Risks, interventions, and costs in early life health and development

RISKS, INTERVENTIONS, AND COSTS IN EARLY LIFE HEALTH AND DEVELOPMENT

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Abstract

Reductions in child mortality over the past decades have been impressive globally. With declining mortality rates, interest in child development has been increasing. However, evidence on the magnitude of the burden of poor child development, as well as the knowledge bases regarding the most cost-effective interventions and key target populations are still limited.

In the first paper of this thesis, "Human capital loss attributable to stunting risks: A systematic analysis of the impact of risk factors for childhood stunting on schooling and income losses in 137 developing countries", we highlight that alleviating poverty-related risk factors for stunting in low- and middle-income countries may not only benefit children's nutritional status, but also result in increased education and larger labor market incomes in the long run. This work underscores the important impacts of early life investment and identifies key areas of intervention for governments and stakeholders.

In the second paper, "The impact of parsimonious versus comprehensive cost estimation in cost-effectiveness analysis: Economic evaluation of a kangaroo mother care program in Mali", we show ways in which costs are frequently underestimated in cost-effectiveness analyses. In our case study, we find that failing to account for administrative costs, demand-creation costs, and costs to patients' families results in cost-effectiveness ratios that are orders of magnitude smaller than if costs were comprehensively accounted for. This work suggests that existing cost-effectiveness estimates may need to be reviewed, and future studies should focus on comprehensive costing data collection in order to provide reliable evidence for resource allocation.

Recognizing the importance of early intervention in child development, in the third paper, "Can placental characteristics predict child development delays? Findings from São Paulo Western Region Cohort Study", we examine the relative ability of birth characteristics from hospital records, maternal risk

factors measured in surveys, and placental characteristics from pathology exam records to predict developmental delay at age three years. We find that placental characteristics have additional predictive ability of developmental adversity and may provide a novel opportunity to identify infants who would benefit from developmental intervention, helping maximize the impact of targeted programs.

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Introduction

Child health and development

Over the past several decades, there have been massive international efforts to reduce deaths among children. This was reinforced by the Millennium Development Goals (MDGs), whose primary health focus was on improved survival, and led to impressive declines in child mortality.[1] Specifically, deaths among children under five years of age declined from 143 per 1000 live births to 44 per 1000 live births between 1970 and 2013.[1]

Despite these remarkable improvements in survival, poor childhood growth and development remains a global challenge.[2,3] In 2010, nearly half of all children ages 3 and 4 years in low- and middle-income countries failed to meet their physical, cognitive, and/or socioemotional developmental potential.[4] While there are many ways to measure poor child growth and development, there are no universally-accepted measures.[5] That said, suboptimal physical growth is often measured by the presence of stunting (height-for-age below -2 standard deviations of the global growth standard median[6]). Stunting is widely measured and has strong correlations with other developmental metrics including cognition and motor scores,[7] and is therefore often used as a proxy measure for poor child development.

Early life developmental deficiencies lead to reductions in educational attainment, work capacity, and income.[8–12] In fact, an estimated US$177 billion is lost each year in lifetime wage earnings in low- and middle-income countries due to early childhood growth faltering alone.[13]

Recognizing this burden, the global policy sphere appears to be moving toward an increased focus on child development. Specifically, global strategies to improve women and children's health have transitioned to the overarching theme of "survive, thrive, transform"[14] from merely a focus on survival.[15] Similarly, the World Bank has highlighted the importance of considering human capital in the overall accounting of the wealth of nations,[16] suggesting a transition from rankings based on mortality alone, for

example. These changes in global policy focus underscore the importance of improving child development and signal a broader policy appetite for child development efforts.

Making well-informed, cost-effective progress in child development will require systematic measurement of the causes and effects of poor childhood outcomes in order to identify priority areas, and identification of cost-effective interventions for scale-up. This also requires a better understanding of the potential utility of prediction modeling in early child development to assess whether certain risks or characteristics measured early on can predict later delays. Below, we discuss each of these research areas as well as the contribution of this thesis in detail.

Systematic measurement of the impacts of risks for poor developmental outcomes

One of the first steps in priority-setting should be measurement. In order to identify target areas to improve child health and development, it is important to systematically and comprehensively quantify the leading causes and consequences of poor developmental outcomes at a global scale. Quantification of the risks for poor child development is important to highlight key risk factors that need to be addressed to improve outcomes and allow for the identification of regions and countries that may benefit from additional support.

Fortunately, previous work has identified key risk factors for poor childhood growth, and quantified their impact on stunting.[17] However, as previously described, the impact of the risks for poor growth extends beyond childhood to educational attainment and income, yet this has not been systematically quantified. The first paper of this dissertation expresses the impact of risk factors for poor growth in terms of the tangible metrics of education and income loss, and highlights the massive human capital ramifications of poor child development, underscoring the importance of continued policy attention in this area.

Identifying cost-effective interventions for child health and development

Given limited resources and the magnitude of the impact of poor child development, implementing interventions that are low in cost and high in impact is imperative. Early childhood has been identified as

the best time to intervene in terms of cost-effectiveness of interventions,[18–20] and interventions aimed at increasing preschool attendance, for example, have been deemed cost-saving.[18]

While cost-effectiveness analyses (CEAs) can provide valuable evidence to inform allocation of limited resources to maximize health gain, these analyses are subject to several common limitations. The usefulness of CEAs depends highly on how comprehensive and valid they are, which in turn depend on the key data inputs, analytic choices, assumptions and values that are incorporated into estimates of intervention effects and costs. In addition, in order to accurately use CEAs to choose one intervention over another, the methods used and the scope must be comparable.[21,22] At present, much of the CEA literature uses varying methods and fails to account for key costs.[23,24] This type of inconsistency and lack of comprehensiveness may have an important impact on the estimated cost-effectiveness of interventions, but this has not yet been examined. The second paper of this dissertation provides the first empirically-based CEA of a kangaroo mother care program, and demonstrates the magnitude of the bias generated by failing to account comprehensively for costs.

Predicting poor developmental outcomes

Predicting the risk of future health outcomes can help guide clinical and public health intervention by targeting high-risk subgroups of the population. The field of cardiovascular research has used prediction modeling for the past several decades.[25] Researchers use information on individuals' risk profiles to predict their risk of cardiovascular outcomes, and national and international guidelines recommend prophylaxis according to risk level.[26,27] This type of strategy is still new to the field of child development,[28] but the potential impact of its expansion seems large.

Early intervention is key to improve child development outcomes.[29] The First 1000 days (from conception to age two years) have been highlighted as a crucial developmental period, and interventions during this time can have long-term, cost-effective benefits.[8,18–20] Given limited resources and the magnitude of the

impact of poor child development, intervening early among children most at risk for poor outcomes is likely to generate impact that is even more cost-effective.

However, before such benefits can be realized, progress is required in risk prediction modeling for child development. While decades of research have documented the associations between various risk factors and poor developmental outcomes,[30–35] using these risks in multivariable prediction modeling is still nascent. In addition, the recent explosion in the availability and use of electronic medical records and "big data" in healthcare[36,37] suggests that there may be innovative opportunities going forward to use novel data in risk prediction. The final paper of this thesis tests the ability of placental characteristics from pathology exam records to predict adverse development outcomes among children, finding that these characteristics are equally effective predictors as maternal characteristics measured in surveys.

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Paper 1: Human capital loss attributable to stunting risks: A systematic analysis of the impact of risk factors for childhood stunting on schooling and income losses in 137 developing countries

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Abstract

Background

Child mortality continues to decline globally, which has resulted in greater focus on early-life interventions to support broader child health, well-being, and human capital development. Previous work has quantified the relative impact of poverty-related risk factors on stunting, but the limiting impact of these risk factors on human capital (capacities that lead to economic productivity) can persist through adulthood and has not been systematically examined. To fill this gap and help identify areas of potential

cost-savings, we estimated the national, regional and global schooling and income losses associated with poverty-related risk factors in 137 developing countries.

Methods and Findings

We examined 18 risk factors for stunting grouped into 5 groups: maternal nutrition and infection, teenage motherhood and short birth intervals, fetal growth restriction and preterm birth, child nutrition and infection, and environmental factors. We estimated the schooling losses and lifetime wage income losses associated with each risk factor based on the fraction of stunting attributable to each risk and risk group, the association between stunting and schooling, and country-specific wages and income returns to education in 2010.

Among the 18 individual risk factors, term, small-for-gestational age (TSGA) was responsible for the largest human capital impact, resulting in US$41.6 (95% confidence interval 31.7, 52.8) billion of lost wages during the lifetime of a birth cohort across all developing countries, equivalent to US$338 per child. Childhood diarrhea accounted for US$28.5 (11.4, 47.3) billion (US$232 per child) and unimproved sanitation for US$24.5 (19.2, 30.4) billion (US$199 per child) of lost wages. Among the five risk factor groups, the group of fetal growth restriction and preterm birth had the greatest impact on income loss at US$59.1 (46.3, 73.3) billion. This risk group was associated with 26.5 (95% confidence interval 21.1, 32.5) million years of schooling lost worldwide, while the teenage motherhood and short birth interval risk group was responsible for the smallest loss, at 1.6 (1.3, 1.9) million lost years of schooling. Since these risks may impact schooling and wages through pathways other than stunting, our results should be considered conservative estimates of their true impact on schooling and wages.

Conclusions

Alleviating poverty-related risk factors for stunting in developing countries may not only benefit children's nutritional status, but also produce cost-savings in the long-term through better educational

attainment. We encourage a broader quantification of the impact of risks and disease to include effects on human capital.

Introduction

Over the past several decades, there have been substantial investment and international efforts to reduce child mortality. This was bolstered by the Millennium Development Goals (MDGs), which focused on improved survival, and led to impressive declines in child mortality.[1]

Despite these remarkable improvements in child survival, suboptimal childhood growth and development remains a global challenge.[2] In 2010, nearly half of all children ages 3 and 4 years in low- and middle-income countries failed to meet their physical, cognitive, and/or socioemotional developmental potential.[3] These early life growth and development adversities can have substantial effects across the lifespan and lead to poor health and cognitive ability, and reductions in educational attainment, work capacity, and income.[4–8]

Perhaps in recognition of this, global strategies to improve women and children's health have transitioned to the overarching theme of "survive, thrive, transform"[9] from merely a focus on survival.[10] Similarly, the World Economic Forum's 2016 Human Capital Report states "A nation's human capital endowment — the knowledge and skills embodied in individuals that enable them to create economic value — can be a more important determinant of its long-term success than virtually any other resource".[11] While human capital has been defined in slightly different ways over the past several centuries, its definition almost always includes reference to educational attainment and income earning potential.[12] In addition to declaring investment in human capital as one of the three methods to achieve the World Bank's goals of ending poverty and boosting shared prosperity,[13] the Bank leadership highlights the importance of considering human capital in the overall accounting of the wealth of nations.[14] To better align the measurement of the burden of risk factors with this agenda, we propose that human capital (not just morbidity and mortality, as is standard[15–18]) also be considered when assessing the impact of a given risk factor.

Several previous studies have examined the role of poverty-related risk factors on childhood growth. A recent study identified key risk factors for stunting (defined as a height-for-age z-score [HAZ] more than

2 standard deviations below the global reference median[19]),[20] a condition affecting about 30% of children under age 5 years worldwide.[21] There is also strong evidence that risks for stunting may affect human capital. For example, previous research has examined the impact on schooling of specific risk factors such as preterm birth,[22] diarrhea,[23] clean water and sanitation,[24] or breastfeeding, [25,26] in one or a few countries. Similarly, a few studies have documented the economic consequences of individual risk factors such as low birthweight,[27] preterm birth,[28,29] or maternal underweight.[30] Other studies show the economic impacts of micronutrient or macronutrient supplementation interventions.[31,32] all in a few selected countries. However, all of these analyses focused on individual countries or a group of 17 high-stunting-burden countries and had important methodological limitations. For example, in these studies, the effect on schooling was only measured by impacts on college education[22] or school performance[23] and the financial impacts were only assessed by hospital costs[30] or were limited to adult wages.[22]

To address these limitations, we systematically estimated the impact of poverty-related risk factors, through stunting, on measures of human capital. Specifically, we estimated the national, regional and global wage income and schooling losses associated with 18 risk factors in 137 developing countries.

Methods

We estimated the impact of 18 risk factors for stunting and 5 risk factor groups jointly (Table 1.1) on schooling and wage income losses in 137 developing countries. Based on an extensive literature review, we selected risk factors that are modifiable, and have high-quality data on their exposure in developing countries and strong evidence on their effect size on stunting ("convincing" or "probable" evidence for a causal relationship with stunting; see Appendix Table 1.1 and additional details in Danaei et al[20]). While 18 are presented here, a separate paper examines the impact of four additional psychosocial risk factors for stunting on subsequent wage income loss (maternal education, maternal depression, intimate partner violence, and orphanhood). The countries in the analysis were included based on their designation as "developing" by the Global Burden of Disease Study.[33] The countries and their associated regions and sub-regions are presented in Appendix Figure 1.1. The impacts of these risk factors on stunting were

estimated for entire birth cohorts in these countries, based on the number of children born in 2010 (data on cohort size were provided by the United Nation's Population Division World Population Prospects 2015 Revision[34]). This work builds on the methods and results of two recent reports,[20,35] and extends those analyses to estimate the country-level human capital loss for each birth cohort that can be attributed to each risk factor through its impact on stunting, schooling, and wage income.

