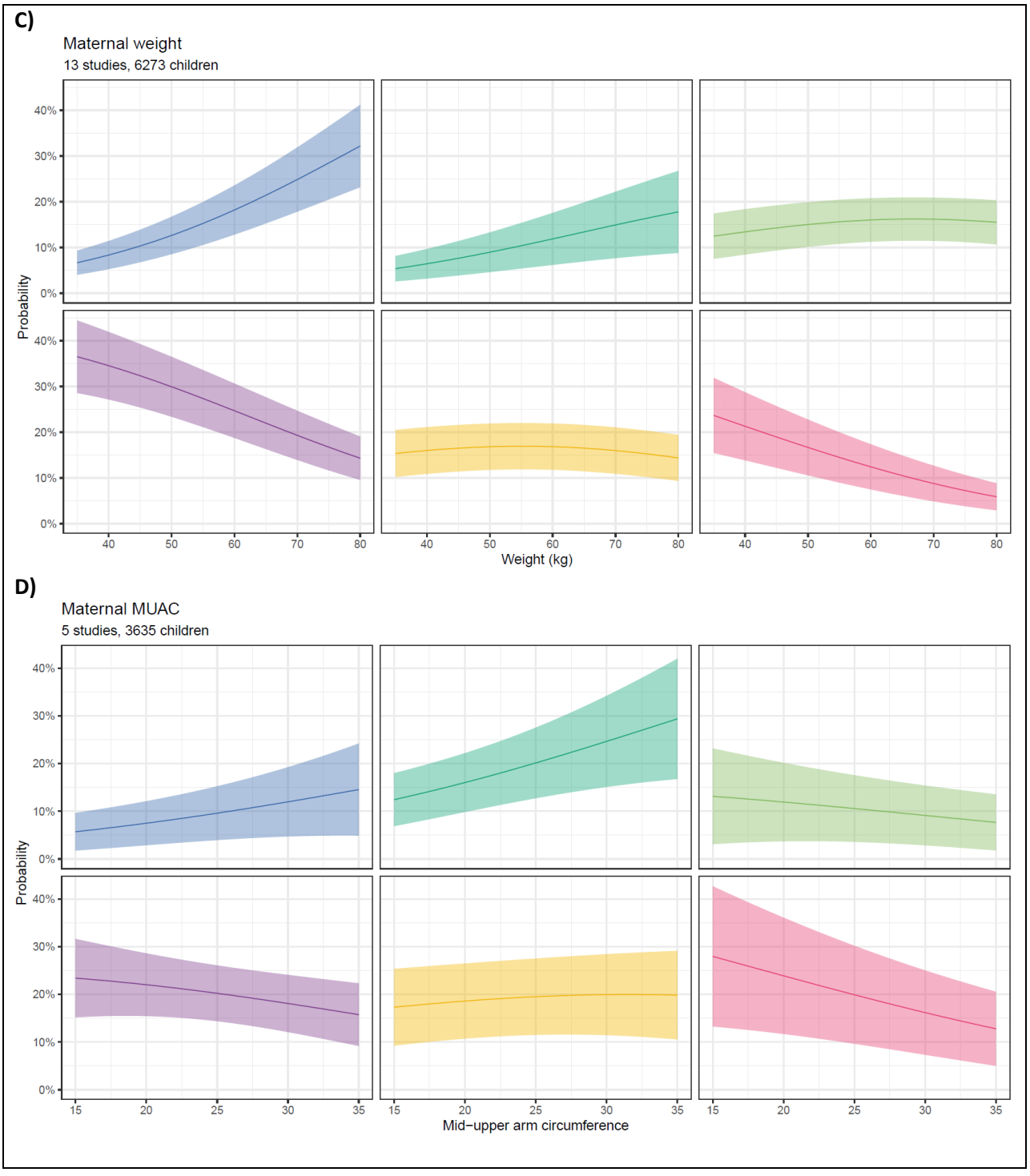

C)
Birthweight
25 studies, 26306 children
Probability
50%
40%
30%
20%
10%
0%
2000
2400
2800
3200
Birthweight (g)
D)
Birth length
19 studies, 13569 children
Probability
100%
75%
50%
25%
0%
40
45
50
55
60
Birth length (cm)
Delayed HAZ loss & fast WHZ recovery
HAZ maintenance & ongoing WHZ recovery
Ongoing HAZ loss & WHZ maintenance
Ongoing HAZ loss & halted WHZ loss
Ongoing HAZ loss & fast WHZ loss
Delayed HAZ loss & fast WHZ loss

Figure 6. Probability of cluster membership based on maternal characteristics. Panels A-D each show the predicted probability for different factors.




