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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Troeger C, Colombara DV, Rao PC, et al. Global disability-adjusted life-year estimates of long-term health burden and undernutrition attributable to diarrhoeal diseases in children younger than 5 years. *Lancet Glob Health* 2018; **6**: e255–69.

Supplementary material for Global disability-adjusted life-year estimates of long-term health burden and undernutrition attributable to diarrhoeal diseases

5 This document provides supplementary material for the manuscript *Global disability-adjusted life-year estimates of long-term health burden and undernutrition attributable to diarrhoeal diseases*. The information in the document is intended to provide additional detail for data extraction and modeling strategy.

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Details on modeling in GBD 2016

The Global Burden of Disease study 2016 provides comprehensive and internally consistent epidemiological estimates for over 300 causes of death and disability, 90 risk factors, for 195 locations, by year, sex, and four age groups under 5 years old. Detailed descriptions of all GBD methods have been previously published.¹⁻⁴ Mortality due to diarrhoeal diseases was estimated using the Cause of Death Ensemble modeling framework (CODEm)^{2,5} and diarrhoea incidence, prevalence, and recovery were estimated with DisMod-MR 2.1 (DisMod), a Bayesian meta-regression tool.⁶ More detail on diarrhoea modeling in GBD can be found several places including the GBD 2015 diarrhoea capstone manuscript,¹ the GBD 2016 cause of death publication² methods appendix (p. 58) and the GBD 2016 non-fatal publication³ methods appendix (p. 54). The diarrhoea incidence, mortality, years of life lost (YLLs), years lived with disability (YLDs), and disability-adjusted life years (DALYs) estimated in the GBD 2016 framework are referred to herein as *acute DALYs* to differentiate them from DALYs associated with growth impairment which will be referred to as *long-term sequelae DALYs*. DALYs associated with growth impairment will be described in more detail below; we estimated these DALYs as part of the GBD 2016 and estimated these DALYs attributable to diarrhoea in children under-5.

We previously estimated DALYs due to childhood undernutrition in GBD 2016.⁴ Childhood undernutrition is modeled using three indicators: stunting, wasting, and underweight. These indicators are based on categorical definitions from the WHO 2006 growth standards for children under-5 using z-scores from an international reference population. For each country, year, sex, and age, we modeled the mean z-score and the prevalence of moderate (less than 2 standard deviations below the reference mean) and severe (less than 3 standard deviations below the reference mean) undernutrition using spatiotemporal Gaussian process regression (ST-GPR). More detail on modeling childhood growth failure in GBD 2016 can be found on p. 73 of the risk factors publication methods appendix.⁴

Childhood undernutrition is associated with three outcomes in GBD 2016: diarrhea, lower respiratory infections, and measles (risk-outcome pairs). The relative risks for these risk-outcome pairs were derived from a pooled cohort analysis.^{4,7} Undernutrition indicators are highly correlated in a population and so the relative risks were adjusted to account for covariance between them by simulating a joint distribution of the three indicators using the distributions extracted from the countries that were included in the original relative risk cohort analysis (individual-level data from Demographic and Health Survey [DHS] microdata). We extracted the interaction terms from the analysis and adjusted the RRs by minimizing the error between the crude (from pooled cohort) and expected RRs derived from our simulation (more information available in the GBD 2015 risk factors manuscript, methods appendix p. 34).⁸

Details on modeling mortality, morbidity, YLLs, YLDs, and DALYs due to measles and lower respiratory infections can be found in the GBD 2016 cause of death methods appendix (p.83 and p. 67, respectively)² and in the GBD 2016 non-fatal methods appendix (p.97 and p. 66, respectively),³ and lower respiratory infections in the GBD 2015 LRI publication.⁹

We attributed 100% of protein-energy malnutrition (PEM) to childhood wasting and underweight but not stunting. PEM mortality was modeled as a sub-category of total nutritional deficiencies in CODEm and PEM prevalence is back-calculated as a composite of marasmus and kwashiorkor using the case fatality ratio and mean duration of illness (GBD 2016 cause of death manuscript methods appendix p. 117).²

Systematic Review

Our primary long-term outcomes of interest were changes in Z-scores of height or length for age (HAZ), weight for age (WAZ), and weight for height (WHZ) subsequent to DD. We defined mild, moderate, and severe stunting, underweight, and wasting as -1 to -2, -2 to -3, and <-3 Z-scores of HAZ,

80 WAZ, and WHZ, respectively. When possible, HAZ, WAZ, and WHZ were defined according to the World Health Organization (WHO) 2006 growth charts¹⁰, rather than the CDC 2000¹¹ or the 1977 National Center for Health Statistics (NCHS) growth charts. We selected these outcomes because they are health related, quantifiable, have sufficient literature or available microdata for meta-analyses, and are available in the Global Burden of Disease Study (GBD).¹²⁻¹⁴

85 Search strategy

We conducted a series of systematic reviews to address three questions to inform our DD DALYs estimates. We sought to quantify the change in HAZ, WAZ, and WHZ due per day of early childhood (under 5 years of age) diarrhoea. Based on these questions, we performed detailed literature searches using EBSCO, Embase, and PubMed databases (Supplementary Table 1). We also examined the references list of a 2015 meta-analysis for additional publications¹⁵ and performed analyses on microdata that we obtained for this study. There was no restriction on publication date. The search terms used were the following.

95 PubMed:

(diarrh[Title/Abstract] or "gastroenteritis"[Title/Abstract] or "acute enteritis"[Title/Abstract] or gastrit*[Title/Abstract]) and ("intellectual impairment"[Title/Abstract] or "cognitive impairment"[Title/Abstract] or "child development"[Title/Abstract] or "personality development"[Title/Abstract] or "academic achievement"[Title/Abstract] or "verbal fluency"[Title/Abstract] or "learning"[Title/Abstract] or memory[Title/Abstract] or "psychosocial"[Title/Abstract] or "developmental disorder"[Title/Abstract])*

105 Embase:

(diarrh:ab or diarrhoea:ab or 'gastroenteritis':ab or 'acute enteritis':ab or gastrit*:ab) and (stunting:ab or wasting:ab or malnutrition:ab or 'child growth':ab or 'child nutrition':ab or underweight:ab or weight:ab) and ('prospective study':ab or 'retrospective study':ab or 'cohort analysis':ab or 'case control study':ab or 'randomized control trial':ab) and [humans]/lim*

110 EBSCO:

AB (diarrhoea or diarrhoeal or diarrhoea or gastroenteritis) AND AB (stunting or wasting or development or growth or underweight or malnutrition or "height" or "weight") AND AB (child or infant or baby)

Data extraction

115 From our search terms, we identified 1355 titles from PubMed, 390 titles from Embase, and 1011 titles from EBSCO. We screened titles and abstracts identified in our systematic review to identify articles for a full-text review. After deduplication, we screened 539 articles and identified articles that provided information on weight, height, and diarrhoea. After full text review, we extracted information from 17 studies that provided height or weight change due to diarrhoea (**SI Table 1**). To extract information from the articles, we used a standardized database to extract the title, journal, volume, issue, pages, publication date, abstract, location(s), study year(s), exposure and outcome ages, descriptions of exposure and outcome measures, cohort identifiers, table or figure numbers, point estimates, and standard errors (SE) or confidence intervals (CI). When crude and adjusted estimates were provided, we extracted both. We did not assess study quality.

125 Exclusion criteria

We excluded exposures, whether DD or undernutrition, that occurred older than age five and outcomes assessed older than age 12. We limited our analysis to studies which could assess nutritional status in terms of continuous HAZ, WAZ, and WHZ. We excluded studies that limited these assessments to dichotomized variables such as “stunting”, “underweight”, and “wasting.” We also excluded studies that solely assessed micronutrient supplementation, community health education, psycho social stimulation, WASH and nutritional interventions, helminthic infection, and breastfeeding as DD risk factors. We had no exclusions for publication date or language.

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Additional data sources

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We supplemented the literature review above with original analyses of individual-level observational data from cohort studies (**SI Table 1**). Changes in HAZ, WAZ, and WHZ per day of diarrhoea were assessed in a birth cohort in Vellore, India, a *Cryptosporidium* study in Bangladesh to assess the association between diarrhoea and undernutrition, The Performance of Rotavirus and Oral Polio Vaccines in Developing Countries (PROVIDE) Study in Bangladesh, and a birth cohort in Bangladesh.¹⁶⁻¹⁹ In addition, we included individual level data from the Etiology, Risk Factors, and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health (MAL-ED) Study child cohort.²⁰

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For each dataset, we calculated the difference in HAZ, WAZ, and WHZ between consecutive anthropometric measures. We used panel regression to estimate the average change in these measures per day of diarrhoea *between* anthropometric measurements, adjusted for the number of days between measures, the baseline HAZ/WAZ/WHZ measure, and the child’s age in months. All of our panel regressions used a maximum likelihood random-effects estimator.

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SI Table 1. Source data list.