Table 1.1: Risk factors included in the analysis and their definitions

Risk factors	**Definition**
Maternal nutrition and infection	
Maternal short stature	Maternal height <160cm
Maternal underweight	Maternal BMI <18.5 kg/m^2
Maternal malaria	Malaria in pregnancy
Maternal anemia	Maternal hemoglobin <110g/L
Teenage motherhood and short birth intervals	
Teenage motherhood	Maternal age at delivery <20 years
Short birth intervals	<24 months between consecutive births
Fetal growth restriction and preterm birth	
Preterm, small-for-gestational age (PSGA)	Birth before 37 weeks of gestation and weight <10^{th} percentile for gestational age
Preterm, appropriate-for-gestational age (PAGA)	Birth before 37 weeks of gestation and weight ≥10^{th} percentile for gestational age
Term, small-for-gestational age (TSGA)	Birth at or after 37 weeks of gestation and weight <10^{th} percentile for gestational age
Low birthweight	Birthweight <2,500g
Child nutrition and infection	
Childhood zinc deficiency	Deficient zinc intake during childhood based on age- and sex-specific zinc requirements
Childhood diarrhea	Mean number of diarrhea episodes per year during childhood
Non-exclusive breastfeeding	Non-exclusive breastfeeding of infants under 6 months of age
Discontinued breastfeeding	Discontinued breastfeeding of children 6-24 months of age
HIV infection without (HAART) before 2 years of age	Child HIV infection without initiation of HAART until after 2 years of age
Environmental factors	
Unimproved sanitation	Lack of access to safe sanitation in the community (based on WHO/UNICEF JMP definition of improved sanitation[36])
Unimproved water	Lack of access to clean water in the community (based on WHO/UNICEF JMP definition of improved water source[36])
Use of biomass fuels	Use of biomass fuels for cooking and heating

Briefly, we had previously estimated the proportion of cases of stunting in 137 developing countries that were attributable to one risk factor or group of risk factors by combining estimates of the prevalence of risk factors and their relative risk for stunting among 2 year olds.[20] Appendix Table 1.2 displays the sources of information on each risk's exposure prevalence and effect size on stunting, which were combined using the epidemiologic methods of Comparative Risk Assessment.[37] This produced estimates of the population attributable fractions (PAFs) of stunting prevalence attributable to each risk. We also estimated the PAFs of stunting prevalence attributable to each of five risk groups; the groups were formed based on the similarity of risks and potential interventions to address them. We used joint PAF calculations[37] to eliminate double-counting of the effects of risks in the same group, and accounted for the fact that the relationship of breastfeeding and zinc deficiency with stunting is mediated through diarrhea.[20,38]

Separately, we had quantified the educational and income impacts of suboptimal childhood growth in terms of years of schooling and wages lost in each country by comparing the observed population HAZs with the global growth standard distribution.[35] To do so, we combined the magnitude of each country's suboptimal HAZ with the effect size from a pooled analysis of cohort studies that found that each standard deviation increase in HAZ at age two was associated with an additional 0.47 years of education (95% confidence interval 0.39, 0.56).[6] This yielded estimates of the years of schooling lost due to suboptimal HAZ in each country. We also estimated the country-specific wage income returns for each additional year of schooling based on a literature review and regression analysis where existing estimates were unavailable.[35] We estimated lifetime wage income based on income per capita in 2010 from the World Bank's World Development Indicator Database[39] and assuming that labor income is roughly equivalent to two-thirds of national income, as is standard.[40,41] We assumed 3% discounting and 2% net wage growth per year to quantify the net present value (NPV) of future wages over a lifetime.[35]

Here, we extended these results by multiplying the country-specific PAFs of stunting attributable to each risk and risk group by the estimated years of schooling lost and the lifetime wage income lost associated

with suboptimal country-specific population-level HAZ. Because the relationship between HAZ and stunting prevalence is linear (see Appendix Figure 1.2 for further description and visualization), and the factors used to estimate the impact on schooling and wages are simply linear transformations, the PAFs can be directly applied to the lost years of schooling and lost wage income associated with suboptimal HAZ to calculate the schooling and wage losses associated with each risk factor.

We also estimated the schooling and wage loss per child in each country (total years of schooling lost and wage income lost, respectively, divided by the cohort size). To facilitate comparison to other published results, we also calculated population-weighted averages of wages lost per child born across all 137 countries for specific risk factors.

To quantify uncertainty, we used 1000 independent random draws of the estimated PAFs (which incorporates uncertainty in risk factor exposure levels and relative risk) with random draws from years of schooling and total wage income lost due to suboptimal growth (which incorporates uncertainty in the association between HAZ and schooling and the estimates of wage returns to schooling). This allowed us to calculate estimated years of schooling and wage income lost attributable to each risk factor for each draw. The 95% confidence intervals were calculated by using the 2.5^{th} and the 97.5^{th} percentiles of draws. All analyses were conducted using STATA SE version 13.1. This study was exempt from Institutional Review Board review.

Results

Among the 18 selected, the most prevalent risk factors for stunting were nonexclusive breastfeeding (prevalence of 66% across all developing countries), use of biomass fuels (56%), and unimproved sanitation (47%). The risk group of fetal growth restriction and preterm birth was associated with 26.5 (95% confidence interval 21.1, 32.5) million years of schooling lost worldwide, followed by environmental factors with 17.6 (14.2, 21.5) million, maternal nutrition and infection with 11.8 (9.1, 15.0) million, and child nutrition and infection with 11.0 (4.9, 17.8) million. The teenage motherhood and short birth interval risk group was responsible for the smallest loss, at 1.6 (1.3, 1.9) million lost years of

schooling. Appendix Figure 1.3 shows the estimates of the lost years of schooling attributable to each of the 5 risk factor groups by country.

Term, small-for-gestational age (TSGA) was the individual risk factor responsible for the largest economic cost, resulting in US$41.6 (95% confidence interval 31.7, 52.8) billion of lost lifetime wages per birth cohort across all developing countries. Childhood diarrhea accounted for US$28.5 (11.4, 47.3) billion and unimproved sanitation for US$24.5 (19.2, 30.4) billion lost. The rankings by individual risk factor are presented in Figure 1.1 and by risk groups in each region in Table 1.2. We omit low birthweight from the presentation of the main findings given that its effect is seen in the combination of TSGA and PSGA (though we present it in Appendix Table 1.3 for reference).

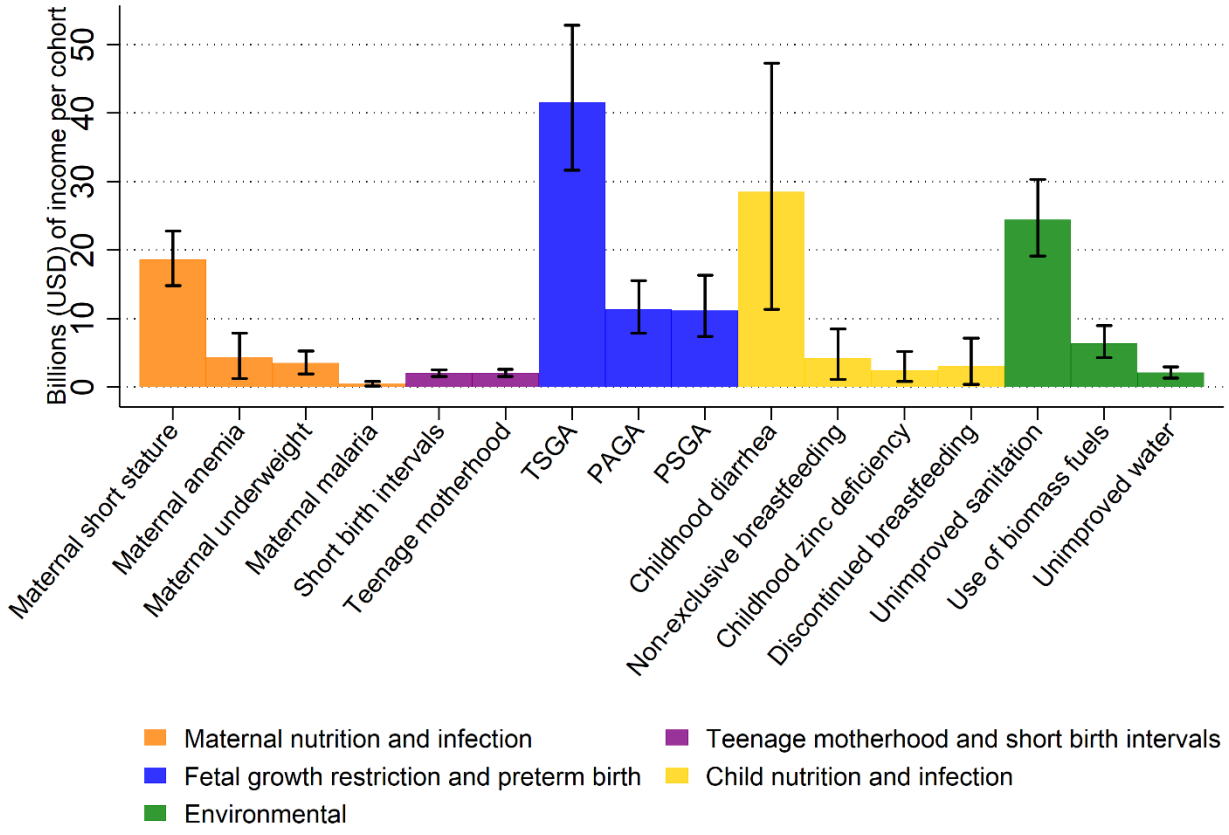


Figure 1.1: Lifetime economic cost (US$) of each risk factor* for the cohort of children born in 2010 in 137 countries, grouped by risk factor category

* HIV infection without HAART before 2 years of age is not included because data are only available for 45 countries

Table 1.2: Lifetime economic cost (US$ millions per birth cohort) of risk factors by region for the cohorts of children born in 2010 (95% confidence intervals in parentheses)

Risk/risk group	Prevalence (%) of risk in developing countries	All developing countries	South Asia	Sub-Saharan Africa	North Africa and Middle East	Latin America and Caribbean	East Asia and Pacific	Central Asia
Maternal nutrition and infection		**26,045 (20286, 32756)**	**10,176 (7002, 14212)**	**4456 (3377, 5659)**	**1705 (1112, 2351)**	**5071 (3239, 7280)**	**4464 (3048, 6001)**	**172 (103, 246)**
Maternal short stature	8	18592 (14837, 22785)	6055 (4266, 7981)	2729 (2196, 3263)	1404 (932, 1912)	4461 (2907, 6247)	3802 (2629, 5066)	140 (86, 194)
Maternal underweight	14	3531 (1980, 5321)	2433 (1350, 3847)	493 (276, 757)	74 (38, 127)	154 (66, 292)	368 (197, 584)	9 (3, 18)
Maternal malaria	8	523 (185, 866)	0 (0, 0)	505 (179, 837)	18 (6, 33)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Maternal anemia	40	4386 (1291, 7930)	2341 (759, 4396)	888 (260, 1588)	233 (65, 477)	510 (129, 1098)	389 (111, 733)	25 (6, 54)
Teenage motherhood and short birth intervals		**4137 (3203, 5203)**	**1122 (799, 1483)**	**764 (608, 916)**	**363 (238, 500)**	**1304 (773, 1903)**	**539 (327, 768)**	**46 (27, 63)**
Teenage motherhood	14	2091 (1619, 2626)	553 (393, 733)	433 (345, 521)	123 (79, 171)	760 (465, 1107)	207 (129, 290)	15 (9, 22)
Short birth intervals	18	2067 (1589, 2596)	575 (409, 759)	335 (265, 405)	242 (158, 332)	552 (314, 808)	334 (200, 486)	31 (18, 43)
Fetal growth restriction and preterm birth		**59134 (46285, 73259)**	**21491 (15412, 28252)**	**11835 (9379, 14346)**	**5068 (3115, 7133)**	**10683 (6274, 15858)**	**9404 (6551, 12755)**	**654 (375, 939)**
Preterm, small-for-gestational age	2	11219 (7461, 16351)	3043 (1776, 4762)	1778 (1145, 2679)	1160 (609, 1890)	2594 (1371, 4312)	2489 (1414, 4020)	154 (79, 256)
Preterm, appropriate-for-gestational age	9	11361 (7904, 15554)	2788 (1750, 4217)	2402 (1628, 3393)	1142 (679, 1762)	2604 (1408, 4199)	2287 (1282, 3494)	139 (71, 226)
Term, small-for-gestational age	24	41581 (31700, 52816)	17733 (12338, 23647)	8628 (6578, 10753)	3175 (1927, 4581)	6194 (3460, 9438)	5444 (3705, 7605)	409 (223, 620)

Table 1.2 (Continued)

Risk/risk group	Prevalence (%) of risk in developing countries	All developing countries	South Asia	Sub-Saharan Africa	North Africa and Middle East	Latin America and Caribbean	East Asia and Pacific	Central Asia
Child nutrition and infection		**29486 (12767, 48125)**	**6360 (2545, 11029)**	**5801 (2566, 9705)**	**2805 (1160, 5002)**	**9576 (3669, 17750)**	**4429 (1744, 7999)**	**515 (206, 890)**
Childhood zinc deficiency	22	2436 (875, 5230)	557 (231, 971)	395 (159, 710)	399 (124, 1086)	640 (199, 1587)	428 (145, 1007)	17 (6, 38)
Childhood diarrhea	2.9[+]	28504 (11414, 47293)	6112 (2328, 10784)	5630 (2337, 9546)	2640 (990, 4851)	9368 (3439, 17415)	4245 (1605, 7818)	508 (198, 884)
Non-exclusive breastfeeding	66	4216 (1164, 8531)	669 (-297, 1762)	785 (193, 1718)	344 (45, 804)	1683 (450, 3623)	664 (124, 1548)	72 (11, 167)
Discontinued breastfeeding	31	3133 (473, 7209)	457 (59, 1195)	402 (59, 937)	281 (39, 662)	1433 (205, 3435)	502 (73, 1246)	58 (9, 133)
Late HAART initiation for childhood HIV*	0.03	42 (16, 107)	1 (0, 2)	41 (15, 106)				
Environmental factors		**31494 (24974, 39046)**	**12913 (9149, 17252)**	**8649 (6935, 10544)**	**754 (506, 1043)**	**3640 (2263, 5332)**	**5449 (3101, 8288)**	**88 (60, 122)**
Unimproved sanitation	47	24466 (19172, 30374)	9579 (6737, 12948)	6646 (5288, 8151)	604 (388, 855)	3112 (1874, 4632)	4466 (2314, 7162)	59 (38, 82)
Unimproved water	17	2133 (1363, 3020)	479 (262, 754)	956 (599, 1362)	108 (59, 167)	237 (136, 381)	336 (177, 555)	17 (9, 28)
Use of biomass fuels	56	6383 (4304, 9031)	3637 (2268, 5371)	1572 (1068, 2153)	54 (24, 99)	331 (182, 533)	776 (470, 1173)	14 (4, 27)

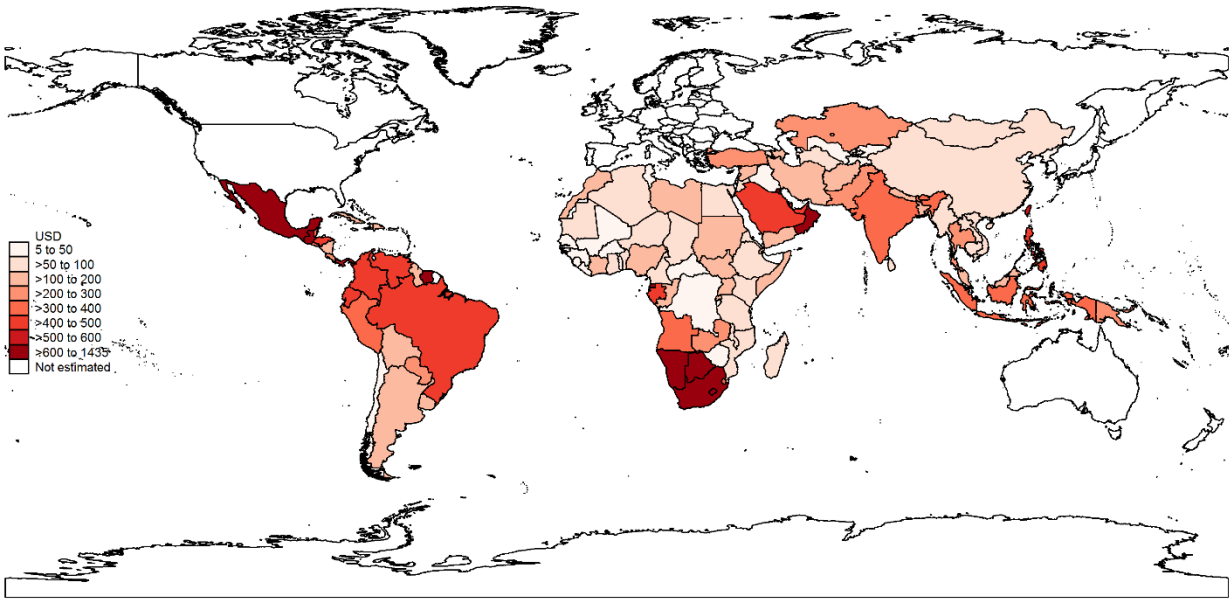
*Only estimated for 45 countries due to data availability
[+] Mean number of episodes per year per child (not prevalence)

The risk factor group with the greatest aggregate wage loss was fetal growth restriction and preterm birth, with US$59.1 (46.3, 73.3) billion lost (Table 1.2). Second were the environmental risk factors at US$31.5 (25.0, 39.0) billion, followed closely by child nutrition and infection at US$29.5 (12.8, 48.1) billion. Maternal nutrition and infection risk factors contributed US$26.0 (20.3, 32.8) billion of lost wages, and teenage motherhood and short birth intervals contributed the smallest cost at US$4.1 (3.2, 5.2) billion.