C)
Maternal weight
13 studies, 6273 children
Probability
40%
30%
20%
10%
0%
40
50
60
70
80
Weight (kg)
D)
Maternal MUAC
5 studies, 3635 children
Probability
15
20
25
30
35
Mid−upper arm circumference

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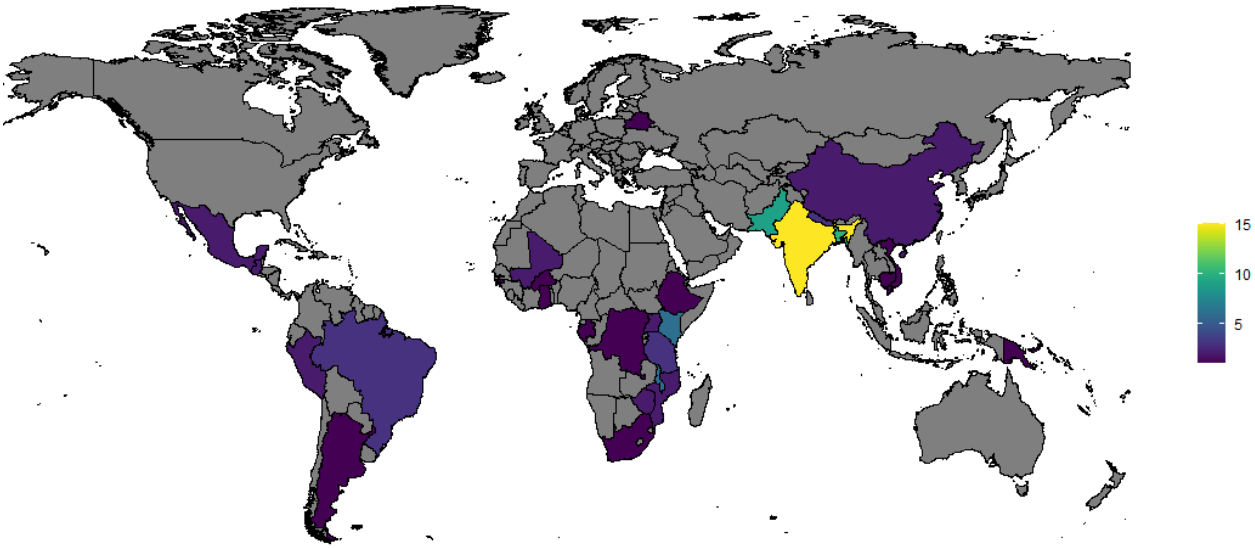
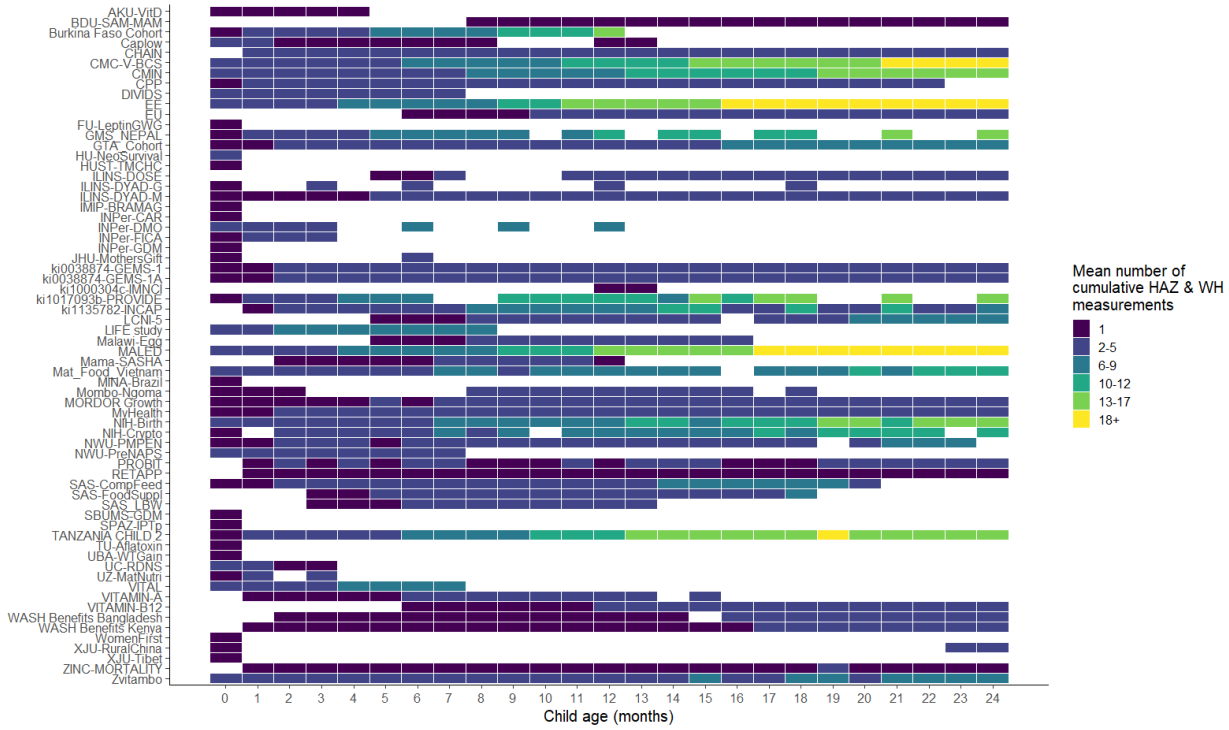
Supplementary information

