Quantifying the proportion of child growth failure attributable to low birth weight and short gestation

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Abstract

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Child growth failure is associated with poor health outcomes, including premature death, increased susceptibility to disease in childhood, and cognitive and motor loss in adulthood. Low birth weight and short gestation are two risk factors that are likely associated with the risk of child growth failure. However, some major comparative risk assessments, such as the risk assessment conducted by the Global Burden of Disease, do not account for the mediation between child growth failure, low birth weight, and short gestation in their estimations of attributable burden. This analysis aims to quantify the proportion of child growth failure attributable to low birth weight and short gestation as a first step towards disentangling the contributions of child growth failure and poor fetal growth towards disease burden. In this analysis, the proportion of child growth failure attributable to low birth weight and short gestation is also used to model how interventions aimed at increasing birth weight and gestational age could lead to averted cases of child growth failure.

Introduction

In 2017, 19.56% (17.64 – 21.25%) of the global disease burden (DALYs) among children under five was attributed to child growth failure.[1] Child growth failure – the failure of a child to attain the average growth experienced by his or her peers – is shown to be associated with poor health outcomes, including premature death, increased susceptibility to disease in childhood, and decreased cognitive and motor capabilities in adulthood.[2] Child growth failure is typically divided into three classifications: stunting (short stature for age), wasting (low weight for height), and underweight (low weight for age).

Child growth failure disproportionately affects children in low and middle-income countries, and the cognitive loss attributed to child growth failure can contribute to stalled progress towards strengthening population-level human capital and socioeconomic status.[3] Preventing child growth failure has become a priority in the global health community; of the six Global Nutrition Targets for 2025 set by the World Health Organization in 2012, two targets explicitly focus on child growth failure: 1) to "achieve a 40% reduction in the number of children under-5 who are stunted", and 2) to "reduce and maintain childhood wasting to less than 5%".[4]

Nutrition-specific interventions aimed at reducing child growth failure are targeted at various periods of child development, from promotion of optimal breastfeeding at infancy to Vitamin A supplementation during childhood.[5] It is also widely recognized that child growth failure can be prevented by intervening in the fetal period, before a child is born.[6] Birth weight and gestational age are markers of growth in the fetal period and are shown to be associated with child growth failure, even several years after birth. [3] These associations provide evidence that a portion of the burden attributable to child growth failure is also attributable to low birth weight and short gestation.

The Global Burden of Disease (GBD) Comparative Risk Assessment models both the attributable burden due to child growth failure risk factors and the attributable burden due to low birth weight and short gestation risk factors. Despite evidence of association between child growth failure and low birth weight and short gestation, the GBD analysis does not allow for mediation between the two groups of risk factors; burden attributed to low birth weight and short gestation risk factors is limited to the first 28 days of life, and burden attributed to child growth failure is limited to after 28 days.[1] Quantifying the proportion of child growth failure attributable to low birth weight and short gestation is an initial step towards more accurately parsing out the proportion of burden under-5 attributable to low birth weight and short gestation and the proportion of burden under-5 attributable to child growth failure. Furthermore, quantifying this proportion can also contribute to analyses aimed at understanding how changes in interventions affecting gestational age and birth weight can lead to averted cases of child growth failure. To those ends, the primary aims of this analysis were to:

1. Calculate the proportion of moderate-to-severe child growth failure attributable to birth weight and gestational age.
2. Calculate cases of moderate-to-severe child growth failure averted under scenarios of shifting birth weight and gestational age exposure.

Methods

Attributable fractions were calculated to estimate the proportion of moderate-to-severe child growth failure attributable to 1) low birth weight and 2) short gestation in 204 countries and 839 subnational locations among males and females aged 1-4 years in 2017. Attributable fractions were estimated for all risk-outcome pairings of two risk factors (birth weight and

gestational age) and three child growth failure outcomes (moderate-to-severe stunting, wasting, and underweight). The exposure and outcome definitions used in this analysis are listed in Table 1.