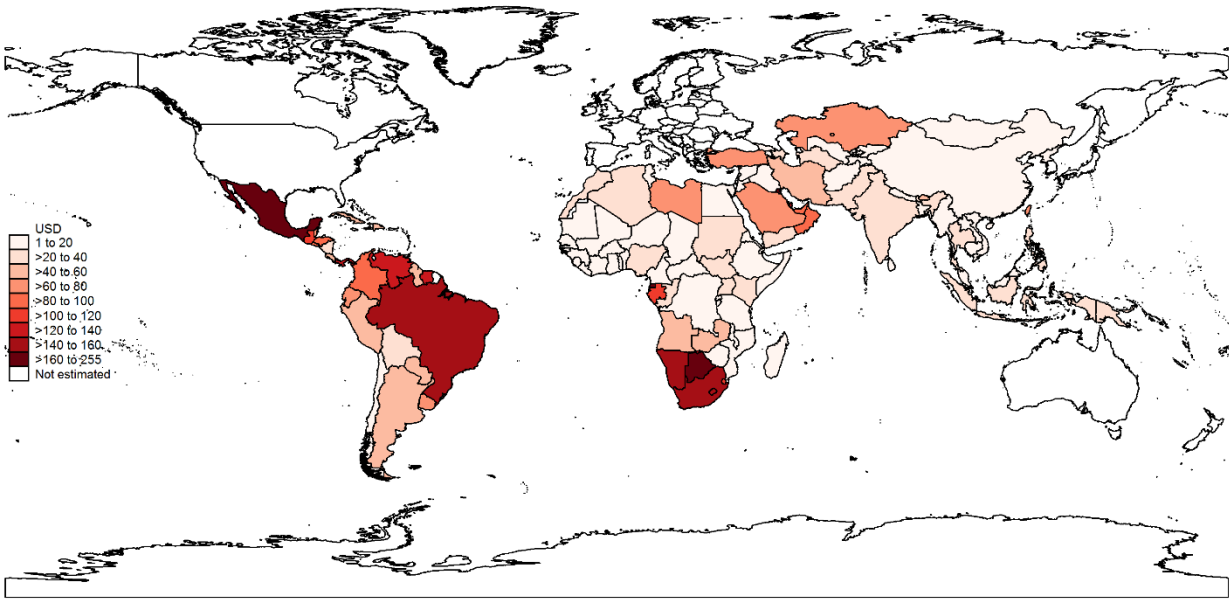
At the regional level, risk-factor specific wage loss estimates varied widely. While the cost for the risk group of fetal growth restriction and preterm birth ranked first for all regions, it ranged from US$21.5 (15.4, 28.3) billion in South Asia to US$0.7 (0.4, 0.9) billion in Central Asia (Table 1.2). The wage loss due to the group of child nutrition and infection risk factors in the Latin America/Caribbean region ranked highest (US$9.6 billion, 95% CIs: 3.7, 17.8), followed by South Asia (US$6.4 billion, 95% CIs: 2.5, 11.0).

Figure 1.2 (A through E) shows the large variations in the wages lost per individual born in 2010 in each country attributable to each of the five risk factor groups. In the child nutrition and infection risk factor group as an example, the countries with the largest individual-level wage losses were Equatorial Guinea, Mexico, Qatar, Antigua and Barbuda, Botswana, and Turkey, which all lost more than US$1,000 in lifetime wages per child due to these risk factors. While the confidence intervals are wide, these differed greatly from the smallest wage losses for this group: Liberia, Togo, Sri Lanka, Iraq, and Democratic People's Republic of Korea, at less than US$40 per child.

Figure 1.2: Lifetime economic cost (US$) of risk factor groups for each child born in 2010, (A) Maternal nutrition and infection; (B) Teenage motherhood and short birth intervals; (C) Fetal growth restriction and preterm birth; (D) Child nutrition and infection; (E) Water, sanitation, and biomass fuel use

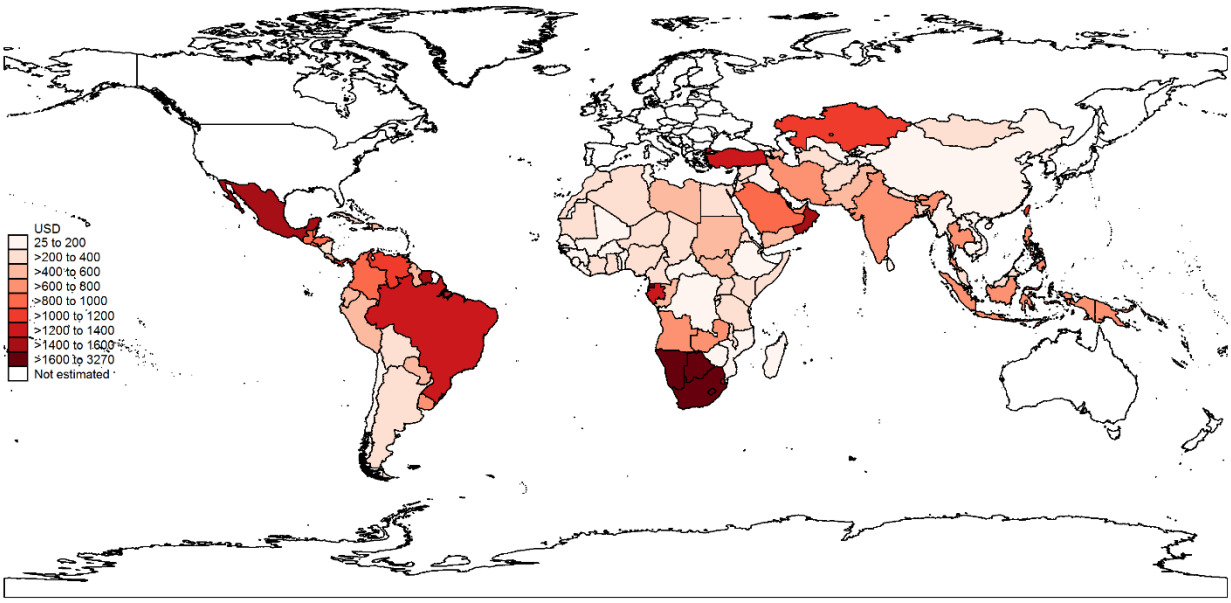

USD
5 to 50
>50 to 100
>100 to 200
>200 to 300
>300 to 400
>400 to 500
>500 to 600
>600 to 1435
Not estimated

A)

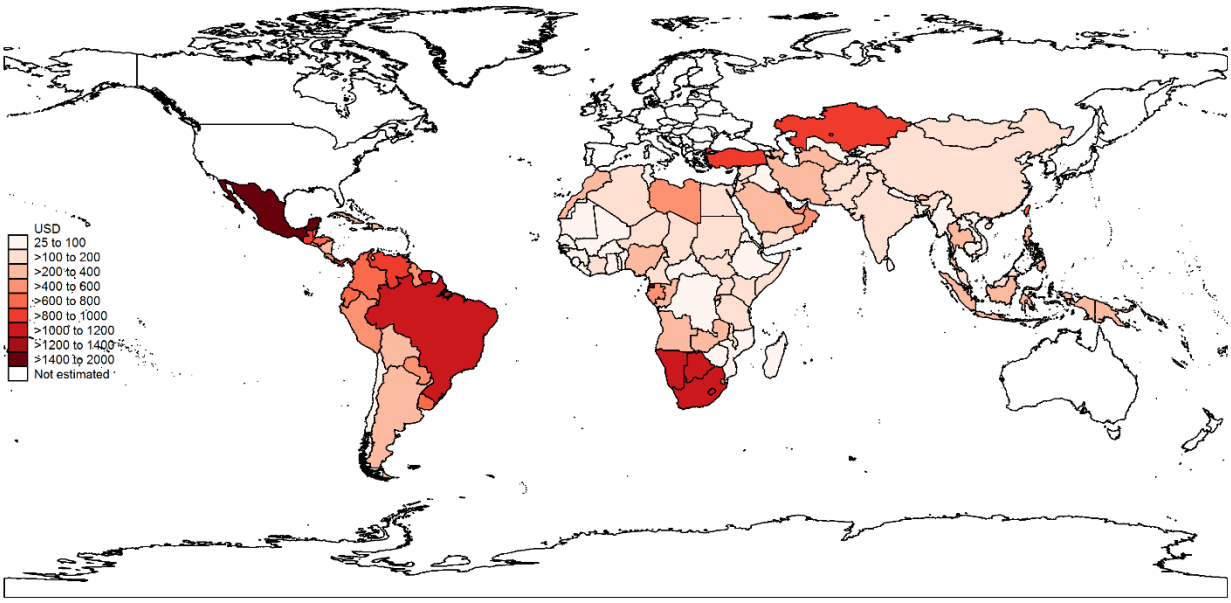

USD
1 to 20
>20 to 40
>40 to 60
>60 to 80
>80 to 100
>100 to 120
>120 to 140
>140 to 160
>160 to 255
Not estimated

B)

Figure 1.2 (Continued)

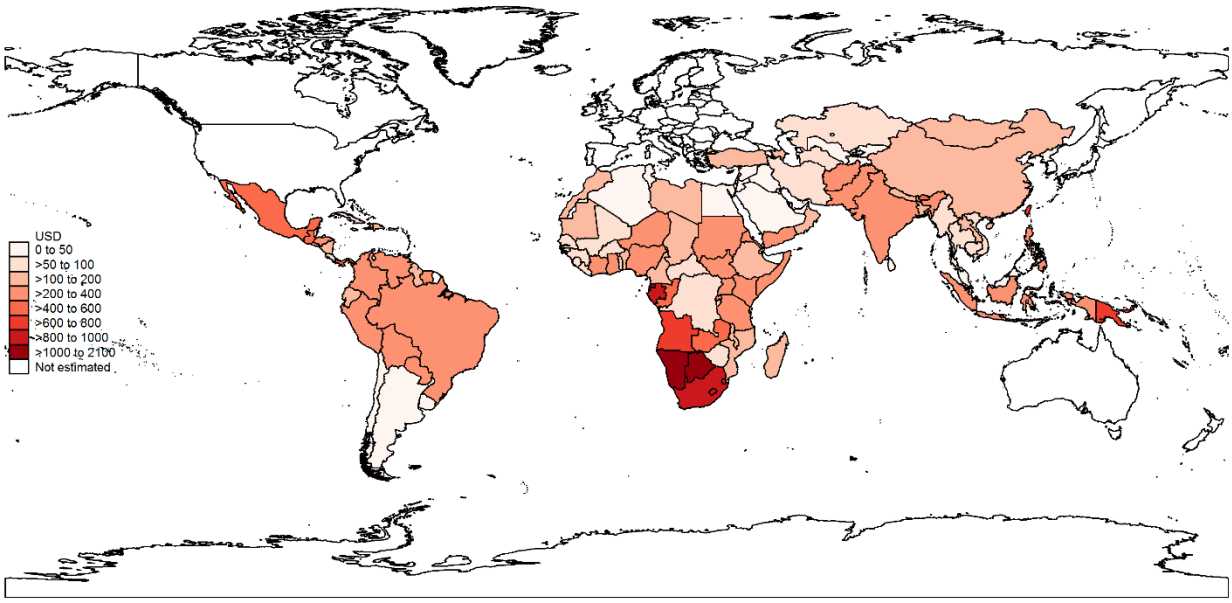


C)



D)

Figure 1.2 (Continued)



E)

At the individual level, the lifetime wages lost per child ranges from a developing country average of US$338 (95% CIs: 258, 430) for TSGA to US$4 (95% CIs: 2, 7) for maternal malaria. Appendix Table 1.3 provides estimates of the wage losses for each country and each risk factor.

Discussion

This analysis demonstrates that risk factors for poor child growth and development are associated with a substantial loss of global human capital. Across 137 developing countries, fetal growth restriction as measured by term, small-for-gestational age (affecting approximately 30 million out of 123 million infants) was estimated to lead to more than US$40 billion lost in lifetime wages for each birth cohort. The second and third leading risk factors were diarrhea and unimproved sanitation. The lost years of schooling and cost of lost wages associated with the risk group of fetal growth restriction and preterm birth is the highest of all groups at 26 million years of schooling lost and US$59 billion of lost wages, which is double the GDP of entire countries (such as Cameroon in 2015).[42] The global economic burden of fetal

growth restriction and preterm birth through stunting and schooling is nearly one third of the US$177 billion lost due to stunting overall.[35] These results can be interpreted as estimates of both the lifetime wage losses associated with the presence of each risk factor, and the potential financial benefits of eliminating each risk factor.

Our findings also interestingly suggest that the leading risks for the burden of stunting are not necessarily the factors causing the largest wage income loss. While fetal growth restriction and preterm birth cause both the largest number of cases of stunting[20] and the largest wage loss, this parallel ranking does not hold true for all factors. Specifically, the second largest number of stunting cases were attributable to unimproved sanitation, followed by diarrhea,[20] but because poor sanitation has a larger prevalence in countries with lower wages (such as in sub-Saharan Africa), the lifetime wage income loss associated with diarrhea is larger than that for poor sanitation. This same phenomenon explains why the wage losses associated with environmental risks is highest in South Asia even though the prevalence of environmental risk factors is greatest in sub-Saharan Africa, and why the wage loss in the Latin America/Caribbean region ranks highest for the risk group of child nutrition and infection (despite lower prevalence of risks and smaller population than in South Asia). Similarly, countries such as Democratic People's Republic of Korea, State of Palestine, and Iraq have relatively small economic losses associated with many risks compared with similar countries, not because the burden of stunting or its risk factors are small, but rather due to low wages and low estimates of returns to education. While the ranking of risk factors remains the same within each country irrespective of the outcome examined (stunting, schooling, or wage income), these examples also importantly demonstrate that quantifying impacts on human capital loss may result in different global and regional priority setting than if impacts were quantified by morbidity alone, further underscoring the importance of estimating human capital effects.

Although this analysis was not designed to assess the cost-effectiveness or cost-benefit of interventions, it can highlight potential areas where the 'cost of action' may be significantly less than the 'cost of inaction'. Our estimates of the lower bound of uncertainty for wage loss can be interpreted as the upper

bound of investment on risk elimination that would still lead to positive returns. Specifically, if a highly-effective intervention package costs less per capita than the lower bound of the estimated wage loss reported here, the intervention package may provide cost savings. For example, it is estimated that 95% coverage of iron supplementation for pregnant women in sub-Saharan Africa would cost 177 million in 2000 international dollars[43] (approximately 224 million in 2010 US$). Given our estimate of wage loss due to maternal anemia of US$861 million (in 2010 US$) for sub-Saharan Africa, and assuming that iron supplementation reduces anemia by 47%,[44] this suggests that providing iron supplementation to pregnant women in the region could result in a roughly US$160 million net benefit over the lifetime of the cohort born in 2010 (i.e. (861 * 0.47 * 0.95) – 224).

