

Quantifying the Burden of Malnutrition in Children with Orofacial Clefts: SUMMARY REPORT

FINAL Report

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Summary Report

Introduction

Orofacial clefts are among the most common congenital conditions around the world, with a global prevalence of 1.41 per 1000 live births.¹ An estimated 195,000 (125,000–295,000) babies are born with clefts each year, and 4.62 (3.76–5.67) million persons are living with unrepaired or inadequately repaired clefts.² Structural abnormalities range in presentation from a small notch in the upper lip (incomplete cleft lip), to a gap in the lip that extends through the upper gum and into the nostril (complete cleft lip), to a wide and complete opening that extends from the palate through the gums and the lip (cleft lip and palate).³ These various conditions can have a significant impact on the health and subsequent quality of life for affected individuals.

A principal effect of orofacial clefts is difficulty with feeding and thus obtaining the proper nutrition. The presence of a cleft reduces an infant's ability to create suction, which is needed for breast feeding or bottle feeding. Swallowing can also be problematic, leading to excessive air intake, choking, gagging, and other forms of discomfort.⁴ Collectively, these challenges result in diminished intake of food and low caloric gain. In combination with heightened energy expenditure during feeding, a negative energy balance can occur.⁵ Infants and children with cleft lip and/or palate are at an elevated risk of growth failure,⁶ with variable growth outcomes according to the type of cleft, age, and sex.⁷ The likelihood of undernourishment and associated growth difficulties is even greater in low- and middle-income countries, where malnutrition is common.^{8–10}

Feeding interventions for individuals with cleft conditions have been designed to address growth-related problems. Among these, specialized equipment and education for parents have been beneficial.^{11,12} Psychosocial risk assessments and patient tracking efforts to frequently monitor weight have also resulted in positive outcomes, even among high-risk patient families.⁵ Surgical cleft repair is largely successful in promoting weight gain, with little risk of surgical complications or downstream feeding limitations.^{13,14} Furthermore, early surgical repair (< 3 months) has recently been reported to improve weight gain relative to traditional timing of surgery (3–6 months).¹⁵ To better target these services and treatment modalities, it is critical to understand the combined burden of malnutrition and clefts, with an ultimate goal to reduce the prevalence of malnutrition and stunting in individuals affected by orofacial cleft abnormalities.¹⁶

As the global leader in the estimation of burden of diseases, injuries and risk factors, the Institute for Health Metrics and Evaluation (IHME) at the University of Washington is excited to support Smile Train in these aims.

Objective

Our objective was to estimate the global burden of child growth failure (CGF), a specific subset of undernutrition, in the population with orofacial clefts and to quantify the contribution that growth failure in these individuals has to the overall global burden of malnutrition. Many groups use the term “malnutrition” to refer to the collection of stunting, underweight, and wasting. Within the GBD, we label this as CGF to reflect the fact that poor growth in childhood can result from many different etiologies, not simply inadequate caloric intake. Due to a comparative sparsity of height data, we focused exclusively on underweight status as a proxy for malnutrition in this analysis. Utilizing patient data compiled by Smile Train and incorporating methodology, data, and infrastructure from IHME's Global Burden of Disease (GBD) Study, we generated consistent and comparative modelled estimates for all countries on the rate of malnutrition in children younger than 5 by age, sex, location, and year. This work represents the first set of globally comparative estimates to assess orofacial clefts and nutrition status, which can be used by Smile Train and other partners in their strategy for inclusive nutrition programs and comprehensive cleft care to support mothers and babies impacted by clefts.

Approach

Overview and Flowchart

We extracted, processed, and standardized cleft patient data from Smile Train Express. These data included weight and age observations for the past 20 years, and height since 2021. We modified the data as necessary to align with IHME's GBD modeling demographic groups, which included assigning ages to GBD age ranges, designating sex as male or female, matching location information to GBD regions, and binning according to year. We then incorporated the adjusted data into a meta-regression model to generate global estimates of the rate of underweight in cleft patients younger than 5 years, stratified by age, sex, location, and year. **Figure 1** illustrates our approach to estimation.