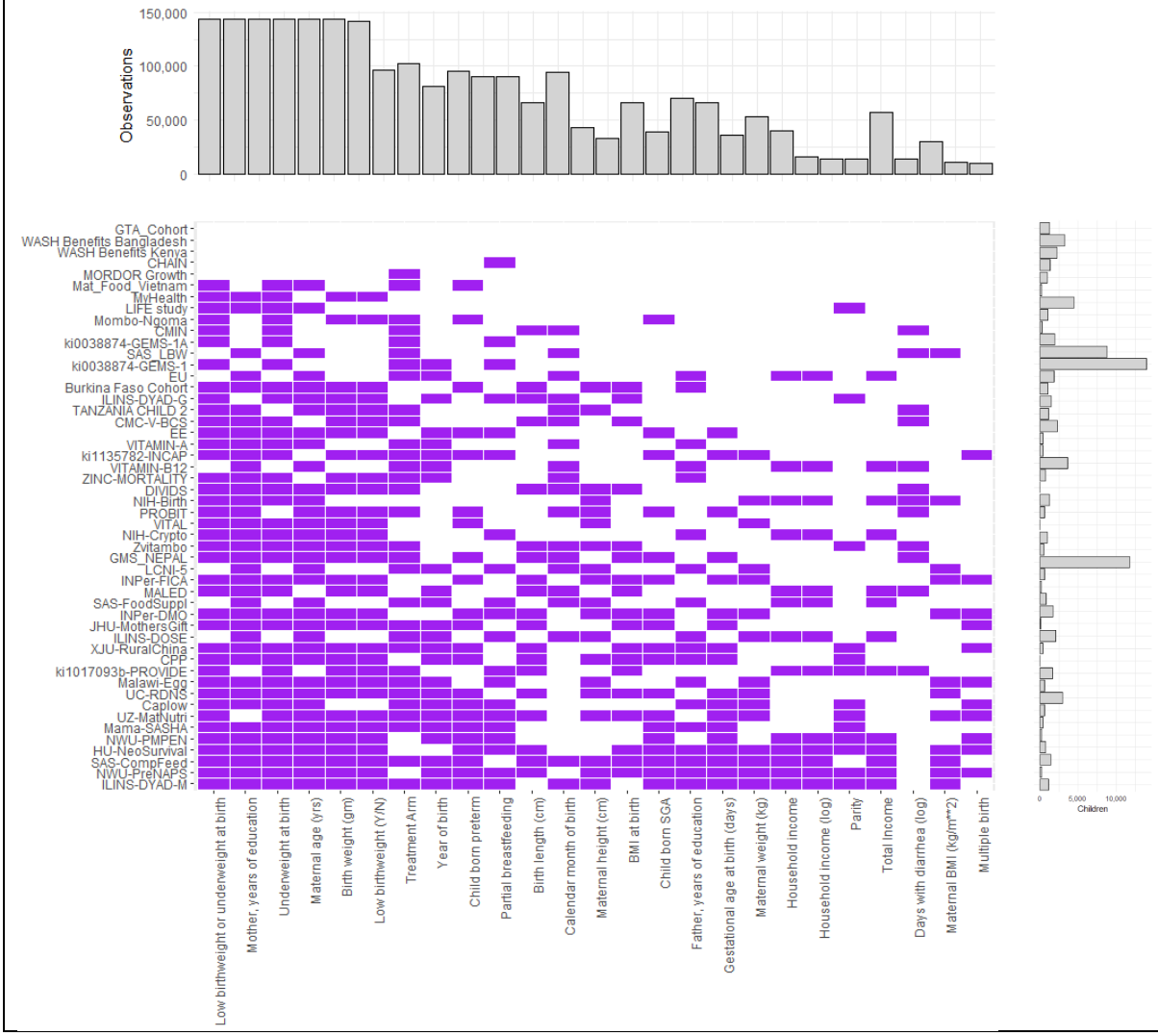
SI Figure 1. Geographical distribution of studies included in pooled dataset.