Table 1: Exposure and Outcome Definitions

Outcomes	
Stunting	*z*-score more than two standard deviations below the global median of a reference height-for-age distribution, as defined by the 2006 WHO Child Growth Standards
Wasting	*z*-score more than two standard deviations below the global median of a reference weight-for-height distribution, as defined by the 2006 WHO Child Growth Standards
Underweight	*z*-score more than two standard deviations below the global median of a reference weight-for-age distribution, as defined by the 2006 WHO Child Growth Standards
Exposures	
Low Birth weight	Defined as birth weight less than the birth weight level with the lowest risk of experiencing child growth failure. For this analysis, birth weight was binned into seven categories: [0, 1500) grams, [1500, 2000) grams, [2000, 2500) grams, [2500, 3000) grams, [3000, 3500) grams, [3500, 4500) grams, [4500,) grams. The [4500,) gram category was identified as the *Theoretical Minimum Risk Exposure Level* (TMREL), or the birth weight level with the lowest risk of experiencing child growth failure. Any birth weight less than the TMREL was considered as low birth weight in this analysis.
Short gestation	Defined as gestational age less than the gestational age level with the lowest risk of experiencing child growth failure. For this analysis, gestational age was binned into five categories: [0, 28) weeks, [28, 32) weeks, [32, 37) weeks, [37, 42) weeks, [42,) weeks. The [37, 42) gestational age category was identified as the *Theoretical Minimum Risk Exposure Level* (TMREL), or the gestational age level with the lowest risk of experiencing child growth failure. Any gestational age birth weight less than the TMREL was considered as short gestation in this analysis. Although burden attributable to the [42,) gestational age category was modeled in this

	analysis, it did not contribute to the burden attributable to short gestation.

Calculations of attributable fractions requires estimation of exposure and relative risk. Odds ratios, modeled using logistic regression, were used to approximate the relative risks of moderate-to-severe child growth failure due to birth weight and gestational age. The exposure of birth weight and gestational age were modeled as part of the Global Burden of Disease analysis. Attributable fractions were estimated for four additional scenarios of shifted birth weight and gestational exposure, using the odds ratios calculated in this analysis.

To estimate cases of child growth failure attributable to low birth weight or short gestation for the exposure scenarios, the calculated attributable fractions were applied to the prevalent cases of stunting, wasting, and underweight among male and female children aged 1-4 in 2017, by location, as modeled by the Global Burden of Disease project.

Input data sources

Data sources underlying the GBD-modeled exposure distributions of birth weight and gestational age and prevalence of moderate-to-severe stunting, wasting, and underweight are described by the GBD. The birth weight and gestational age odds ratios were modeled using data from Demographic Health Surveys (DHS), spanning 69 countries and the years 1986 – 2017, with individually linked birth weight, child weight and height, and age in weeks at time of measurement. The height-for-age, weight-for-age, and height-for-weight Z-scores were calculated using the 2006 WHO Child Growth Standards. Individuals with Z-scores more than 2 standard deviations below the median on the height-for-age, weight-for-age, and height-for-weight reference distributions were classified as moderate-to-severely stunted, underweight, and

wasted, respectively. Only data from children ages 1-4 years at the time of weight and height measurement were kept. Data for children under 1 year were dropped because the association between birth weight and child growth failure Z-score appears to differ by week under the age of 1 by preterm and low birth weight status; however, the relationships stabilizes between 1-4 years (Figure 1). Because the association did not vary by age between 1-4 years, the odds ratio of experiencing child growth failure was modeled as age-invariant between 1-4 years.

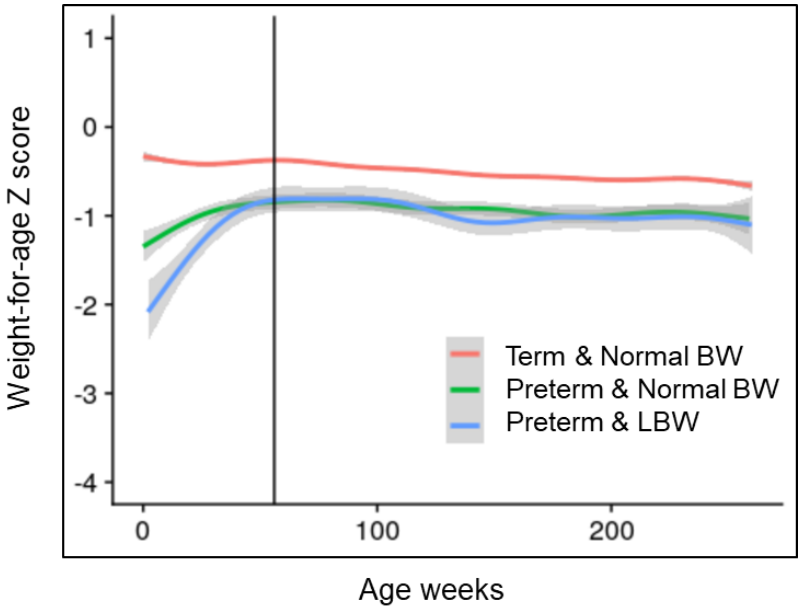

Figure 1: Association between weight-for-age Z score differs by age for individuals born low birth weight and preterm