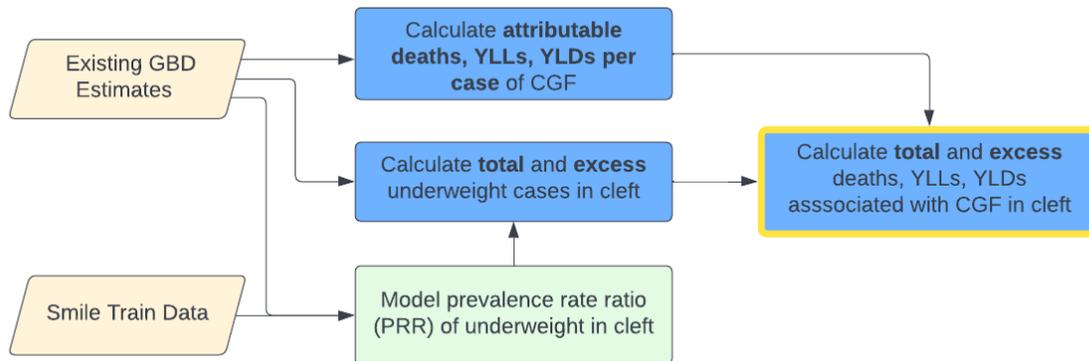


Figure 1. Simplified estimation flowchart for quantifying the burden of malnutrition in children with orofacial clefts.

We matched these underweight rates in children with clefts with the existing corresponding general population estimates of underweight prevalence rates from the GBD. Then we estimated the following:

- **Comparative risk of malnutrition in those with clefts:** We calculated the prevalence rate ratio (PRR) by dividing the rate of underweight condition in the under-5 population with orofacial clefts by the underweight rate in the entire under-5 population.
- **Comparative malnutrition burden in those with clefts:** We compared the total number of children with malnutrition and the number with **both** cleft condition and malnutrition to generate the proportion of total malnutrition that is associated with orofacial clefts. We used this proportion, as well as the PRR above, to calculate the number of “excess” cases of malnutrition in those with clefts.
- **Health consequences of malnutrition in those with clefts:** We evaluated the health consequences of malnutrition in individuals with clefts by leveraging GBD-analyzed relationships between malnutrition and subsequent malnutrition-related illness and death. We applied this to the total and “excess” number of malnutrition cases in children with orofacial clefts, allowing us to estimate the health consequences of malnutrition specifically in the cleft population.

The outputs of this work are estimates of the burden of underweight condition in children younger than 5 years with orofacial clefts. These estimates encompass relative rates of underweight in those with clefts, total children with underweight status and cleft occurrence, excess malnutrition cases in those with clefts, and the associated malnutrition-related consequences including deaths and disease burden. These results are detailed by country,

age, sex, and year. We also provide the extracted and harmonized datasets, written reports, analytic code, and summary tables and figures for use by Smile Train in their 2022 State of the World’s Cleft Care.

GBD Inputs

Overview of the Global Burden of Disease

The GBD is the largest systematic study that quantifies the comparative magnitude of health loss due to diseases, injuries, and risk factors by age, sex, and geographies for specific points in time. With a vision for all lives to be lived in full health, IHME uses the GBD to assess how 369 diseases and injuries and 87 risk factors contribute to health loss in 204 countries and selected subnational locations—producing regular estimates of all-cause mortality, deaths by cause, years of life lost due to premature mortality (YLLs), years lived with disability (YLDs), and disability-adjusted life years (DALYs). The most recent iteration of GBD included estimates from 1990 to 2020 for each of 25 distinct age groups from birth to 95+ years and for two sexes, separately.