SI Figure 2. Data sources for fitting latent trajectory classes for height-for-age and weight-for-height z-scores.



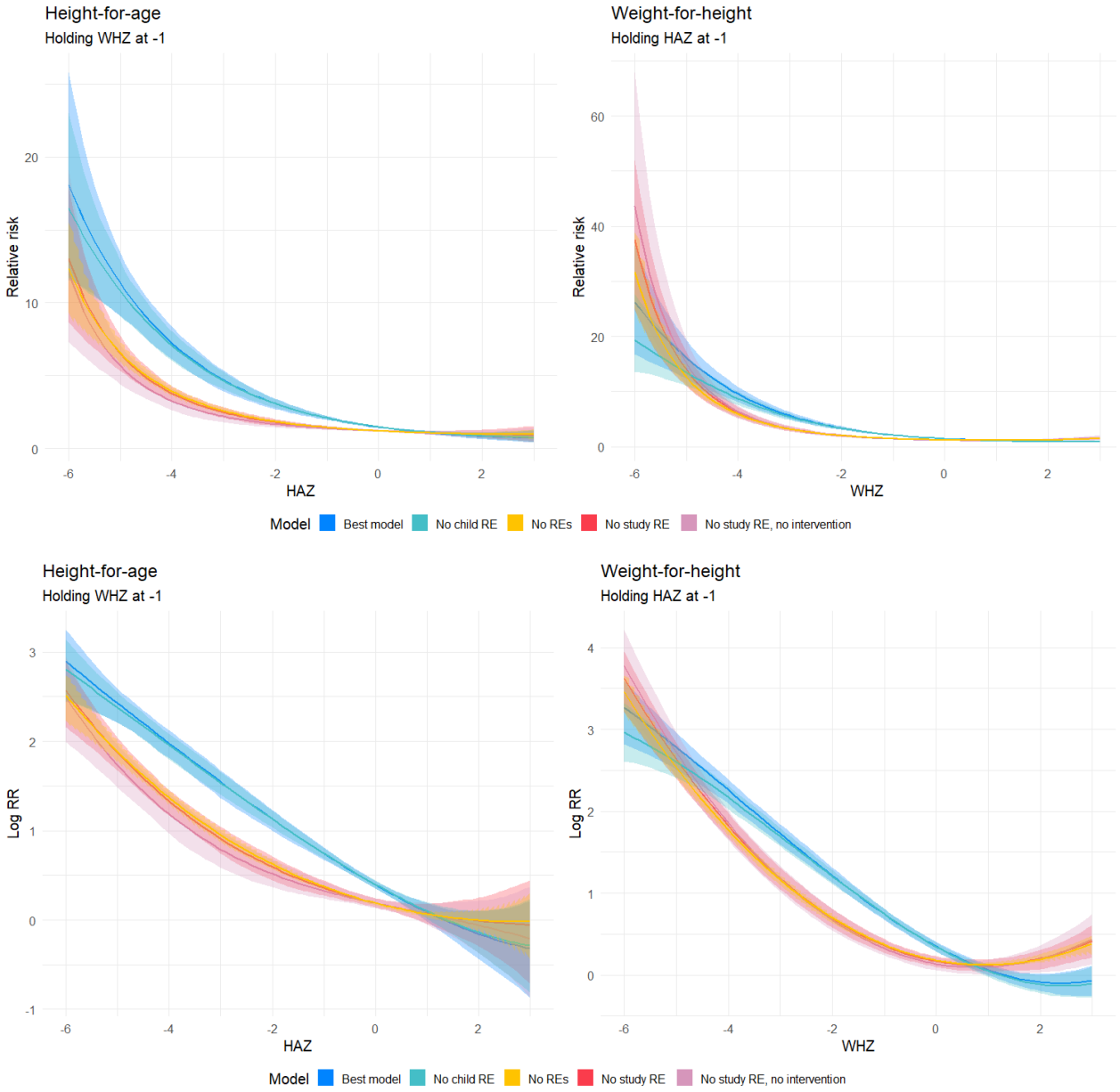
SI Figure 3. Data sources for predicting vulnerability class membership