First Author	Location	Years	Age range (years)	Input	Type
Assis ²¹	Brazil	1990 - 1991	0.5 to 4	HAZ, WAZ	Literature
Bairagi ²²	Bangladesh	1975 - 1976	1 to 4	HAZ, WAZ	Literature
Becker ²³	Bangladesh	1978 - 1979	0.5 to 2.7	WAZ	Literature
Black ²⁴	Bangladesh	1978 - 1979	0.5 to 4	HAZ, WAZ	Literature
Donowitz ¹⁶	Bangladesh	2008 - 2014	0 to 6	HAZ, WAZ, WHZ	Microdata
Faruque ¹⁷	Bangladesh	2014 - 2016	0 to 2	HAZ, WAZ, WHZ	Microdata
Kattula ¹⁸	India	2009 - 2013	0 to 3	HAZ, WAZ, WHZ	Microdata
Kirkpatrick ¹⁹	Bangladesh	2011 - 2014	0 to 2	HAZ, WAZ, WHZ	Microdata
Kotloff ²⁵	The Gambia, Mali, Kenya, Mozambique, Pakistan, India, Bangladesh	2007 - 2011	0 to 5	HAZ	Literature
Lee ²⁶	Peru	2002 - 2006	0 to 6	HAZ, WAZ	Literature
Lima ²⁷	Brazil	1989 - 1993	0 to 3	HAZ, WAZ	Literature
MAL-ED Network ²⁸	Bangladesh, Brazil, India, Nepal, Pakistan, Peru, South Africa, Tanzania	2009-2014	0 to 2	HAZ, WAZ, WHZ	Microdata
Moffat ²⁹	Nepal	1995	0 to 5	HAZ, WAZ	Literature
Molbak ³⁰	Guinea-Bissau	1987 - 1990	0 to 2	HAZ	Literature
Mondal ³¹	Bangladesh	1999 - 2002	2 to 5	HAZ, WAZ	Literature
Moore ³²	Brazil	1989 - 1998	0 to 2	HAZ	Literature
Moore ³³	Brazil	1989 - 2000	0 to 10	HAZ, WAZ, WHZ	Literature
Moy ³⁴	Zimbabwe	1992 - 1993	0 to 1.2	HAZ, WAZ	Literature
Sawadogo ³⁵	Burkina Faso	2003 - 2005	0.5 to 2	HAZ	Literature
Walker ³⁶	Jamaica	1989 - 1991	0.8 to 2	HAZ, WAZ	Literature
Weisz ³⁷	Malawi	2009 - 2010	0.5 to 1.5	HAZ, WAZ	Literature
Wierzbna ³⁸	Egypt	1993 - 1995	1 to 3	HAZ, WAZ, WHZ	Literature

165 **Data transformations**

For the diarrhoea to undernutrition analysis, we aimed to identify data that measured the change in nutritional status (e.g., HAZ) per day of diarrhoea. For estimates of change in nutritional status per episode of diarrhoea, the coefficient and standard error (SE) were divided by the mean number of days per episode of DD in that study. If the authors provided a range, we used the median of that range. When only a lower limit was provided, we used that lower limit. We assumed an average duration of 4.3 days per diarrhoeal episode when the days per episode could not be estimated from the study, consistent with the mean duration of diarrhoea episodes in GBD 2016.³ When estimates were based on diarrhoea prevalence (percent of days with diarrhoea), we multiplied the estimate by the number of days in that period, while assuming 30 days per month. Estimates based directly on changes in anthropometric measures (i.e., height in cm) were adjusted by dividing the coefficients and SE by the

standard deviation (SD) for that metric at a particular age from the WHO Growth Charts.¹⁰ The age was defined as the midpoint of the age range in the study and female growth charts were used for mixed populations of males and females.

180 We needed beta coefficients and SEs for our meta-analyses. When possible, we converted correlation coefficients to beta coefficients:

$$\beta = \text{Correlation}(X, Y) * \frac{SD(X) * SD(Y)}{\text{Variance}(X)}$$

When a publication provided a beta coefficient and p-value, we calculated the standard error as:

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$$\text{Standard Error} = \frac{\beta}{Z}$$

Where:³⁹

$$Z = -0.862 + (0.743 - 2.404 * \ln(p))^{0.5}$$

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Meta-analysis

215 We performed a series of random-effect meta-analyses to determine the effect per day of
diarrhoea on height-for-age, weight-for-age, and weight-for-height among children under-5 (**SI Figures
1-3**). We used the most detailed available information from the extracted literature sources in terms of
age and location in the meta-analyses. All meta-analyses were performed in R v3.3.2 using the
'metaphor' package.