GBD Cause Estimation of Orofacial Clefts

The GBD study includes estimates of the incidence, prevalence, and mortality due to orofacial clefts. These are constructed within the “causal” framework of GBD, where each death or morbidity has a single underlying cause, and all diseases are analyzed in a mutually exclusive and collectively exhaustive fashion to provide a comprehensive assessment of levels and trends of health loss across populations. Details of how orofacial cleft models were developed are in the Appendix of this report. Briefly, we used cause of death data sources such as vital registration (VR), verbal autopsy (VA), and surveillance data in our attempt to identify all the available data for deaths directly attributed to an orofacial cleft condition—noted as the primary underlying cause of death. We standardized these data to ensure comparability and quality. We then proposed a diverse set of models within a cause of death ensemble modeling framework, confirming that basic plausibility criteria were met. These models were assessed for predictive validity and then used to compute YLLs, or years lost due to premature mortality, and cause-specific deaths. To estimate the nonfatal disease burden associated with orofacial clefts, we used data from systematic reviews, surveys, and disease registries. These data were adjusted and standardized (i.e., checked for consistency across incidence, prevalence, and mortality) before performing a meta-regression based on a compartmental model of disease. We modeled the epidemiological characteristics of orofacial clefts. Then, following a comorbidity correction, we were able to generate estimates of the health loss due to cleft conditions.

GBD Risk Factor Estimation of Child Growth Failure

GBD produces estimates of CGF, a risk factor group. The three sub-components of CGF that we model include stunting (defined by a height-for-age Z score), wasting (defined by a weight-for-height Z score), and underweight (defined by a weight-for-age Z score), each of which is analyzed separately and in an internally consistent manner. Though data constraints led us to focus on underweight condition for this analysis, we include here the full details of CGF estimation for completeness. CGF is estimated as part of the “comparative risk assessment” framework of GBD, where the population health impact of individual causal risk factors is evaluated by quantifying the exposure to each risk factor and the individual-level, outcome-specific consequences of being exposed to that risk factor.

The GBD approach quantifies burden for risk factors using a technique called population attributable fraction (PAF), whereby the population-level impact of a risk factor can be estimated given knowledge of the exposure and relative risk of an outcome. Evidence of the causal relationships between risks and outcomes are carefully scrutinized on a case-by-case basis, and only those with sufficient causal evidence are retained in the final

estimates. Multiplying the PAF and the rates of specific outcomes leads to an estimation of the attributable burden of a given outcome linked to a specific risk factor. Summing across all outcomes provides a measure of the total health burden associated with an individual risk factor (in terms of YLLs, YLDs, and DALYs). Unlike GBD causes, GBD risk factors are not analyzed in a manner that allows for results to be readily summed across risks. For this reason, there is an additional step to simulate the mediation, or overlap, between related risks and thereby allow for GBD quantification of the total attributable burden to all component risks combined—in this case, stunting, wasting, and underweight.

We followed a four-step modeling process to generate our stunting, wasting, and underweight exposure estimates. First, we used ensemble modeling to fit a series of distributions to each microdata source. Second, we modeled prevalence of mild, moderate, and severe CGF (based on established levels of statistical deviation from the World Health Organization's Child Growth Standards¹⁷) and mean Z score values using a time series modeling strategy. This allowed us to generate estimates for each age group, sex, year, and location. Next, we derived the variance corresponding to each of the predicted mean and prevalence values and calculated probability density functions (PDFs). Finally, PDFs were integrated to determine the prevalence associated with mild, moderate, and severe CGF.

The outcomes paired with CGF risks include lower respiratory infections (LRI), diarrhea, and measles and protein-energy malnutrition (PEM). 100% of protein-energy malnutrition was assumed to be attributable to each of underweight and wasting. The relative risks (RR) for CGF are derived from a pooled analysis of 10 prospective cohort studies by Olofin and colleagues,¹⁸ a pooled cohort analysis of all-cause mortality by McDonald and colleagues,¹⁹ and 15 longitudinal studies from the Bill and Melinda Gates knowledge integration database.²⁰ To account for high correlation between stunting, wasting, and underweight, a joint distribution of the indicators was created. From this, 1000 RR draws for each univariate indicator and severity level were generated, and the univariate RRs were adjusted for diarrhea, LRI, and measles to account for interactions between the CGF indicators. Lastly, RRs were adjusted using RR optimization to minimize error and account for joint distribution and interactions between indicators and outcomes.