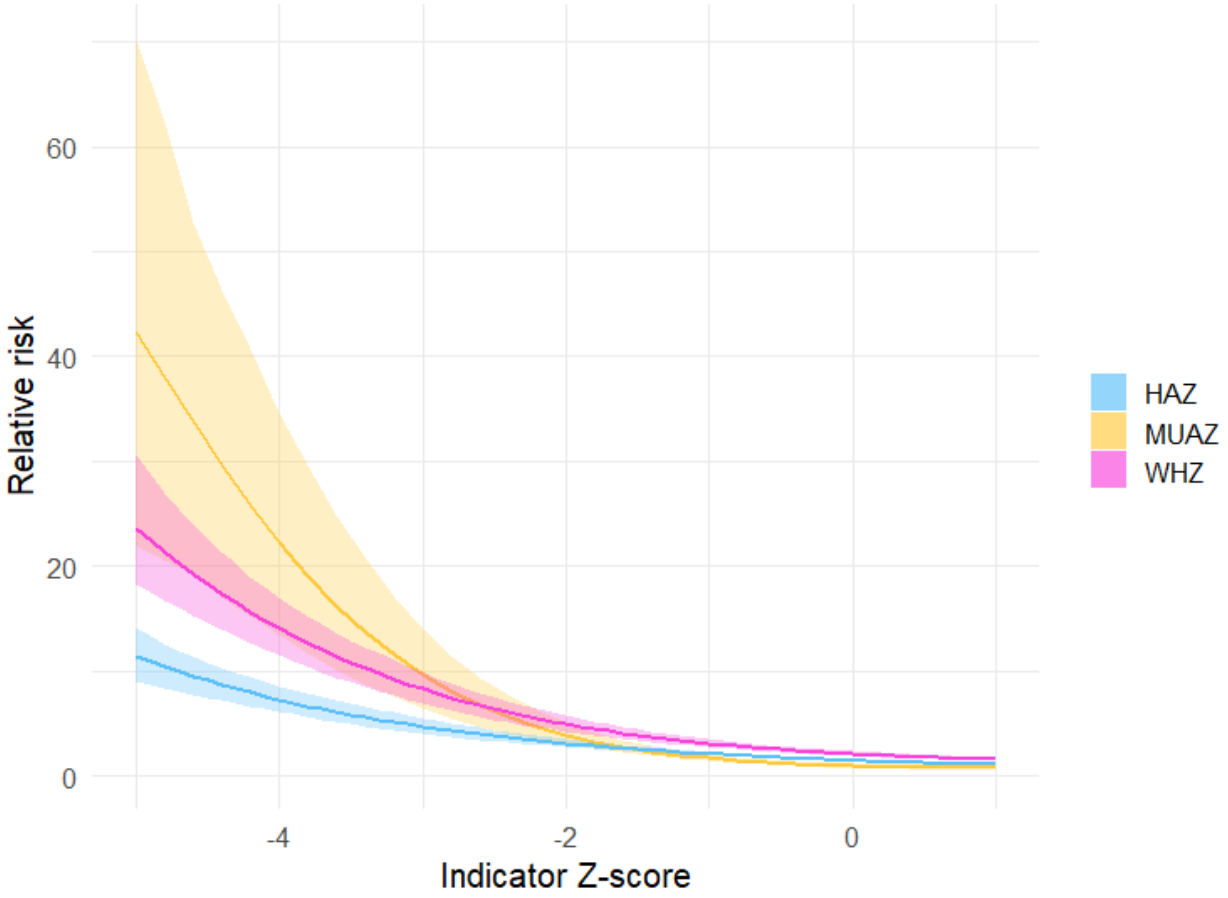
SI Table 1. Fit statistics from mortality incidence model with differing degrees of polynomials for HAZ & WHZ.