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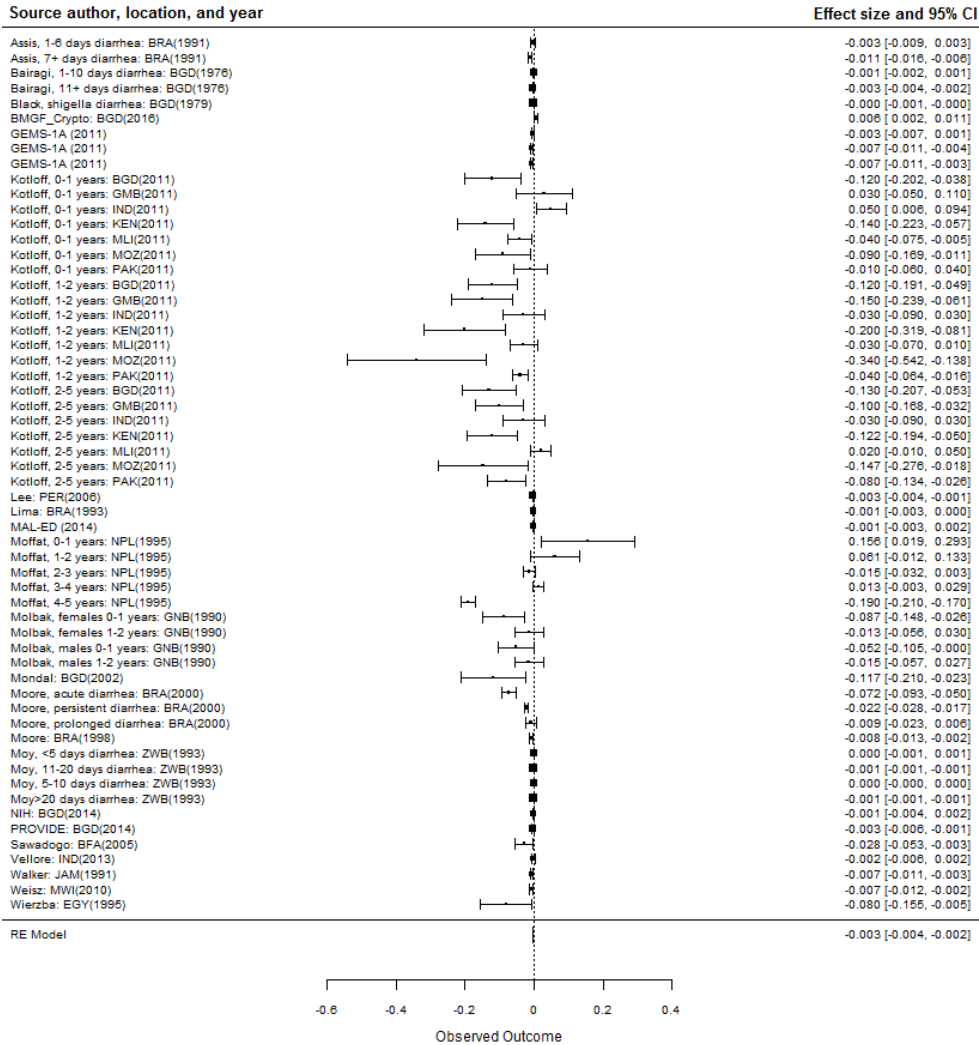
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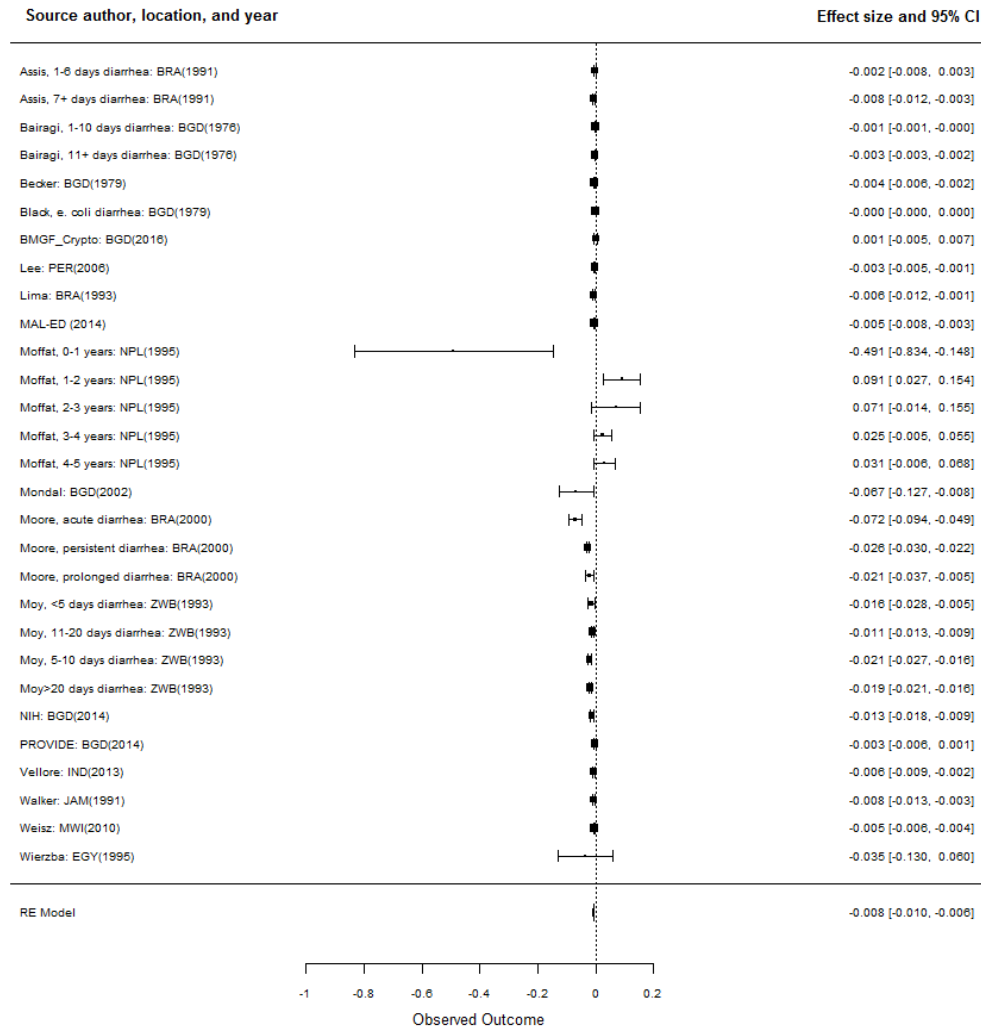
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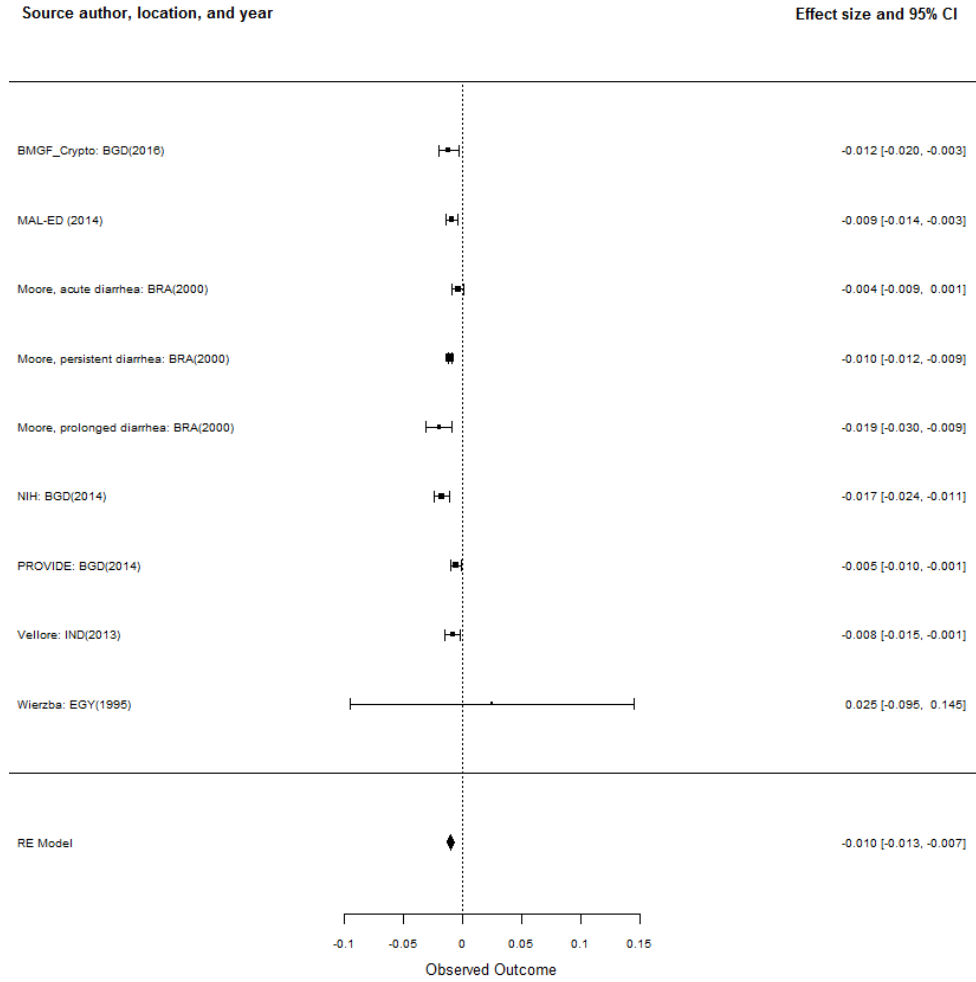
SI Figure 1. Forest plot of the relationship between height-for-age z-scores (HAZ) per day of diarrhoea.
 The random-effects meta-analysis uses input data at the finest granularity reported by study authors.
 Where individual-level data were available, a summary value by age group was used.



SI Figure 2. Forest plot of the relationship between weight-for-age z-scores (WAZ) per day of diarrhoea. The random-effects meta-analysis uses input data at the finest granularity reported by study authors. Where individual-level data were available, a summary value by age group was used.

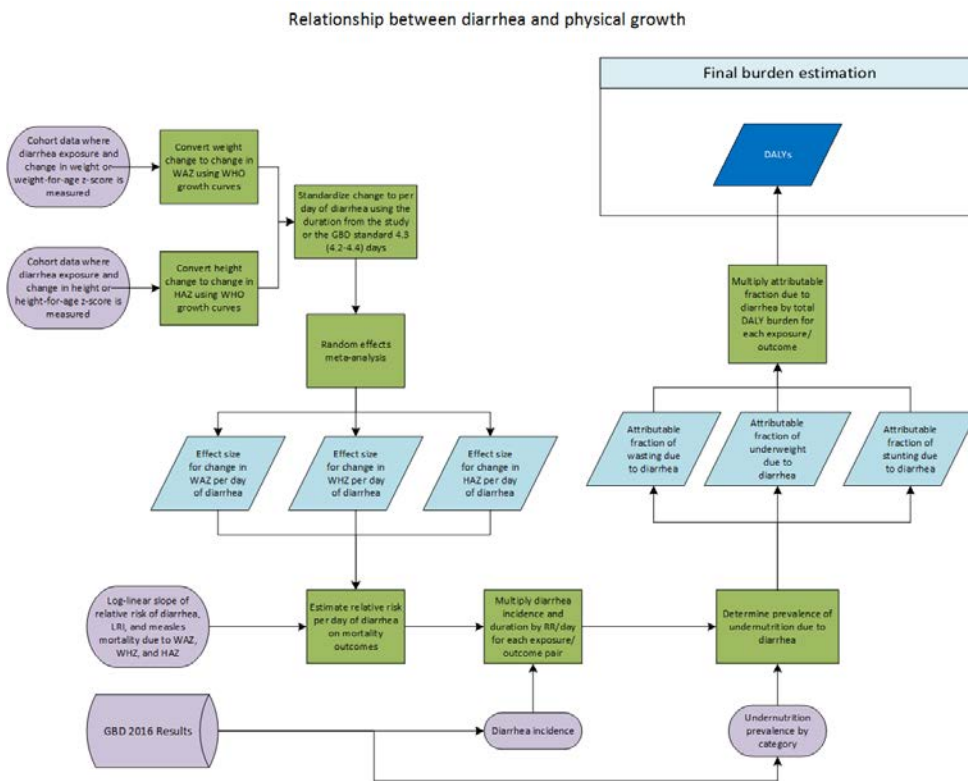


SI Figure 3. Forest plot of the relationship between weight-for-height z-scores (WHZ) per day of diarrhoea. The random-effects meta-analysis uses input data at the finest granularity reported by study authors. Where individual-level data were available, a summary value by age group was used.



Statistical analysis

270 **Flowchart 1.** Analytic flowchart for estimating the effect of diarrhoea on physical growth and childhood undernutrition and subsequent disability-adjusted life years (DALYs) associated with undernutrition due to diarrhoeal diseases.



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Using the results of our systematic review and microdata analyses, we conducted a random effects meta-analysis. When available, we used multivariate-adjusted estimates rather than crude estimates from the literature review in our analyses.