Our results can also be used to examine potential cost-savings at the individual level. For example, if zinc supplementation during 'child health days' costs between US$0.60 and US$1.80 per child,[45] and reduces zinc deficiency by 51%,[46] then the US$20 per infant wage loss associated with zinc deficiency from our analysis suggests that intervening may be highly cost-saving. Specifically, using the upper estimate of US$1.80, we might expect approximately US$8 of savings per child (i.e. (20 * .51) – 1.80).

Finally, as a third example, the wage losses can be used at the country-level and compared to country-level cost of intervention. Hansen et al reported that providing a combined intervention of intermittent preventive treatment in pregnancy (IPTp) and insecticide-treated nets (ITNs) to pregnant women in Uganda costs US$ 2.48 per pregnant woman.[47] Our estimate of the wage loss associated with maternal malaria is a much higher US$11 per capita in Uganda. While the IPTp-ITN package will not be 100% effective against malaria during pregnancy, our estimate of the wage loss attributable to maternal malaria is also an underestimate as it only assesses income loss through stunting and education. Thus, the combination of these results seems to suggest that the economic benefit of intervening on maternal malaria may outweigh the cost of this intervention. The country- and risk-specific wage income losses are available in Appendix Table 1.3 and can serve as a guide for each country to identify risk factors that result in substantial economic loss.

Our findings are not directly comparable but generally consistent with previous analyses. Alderman and Behrman estimate that the economic benefit of eliminating low birthweight is US$510 per infant, which incorporates averted health care costs.[48] This is similar to our estimate of the summed economic cost of PSGA and TSGA (closely related to low birthweight), which is approximately US$418 per child (the population-weighted average across 137 developing countries). Our findings are also generally consistent with a previous cost-benefit analysis of a package of 10 nutrition interventions to prevent stunting in 17 developing countries which found large positive returns[32] (this study builds off a *Lancet Maternal and Child Nutrition Series* paper estimating that 90% coverage of these interventions in 34 key countries would cost approximately US$9.6 billion[49]). Other studies that have examined the benefit-cost ratios of universal access to clean water and sanitation,[50] or the overall economic impact of malaria in Africa,[51] find economic burdens associated with these risks several times larger than our analysis does. In the case of water and sanitation, we examine their economic burden through their impact on childhood stunting alone (and not directly from diarrhea or from lost time in transit to seek water, for example). In the case of malaria, this discrepancy is because our estimates encompass the economic burden of *maternal* malaria only and because our analytical approach is more conservative (i.e. tracing the impact through the specific substantiated causal pathway of risks to stunting to education to income, rather than using macro-level associations).

Limitations

Like other global quantifications of risk factor effects, our study has several limitations. We were unable to include risk factors that lacked adequate country-level exposure data or reliable relative risk estimates (e.g. prenatal alcohol use or lead exposure). We also used risk exposure levels in related populations when prevalence in the precise population of interest were unavailable (such as short stature and underweight among women of reproductive age rather than among pregnant women). As is standard in global studies, nearly all of the risk exposure estimates from the literature were based on some amount of modeling given lack of available data for all countries (as visible in the data source description for each

risk exposure in Appendix Table 1.2). While we incorporated the uncertainty from these modeled risk factor estimates in our analysis of their human capital ramifications, the underlying raw data and models all likely have different limitations impacting precision and accuracy of the generated estimates. It is also important to note that while we use the highest quality estimates available,[52] the group of risks with the greatest human capital burden (fetal growth restriction and preterm birth group), may also be the risks with some of the lowest data quality underlying the exposure estimates given the difficulty of ascertaining preterm status worldwide.

We estimated losses of lifetime wage income through only one pathway: from risk factors to stunting, to educational attainment, and to future wages; focusing on this pathway meant that we excluded other potential pathways through which risk factors could affect wage earnings (e.g. effect of risks on education or wage earnings through cognition specifically, or the effect of stunting on wage earnings through increased adult height rather than education[53]). Therefore, our results should be considered underestimates of the true wage earning impact of these risk factors, and if other pathways were included in this analysis, the relative importance of certain risk factors could be altered.

While we posit that the economic benefits of intervening on some risks may outweigh the costs, we do not account for the fact that the costs of addressing risks may be primarily accrued by governments or external donors but the benefits (in the form of wages) would mainly be gained by individuals (though some benefits could be reaped by governments in countries that tax income). While this suggests that the incentives to intervene may be misaligned, recent pushes to consider human capital in the accounting of the wealth of nations[14] may help address this mismatch. Finally, while we are more holistically quantifying the impact of risk factors by also estimating the associated losses in schooling and wage income, we are not able to fully capture the effects of risks on all aspects of human capital development, such as quality of education, specific skill acquisition, or other types of knowledge growth.

Our analysis also has several strengths, including its comprehensive nature (including 18 risks in 137 countries) and consistent estimation strategy allowing for cross-country comparison of the educational

and wage loss impacts of risks for stunting. We also propagated uncertainty at every analysis step and quantified the total uncertainty in the estimated impacts on schooling and lifetime wage loss. Our analysis combines the best available evidence on risks for stunting from the epidemiologic literature with the best available evidence on returns to education and wages from the economics literature to generate tangible, policy-relevant estimates of the human capital loss associated with key risk factors for stunting.

Conclusions

We report a consistent and comparable set of estimates for the human capital losses associated with poverty-related risk factors for stunting in children across 137 developing countries. The largest global schooling and wage losses are from TSGA at US$42 billion per birth cohort followed by diarrhea and unimproved sanitation. The magnitude of these losses is a clear demonstration that the vast impact of risk factors extends far beyond morbidity. This, in turn, suggests that failing to extend estimates of risk factor impact to human capital may result in a narrow and underestimated quantification, and also implies that efforts to eliminate these risks should extend beyond the health sector, given that the ramifications for schooling and income are relevant to the education, employment, and finance sectors. Our estimates of the wage income losses for risk factors for stunting, when combined with estimates of the cost of intervening on those risks (coupled with the intervention effectiveness), highlight that many conventional interventions that improve these risk factors may produce cost-savings over the long-term. As the development community continues to expand its focus from improving survival to improving populations' ability to thrive, it is increasingly important to take into account the impact of risk factors on human capital.

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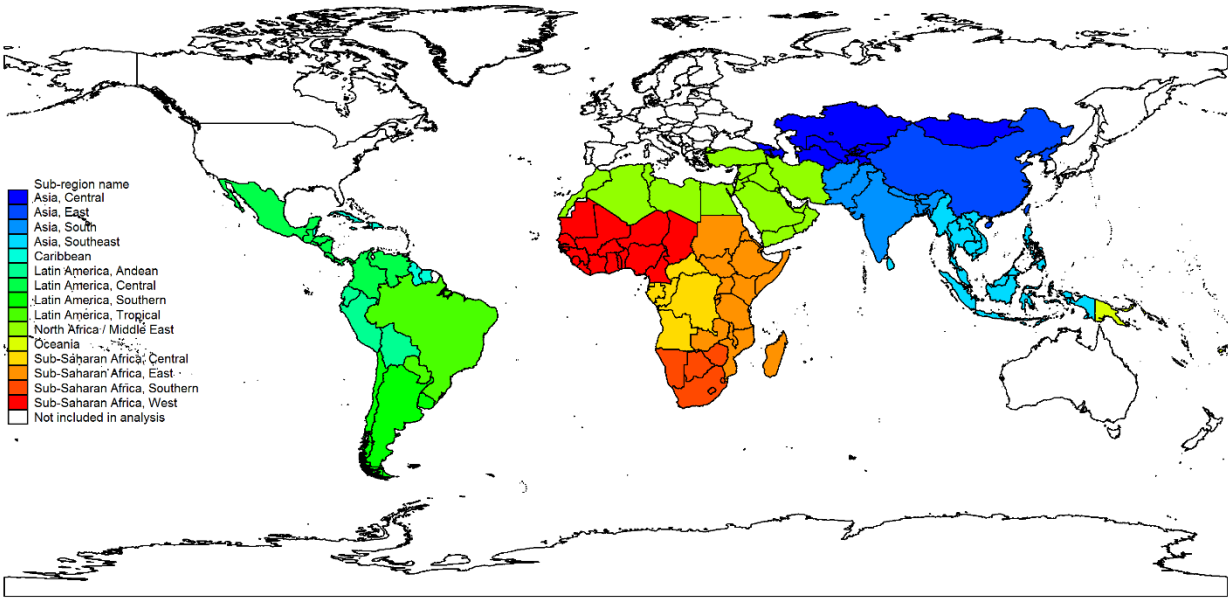
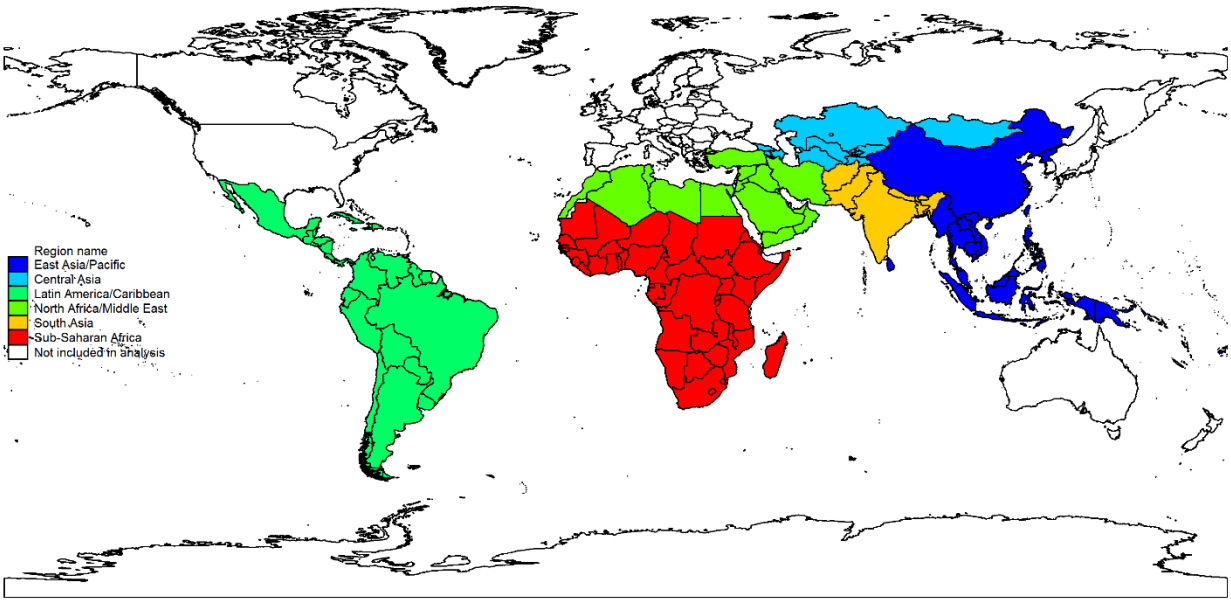
Appendices



A)



B)

Appendix Figure 1.1: The 137 analysis countries in their (A) sub-regions and (B) regions

Appendix Table 1.1: Level of evidence on the relationship between each risk factor and stunting required for inclusion in the analysis (Table reproduced from Danaei et al[20])

Level of evidence	**Empirical evidence**
Convincing	Evidence from more than one study type (e.g. randomized trials and cohort studies). • Evidence from at least two independent randomized trials or cohort studies • No substantial unexplained heterogeneity • Good quality studies to exclude with confidence the possibility of random or systematic error, including confounding, measurement error, and selection bias • Presence of a plausible biological gradient ('dose response') • Strong and plausible experimental evidence (human studies or relevant animal models)
Probable	Evidence from at least two independent randomized trials, cohort studies, or at least five case-control or cross-sectional studies. • Evidence from case-control studies should only be considered if there is consensus among the panel[a] that potential for bias is reasonably low. • Evidence from cross-sectional studies should only be considered if there is consensus among the panel[a] that exposure could not possibly have been affected by the outcome. • No substantial unexplained heterogeneity between or within study types in the presence or absence of an association, or direction of effect • Good quality studies to exclude with confidence the possibility that the observed association results from random or systematic error, including confounding, measurement error, and selection bias • Evidence for biological plausibility

The panel that examined the evidence quality consisted of the members of our core Saving Brains Research Team.

Appendix Table 1.2: Sources of data on the selected risk factors and their effect size for stunting (Table reproduced from Danaei et al[20])

Risk factor	Definition	Evidence on effect size for stunting	Effect size[a] (95% confidence interval)	Source of exposure data
Maternal nutrition and infection				
Maternal short stature	Maternal height <160cm	Pooled analysis of Demographic and Health Surveys (DHS)[54]	Maternal height <145cm: 2.13 (2.10, 2.16) 145-<150cm: 1.78 (1.76, 1.80) 150-<155cm: 1.48 (1.46, 1.49) 155-<160cm: 1.24 (1.23, 1.26)	Modeled height among women 18-49 years of age[55 b, c]
Maternal underweight	Maternal BMI <18.5 kg/m^2	Pooled analysis of population-based cohort studies and WHO perinatal facility-based data from 24 countries[56]	OR for LBW: 1.64 (1.38, 1.94)	Modeled estimates of underweight among women of reproductive age[57 b, d]
Maternal malaria	Malaria in pregnancy	Systematic review of Intermittent Preventive Treatment of malaria in pregnancy (IPTp) RCTs[58 e]	RR for LBW: 1.37 (1.13, 1.63)	Malaria Atlas Project modeled estimates of *Plasmodium falciparum* parasite prevalence[59 b, d]
Maternal anemia	Maternal hemoglobin <110g/L	Systematic review of cohort studies[60]	OR for LBW: 1.29 (1.09, 1.53)	Modeled estimates of hemoglobin concentration among pregnant women[61 b, d]

Appendix Table 1.2 (Continued)

Risk factor	Definition	Evidence on effect size for stunting	Effect size[a] (95% confidence interval)	Source of exposure data
Teenage motherhood and short birth intervals				
Teenage motherhood	Maternal age at delivery <20 years	Pooled analysis of DHS[62]	Maternal age <18 years: 1.20 (1.19, 1.22) 18-19 years: 1.11 (1.10, 1.12)	DHS estimates of teenage motherhood[62]
Short birth intervals	<24 months between consecutive births	Pooled analysis of DHS[62]	Birth spacing <12 months: 1.14 (1.11, 1.67) 12-23 months: 1.11 (1.10, 1.12)	DHS estimates of birth spacing[62]
Fetal growth restriction and preterm birth				
Preterm, small-for-gestational age	Birth before 37 weeks of gestation and weight <10th percentile for gestational age	Meta-analysis of observational cohort studies[63]	4.51 (3.42, 5.93)	Modeled estimates of prevalence of preterm, small-for-gestational age[63 b]
Preterm, appropriate-for-gestational age	Birth before 37 weeks of gestation and weight ≥10th percentile for gestational age	Meta-analysis of observational cohort studies[63]	1.93 (1.71, 2.18)	Modeled estimates of prevalence of preterm, appropriate-for-gestational age[63 b]
Term, small-for-gestational age	Birth at or after 37 weeks of gestation and weight <10th percentile for gestational age	Meta-analysis of observational cohort studies[63]	2.43 (2.22, 2.66)	Modeled estimates of prevalence of term, small-for-gestational age[63 b]
Low birth weight[f]	Birth weight <2500g	Meta-analysis of observational cohort studies[63]	2.92 (2.56, 3.33)	Modeled estimates of low birth weight[63,b]