Model parameters	AIC	BIC	Log-likelihood
(Intercept), poly(fill_haz, h, raw = T)1, poly(fill_haz, h, raw = T)2, poly(fill_haz, h, raw = T)3, poly(fill_whz, w, raw = T)1, poly(fill_whz, w, raw = T)2, poly(fill_whz, w, raw = T)3	21815.99	21894.42	-10901
(Intercept), poly(fill_haz, h, raw = T)1, poly(fill_haz, h, raw = T)2, poly(fill_haz, h, raw = T)3, poly(fill_whz, w, raw = T)1, poly(fill_whz, w, raw = T)2	21815.86	21883.09	-10901.9
(Intercept), poly(fill_haz, h, raw = T)1, poly(fill_haz, h, raw = T)2, poly(fill_whz, w, raw = T)1, poly(fill_whz, w, raw = T)2, poly(fill_whz, w, raw = T)3	21818.54	21885.77	-10903.3
(Intercept), poly(fill_haz, h, raw = T)1, poly(fill_haz, h, raw = T)2, poly(fill_whz, w, raw = T)1, poly(fill_whz, w, raw = T)2	21818.2	21874.23	-10904.1
(Intercept), poly(fill_haz, h, raw = T), poly(fill_whz, w, raw = T)1, poly(fill_whz, w, raw = T)2, poly(fill_whz, w, raw = T)3	21834.58	21890.61	-10912.3
(Intercept), poly(fill_haz, h, raw = T), poly(fill_whz, w, raw = T)1, poly(fill_whz, w, raw = T)2	21834.35	21879.17	-10913.2
(Intercept), poly(fill_haz, h, raw = T)1, poly(fill_haz, h, raw = T)2, poly(fill_haz, h, raw = T)3, poly(fill_whz, w, raw = T)	22038	22094.02	-11014
(Intercept), poly(fill_haz, h, raw = T)1, poly(fill_haz, h, raw = T)2, poly(fill_whz, w, raw = T)	22042.39	22087.21	-11017.2
(Intercept), poly(fill_haz, h, raw = T), poly(fill_whz, w, raw = T)	22085.65	22119.27	-11039.8

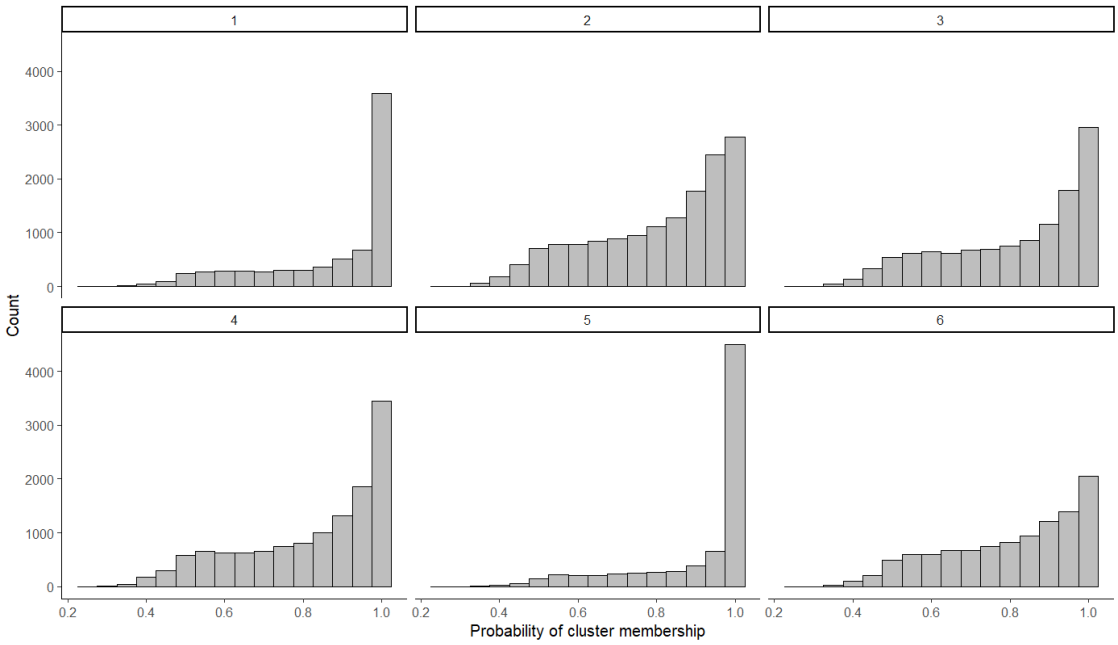
SI Figure 4. Comparing results between full Cox all-cause mortality model and a model dropping children who were in intervention study treatment arms. The best model used in the analysis includes children in intervention and non-intervention arms of trials and includes nested random effects for study/children. That model is compared to separate models without a child random effect, without any random effects, without a random effect for study (but one for children to account for repeated measurements), a model without study random effects and dropping children from intervention arms. Including random effect for study improves the model defined by an analysis of deviance (Chi square test statistic < 1e-15).