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Diarrhoea-associated undernutrition. For the DD to undernutrition analysis, we estimated the log-linear relative risk (RR) of disease and mortality for diarrhoea, lower respiratory tract infection (LRI), and measles per unit change in HAZ, WAZ, and WHZ based on hazard ratios reported in a 2013 pooled analysis (SI Figure 5).⁴⁰ Although hazard ratios may not be equivalent to a risk ratio in many circumstances, we assume that the hazard ratios can be treated similarly to risk ratios in assessing the

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association between a risk and an outcome in estimating an attributable burden.⁴¹ Hazard ratios will be referred to generally as a relative risk (RR) in this manuscript. The relative risks for stunting and wasting are adjusted to account for their covariance with each other and with underweight.¹⁴ Undernutrition indicators are highly correlated in a population and so the relative risks were adjusted to account for covariance between them by simulating a joint distribution of the three indicators using the distributions extracted from the countries that were included in the original relative risk cohort analysis (individual-level data from Demographic and Health Survey [DHS] microdata). We extracted the interaction terms from the analysis and adjusted the RRs by minimizing the error between the crude (from pooled cohort) and expected RRs derived from our simulation (more information available in the GBD 2015 risk factors manuscript, methods appendix p. 34).⁸ We then calculated an outcome-specific population attributable fraction (PAF) for each age group under 5 years and for each year, sex, and location where:

$$PAF = 1 - \frac{1}{Diarrhoea\ incidence * Episode\ Duration * \frac{\Delta Zscore}{day\ of\ diarrhoea} * RR}$$

Where *Diarrhoea incidence* is the modeled number of episodes per child-year in GBD 2016, *Episode duration* is the mean duration in days per diarrhea episode, $\Delta Zscore$ is the unit change per day of diarrhea, and *RR* is the relative risk of each outcome per unit change in z-score. The overall undernutrition PAF for each outcome was calculated as:

$$PAF_{malnutrition} = 1 - [(1 - PAF_{WAZ}) * (1 - PAF_{HAZ}) * (1 - PAF_{WHZ})]$$

We multiplied the DD, LRI, and measles undernutrition PAFs by the GBD 2016 total estimated DALYs associated with those outcomes.⁴² Uncertainty in the final DALYs estimates was calculated using 1000 draws of the input parameters including DD incidence, effect size from the meta-analyses, and relative risk of the outcome. Our final DALYs point estimate is the mean DALYs estimate, with the upper and lower uncertainty intervals (UI) defined by the 2.5 and 97.5 percentiles of the estimates, respectively.

To estimate the attribution of diarrhoea on protein-energy malnutrition, we used a counterfactual approach to define the percent change in the cumulative density from a normal distribution. From GBD 2016, we used the estimated prevalence of mild, moderate, and severe underweight and wasting for each age group under five, each location, both sexes, and the years 1990, 1995, 2000, 2005, 2010, and 2016. We converted the prevalence of undernutrition categories to z-scores. We then estimated the z-score shift per day of diarrhoea based on the GBD 2016 estimated diarrhoea incidence and the effect sizes from our meta-analysis. We defined the counterfactual prevalence of wasting or stunting as the difference in the observed and z-score-shifted prevalences. The PAF was the percent difference in the observed and counterfactual prevalence estimates (**SI Figure 4**).

We estimated protein energy undernutrition (PEM) DALYs attributable to DD using 1000 draws of DD incidence, PEM DALYs, and the prevalence of underweight and wasted children from GBD 2016. We defined underweight and wasting as the cumulative prevalence of mild, moderate, and severe measures. We multiplied the estimated change in WAZ and WHZ due to one day of diarrhoea from the meta-analysis by the estimated diarrhoea incidence from GBD 2016 times the duration in days per episode (4.3 days on average, range: 4.2-4.4 days)⁴³ to calculate the change in underweight and wasting due to diarrhoea, respectively. We defined the counterfactual prevalence of underweight in children as:

$$Prevalence_{counterfactual} = Prevalence + \frac{\Delta Zscore}{day\ of\ diarrhea} * Diarrhea\ Incidence * Episode\ Duration$$

and calculated the PAF as

$$PAF = \frac{Prevalence(Counterfactual) - Prevalence(GBD\ 2016\ Estimate)}{Prevalence(GBD\ 2016\ Estimate)}$$

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The PAF for wasting was calculated in a parallel manner using WHZ. PEM DALYs attributable to DD were calculated by multiplying the PAF by the total PEM DALYs, again taking the mean as our point estimate and the 2.5 and 97.5 percentiles as the lower and upper UI limits. All analyses used two-sided statistical tests and were conducted using Stata/SE 13.1 and R version 3.3.2.

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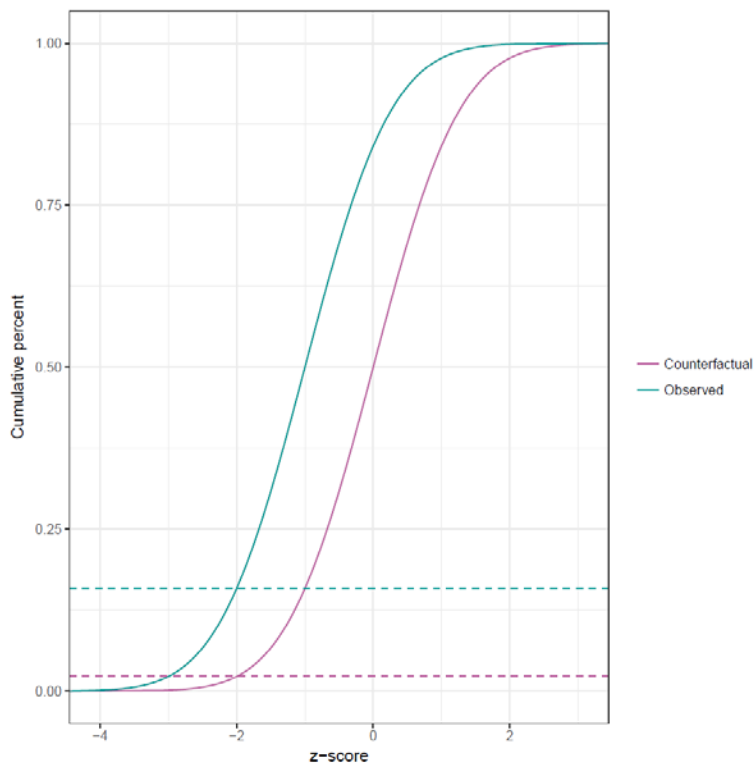
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360 **SI Figure 4.** This figure shows the analytic strategy for evaluating the counter-factual attributable
fraction for the impact of diarrhoea on weight-for-age and weight-for-height. The cumulative density
curves show the observed (blue) and counterfactual prevalence. The counterfactual curve is set to mean
0 and standard deviation 1 and the observed curve is a hypothetical population with a mean of -1
and standard deviation of 1. The prevalence of wasting in this example is the area below -2 standard
deviations. Shifting the curve to the right (counterfactual curve) decreases the prevalence of wasting.
365 The percent difference in the prevalence of wasting (dashed lines) is the population attributable
fraction.



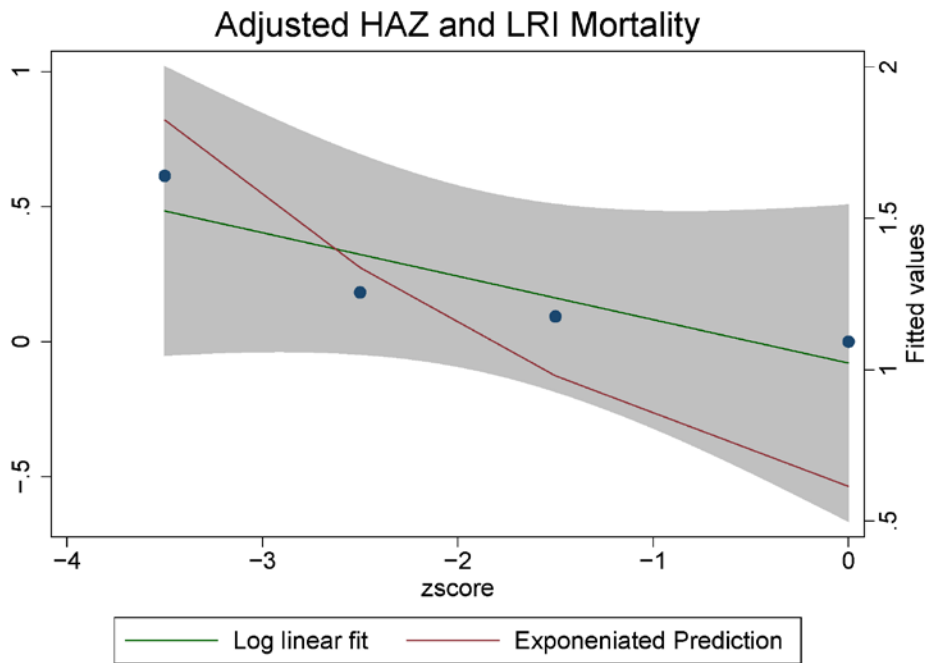
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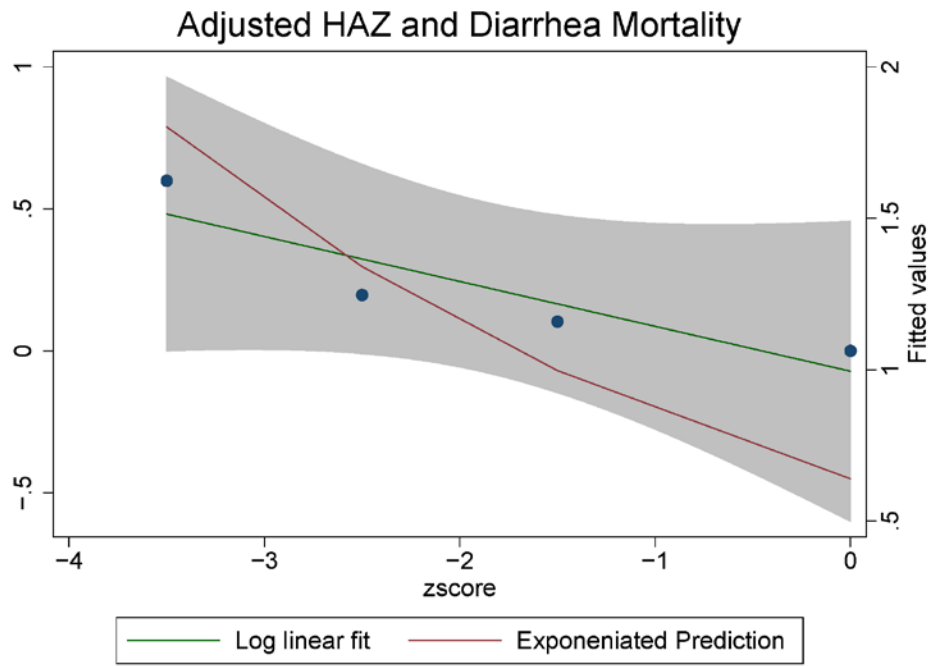
SI Figure 5. The adjusted hazard ratios for mortality, from Olofin et al 2013, for each risk-outcome pair is shown. Fit was evaluated in log-space (primary y-axis) and the plots also show the exponentiated prediction (secondary y-axis). The log-linear slope represents the per z-score unit change in the hazard ratio of mortality.