Birth weight and gestational age imputation

Birth weight was missing in 47% of the data. Descriptive analysis showed that lower birth weights were more likely to be missing than higher birth weights. Under the assumption that birth weight could be modeled from additional covariates in the data set, birth weight was imputed using the Amelia package. The covariates used in the birth weight imputation were:

survey year, urbanicity, sex, age in weeks, method of birth weight recall (self-report or birth weight card), birth order, pregnancy status of mother at time of interview, number of years of maternal education, number of years of paternal education, maternal age, maternal weight, maternal height, access to treated water, access to shared sanitation, and household wealth category.

The DHS does not capture information on gestational age. To impute gestational age per birth weight data point, the GBD models of the joint distribution of gestational age and birth weight by location, year, sex were utilized. For every birth weight data point, one thousand draws of the gestational age distribution conditional on data point's birth weight were used to impute gestational age for that data point. The analysis was conducted on the 1000 imputations with uncertainty carried through and incorporated into the final estimates.

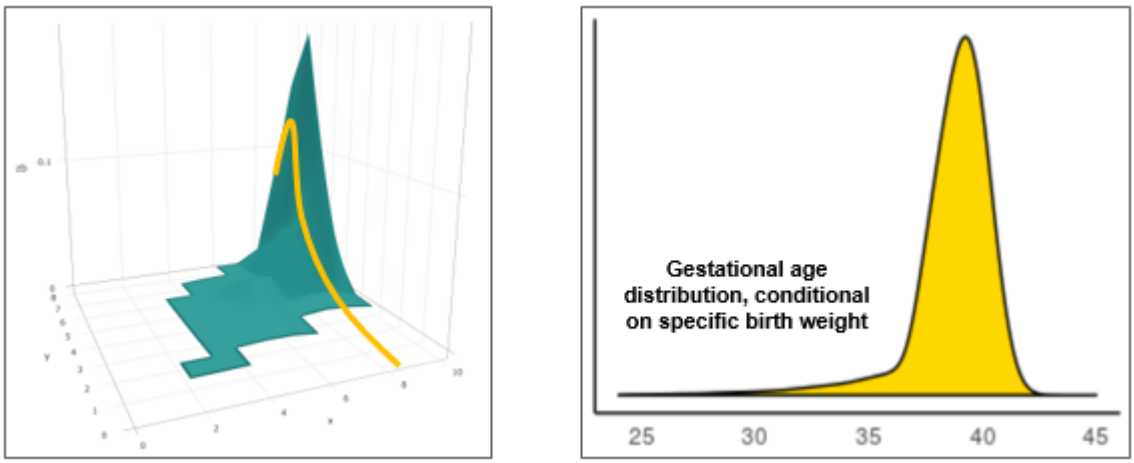

Figure 2: Schematic of using the joint distribution to take draws from the gestational age distribution, conditional on the birth weight of the data point

Modeling Odds Ratios

Logistic regression was used to model the gestational age and birth weight odds ratios with dummy variables on each categorical bin (see Table 1 for risk categories for birth weight and gestational age), using the equation below:

$$log\left(\frac{p}{1-p}\right) = \beta_0 + \sum_{i=1}^{k} \beta_i x_i + e$$

The theoretical minimum risk exposure level (TMREL) was set as the reference category in the regression. The TMREL for birth weight was set as [4500,) grams, and the TMREL for gestational age was set as [38, 42).