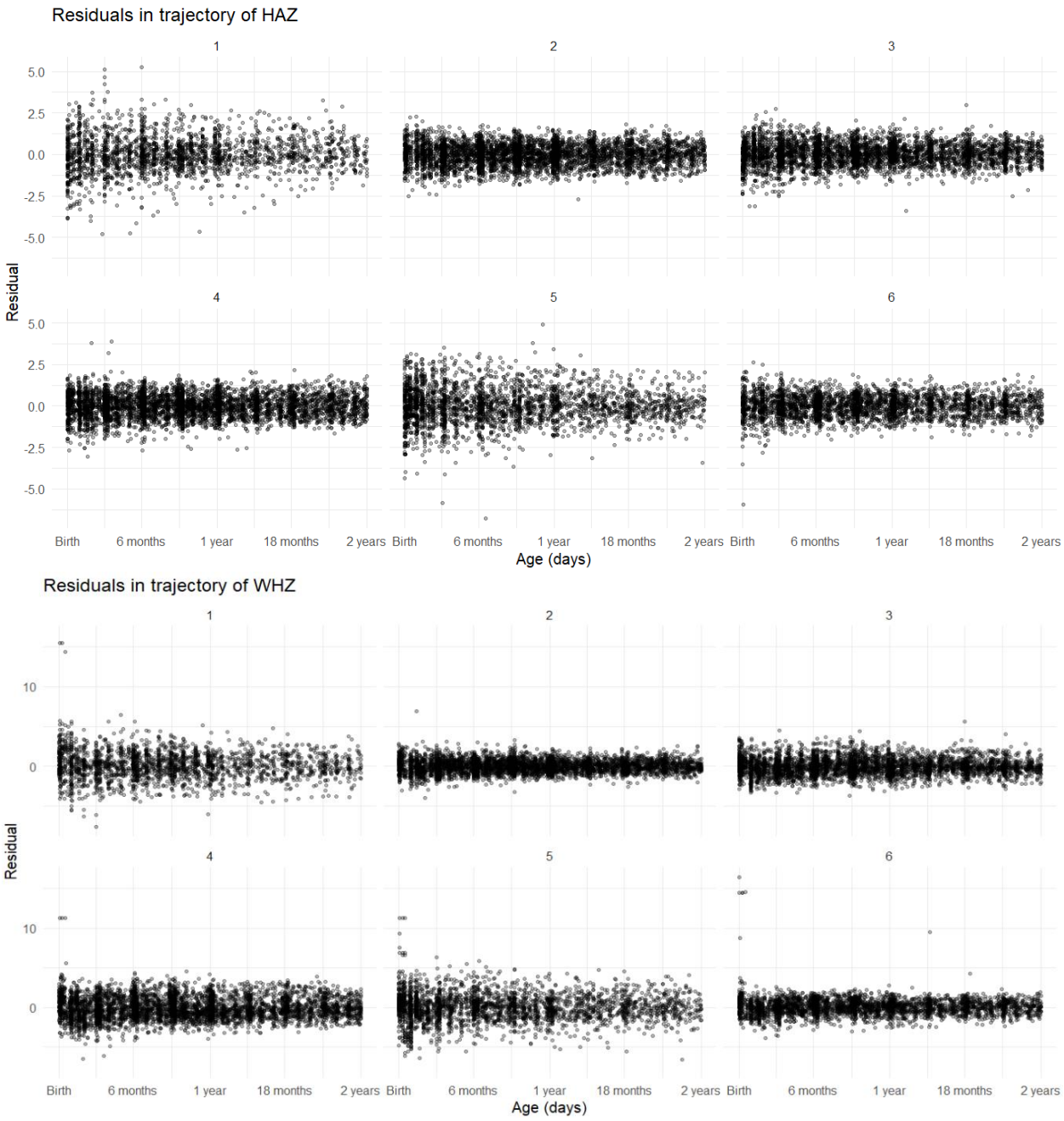
SI Figure 5. Relative risks of all-cause mortality for mid-upper arm circumference for age z-scores, adjusted for HAZ and WHZ and using the same model structure in a Cox proportional hazards survival model as the primary results.



SI Figure 5. The probability of membership in the cluster assigned to each child in the analysis, facetted by cluster.



SI Figure 6. Residuals in HAZ and WHZ trajectory by latent class. Figures are subset to the same 5000 individuals to assist in interpretability of plots.



Conclusion

Overall summary

Too many children die every year. Many of those deaths are among children with suboptimal growth in height and weight in the first two years of life. These children are vulnerable to poor health and developmental outcomes. This dissertation sought to improve the quantification and measurement of the magnitude and trajectory of this vulnerability. It surveyed the existing landscape of longitudinal growth studies and applied several appropriate statistical models to account for repeated measurements of height and weight. It demonstrated that poor growth is a substantial, non-linear risk factor for infectious disease burden and described how that burden is massive on a population level. This dissertation created a vulnerability metric to describe how growth affects an individual child's trajectory in the first two years of life and a corresponding risk of mortality based on that growth. The most vulnerable children are those born small or premature and those born to marginalized or undernourished mothers. This dissertation is a step towards a quantitative, specific, and robust framework for understanding childhood vulnerability and understanding how to target effective interventions to improve growth and reduce child mortality.