Comment [CT1]: Cite this!

A)

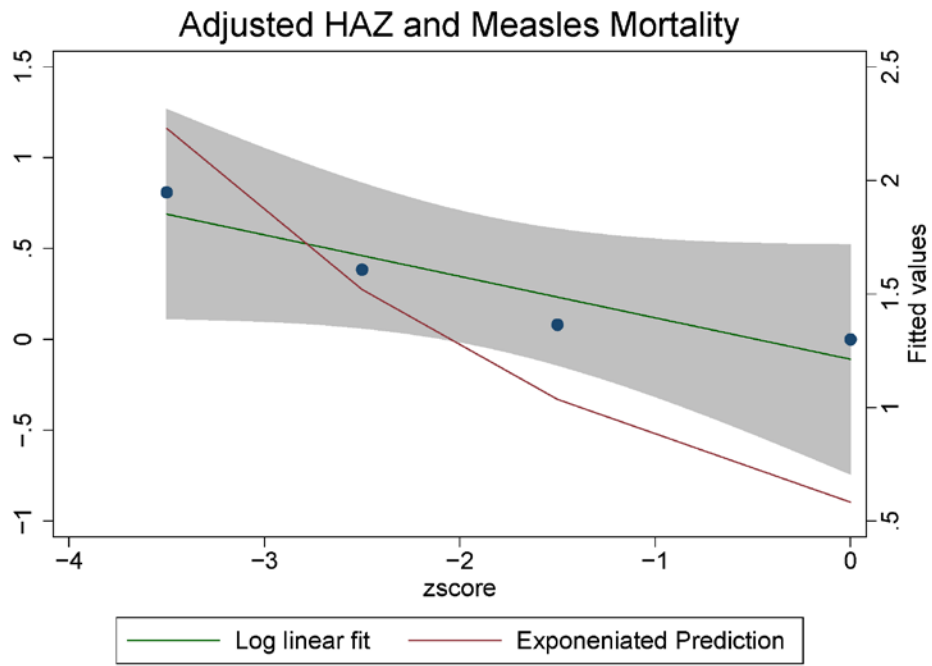


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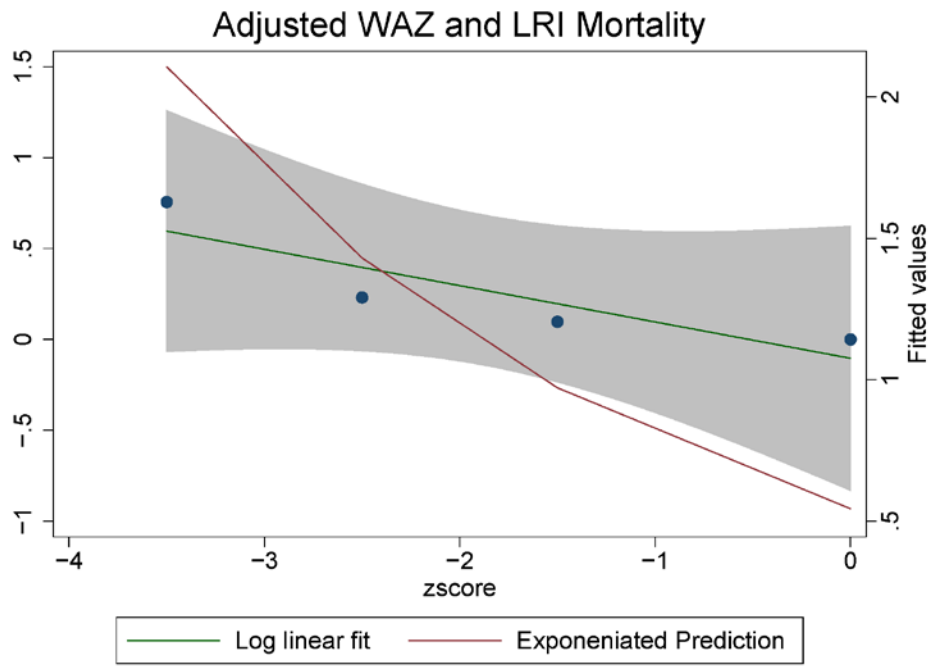


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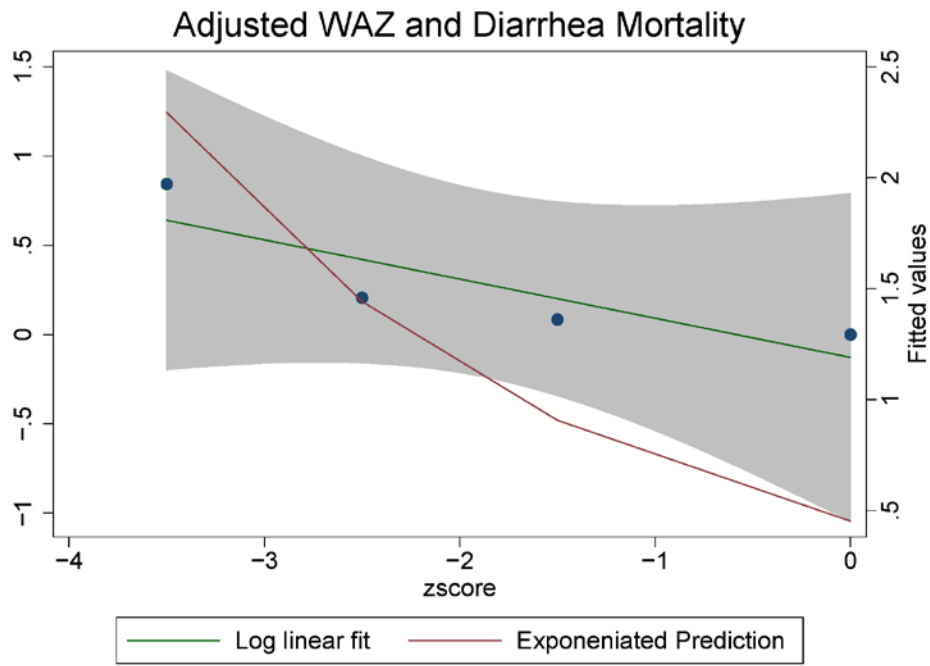
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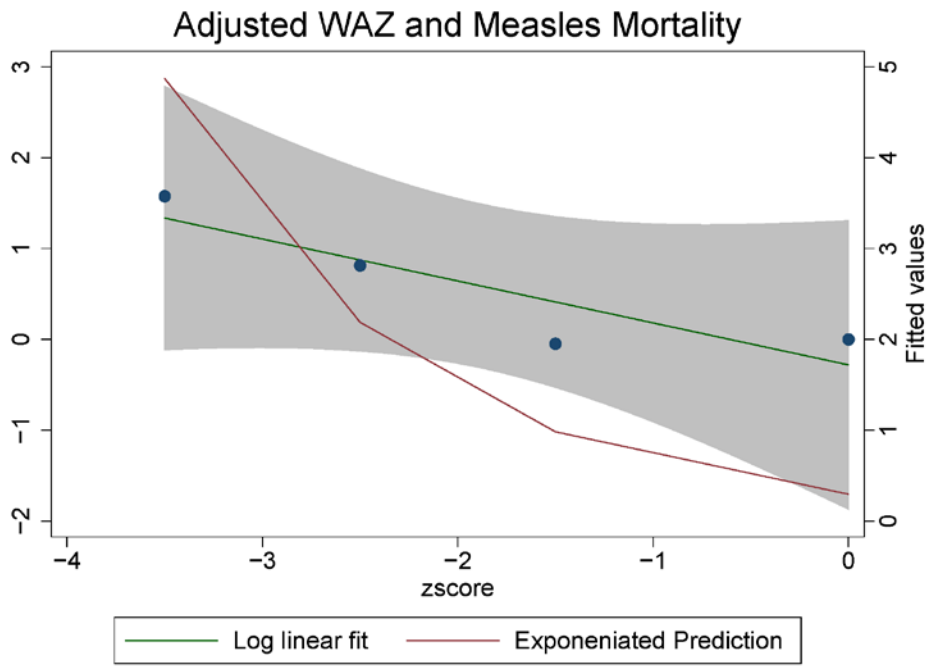
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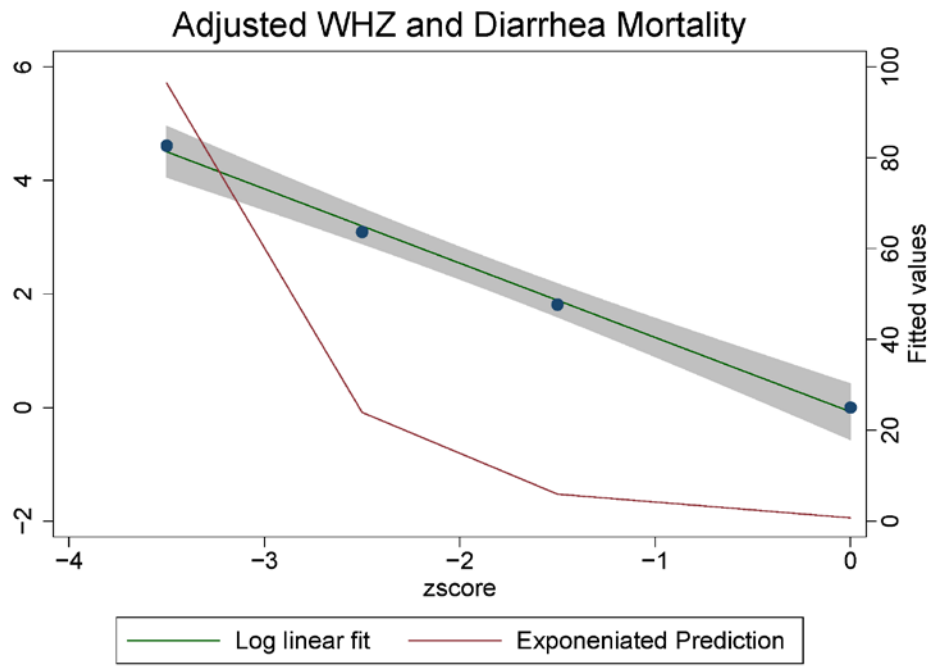