Estimation of Attributable Fractions

Attributable fractions for the six combinations of risk-outcome pairs (low birth weight and stunting, low birth weight and wasting, low birth weight and underweight, short gestation and stunting, short gestation and wasting, and short gestation and underweight) were calculated for each unique location-sex in 2017 among children aged 1-4. GBD-modeled birth weight and gestational age distributions were used as the exposure, and the odds ratios modeled in this analysis were used as the relative risk in the attributable fraction calculations. Attributable fractions were calculated using the method proposed by Greenland and Drescher[7] of obtaining attributable fractions directly from regression models. In brief, attributable fractions are calculated by, for each level of the risk factor:

1. Re-classifying the exposed individuals as unexposed
2. Estimating the predicted probability of disease for each individual using the predicted probability of disease calculations below. Due to the re-classification of individuals who

were exposed at that risk factor level as unexposed in Step 1, the coefficient for that risk level is dropped.

$$Predicted\ probability\ of\ disease = \frac{1}{1 + e^{-(a+\beta' X_i)}}$$

3. The predicted probability of disease for all individuals are summed to estimate the *Expected* cases of child growth failure.
4. The *Observed* cases of child growth failure is the number of cases of observed using the original exposure distribution.
5. The attributable fraction for that risk level is calculated as: *(Observed – Expected) / Observed.*

Using steps 1-5, attributable fractions are calculated for each level of the risk factor, for both the short gestation and low birth weight risks.

Estimation of Attributable Cases

Attributable fractions for each risk-outcome pairing, by location-sex in 2017, were applied to the GBD-modeled number of cases of the outcome (wasting, underweight, or stunting) among child aged 1-4 in 2017, by location-sex. The sum of the attributable cases for each location represented the total global number of attributable cases due to low birth weight or short gestation. In the gestational age model, an attributable fraction was calculated for the single gestational age level longer than the gestational age TMREL, and these cases were excluded from the calculation of attributable cases due to short gestation.

Estimation of Averted Cases per scenario

Four additional scenarios were of shifting birth weight and gestational age exposure were constructed (Table 2). To calculate averted cases, attributable fractions for each location-sex were recalculated using the new exposure in each scenario. The difference between the attributable cases due to "unchanged" exposure and the attributable cases due to each scenario represented the cases of stunting, wasting, or underweight averted due to changes in birth weight or gestational age in that scenario.

Table 2: Description of scenarios of shifted birth weight and gestational age

Scenario	
Unchanged exposure	No changes to modeled birth weight and gestational age exposure
Naïve	Birth weight increased by 250 grams across all births, gestational age increased by 2 weeks across all births
Proportional increase towards TMREL	Increase birth weight and gestational age across all births to be 10% closer to the TMREL
Focus on extreme cases	Move all births out of the most extreme birth weight and gestational age category into TMREL
Focus on near-TMREL cases	Move all births 250 grams from birth weight TMREL and 2 weeks from gestational age TMREL to TMREL

Results

Globally, among children aged 1-4 in 2017, 44% (35 – 53%) of childhood wasting was attributable to birth weight, 43% (36 – 52%) of childhood underweight was attributable to birth weight, and 20% (16 – 24%) of childhood stunting was attributable to birth weight. The attributable fractions of child growth failure due to gestational age were lower, with 6% (2 – 11%) of childhood wasting attributable to short gestation, with 6% (4 – 10%) of childhood underweight, and 2% (1 – 10%) of childhood stunting attributable to short gestation.

Table 3: Global number of cases and proportion of chlid growth failure attributable to low birth weight and short gestation

	Cases attributable to birth weight	Proportion of cases attributable to birth weight
Stunting	4,420,000 (3,540,000 – 5,350,000)	0.205 (0.164 - 0.248)
Wasting	5,520,000 (4,400,000 – 6,720,000)	0.439 (0.35 - 0.535)
Underweight	6,130,000 (4,990,000 – 7,360,000)	0.439 (0.358 - 0.527)
	Cases attributable to gestational age	Proportion of cases attributable to gestational age
Stunting	521,000 (304,000 – 759,000)	0.0241 (0.0141 - 0.0352)
Wasting	723,000 (207,000 – 1,430,000)	0.0575 (0.0165 - 0.114)
Underweight	937,000 (517,000 – 1,460,000)	0.0671 (0.0371 - 0.105)

South Asia and Western Sub-Saharan Africa have the highest proportion of child growth failure attributable to birth weight. South Asia has the highest proportion of childhood growth failure attributable to gestational age. The regional pattern of DALYs attributable to stunting, underweight, and wasting mirrors the regional pattern of the proportion of child growth failure attributable to birth weight and gestational age, indicating that the regions with the highest overall health burden attributable to child growth failure also have a higher percentage of child growth failure attributable to birth weight and gestational age.