Future directions

I will be submitting each Chapter for publication in academic journals. I believe that the work contained in this dissertation advances the field and I am proud of what I have accomplished.

Several limitations were identified within each chapter of this dissertation which warrant additional research. For example, Chapter 2 quantified cause-specific mortality risk for each CGF metric, *independently;* risk estimates for HAZ, WAZ, and WHZ were estimated separately from each other. There is, however, substantial covariance between these indicators. Children that are tall will, by necessity,

weigh more than children who are shorter but of the same weight-for-height. Further, Chapter 3 showed that there is a non-linear relationship between HAZ and WHZ in the risk of all-cause mortality. It is likely that this would also be true for cause-specific mortality estimated in Chapter 2. Modeling advances in the Bayesian meta-regression tool used for Chapter 2 relative risk estimates would need to be built to account for joint estimates of HAZ and WHZ, for example. Modifying the risk estimates to account for this dependence in CGF metrics might change the overall burden of disease attributable to it, or at least change how that is distributed within populations. Also from Chapter 2, there are at least 8 prospective studies that measured childhood growth and risk of infectious disease mortality that were not directly used in the meta-regression. Contacting these study authors and requesting the primary data to be included in this analysis might improve the modeled estimates.

We used height and weight as growth indicators associated with vulnerability. Testing the association between another metric, the mid-upper arm circumference (MUAC), with vulnerability should be explored. There is some evidence that this is a stronger indicator of acute malnutrition than low WHZ and is more accurate across measurements. Measuring a child's length or height is difficult as infants tend to squirm, and it is challenging to put them in a position with a straight spine. In contrast, a simple string and ruler can be quickly and reliably used to measure MUAC. Child MUAC is not as frequently collected in longitudinal studies, but it is warranted in future cohorts and in future analyses of vulnerability.

Chapter 3 used a robust approach to quantify vulnerability. However, vulnerability in this analysis was limited to the risk of all-cause mortality. There are other non-fatal negative outcomes of poor growth in early childhood including long-term educational and economic prospects. Vulnerability might also be extended to susceptibility to specific diseases that may require treatment including hospitalization. Considering the likelihood of suboptimal educational attainment, economic potential, or treatment costs could be used to create a vulnerability index representing this wider range of outcomes.

Chapter 3 considered a wide array of factors that might be associated with vulnerability levels and trajectories among children younger than 2 years and identified maternal characteristics and fetal development as some of the most important. Maternal health is underfunded and understudied, leaving a dearth of evidence to better understand how intergenerational vulnerability is linked. It is exceedingly likely that intersectional interventions to improve women's equality, education, and overall health are connected to early childhood vulnerability. However, the data available for this analysis generally lacked meaningful variables that might describe maternal characteristics beyond anthropometry and education. Data on maternal hemoglobin, blood pressure, micro- and macro-nutrient intake, family planning agency, and economic equality indicators could be highly informative in identifying what makes children vulnerable.

There are additional metrics from vulnerability trajectories that could be of practical public health importance. For example, the prevalence of vulnerability clusters could be estimated using population-representative surveys such as the Demographic and Health Survey (DHS). One might hypothesize that vulnerability cluster prevalence would vary by time and geography. Modifying the latent class analysis to test for out-of-sample predictions, using one or several sets of anthropometric measurements in the first few months of life to predict future vulnerability values would be useful to identify the most at risk children early in their lives, ideally with more specificity than simply based on their birth size and gestational age.

Finally, although this analysis used all available data on childhood growth and mortality, the results may not be generalizable to all children everywhere. Each community has a different environment resulting in different lived experiences for the women and children that live in them. Additional studies should be identified and added to this pooled cohort. Further effort to standardize other variables, like maternal characteristics, but also demographic and biological ones might reveal additional associations between growth and vulnerability. Lastly, methodology to test the predictive ability of our models, such as cross-

validation, should be tested to evaluate the validity of our findings to communities outside of those included in the pooled analysis.

This dissertation does not close the book on quantifying cross-sectional and longitudinal childhood vulnerability. It is, perhaps, an opening chapter. There is more work to be done. The results are urgent for all children who suffer from childhood growth failure.