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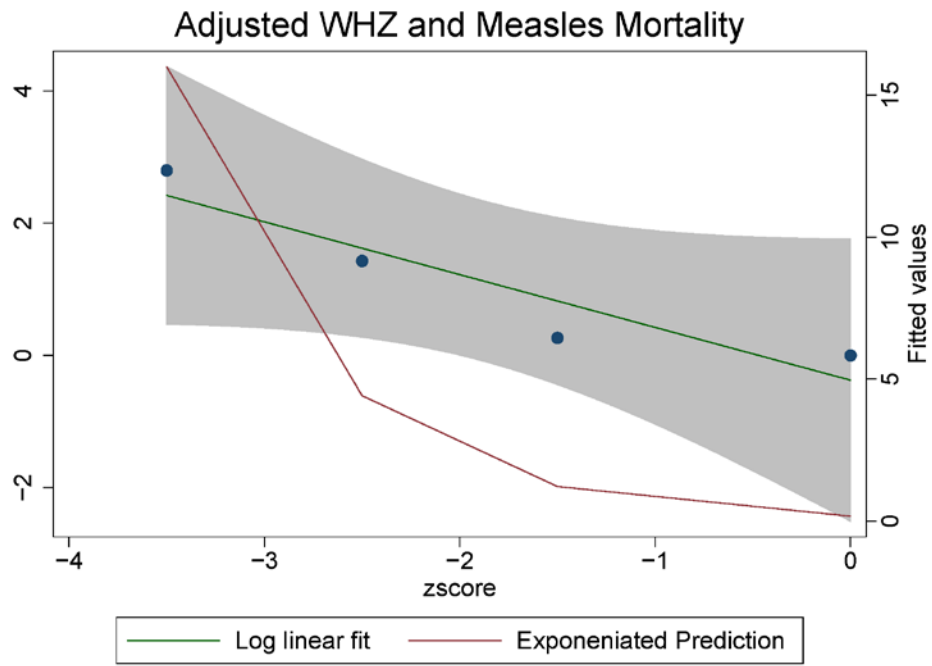


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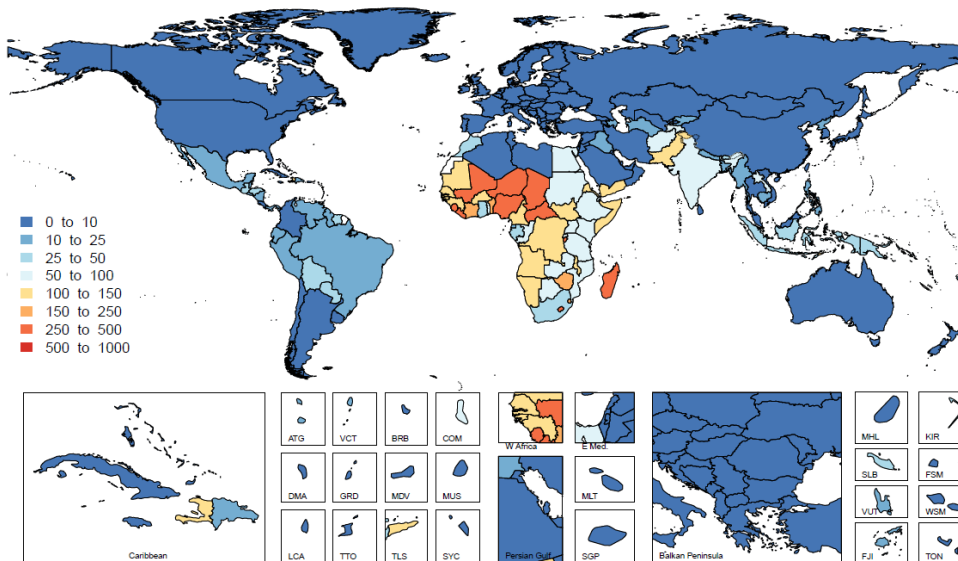
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Supplementary results

Table 1. Effect sizes from the systematic review and meta-analyses of the effect of diarrhoea on physical growth.

Measured Association	Estimate	Standard Error	Lower	Upper	p-value
Diarrhoea and HAZ	-0.00327	0.000433	-0.00412	-0.00242	4.43E-14
Diarrhoea and WAZ	-0.00774	0.000982	-0.00966	-0.00581	3.19E-15
Diarrhoea and WHZ	-0.00964	0.001482	-0.01254	-0.00673	7.78E-11

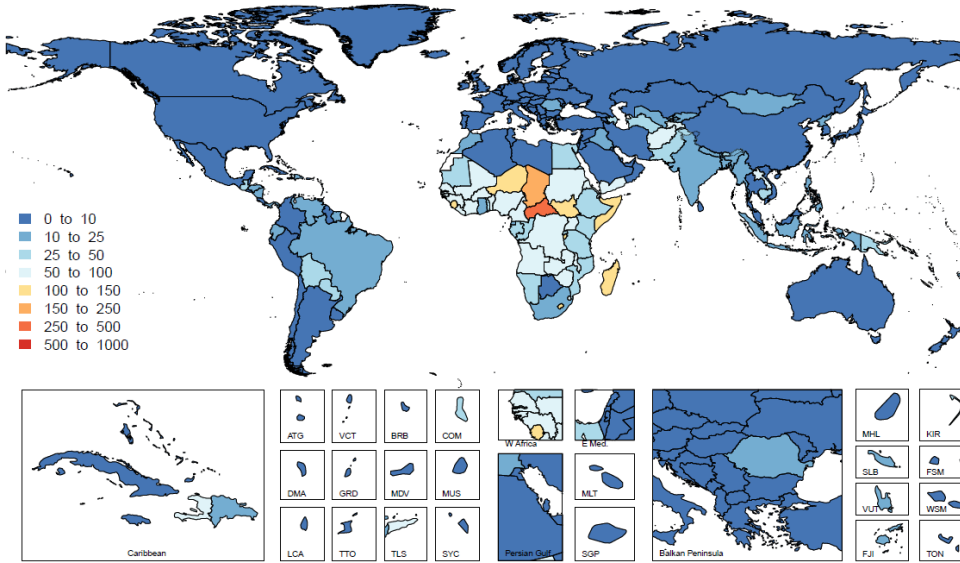
410 **Acute diarrhoeal disease DALYs per 1000 under-5 in 2016.** This map shows the acute diarrhoea DALYs (diarrhoea incidence and mortality) per 1,000 children under-5 years old in 2016.



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Long-term sequelae diarrhoeal disease DALYs per 1000 under-5 in 2016. This map shows long-term sequelae diarrhoea DALYs, due to growth impairment, per 1,000 children under-5 years old in 2016.