Analysis of CGF in the Smile Train Surgical Database

Overview of the Smile Train Database

The digital database, Smile Train Express, contains patient information corresponding to 60 low- and middle-income countries where Smile Train offers essential care services. There are 20 years of weight and age data, obtained from children at the time of cleft surgery. Height data have been recorded since 2021.

Data Extraction and Processing

We used R statistical software to import Smile Train's patient and surgical datasets and conduct all subsequent analyses. We merged these datasets according to patient ID and extracted relevant information including birth date, sex, country, weight, and height, among others. Data were subjected to adjustment and standardization procedures, including assignment into GBD age, sex, and location categories. Age calculations were conducted using date of birth relative to evaluation, admission, and surgery dates. The appropriate age calculation was then used to extract child Z scores. Duplicate patient entries in the dataset were dropped, and primary surgical encounters were retained for merging with GBD outputs and calculating the attributable burden of malnutrition in those with orofacial clefts. We developed and implemented an approach for correcting errors in dates corresponding to evaluation, admission, and operation. For height and weight data, we used measurements obtained from the evaluation encounter and admission interchangeably to impute missing values as possible. Additionally, we corrected decimal errors in weights using WHO clinical growth charts.^{17,21} These data were then

used to calculate height-for-age Z score (HAZ), weight-for-age Z score (WAZ), and weight-for-height Z score (WHZ).

Modeling

After the processing of Smile Train data was completed, we calculated the prevalence of moderate underweight condition ($WAZ < -2$) for each country in the dataset according to age, sex, and year. We paired these prevalence rates with GBD 2020 estimates of moderate underweight prevalence in order to calculate the prevalence rate ratio (PRR). Global trends in PRR were assessed using an advanced meta-analytic tool called Meta-Regression Bayesian Regularized Trimmed (MR-BRT),²² which is a mixed-effects modeling tool that incorporates priors in the form of regularization or constraints in the optimization, optional automatic likelihood-based outlier detection, and predictive covariates. We tested several predictive covariates including Healthcare Access and Quality Index,²³ Socio-demographic Index,²⁴ and Universal Health Coverage Index.²⁵ We also explored several models that accounted for the differential effects of age, sex, and location. We found that a fourth covariate, GBD underweight prevalence, had the strongest relationship with PRR—warranting its inclusion in the model. Our final model had fixed effects on sex and age group, and a dose response linear fixed effect on logit-transformed prevalence of underweight in the general population, with 30% trimming.

Estimating the Burden of Malnutrition in Individuals with Orofacial Clefts

We used inputs from GBD and PRR predictions from the MR-BRT model described in Appendix 1 Section 1.2 to estimate the total and excess burden of malnutrition in those with orofacial clefts. GBD estimates used included prevalence of orofacial clefts, moderate underweight prevalence, and underweight-attributable deaths, years of life lost (YLLs), and years lived with disability (YLDs) for each condition with a causal relationship to underweight (measles, LRIs, diarrhea, and PEM). Formulas for these calculations and additional details are provided in Appendix 1 Section 1.2. We also used GBD population estimates to determine rates of outcomes and total counts.

PRR was used to calculate the total and excess rate (and cases) of underweight in those with clefts using the formula in Appendix 1 Section 1.2. We approximated the number of attributable deaths, YLLs, and YLDs associated with the underweight condition in the cleft population by first calculating each of these three health consequences of moderate underweight condition from overall GBD results. Then, to quantify the attributable burden of malnutrition in those with clefts, we multiplied deaths per underweight case, YLLs per underweight case, and YLDs per underweight case by the estimated total and excess number of underweight cases specific to the cleft population. This yielded attributable burden counts by cause, location, year, age group, and sex for the years 2000 to 2020.