The modeled odds ratios of birth weight increase as birth weight decreases from the TMREL, except between the category of [0, 1500) grams and [1500, 2000) grams for moderate-to-severe stunting. The modeled odds ratios of gestational age are lower than the birth weight odds ratios and have greater overlap of uncertainty intervals between the outcomes and also between the levels of gestational age.

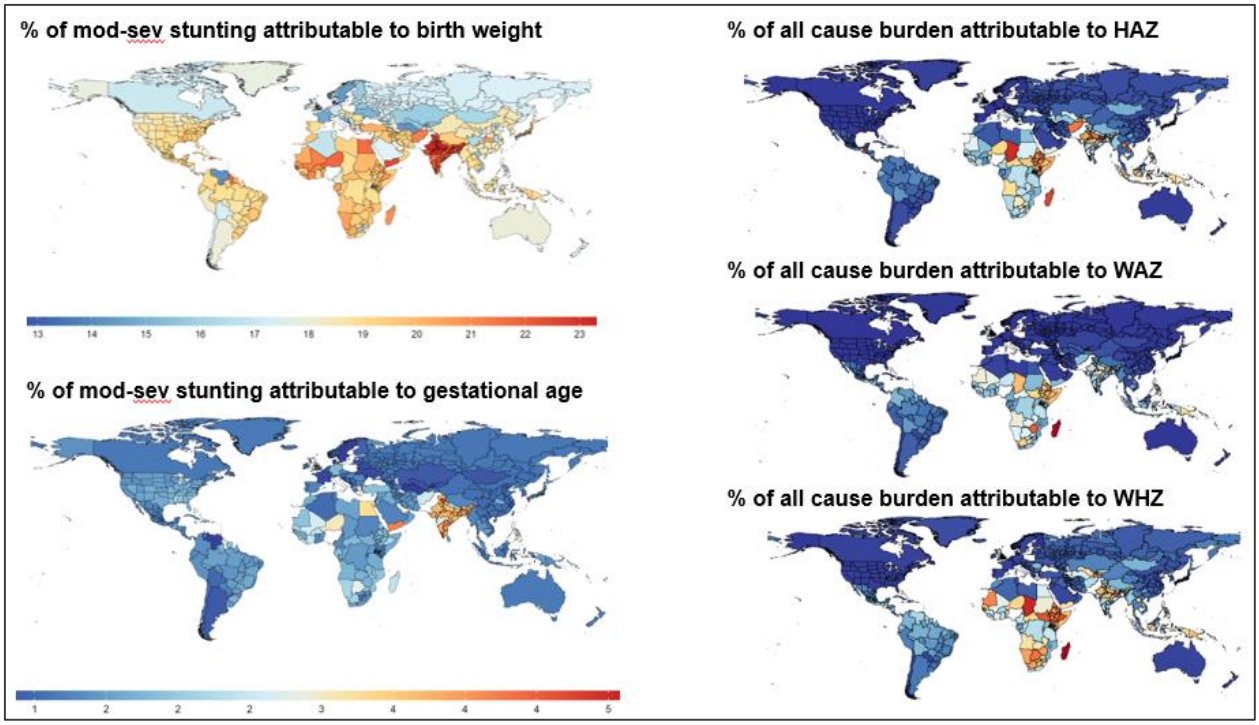

Figure 3: Regional pattern comparison of child growth failure attributable to low birth weight and short gestation (left) and all-cause burden attributable to child growth failure (right)