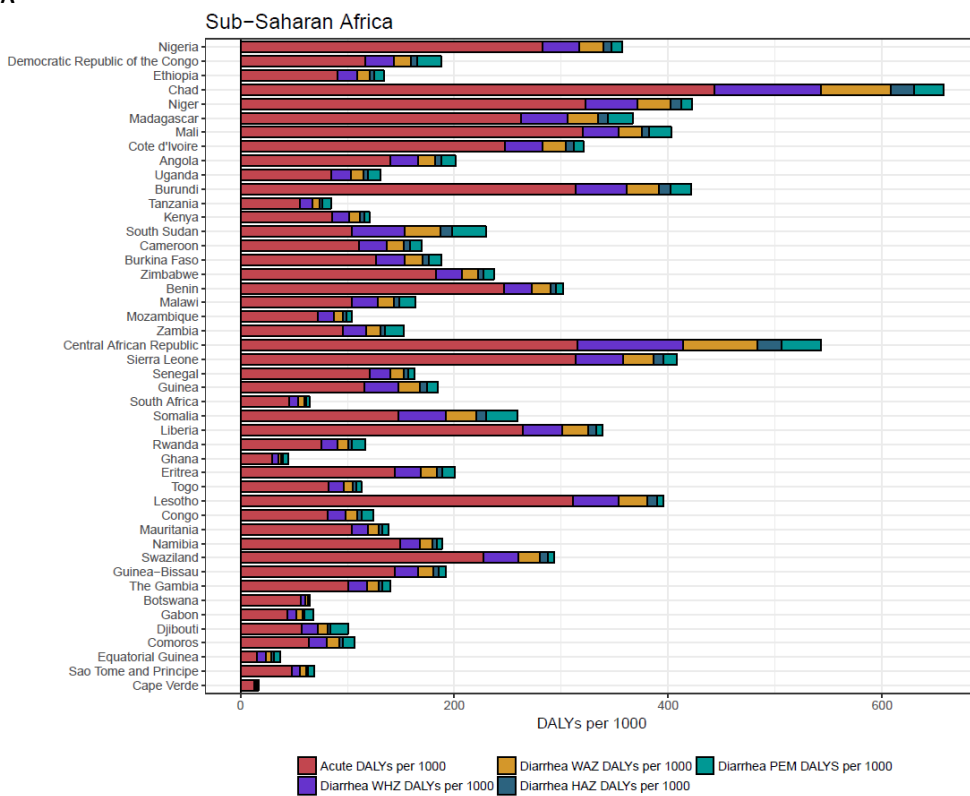
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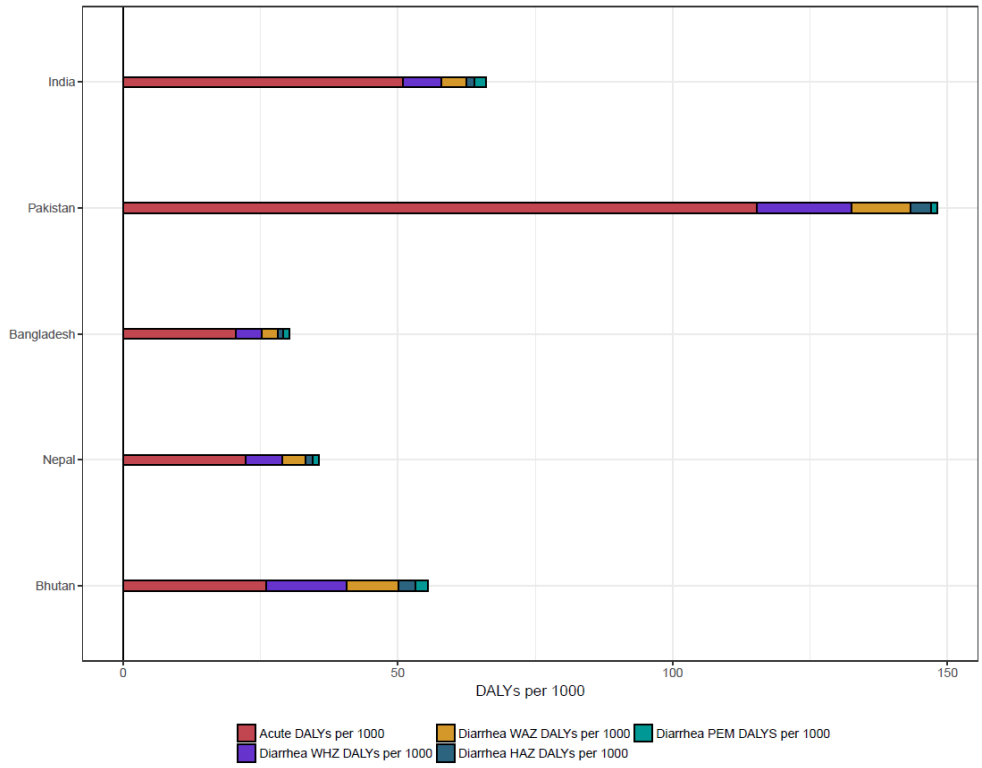
440 **Diarrhoea DALYs per 1000 by sequelae source and GBD super-region among children under 5 years old in 2016.** Acute DALYs represent the burden of diarrhoea before considering the long-term sequelae associated with physical growth impairment. Diarrhoea WHZ, WAZ, and WHZ DALYs represent the burden of diarrhoea due to its effect on weight and height and the subsequent risk of morbidity and mortality due to impaired physical growth. Protein-energy malnutrition (PEM) DALYs represent the burden of disease due to low weight caused by diarrhoea. Countries are ordered from top to bottom by the total number of DALYs due to diarrhoeal diseases in 2016.