Results

Figure 2 shows mapped results for children younger than 5 years for males and females combined in the year 2020, including the prevalence of orofacial clefts overall, prevalence of moderate underweight condition ($WAZ < -2$), PRR of underweight in the cleft population, total and excess prevalence of underweight in the cleft population, and death rate associated with total and excess underweight condition in the cleft population, and total deaths attributable to underweight in the cleft population. Figure 3 illustrates annual and cumulative total and excess burden of underweight condition in those with clefts, quantified in terms of cases and deaths

The highest cleft prevalence rates in 2020 were found across the countries of the North Africa / Middle East region, extending into Central Asia and South Asia. Cleft prevalence rates were moderately lower in sub-Saharan Africa, but still affected nearly 1 per 1000 children in many of those countries (Figure 2, top row, left). GBD

found that rates of moderate underweight condition were highest in Africa, extending from the Sahel to the Horn of Africa, and similarly affecting individuals in Yemen and the countries of South Asia (Figure 2, top row, right); in some cases, we observed rates as high as 1 in 3 children overall being underweight in the population. A number of countries in Southeast Asia and Oceania, including Indonesia and Papua New Guinea, also had high rates of underweight in children. The global pooled PRR was 2.15 in the year 2020 for children younger than 5 years for both sexes combined. This was an increase from a global pooled PRR of 1.86 in 2000. The lowest PRR estimates in 2020 were for Timor-Leste, Yemen, and Niger, all of which had $PRR \leq 1.5$. Next was India, with PRR of 1.54 in 2020, which was an increase from 1.31 in 2000. The countries with the highest PRR in 2020 were New Zealand and Australia, with values of 11.93 and 13.16, respectively (Figure 2, second row), followed by other high-income countries with low population rates of underweight condition. Combining PRR with population level estimates of cleft anomalies and underweight condition, we were able to see that those with clefts in sub-Saharan Africa, south Asia, Oceania, and southeast Asia had the highest total rates of underweight (Figure 2, third row, left) and excess rates of underweight (Figure 2, third row, right). Combining further with deaths per case of underweight from GBD, we saw the total and excess burden again was concentrated in the areas with the highest malnutrition rates, namely peri-Saharan African countries, Somalia, Pakistan, and India (Figure 2, bottom row left [total] and right [excess]).

There were just over 600,000 children younger than 5 years living with clefts in the year 2020, a number that has remained relatively unchanged since 2000. While the total number of cases of underweight condition in the cleft population declined in these two decades, the excess number remained static or slightly increased and in 2020 was just under 100,000 worldwide (Figure 3, top). Owing likely to outsized improvements in prevention and syndromic management of malnutrition-related illnesses (measles, diarrhea, lower respiratory infections), the decline in deaths was more substantial from 2000 to 2020, yet there were still an estimated 525 excess and 1,040 total malnutrition-related deaths in children with clefts in 2020. There were cumulatively nearly 21,000 cumulative excess malnutrition-related deaths in children with clefts from 2000 to 2020 and more than 46,000 total malnutrition-related deaths in those with clefts (Figure 3, bottom).