Appendix Table 1.2 (Continued)

Risk factor	Definition	Evidence on effect size for stunting	Effect size[a] (95% confidence interval)	Source of exposure data
Child nutrition and infection				
Childhood zinc deficiency	Deficient zinc intake during childhood based on age- and sex-specific zinc requirements	Systematic review of preventive zinc supplementation trials[64]	Mean decrease in HAZ: 0.06 (0.02, 0.10) [g, h]	Modeled estimates of zinc deficiency[65 b]
Childhood diarrhea	Mean number of diarrhea episodes per year during childhood	Pooled analysis of prospective cohort studies[66]	OR for stunting per one additional diarrhea episode: 1.025 (1.01, 1.04)	Modeled estimates of mean number of diarrhea episodes per child per year[67 b]
Non-exclusive breastfeeding	Non-exclusive breastfeeding of infants under 6 months of age	Systematic review of observational studies[64]	RR for diarrhea; not breastfed: 2.65 (1.72, 4.07) partially breastfed: 1.69 (1.03, 2.76) predominantly breastfed: 1.26 (0.81, 1.95)	Modeled estimates of prevalence of non-exclusive breastfeeding[68 b]
Discontinued breastfeeding	Discontinued breastfeeding of children 6-24 months of age	Systematic review of observational studies[64]	RR for diarrhea: 1.32 (1.06, 1.63)	Modeled estimates of prevalence of discontinued breastfeeding[68 b]
HIV infection without highly active antiretroviral therapy (HAART) before 2 years of age	Child HIV infection without initiation of HAART until after 2 years of age	Systematic review of observational studies (described in S4 Text of Danaei et al[20])	Mean decrease in HAZ: 0.63 (0.46, 0.80)[h]	UNAIDS modeled estimates of prevalence of HIV infection and HAART coverage[69 i]

Appendix Table 1.2 (Continued)

Risk factor	Definition	Evidence on effect size for stunting	Effect size[a] (95% confidence interval)	Source of exposure data
Environmental factors				
Unimproved sanitation	Lack of access to safe sanitation in the community (based on WHO/UNICEF JMP definition of improved sanitation) [j]	Pooled analysis of DHS[70]	1.37 (1.33, 1.41)	Modeled estimates of access to sanitation[71] [b]
Unimproved water	Lack of access to clean water in the community (based on WHO/UNICEF JMP definition of improved water source) [j]	Pooled analysis of DHS[70]	1.09 (1.06, 1.12)	Modeled estimates of access to safe drinking water[71] [b]
Use of biomass fuels	Use of biomass fuels for cooking and heating	Systematic review of RCTs and observational cohorts[72]	OR for LBW: 1.40 (1.26, 1.54)	Modeled estimates of proportion of households relying mainly on biomass fuel for cooking[73] [b]

[a] All effect sizes are reported as odds ratios for stunting unless otherwise stated.

[b] For these risk factors, exposure data were missing for 6 or fewer of the 137 developing countries (primarily small island nations) and these were imputed using sub-regional or regional averages.

[c] In order to generate estimates of maternal height in categories corresponding to the RR categories, we used estimates of the mean height (and its uncertainty) and standard deviation (SD) of height (and its uncertainty) for each country. Using data for women age 18 to 49 in 2010, incorporating the assumption that height declines linearly per year after age 18 by 0.03562155cm (as provided by the authors [55]), we calculated (population-weighted) estimates of the mean and SD of height of women of reproductive age in each country in 2010. Assuming that height follows a normal distribution, we calculated the fraction of women falling into each height category listed above using the mean and SD of height in each country. Using the uncertainty around the mean and SD of height, we propagated uncertainty at every step using 1000 simulations. The standard deviation used for this calculation is available in S1 Table of Danaei et al[20], and the means are available from the Non-Communicable Disease Risk Factor Collaboration website.[74]

[d] Input exposure data for maternal underweight, anemia, and malaria are available in S1 Table.

[e] Given the lack of an available RR of malaria on childhood stunting, the inverse of the effect of IPTp on childhood stunting was used as a conservative approximation.

[f] For this analysis, LBW is used only as a mediator because the main effects are nearly entirely encompassed by the combination of the effects of term, small-for-gestational age; preterm, small-for-gestational age; and preterm, appropriate-for-gestational age.

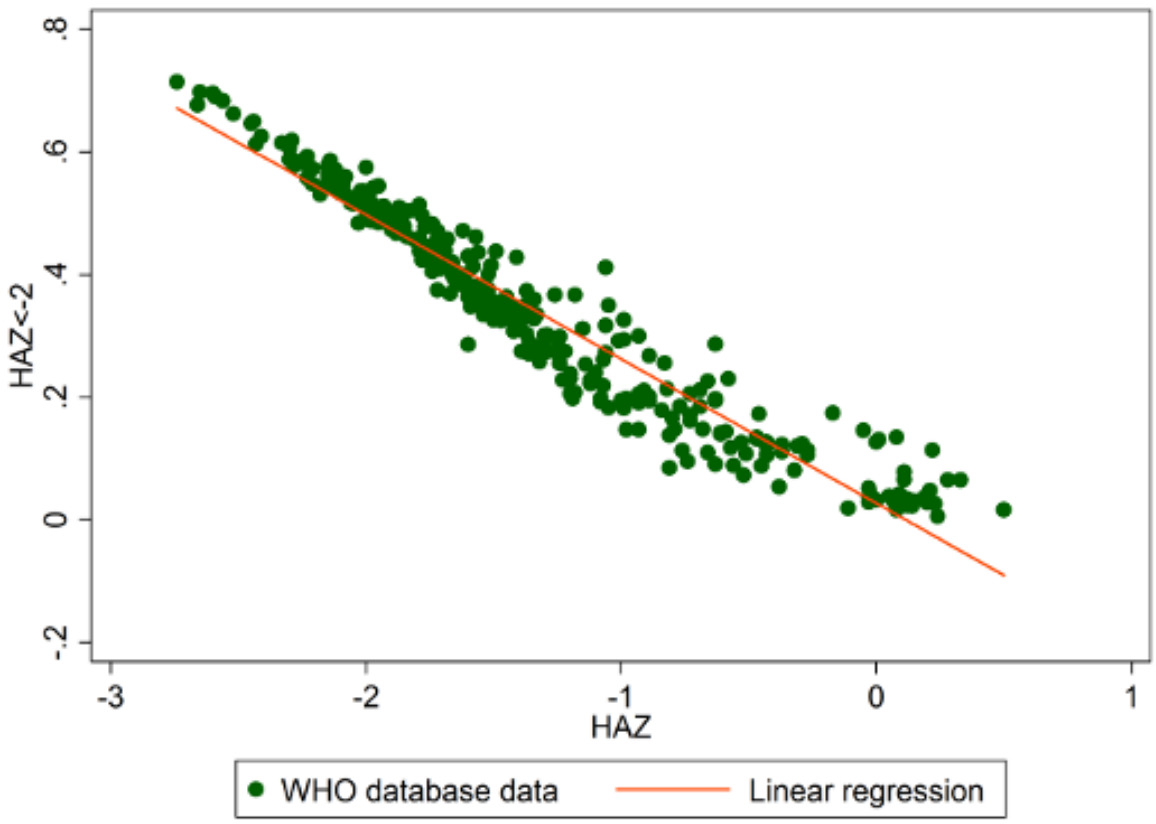
[g] For zinc deficiency, the available effect size was a decrease in linear growth of 0.19cm (95% confidence intervals: decrease of 0.08 to 0.3)[64] among zinc-deficient children compared to those without zinc deficiency. We converted this effect size into an HAZ shift by dividing it by the standard deviation of height among children aged 21 months (the mean age of children in the zinc deficiency meta-analysis) from the WHO Child Growth Standards.[19] The estimated mean HAZ shift of 0.06 was then converted into a relative risk as described in footnote h below.

[h] For zinc deficiency and late HAART initiation for HIV, the effect sizes were available as mean differences in HAZ between the exposed and the unexposed, but not as RRs. To convert HAZ shifts into relative risks, we used the observed population mean HAZ and estimated a counterfactual HAZ had there been no zinc deficiency/late HAART initiation by subtracting off the HAZ shift attributable to each of these risks from each country's observed mean HAZ. We converted observed country-level estimates of mean HAZ among children under 5 to mean HAZ among children age 2 as described in S2 Text of Danaei et al[20, 21,75]. For zinc and HIV separately, we then translated the two mean HAZ levels for each country into stunting prevalence by using the linear regression crosswalk described in S3 Text [75] and shown in S1 Fig of Danaei et al.[20] We used the ratio of the counterfactual to the observed stunting prevalence generated from the crosswalk as a country-specific estimate of the RR.

[i] Using data available in the UNAIDS Report on the Global AIDS Epidemic 2013 on the number of HIV-infected children on HAART and not on HAART, and assuming that that 75% of HIV-infected children on HAART initiate treatment before 2 years of age, we calculate the fraction of HIV-infected children age 2 who are not yet on HAART (the exposure of interest) using this equation: HIV prevalence among children * (1 – HAART coverage among children) + HIV prevalence among children * HAART coverage among children * 25%. The data inputs (as shared with the authors) are available in S1 Table.

[j] The WHO/UNICEF Joint Monitoring Programme (JMP) for Water Supply and Sanitation provides specific definitions of improved water and sanitation.[36] Improved water sources are piped water into dwelling, piped water into yard/plot, public tap or standpipe, tubewell or borehole, protected dug well, protected spring, and rainwater. Improved sanitation is flush toilet, piped sewer system, septic tank, flush/pour flush to pit latrine, ventilated improved pit latrine, pit latrine with slab, composting toilet, and flush/pour flush to unknown place.[36] This classification is used by Fink et al[70] to create the relative risks used for this analysis. The prevalence of exposure to improved water and sanitation (as shared with the authors; we subtracted these values from 100 to calculate prevalence of exposure to unimproved water and sanitation) used as inputs into this analysis are available in S1 Table of Danaei et al.[20]

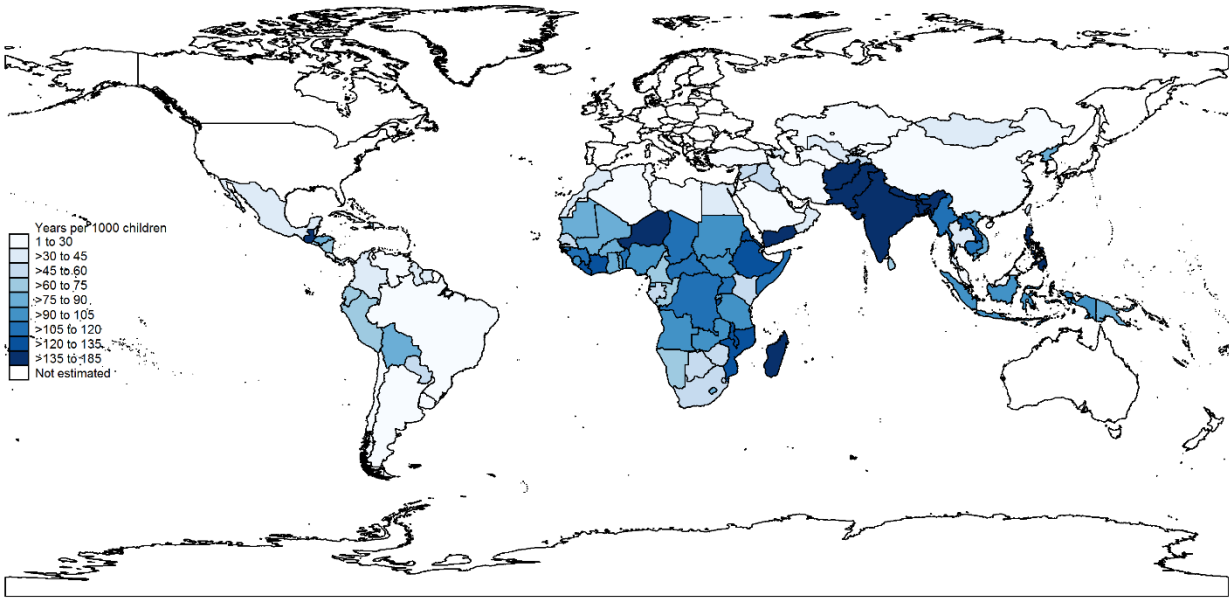
HAZ: height-for-age z-score; OR: Odds Ratio; RR: relative risk; LBW: low birth weight; BMI: body mass index; DHS: Demographic and Health Surveys; RCT: randomized control trial; HIV: Human Immunodeficiency Virus



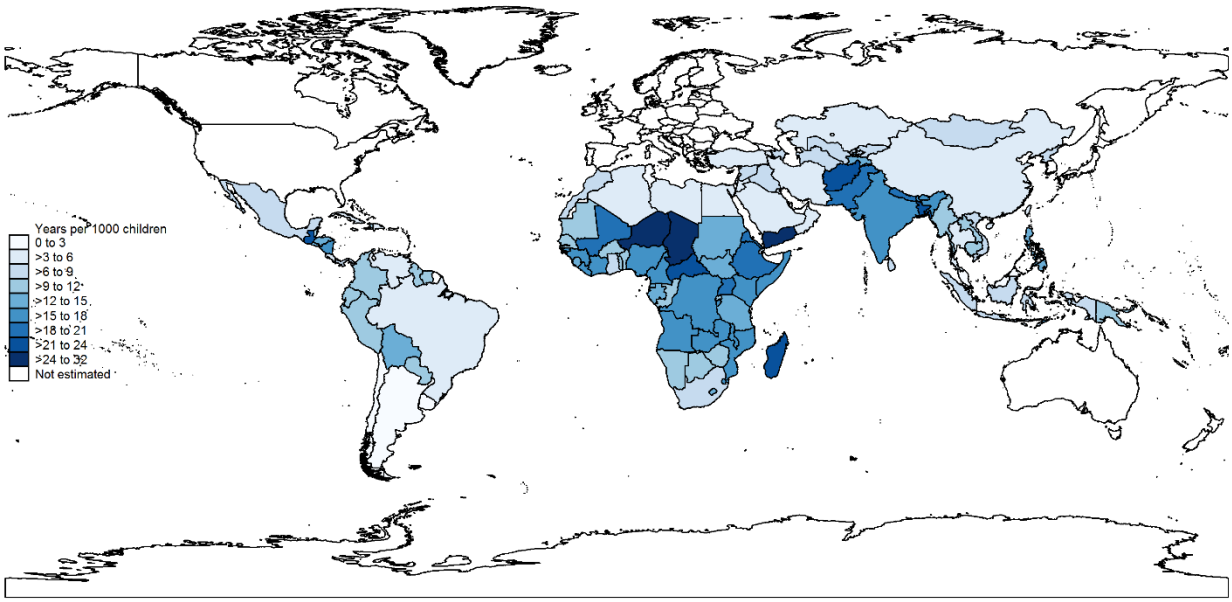
Appendix Figure 1.2: Linear relationship between HAZ and stunting prevalence*

* In order to apply the stunting PAF to the economic burden associated with stunting, the relationship between height-for-age Z-scores (HAZ) and stunting (height-for-age Z-score less than -2) prevalence must be roughly linear. To assess the veracity of this assumption, we used 309 (nationally representative, for both sexes) data points from the WHO Database on Child Growth and Malnutrition[75] from 120 countries and 15 years (2000-2014) where mean HAZ and stunting prevalence were estimated for the same population. The raw data and a linear regression model fit are presented below. While not perfectly linear at the extremes, we are confident that the relationship between stunting and HAZ is approximately linear over the range of stunting values applicable to the 137 developing countries in this analysis. We also used a spline fit to capture this relationship and the results remained the same.