445 **A**

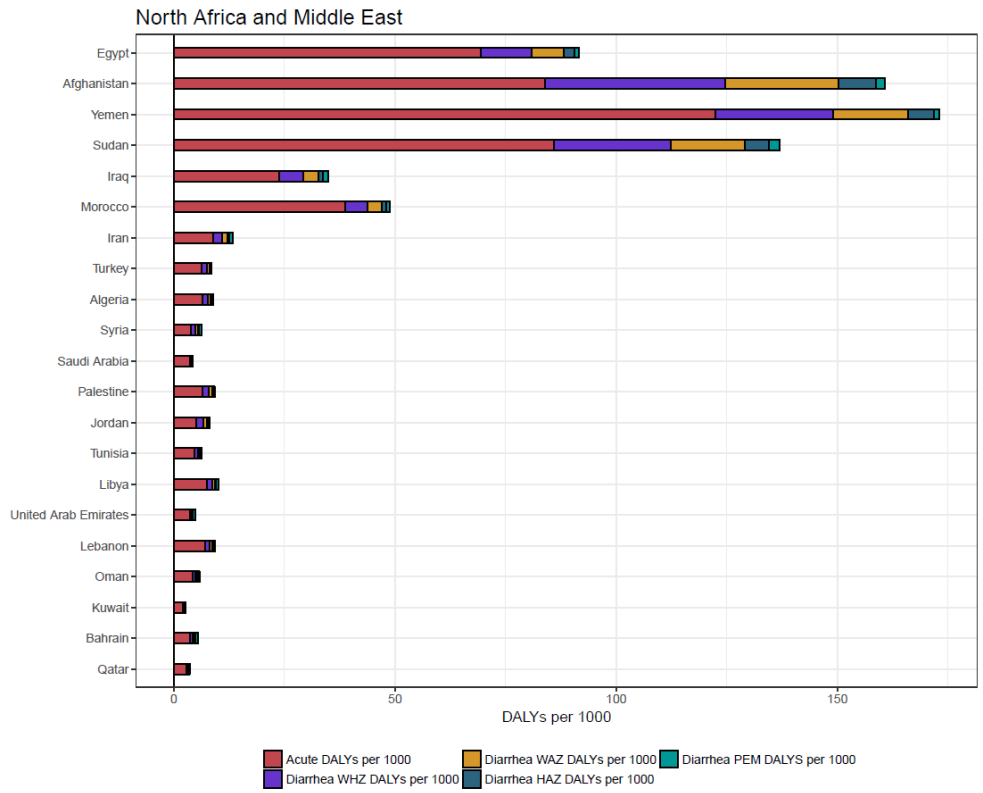


B

South Asia

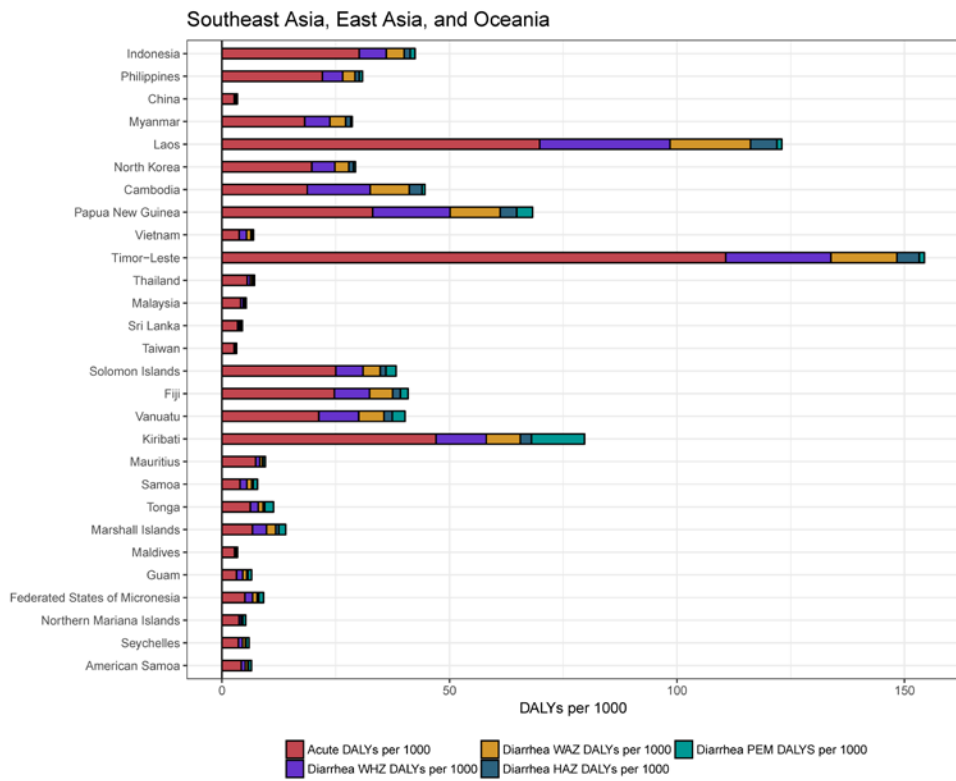


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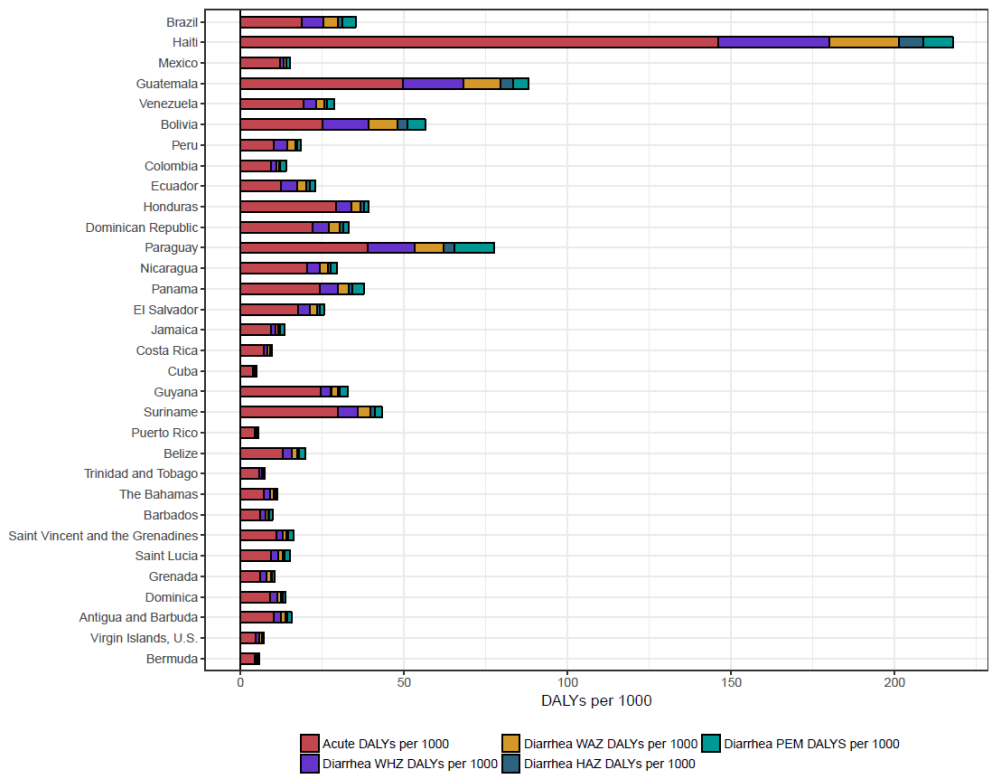
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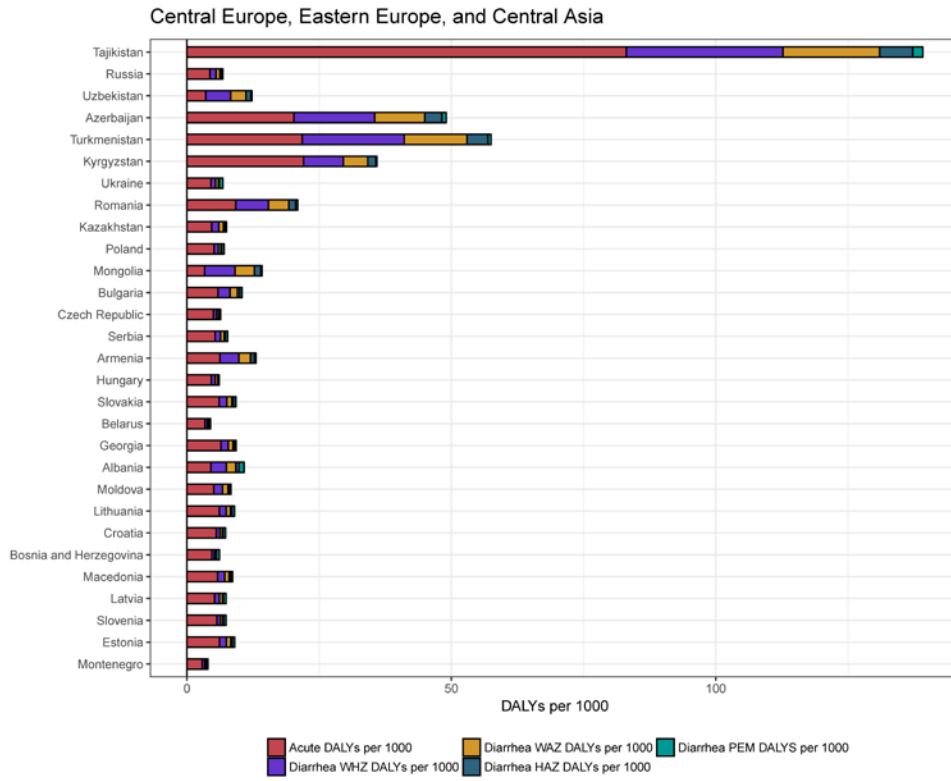
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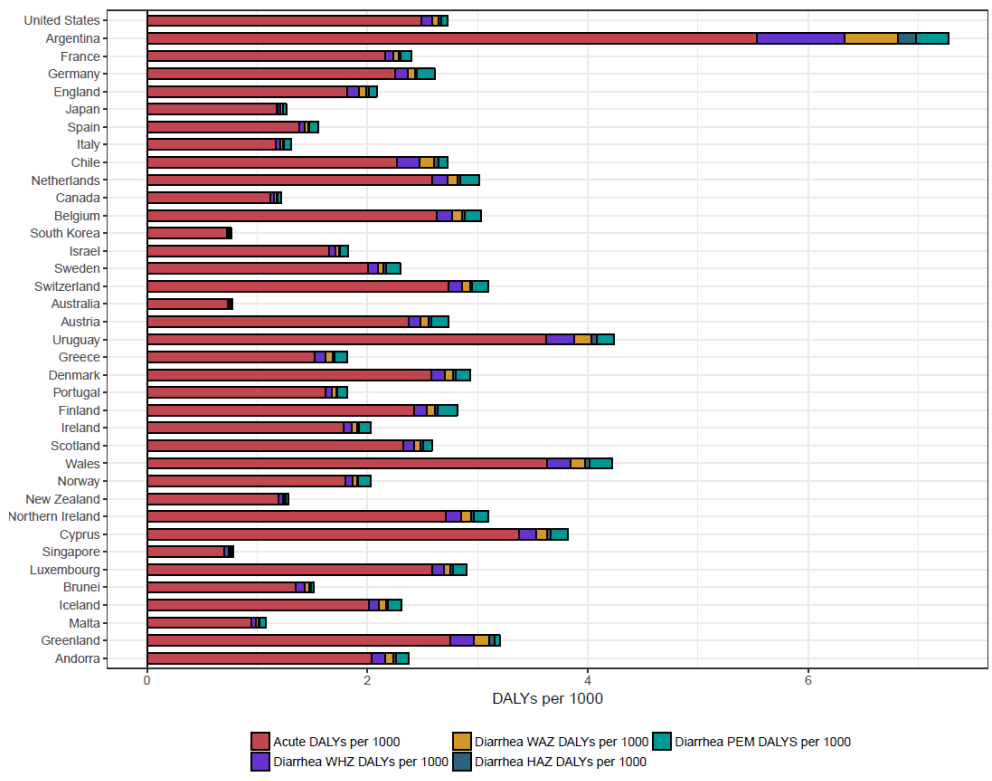
Latin America and Caribbean





G

High-income



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mortality, and aetiologies of diarrhoeal diseases: a systematic analysis for the Global Burden of
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national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195
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