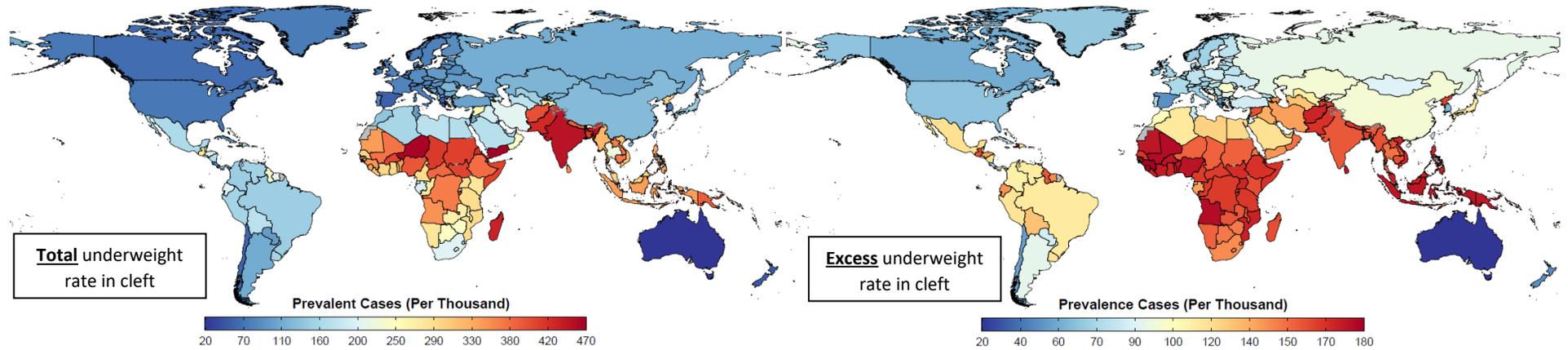
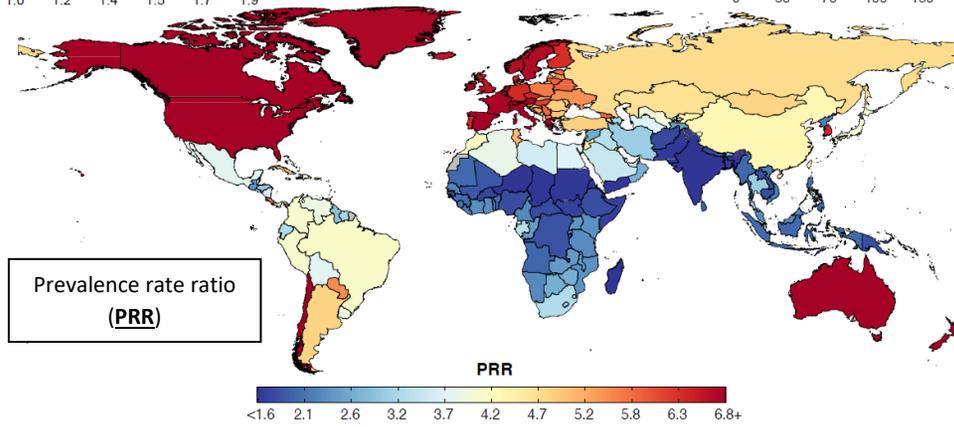
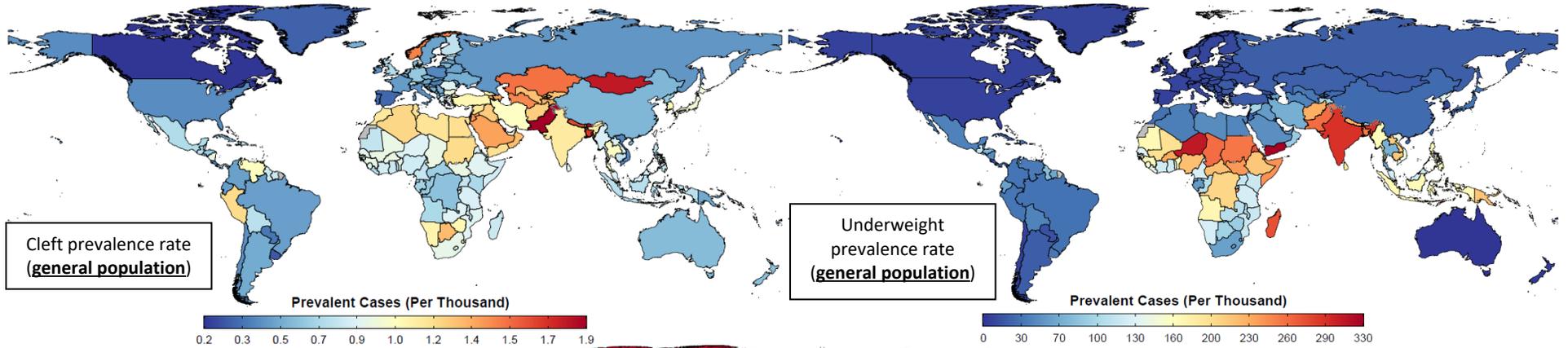
Implications of the Findings

Malnutrition in the cleft population is categorically worse than that in the general population in all scenarios. Based on our analysis of Smile Train data, at the global level, children with clefts were 2.15 times more likely to be underweight than were all children younger than 5 years. There were nearly 200,000 children globally who were living with clefts and were underweight in 2020. This number has changed very little since the year 2000, and over that period of time, there were more than 1.8 million excess cases of underweight condition in the cleft population. We estimated there were 21,000 deaths, 1.8 million YLLs, and 54,000 YLDs associated with the excess underweight condition in children with clefts.