Appendix Figure 1.3: Years of schooling lost (per 1000 children) attributable to risk factor groups (A) Maternal nutrition and infection; (B) Teenage motherhood and short birth intervals; (C) Fetal growth restriction and preterm birth; (D) Child nutrition and infection; (E) Water, sanitation, and biomass fuel use


Years per 1000 children
1 to 30
>30 to 45
>45 to 60
>60 to 75
>75 to 90
>90 to 105
>105 to 120
>120 to 135
>135 to 185
Not estimated

A)


Years per 1000 children
0 to 3
>3 to 6
>6 to 9
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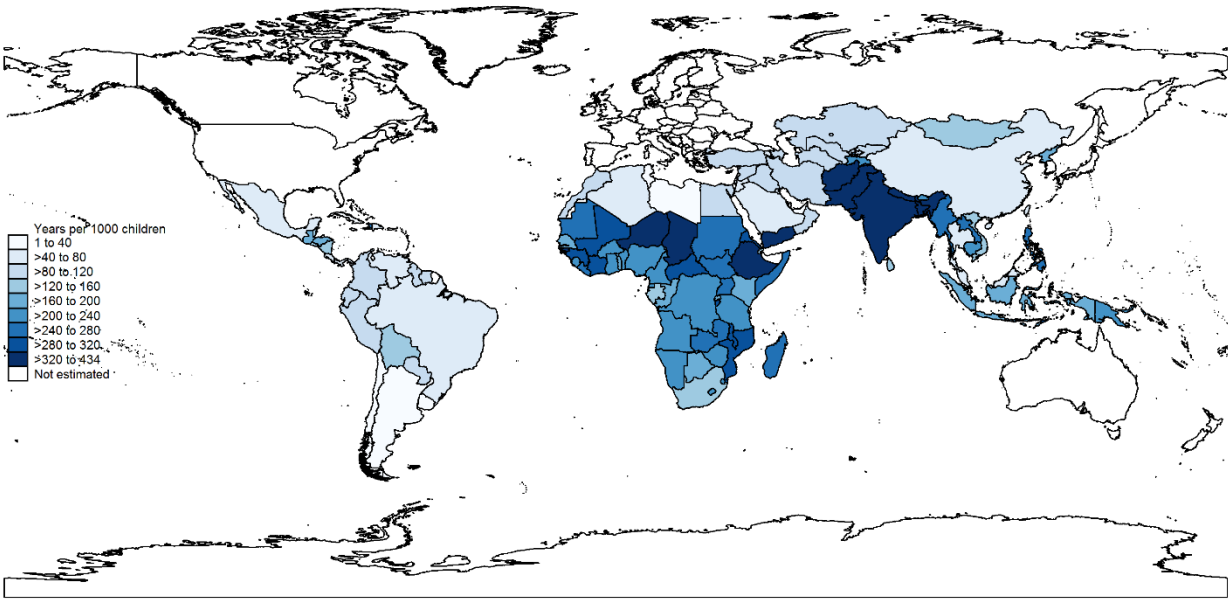
>18 to 21
>21 to 24
>24 to 32
Not estimated

B)

Appendix Figure 1.3 (Continued)



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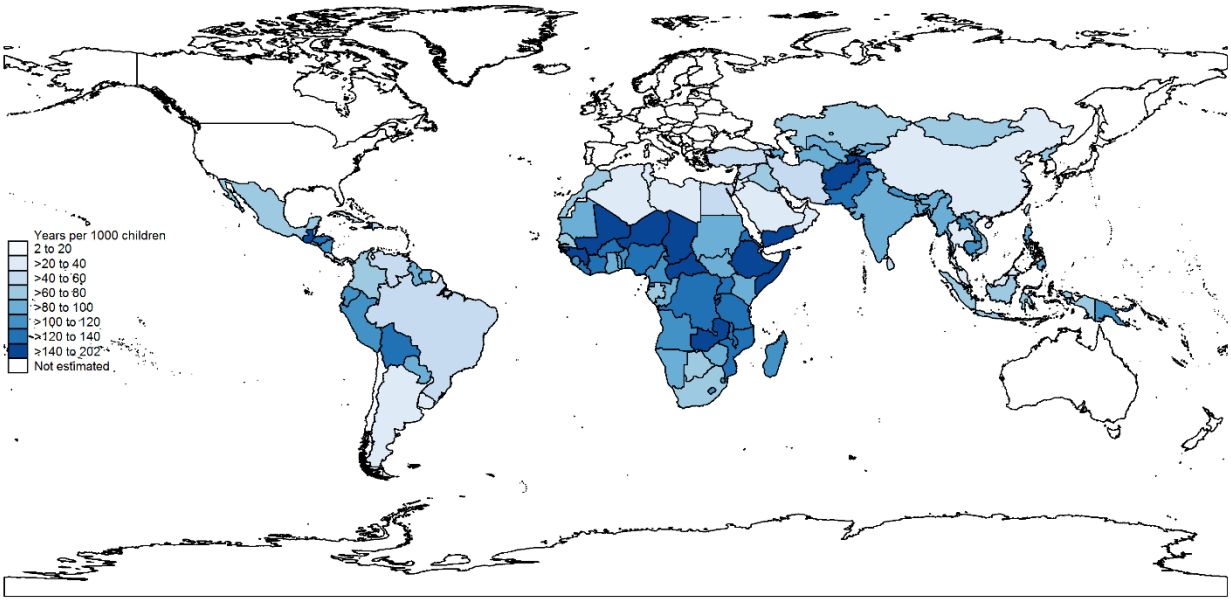

D)

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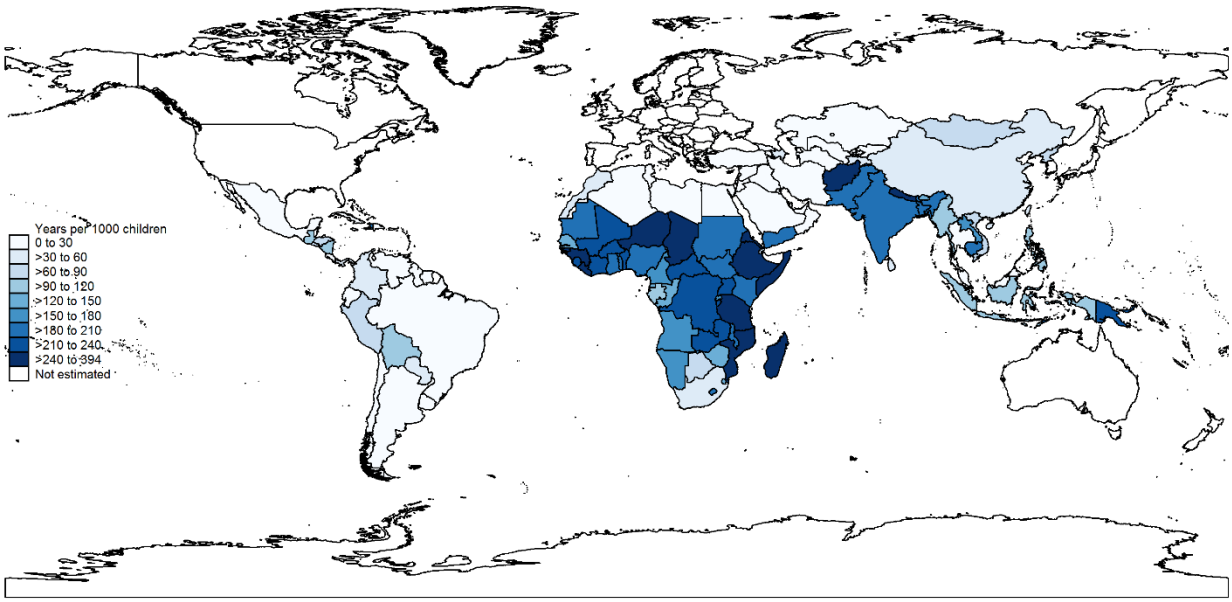

E)

Appendix Table 1.3: Country-level estimated lifetime wage income loss associated with each risk factor (95% confidence intervals in parentheses) per child born in 2010 ($US) for the maternal nutrition and infection, teenage motherhood and short birth intervals, and fetal growth restriction and preterm birth risk groups

Country name	Maternal short stature	Maternal under-weight	Maternal malaria	Maternal anemia	Teenage mother-hood	Short birth intervals	Low birth-weight	Preterm, small-for-gestational age	Preterm, appropriate-for-gestational age	Term, small-for-gestational age
Afghanistan	65 (46, 85)	24 (11, 38)	0 (0, 0)	24 (6, 45)	10 (7, 13)	7 (5, 10)	212 (168, 256)	41 (7, 84)	37 (7, 71)	241 (165, 329)
Algeria	65 (14, 117)	4 (1, 11)	4 (1, 10)	10 (1, 28)	7 (1, 12)	15 (3, 27)	124 (25, 228)	42 (5, 99)	58 (9, 131)	133 (26, 247)
Angola	235 (140, 350)	36 (11, 73)	19 (6, 35)	56 (15, 115)	34 (21, 49)	23 (14, 34)	468 (275, 704)	115 (22, 247)	154 (32, 311)	542 (310, 822)
Antigua and Barbuda	792 (206, 1465)	19 (0, 51)	0 (0, 0)	72 (9, 188)	122 (33, 221)	86 (23, 154)	917 (251, 1648)	356 (61, 805)	323 (62, 625)	833 (212, 1647)
Argentina	99 (9, 190)	3 (0, 8)	0 (0, 0)	16 (1, 47)	24 (2, 47)	17 (2, 33)	216 (20, 432)	80 (11, 126)	84 (7, 173)	198 (19, 440)
Armenia	46 (22, 69)	2 (0, 5)	0 (0, 0)	7 (1, 15)	3 (2, 5)	6 (3, 9)	93 (44, 143)	48 (7, 104)	43 (2, 97)	106 (53, 166)
Azerbaijan	103 (53, 147)	5 (1, 11)	0 (0, 0)	18 (4, 37)	11 (6, 16)	20 (10, 29)	211 (107, 309)	90 (14, 188)	83 (14, 174)	275 (124, 454)
Bahamas	945 (7, 1874)	40 (0, 115)	0 (0, 0)	157 (0, 438)	147 (1, 291)	104 (1, 205)	2006 (16, 4061)	579 (5, 1391)	568 (4, 1263)	1695 (13, 3516)
Bahrain	239 (0, 583)	13 (0, 41)	0 (0, 0)	44 (0, 142)	17 (0, 40)	38 (0, 94)	500 (0, 1238)	239 (0, 662)	215 (0, 547)	508 (0, 1308)
Bangladesh	87 (66, 110)	27 (18, 39)	0 (0, 0)	24 (7, 43)	14 (11, 18)	3 (2, 4)	194 (142, 255)	43 (24, 70)	38 (23, 59)	199 (145, 263)
Barbados	298 (82, 543)	47 (7, 116)	0 (0, 0)	155 (13, 424)	149 (41, 272)	105 (28, 187)	2041 (542, 3692)	600 (131, 1285)	593 (129, 1195)	1757 (454, 3293)

Appendix Table 1.3 (Continued)

Country name	Maternal short stature	Maternal under-weight	Maternal malaria	Maternal anemia	Teenage mother-hood	Short birth intervals	Low birth-weight	Preterm, small-for-gestational age	Preterm, appropriate-for-gestational age	Term, small-for-gestational age
Belize	287 (174, 427)	20 (3, 45)	0 (0, 0)	50 (12, 90)	45 (27, 67)	32 (19, 47)	730 (426, 1115)	185 (65, 355)	182 (71, 345)	608 (334, 1002)
Benin	24 (17, 32)	6 (2, 10)	14 (5, 24)	14 (4, 24)	3 (2, 4)	3 (2, 4)	87 (60, 120)	16 (4, 31)	22 (6, 42)	91 (61, 126)
Bhutan	241 (187, 305)	27 (11, 49)	0 (0, 0)	41 (11, 79)	29 (22, 36)	22 (17, 28)	347 (255, 448)	124 (12, 250)	120 (13, 241)	445 (298, 625)
Bolivia	179 (136, 228)	2 (0, 4)	0 (0, 0)	13 (4, 25)	18 (13, 23)	14 (11, 18)	134 (96, 181)	76 (39, 127)	75 (42, 120)	145 (84, 218)
Botswana	429 (287, 583)	99 (25, 203)	29 (9, 54)	169 (35, 370)	120 (81, 164)	48 (32, 66)	1990 (1301, 2751)	574 (198, 1076)	791 (301, 1418)	1739 (1036, 2632)
Brazil	350 (25, 674)	24 (2, 58)	0 (0, 0)	69 (0, 197)	79 (6, 154)	67 (5, 131)	823 (57, 1631)	308 (16, 716)	309 (21, 697)	744 (55, 1558)
Burkina Faso	11 (8, 15)	5 (2, 8)	11 (4, 19)	8 (2, 14)	3 (2, 4)	2 (1, 3)	53 (37, 72)	13 (6, 24)	19 (10, 30)	60 (41, 84)
Burundi	33 (24, 43)	5 (2, 10)	2 (1, 3)	6 (1, 11)	2 (1, 2)	4 (3, 5)	67 (47, 91)	16 (3, 35)	23 (3, 45)	80 (55, 111)
Cambodia	44 (34, 54)	5 (2, 8)	0 (0, 0)	7 (2, 12)	2 (2, 2)	3 (2, 3)	53 (38, 68)	24 (3, 51)	22 (3, 42)	66 (42, 95)
Cameroon	39 (27, 53)	7 (3, 13)	17 (6, 31)	18 (5, 33)	11 (8, 15)	8 (5, 11)	143 (97, 197)	41 (12, 78)	57 (20, 102)	157 (102, 222)
Cape Verde	33 (8, 61)	6 (1, 14)	0 (0, 0)	12 (1, 29)	11 (3, 19)	8 (2, 15)	106 (26, 196)	55 (10, 128)	72 (16, 154)	103 (24, 202)
Central African Republic	22 (15, 30)	6 (2, 12)	8 (3, 14)	10 (3, 18)	5 (4, 7)	4 (3, 6)	74 (48, 104)	17 (1, 38)	23 (2, 46)	87 (56, 124)
Chad	24 (14, 34)	16 (6, 27)	6 (2, 11)	23 (6, 45)	9 (5, 12)	7 (5, 11)	178 (104, 259)	27 (2, 59)	36 (4, 79)	179 (102, 263)

Appendix Table 1.3 (Continued)