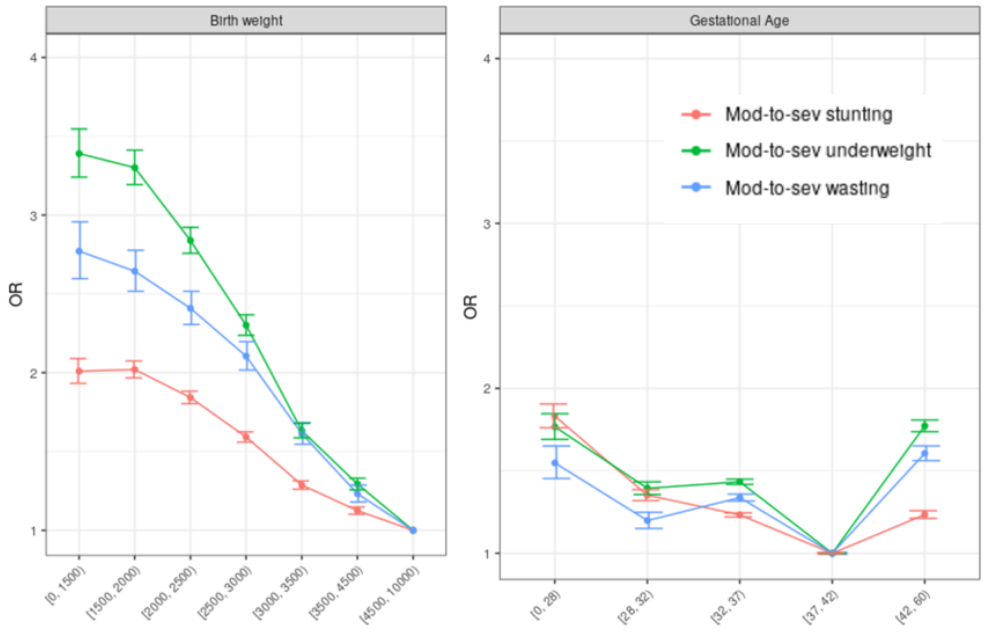

Figure 4: Modeled odds ratios of child growth failure, by birth weight and gestational age

Scenario Comparisons

The proportional increase of birth weight towards TMREL compared to the other three scenarios yielded more than double the number of cases of childhood undernutrition averted that were attributable to changes in birth weight. Shifting the near-TMREL cases led to the least change in cases of childhood undernutrition averted that were attributable to changes in birth weight. Conversely, naïve shifts and shifts near-TMREL for gestational age led to more cases of childhood undernutrition averted that were attributable to gestational age.