The estimates presented here can plausibly be considered a lower bound of the full burden of malnutrition in children with orofacial clefts for several reasons. First, due to sparsity of longitudinal height data, we did not look at the relationships with wasting and stunting, which also would be expected to show a strong relationship with the nutritional problems of orofacial clefts. Second, the GBD causal relationships do not specifically capture the potential connection between underweight and other respiratory problems, most specifically upper respiratory infections and otitis media, which would be hypothesized to have similar risk relationships, or the known associations between orofacial clefts and other congenital syndromes that may make children even more susceptible to illness and death if and when they develop malnutrition. Third, while we developed a comparatively simple model evaluating PRR for moderate underweight condition, it is entirely possible that

children with clefts are disproportionately more likely than their peers without clefts to have severe forms of CGF, which are associated with higher risk of health loss due to LRIs, measles, and diarrhea. Fourth, like GBD, this analysis did not include an assessment of the excess burden associated with being underweight in the neonatal period or past the age of 5 years. It also was not able to quantify other repercussions of malnutrition in childhood, which may include impaired cognitive development, language difficulties, and potential increased risk of early-onset adult metabolic diseases such as high blood pressure, diabetes, and kidney problems.

These findings of increased vulnerability in children with orofacial clefts and malnutrition highlight the importance of prevention, identification, nutritional support, and surgical treatment for children with clefts throughout the world. This is especially true in the current global climate, where the COVID-19 pandemic has led to disruptions of routine vaccination and other health services for children and there are widespread food shortages and unmet basic needs for children and their families.



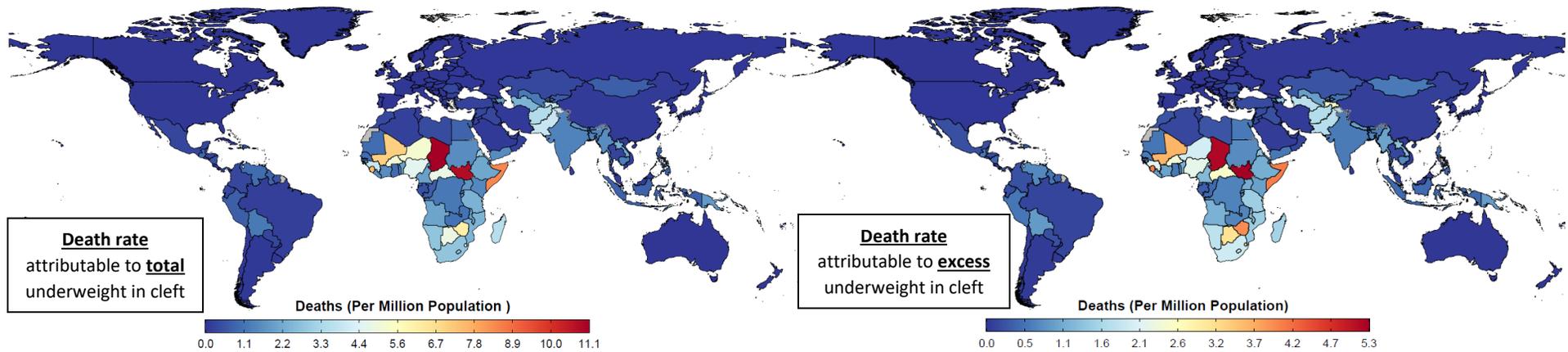


Figure 2: GBD cleft prevalence (top row, left), GBD moderate underweight prevalence (top row, right), PRR of underweight in cleft (second row), total underweight rate in cleft (third row, left), excess underweight in cleft (third row, right), death rate attributable to total underweight (bottom left) and death rate attributable to excess underweight (bottom right) in 2020, under 5 years, both sexes.