Country name	Maternal short stature	Maternal under-weight	Maternal malaria	Maternal anemia	Teenage mother-hood	Short birth intervals	Low birth-weight	Preterm, small-for-gestational age	Preterm, appropriate-for-gestational age	Term, small-for-gestational age
Chile	12 (0, 82)	0 (0, 1)	0 (0, 0)	1 (0, 11)	2 (0, 16)	2 (0, 12)	18 (0, 123)	8 (0, 51)	7 (0, 52)	17 (0, 124)
China	68 (15, 126)	2 (0, 5)	0 (0, 0)	3 (0, 8)	5 (1, 10)	10 (2, 18)	50 (11, 96)	55 (11, 114)	50 (11, 100)	66 (8, 149)
Colombia	375 (279, 485)	15 (5, 29)	0 (0, 0)	54 (13, 108)	71 (52, 92)	28 (22, 34)	650 (452, 884)	215 (125, 334)	220 (140, 324)	596 (387, 869)
Comoros	69 (42, 99)	16 (6, 33)	0 (0, 0)	25 (5, 55)	6 (4, 9)	13 (8, 19)	266 (159, 389)	46 (12, 91)	60 (16, 115)	238 (141, 355)
Congo	91 (50, 135)	24 (9, 45)	27 (9, 53)	44 (13, 87)	20 (11, 30)	8 (5, 12)	303 (157, 457)	94 (35, 177)	126 (53, 228)	306 (156, 471)
Costa Rica	202 (15, 402)	5 (0, 15)	0 (0, 0)	18 (0, 50)	36 (3, 71)	24 (2, 46)	261 (18, 505)	179 (8, 427)	181 (7, 439)	222 (17, 497)
Cote d'Ivoire	49 (34, 68)	12 (5, 22)	51 (19, 87)	32 (10, 60)	13 (8, 18)	6 (4, 8)	226 (151, 321)	48 (10, 99)	64 (15, 127)	239 (157, 343)
Cuba	123 (0, 255)	6 (0, 16)	0 (0, 0)	14 (0, 40)	27 (0, 56)	19 (0, 40)	192 (0, 402)	79 (0, 180)	80 (0, 171)	171 (0, 390)
Democratic People's Republic of Korea	29 (21, 38)	2 (0, 4)	0 (0, 0)	2 (1, 5)	1 (1, 2)	3 (2, 3)	34 (23, 46)	19 (4, 38)	17 (3, 33)	42 (25, 63)
Democratic Republic of the Congo	19 (15, 24)	3 (1, 6)	6 (2, 10)	5 (1, 9)	2 (2, 3)	3 (2, 4)	38 (26, 50)	11 (2, 22)	15 (1, 29)	48 (33, 65)
Djibouti	82 (29, 139)	17 (4, 37)	2 (0, 4)	19 (3, 47)	8 (3, 13)	8 (3, 13)	230 (84, 402)	34 (3, 80)	49 (6, 105)	225 (79, 390)
Dominica	277 (77, 502)	22 (5, 46)	0 (0, 0)	61 (7, 150)	62 (17, 112)	44 (12, 81)	727 (201, 1397)	204 (-46, 578)	221 (-35, 607)	648 (174, 1292)
Dominican Republic	127 (63, 192)	9 (2, 19)	0 (0, 0)	21 (4, 49)	34 (17, 52)	19 (9, 29)	255 (123, 400)	121 (23, 262)	117 (23, 243)	237 (107, 401)

Appendix Table 1.3 (Continued)

Country name	Maternal short stature	Maternal under-weight	Maternal malaria	Maternal anemia	Teenage mother-hood	Short birth intervals	Low birth-weight	Preterm, small-for-gestational age	Preterm, appropriate-for-gestational age	Term, small-for-gestational age
Ecuador	401 (255, 559)	5 (0, 11)	0 (0, 0)	30 (5, 66)	39 (24, 55)	32 (20, 45)	381 (229, 550)	117 (6, 273)	115 (5, 234)	369 (204, 569)
Egypt	74 (37, 114)	1 (0, 3)	4 (1, 9)	10 (2, 21)	7 (3, 11)	9 (5, 14)	123 (59, 194)	41 (13, 77)	55 (17, 108)	120 (54, 211)
El Salvador	348 (265, 434)	11 (2, 23)	0 (0, 0)	39 (8, 83)	49 (37, 61)	32 (25, 41)	518 (381, 686)	229 (16, 488)	219 (1, 461)	427 (267, 613)
Equatorial Guinea	983 (575, 1471)	119 (27, 258)	114 (34, 220)	272 (76, 543)	143 (82, 212)	99 (57, 145)	2030 (1137, 3086)	605 (119, 1317)	831 (229, 1576)	2173 (1184, 3312)
Eritrea	51 (33, 70)	17 (8, 28)	2 (1, 4)	14 (3, 30)	7 (4, 9)	7 (4, 9)	150 (96, 213)	33 (8, 69)	45 (6, 94)	145 (88, 209)
Ethiopia	44 (32, 60)	16 (8, 28)	2 (1, 3)	10 (3, 19)	5 (4, 7)	6 (4, 8)	158 (109, 217)	20 (10, 35)	28 (16, 44)	156 (106, 216)
Fiji	4 (0, 48)	0 (0, 4)	0 (0, 0)	1 (0, 15)	0 (0, 6)	1 (0, 12)	16 (0, 194)	6 (0, 67)	5 (0, 77)	18 (0, 226)
Gabon	224 (107, 354)	46 (12, 100)	43 (12, 85)	137 (34, 279)	78 (37, 123)	38 (18, 61)	926 (427, 1465)	254 (47, 538)	357 (106, 701)	879 (400, 1454)
Gambia	20 (14, 27)	10 (4, 17)	2 (1, 4)	18 (6, 35)	5 (3, 7)	4 (3, 5)	130 (86, 185)	23 (3, 50)	31 (5, 64)	127 (81, 180)
Georgia	8 (0, 18)	1 (0, 3)	0 (0, 0)	2 (0, 6)	1 (0, 3)	3 (0, 6)	31 (0, 73)	14 (0, 38)	13 (0, 32)	38 (0, 99)
Ghana	43 (31, 58)	7 (3, 14)	27 (10, 47)	23 (7, 42)	5 (4, 7)	4 (3, 6)	150 (103, 208)	40 (6, 84)	55 (9, 108)	152 (100, 219)
Grenada	127 (41, 214)	21 (2, 53)	0 (0, 0)	60 (8, 145)	78 (25, 135)	55 (18, 95)	734 (235, 1278)	338 (55, 786)	328 (48, 771)	641 (201, 1181)
Guatemala	664 (449, 888)	13 (2, 26)	0 (0, 0)	51 (12, 112)	52 (35, 70)	58 (39, 79)	610 (400, 854)	195 (78, 350)	192 (76, 329)	586 (351, 885)
Guinea	15 (11, 20)	4 (2, 7)	7 (2, 11)	8 (2, 14)	3 (2, 4)	2 (1, 2)	52 (35, 72)	14 (2, 30)	19 (3, 38)	58 (38, 82)

Appendix Table 1.3 (Continued)

Country name	Maternal short stature	Maternal under-weight	Maternal malaria	Maternal anemia	Teenage mother-hood	Short birth intervals	Low birth-weight	Preterm, small-for-gestational age	Preterm, appropriate-for-gestational age	Term, small-for-gestational age
Guinea-Bissau	18 (12, 24)	7 (3, 13)	4 (1, 7)	12 (3, 24)	3 (2, 5)	3 (2, 4)	100 (65, 140)	12 (3, 24)	16 (4, 32)	100 (64, 142)
Guyana	152 (107, 205)	13 (2, 26)	0 (0, 0)	32 (8, 61)	31 (21, 43)	21 (15, 29)	389 (264, 541)	152 (34, 319)	148 (17, 295)	356 (219, 516)
Haiti	42 (28, 57)	15 (5, 29)	0 (0, 0)	29 (9, 54)	7 (4, 9)	7 (5, 9)	245 (162, 332)	47 (11, 95)	47 (11, 93)	209 (134, 294)
Honduras	400 (285, 523)	17 (4, 34)	0 (0, 0)	36 (8, 79)	53 (37, 69)	33 (23, 44)	606 (419, 826)	237 (27, 475)	236 (39, 461)	525 (323, 766)
India	188 (126, 255)	78 (42, 127)	0 (0, 0)	73 (22, 144)	17 (11, 23)	17 (11, 23)	549 (361, 774)	90 (48, 148)	82 (47, 131)	543 (359, 751)
Indonesia	258 (154, 382)	29 (13, 56)	0 (0, 0)	29 (6, 64)	12 (7, 18)	11 (7, 18)	361 (210, 561)	162 (71, 302)	151 (67, 273)	392 (210, 631)
Iran (Islamic Republic of)	165 (41, 296)	11 (2, 23)	0 (0, 0)	23 (3, 61)	15 (4, 26)	33 (8, 60)	331 (79, 614)	201 (43, 412)	182 (37, 361)	390 (92, 782)
Iraq	23 (13, 30)	1 (0, 2)	0 (0, 0)	2 (0, 5)	1 (1, 2)	3 (2, 4)	24 (13, 33)	10 (1, 21)	10 (0, 20)	34 (16, 53)
Jamaica	8 (0, 40)	1 (0, 8)	0 (0, 0)	4 (0, 24)	4 (0, 18)	2 (0, 13)	50 (0, 258)	15 (0, 83)	15 (0, 87)	43 (0, 225)
Jordan	53 (21, 88)	2 (0, 4)	0 (0, 0)	9 (2, 21)	2 (1, 4)	13 (5, 22)	127 (52, 222)	71 (21, 149)	67 (18, 137)	142 (52, 260)
Kazakhstan	227 (92, 361)	16 (2, 37)	0 (0, 0)	45 (7, 110)	26 (10, 42)	51 (20, 81)	606 (226, 984)	256 (86, 484)	229 (81, 410)	735 (269, 1230)
Kenya	58 (45, 71)	9 (4, 16)	2 (1, 3)	13 (2, 26)	11 (9, 14)	11 (8, 13)	138 (102, 177)	56 (29, 91)	75 (43, 115)	151 (106, 206)
Kiribati	72 (28, 119)	2 (0, 6)	0 (0, 0)	13 (2, 33)	5 (2, 9)	10 (4, 17)	163 (64, 283)	66 (9, 155)	63 (14, 145)	202 (74, 378)
Kuwait	567 (0, 1794)	16 (0, 67)	0 (0, 0)	92 (0, 408)	59 (0, 187)	134 (0, 429)	1385 (0, 4470)	703 (0, 2833)	607 (0, 2475)	1524 (0, 5287)

Appendix Table 1.3 (Continued)

Country name	Maternal short stature	Maternal under-weight	Maternal malaria	Maternal anemia	Teenage mother-hood	Short birth intervals	Low birth-weight	Preterm, small-for-gestational age	Preterm, appropriate-for-gestational age	Term, small-for-gestational age
Kyrgyzstan	12 (4, 21)	1 (0, 2)	0 (0, 0)	2 (0, 5)	1 (0, 2)	3 (1, 5)	24 (8, 46)	14 (2, 33)	13 (1, 29)	30 (10, 61)
Lao People's Democratic Republic	76 (54, 100)	9 (4, 15)	0 (0, 0)	10 (3, 20)	3 (2, 4)	5 (4, 7)	103 (71, 142)	34 (3, 71)	32 (5, 67)	120 (76, 175)
Lebanon	28 (0, 90)	2 (0, 6)	0 (0, 0)	6 (0, 22)	4 (0, 13)	9 (0, 30)	78 (0, 251)	36 (0, 132)	34 (0, 113)	92 (0, 297)
Lesotho	151 (115, 190)	16 (5, 30)	4 (1, 7)	29 (8, 55)	26 (19, 33)	9 (7, 11)	350 (258, 462)	93 (8, 192)	135 (22, 260)	405 (287, 533)
Liberia	16 (12, 21)	3 (1, 5)	5 (2, 8)	6 (2, 11)	2 (2, 3)	2 (1, 2)	42 (29, 58)	10 (1, 21)	14 (2, 28)	42 (29, 59)
Libyan Arab Jamahiriya	163 (53, 271)	5 (0, 11)	11 (2, 24)	20 (2, 49)	20 (6, 32)	45 (15, 75)	262 (85, 437)	138 (7, 321)	194 (18, 420)	269 (79, 494)
Madagascar	60 (44, 77)	12 (6, 21)	2 (1, 4)	11 (3, 22)	8 (6, 10)	6 (4, 7)	126 (90, 169)	29 (6, 58)	39 (9, 74)	118 (81, 161)
Malawi	62 (48, 79)	9 (4, 17)	16 (6, 27)	14 (4, 26)	8 (6, 10)	5 (4, 6)	140 (102, 183)	49 (25, 78)	66 (37, 102)	136 (95, 190)
Malaysia	120 (22, 228)	15 (2, 32)	0 (0, 0)	17 (1, 44)	6 (1, 12)	11 (2, 21)	239 (41, 444)	90 (2, 223)	85 (6, 198)	244 (45, 475)
Maldives	219 (130, 314)	21 (8, 41)	0 (0, 0)	33 (8, 68)	4 (2, 5)	9 (5, 13)	312 (180, 464)	86 (37, 151)	79 (35, 135)	351 (191, 559)
Mali	13 (9, 18)	7 (3, 12)	6 (2, 12)	13 (4, 24)	4 (3, 6)	4 (2, 5)	89 (56, 123)	14 (2, 30)	18 (2, 38)	97 (62, 139)
Marshall Islands	105 (21, 190)	7 (1, 16)	0 (0, 0)	31 (1, 88)	8 (2, 15)	16 (3, 29)	426 (88, 794)	87 (-5, 242)	82 (0, 217)	447 (88, 867)
Mauritania	30 (20, 41)	13 (5, 25)	6 (2, 11)	23 (5, 45)	6 (4, 8)	4 (3, 6)	200 (129, 285)	24 (5, 50)	33 (6, 67)	175 (111, 252)
Mauritius	113 (0, 231)	12 (0, 33)	0 (0, 0)	24 (0, 67)	6 (0, 13)	12 (0, 24)	289 (0, 605)	66 (0, 180)	95 (0, 246)	248 (0, 540)

Appendix Table 1.3 (Continued)