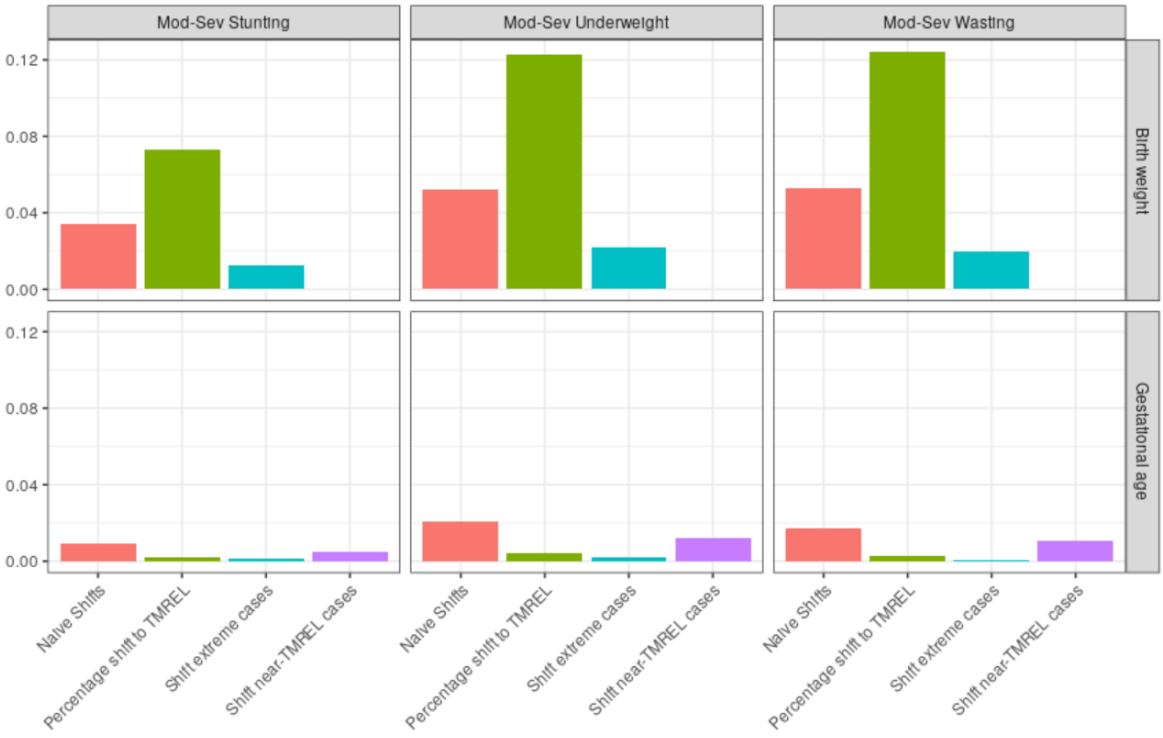

Figure 5: Proportion of child growth failure cases averted, by scenario, outcome, and risk factor

Discussion

Almost half of wasting and underweight and approximately one-fifth of stunting was estimated to be attributable to low birth weight. The proportion of child growth failure

attributable to short gestation was less dramatic, with less than 10% of child growth failure attributable to short gestation. South Asia and Sub-Saharan Africa, the regions with the highest percentage of burden attributable to child growth failure, also have the highest percentage of child growth failure attributable to low birth weight and short gestation. These regions also have the highest count of children experiencing child growth failure. This indicates that interventions aimed at reducing child growth failure by increasing birth weight and length of gestation could have greater impact in those regions.

Models of cases of child growth failure averted through shifted birth weight and gestational age exposure can be used for decision-making exercises on the type of interventions aimed at reducing child growth failure by targeting fetal growth. The results in this analysis show that interventions focused on increasing gestational age would likely be more impactful if focused on small increases to large percentage of births that are near term ("Shift near-TMREL scenario"). Conversely, interventions focused on increasing birth weight would likely avert more cases of child growth failure if they focused on shifting the less prevalent but highest risk births (birth weights less than 1500 grams) to the TMREL.

Several limitations in this analysis should caution against over-interpretation of the results. Odds ratios were used to approximate relative risks, and odds ratios are less accurate as baseline prevalence increases. In the areas with the highest prevalence of child growth failure, the odds ratios and therefore the attributable fractions may be less accurate representations compared to regions with lower child growth failure prevalence. Furthermore, multiple imputation was used to impute almost 50% of the missing birth weight data and all of the gestational age data. Uncertainty was carried through to the final analysis, and the gestational age imputation may have resulted in the overlapping confidence intervals in the gestational age odds

ratios and attributable fractions. Additionally, only data in ages 1-4 were used, and descriptive analysis shows that the association between child growth failure and low birth weight and preterm birth is stronger under 1 year than between 1-4 years of age. Survivor bias may be affected the odds ratios, as only data from the children who have survived to age 1 were used to estimate the odds ratios.

The most significant limitation is that the odds ratios (and thus attributable fractions) were not adjusted for other risk factors, and so the correlation between the risk factor of interest and other risk factors was not accounted for. Because the odds ratios are unadjusted, the model is susceptible to confounding and should be interpreted with caution. The attributable fraction due to low birth weight should be interpreted not as the attributable fraction due *only* to low birth weight, but attributable to low birth weight and all other risk factors associated with low birth weight – including short gestation.

Finally, in the estimation of attributable fractions, the expected cases of child growth failure were re-classified from exposed to unexposed. Underlying this assumption is that those who were exposed, once re-classified as unexposed, were evenly distributed amongst the other risk levels. For example, calculating the attributable fraction due to gestational age less than 28 weeks required re-classifying the individuals with gestational age less than 28 weeks as unexposed and, essentially, redistributing those individuals evenly amongst the other risk levels. However, in reality, if an individual less than 28 weeks became unexposed, it is more likely that the individual would have been born between 28 and 32 weeks of gestation than the other levels of gestational age.

Conclusions

This analysis shows that a proportion of child growth failure is likely attributable to short gestation and low birth weight. The proportion of wasting and underweight attributable to short gestation or low birth weight is higher than the proportion of stunting attributable to short gestation or low birth weight. Quantifying the association between low birth weight, short gestation, and child growth failure can improve the Global Burden of Disease estimates of burden attributable to child growth failure and the estimates of burden attributable to low birth weight and short gestation. Additionally, quantifying the proportion of child growth failure attributable to low birth weight and short gestation can lead to improved decision-making around how to intervene on gestational age and birth weight and prevent downstream cases of child growth failure.

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