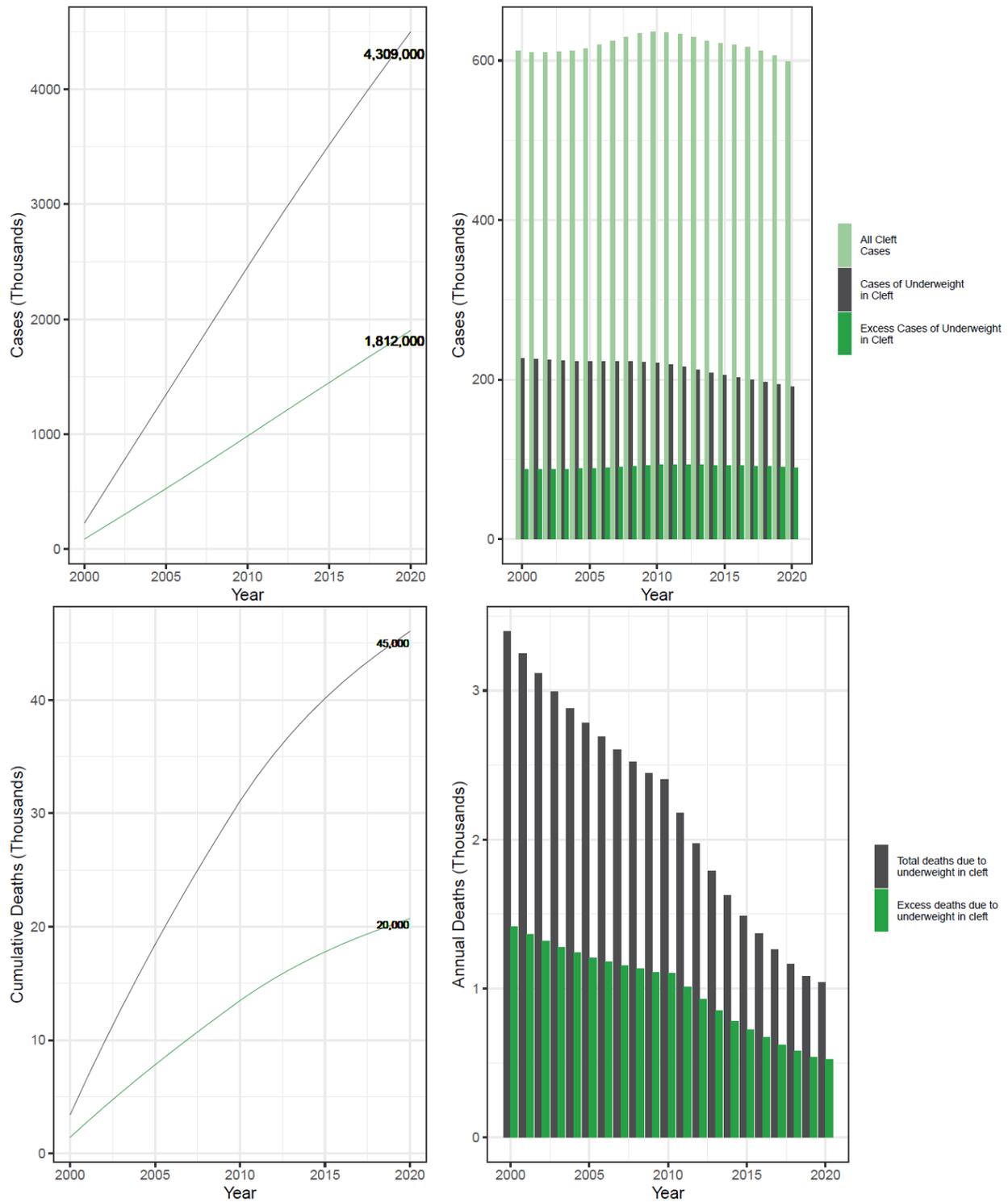


Figure 3: Overall prevalent cases of orofacial clefts, total cases, and excess cases of underweight in cleft (top) and total and excess deaths (bottom) globally in children <5 years, both sexes, cumulative and annually from 2000 to 2020

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