Country name	Maternal short stature	Maternal under-weight	Maternal malaria	Maternal anemia	Teenage mother-hood	Short birth intervals	Low birth-weight	Preterm, small-for-gestational age	Preterm, appropriate-for-gestational age	Term, small-for-gestational age
Mexico	774 (381, 1279)	14 (4, 30)	0 (0, 0)	51 (11, 114)	122 (59, 205)	80 (39, 132)	857 (412, 1464)	356 (153, 646)	361 (163, 643)	781 (353, 1410)
Micronesia (Federated States of)	168 (64, 272)	6 (0, 16)	0 (0, 0)	29 (1, 76)	10 (4, 17)	19 (7, 30)	392 (150, 653)	135 (18, 303)	122 (15, 292)	447 (156, 768)
Mongolia	75 (46, 107)	2 (1, 5)	0 (0, 0)	5 (1, 12)	6 (4, 9)	12 (7, 18)	80 (48, 120)	96 (35, 181)	87 (34, 161)	98 (40, 172)
Morocco	124 (47, 211)	4 (1, 10)	3 (1, 7)	12 (2, 28)	11 (4, 19)	14 (5, 24)	136 (49, 242)	68 (7, 167)	88 (14, 204)	156 (49, 307)
Mozambique	47 (36, 58)	9 (4, 15)	10 (3, 18)	15 (4, 26)	7 (5, 9)	3 (2, 4)	119 (87, 157)	30 (11, 54)	43 (20, 68)	119 (87, 158)
Myanmar	40 (27, 55)	8 (4, 14)	0 (0, 0)	8 (2, 16)	2 (1, 2)	3 (2, 5)	89 (57, 127)	25 (5, 51)	22 (3, 43)	103 (66, 149)
Namibia	441 (297, 592)	136 (54, 242)	24 (8, 44)	189 (43, 404)	95 (63, 128)	49 (33, 66)	2151 (1414, 2958)	500 (104, 1059)	698 (150, 1347)	1927 (1200, 2762)
Nepal	100 (79, 122)	24 (12, 40)	0 (0, 0)	25 (7, 45)	9 (7, 11)	6 (5, 7)	221 (166, 282)	48 (26, 79)	45 (26, 68)	228 (171, 291)
Nicaragua	114 (84, 150)	4 (1, 9)	0 (0, 0)	9 (1, 23)	20 (15, 27)	13 (9, 17)	171 (116, 235)	59 (1, 131)	60 (1, 126)	157 (97, 231)
Niger	29 (20, 39)	18 (8, 31)	12 (4, 21)	29 (8, 54)	7 (5, 10)	7 (5, 9)	207 (143, 293)	20 (-2, 44)	27 (0, 60)	193 (129, 274)
Nigeria	80 (55, 106)	14 (7, 24)	28 (10, 49)	31 (9, 57)	12 (8, 16)	13 (9, 17)	215 (147, 299)	57 (28, 99)	76 (43, 116)	246 (157, 341)
Oman	543 (322, 801)	34 (10, 67)	0 (0, 0)	80 (19, 173)	30 (18, 43)	68 (41, 99)	888 (523, 1332)	432 (190, 806)	397 (177, 703)	907 (483, 1449)
Pakistan	124 (93, 159)	44 (23, 73)	0 (0, 0)	54 (16, 97)	8 (6, 11)	20 (15, 26)	435 (318, 572)	87 (43, 143)	81 (44, 128)	434 (313, 570)

Appendix Table 1.3 (Continued)

Country name	Maternal short stature	Maternal under-weight	Maternal malaria	Maternal anemia	Teenage mother-hood	Short birth intervals	Low birth-weight	Preterm, small-for-gestational age	Preterm, appropriate-for-gestational age	Term, small-for-gestational age
Panama	462 (166, 785)	15 (2, 36)	0 (0, 0)	54 (9, 135)	76 (28, 130)	50 (18, 87)	717 (260, 1276)	236 (66, 503)	236 (71, 474)	649 (221, 1188)
Papua New Guinea	221 (143, 300)	12 (2, 27)	0 (0, 0)	40 (9, 88)	12 (8, 16)	22 (14, 30)	414 (258, 581)	95 (-5, 222)	88 (4, 200)	533 (319, 780)
Paraguay	218 (92, 365)	6 (0, 16)	0 (0, 0)	21 (3, 54)	32 (14, 52)	27 (11, 45)	254 (109, 429)	106 (-9, 279)	104 (-2, 260)	247 (100, 454)
Peru	315 (259, 371)	4 (1, 7)	0 (0, 0)	21 (5, 38)	27 (21, 32)	23 (18, 27)	315 (238, 397)	112 (51, 194)	114 (53, 181)	292 (183, 417)
Philippines	317 (261, 372)	52 (27, 85)	0 (0, 0)	52 (14, 102)	12 (10, 14)	25 (20, 31)	586 (453, 724)	150 (26, 289)	139 (30, 253)	556 (411, 705)
Qatar	399 (0, 1251)	13 (0, 55)	0 (0, 0)	68 (0, 275)	40 (0, 127)	92 (0, 287)	897 (0, 2885)	470 (0, 1885)	430 (0, 1651)	985 (0, 3249)
Rwanda	122 (94, 150)	10 (4, 18)	2 (1, 3)	9 (3, 18)	5 (4, 6)	14 (10, 17)	170 (125, 224)	65 (1, 139)	89 (2, 183)	191 (125, 268)
Samoa	35 (0, 99)	0 (0, 1)	0 (0, 0)	2 (0, 7)	5 (0, 15)	10 (0, 27)	26 (0, 71)	37 (-1, 143)	33 (-4, 126)	37 (0, 126)
Sao Tome and Principe	32 (23, 42)	4 (1, 8)	0 (0, 0)	9 (2, 16)	6 (4, 8)	3 (2, 3)	71 (49, 98)	21 (0, 42)	31 (4, 65)	82 (52, 118)
Saudi Arabia	357 (0, 806)	9 (0, 25)	0 (0, 0)	51 (0, 147)	21 (0, 47)	48 (0, 108)	490 (0, 1114)	140 (0, 375)	133 (0, 328)	572 (0, 1463)
Senegal	12 (9, 16)	8 (4, 15)	4 (1, 7)	17 (5, 29)	4 (3, 6)	3 (2, 5)	108 (74, 146)	15 (-1, 34)	20 (0, 43)	104 (70, 145)
Seychelles	46 (0, 118)	6 (0, 20)	0 (0, 0)	15 (0, 50)	6 (0, 15)	11 (0, 28)	211 (0, 542)	53 (-1, 196)	71 (0, 250)	196 (0, 524)
Sierra Leone	17 (11, 23)	3 (1, 6)	6 (2, 10)	5 (1, 10)	2 (2, 3)	2 (1, 3)	45 (29, 63)	8 (1, 18)	11 (2, 22)	55 (35, 78)
Solomon Islands	119 (89, 153)	6 (1, 14)	0 (0, 0)	24 (4, 51)	6 (5, 8)	12 (9, 15)	271 (193, 355)	90 (8, 184)	85 (11, 171)	284 (184, 406)

Appendix Table 1.3 (Continued)

Country name	Maternal short stature	Maternal under-weight	Maternal malaria	Maternal anemia	Teenage mother-hood	Short birth intervals	Low birth-weight	Preterm, small-for-gestational age	Preterm, appropriate-for-gestational age	Term, small-for-gestational age
Somalia	79 (48, 116)	12 (4, 23)	1 (0, 2)	16 (5, 32)	8 (5, 11)	8 (4, 11)	141 (83, 213)	35 (8, 72)	49 (10, 99)	177 (101, 270)
South Africa	562 (387, 748)	59 (23, 115)	38 (13, 70)	167 (35, 359)	104 (71, 140)	49 (33, 67)	2082 (1383, 2896)	305 (62, 651)	410 (56, 812)	2023 (1285, 2912)
Sri Lanka	53 (39, 69)	8 (4, 14)	0 (0, 0)	7 (2, 14)	2 (2, 3)	4 (3, 5)	100 (69, 135)	28 (11, 54)	26 (10, 46)	103 (66, 145)
St. Lucia	190 (69, 313)	24 (3, 57)	0 (0, 0)	77 (11, 182)	78 (28, 130)	55 (19, 91)	942 (339, 1621)	311 (38, 744)	311 (29, 711)	829 (274, 1506)
St. Vincent	388 (116, 668)	18 (1, 46)	0 (0, 0)	48 (5, 121)	61 (18, 108)	43 (13, 74)	600 (183, 1048)	269 (16, 649)	269 (18, 673)	547 (162, 999)
State of Palestine	10 (1, 19)	0 (0, 1)	0 (0, 0)	2 (0, 5)	1 (0, 2)	2 (0, 4)	24 (3, 44)	10 (1, 20)	10 (1, 19)	26 (3, 49)
Sudan	127 (88, 171)	29 (10, 55)	10 (3, 19)	43 (11, 90)	12 (8, 16)	12 (8, 17)	476 (324, 658)	56 (23, 99)	76 (36, 132)	413 (274, 582)
Suriname	522 (293, 789)	30 (2, 66)	0 (0, 0)	84 (17, 201)	81 (45, 122)	57 (32, 86)	1048 (568, 1594)	302 (106, 573)	304 (116, 579)	970 (500, 1578)
Swaziland	281 (226, 344)	33 (9, 67)	3 (1, 5)	65 (18, 127)	80 (63, 99)	31 (25, 39)	797 (595, 1029)	288 (32, 574)	389 (64, 743)	904 (664, 1211)
Syrian Arab Republic	103 (51, 165)	4 (1, 11)	0 (0, 0)	13 (2, 31)	6 (3, 10)	14 (7, 22)	171 (84, 282)	67 (4, 155)	64 (14, 133)	189 (87, 325)
Taiwan	467 (0, 1055)	26 (0, 72)	0 (0, 0)	35 (0, 97)	27 (0, 61)	50 (0, 113)	476 (0, 1089)	337 (0, 898)	300 (0, 748)	612 (0, 1478)
Tajikistan	17 (8, 28)	1 (0, 3)	0 (0, 0)	2 (0, 6)	1 (1, 2)	3 (1, 5)	31 (15, 53)	18 (4, 39)	16 (2, 38)	42 (18, 76)
Thailand	239 (113, 372)	23 (8, 45)	0 (0, 0)	32 (2, 81)	12 (6, 19)	23 (11, 36)	409 (190, 657)	184 (77, 345)	168 (67, 296)	443 (194, 778)

Appendix Table 1.3 (Continued)

Country name	Maternal short stature	Maternal under-weight	Maternal malaria	Maternal anemia	Teenage mother-hood	Short birth intervals	Low birth-weight	Preterm, small-for-gestational age	Preterm, appropriate-for-gestational age	Term, small-for-gestational age
Timore Leste	93 (20, 179)	15 (2, 35)	0 (0, 0)	9 (1, 24)	3 (1, 6)	10 (2, 19)	139 (30, 276)	45 (3, 127)	42 (2, 102)	163 (33, 323)
Togo	12 (9, 16)	3 (1, 5)	7 (3, 12)	6 (2, 11)	2 (1, 2)	2 (1, 2)	42 (29, 56)	12 (1, 23)	16 (2, 31)	46 (31, 63)
Tonga	22 (0, 53)	0 (0, 1)	0 (0, 0)	6 (0, 21)	7 (0, 18)	13 (0, 34)	87 (0, 216)	74 (0, 230)	70 (0, 231)	110 (0, 324)
Trinidad and Tobago	69 (0, 213)	6 (0, 23)	0 (0, 0)	23 (0, 86)	23 (0, 71)	16 (0, 49)	281 (0, 856)	79 (0, 274)	78 (0, 262)	274 (0, 822)
Tunisia	36 (0, 88)	2 (0, 5)	2 (0, 6)	5 (0, 15)	4 (0, 9)	8 (0, 20)	63 (0, 160)	27 (0, 85)	37 (0, 112)	63 (0, 159)
Turkey	237 (36, 443)	12 (1, 32)	0 (0, 0)	55 (3, 145)	28 (4, 52)	45 (7, 84)	749 (121, 1420)	284 (41, 593)	257 (39, 559)	795 (122, 1568)
Turkmenistan	62 (17, 112)	5 (1, 12)	0 (0, 0)	12 (1, 33)	9 (3, 17)	19 (5, 34)	161 (42, 297)	107 (9, 273)	96 (7, 245)	224 (58, 436)
Uganda	76 (55, 100)	17 (7, 31)	31 (10, 53)	23 (7, 43)	12 (8, 16)	14 (10, 18)	247 (169, 345)	61 (18, 116)	82 (24, 146)	247 (171, 342)
United Arab Emirates	452 (0, 1250)	5 (0, 16)	0 (0, 0)	20 (0, 72)	26 (0, 72)	60 (0, 165)	283 (0, 799)	249 (0, 787)	221 (0, 643)	347 (0, 1076)
United Republic of Tanzania	70 (58, 83)	9 (4, 16)	5 (2, 9)	18 (5, 30)	8 (6, 9)	7 (5, 8)	137 (104, 172)	41 (4, 81)	56 (9, 107)	145 (106, 192)
Uruguay	147 (0, 352)	7 (0, 22)	0 (0, 0)	38 (0, 126)	45 (0, 108)	32 (0, 76)	499 (0, 1239)	186 (0, 492)	184 (0, 461)	420 (0, 1037)
Uzbekistan	28 (10, 48)	2 (0, 3)	0 (0, 0)	4 (1, 10)	2 (1, 4)	6 (2, 10)	44 (15, 75)	26 (5, 60)	24 (5, 52)	59 (19, 109)
Vanuatu	244 (155, 344)	16 (3, 36)	0 (0, 0)	50 (10, 113)	19 (12, 26)	35 (22, 49)	675 (413, 999)	291 (35, 626)	253 (25, 513)	707 (389, 1101)
Venezuela	374 (0, 819)	9 (0, 25)	0 (0, 0)	49 (0, 145)	73 (0, 160)	48 (0, 105)	667 (0, 1490)	253 (-8, 765)	245 (0, 769)	591 (0, 1349)

Appendix Table 1.3 (Continued)

Country name	Maternal short stature	Maternal under-weight	Maternal malaria	Maternal anemia	Teenage mother-hood	Short birth intervals	Low birth-weight	Preterm, small-for-gestational age	Preterm, appropriate-for-gestational age	Term, small-for-gestational age
Viet Nam	84 (58, 112)	8 (4, 13)	0 (0, 0)	5 (1, 11)	3 (2, 5)	6 (4, 9)	71 (47, 98)	44 (8, 91)	40 (5, 85)	89 (44, 148)
Yemen	125 (83, 171)	25 (10, 47)	0 (0, 0)	37 (9, 79)	8 (6, 12)	28 (18, 40)	394 (254, 556)	75 (11, 151)	68 (2, 139)	411 (262, 571)
Zambia	173 (124, 229)	29 (13, 52)	24 (8, 44)	42 (10, 83)	28 (20, 38)	18 (13, 24)	444 (304, 610)	129 (21, 279)	180 (36, 354)	463 (307, 659)
Zimbabwe	19 (8, 30)	3 (1, 6)	2 (0, 4)	6 (1, 13)	4 (2, 7)	1 (0, 2)	64 (24, 109)	23 (8, 45)	31 (11, 55)	65 (26, 115)

Appendix Table 1.4: Country-level estimated lifetime wage income loss associated with each risk factor (95% confidence intervals in parentheses) per child born in 2010 ($US) for the child nutrition and infection and water, sanitation, and biomass fuel use risk groups

Country name	Child-hood zinc deficiency	Childhood diarrhea	Non-exclusive breastfeeding	Discontinued breast-feeding	Late HAART initiation for childhood HIV*	Unimproved sanitation	Unimproved water	Use of biomass fuels
Afghanistan	4 (2, 8)	130 (46, 238)	16 (-5, 43)	9 (1, 24)		146 (100, 201)	27 (15, 44)	52 (35, 71)
Algeria	23 (6, 64)	122 (19, 296)	23 (2, 63)	16 (1, 48)		36 (7, 70)	10 (1, 22)	0 (-2, 2)
Angola	27 (11, 49)	382 (123, 737)	54 (-7, 142)	21 (1, 60)	0 (0, 1)	471 (281, 684)	88 (42, 154)	85 (37, 152)
Antigua and Barbuda	49 (15, 116)	1440 (315, 3060)	261 (17, 701)	227 (19, 599)		292 (69, 603)	16 (3, 35)	0 (-18, 18)
Argentina	18 (1, 88)	304 (26, 740)	28 (-38, 119)	38 (1, 120)		26 (1, 66)	2 (-1, 5)	1 (-3, 6)
Armenia	13 (4, 32)	129 (43, 241)	14 (-12, 45)	20 (3, 49)		21 (10, 35)	1 (-1, 2)	3 (-3, 8)
Azerbaijan	27 (10, 63)	312 (168, 421)	49 (7, 101)	48 (8, 98)		106 (49, 169)	25 (10, 47)	9 (-7, 25)
Bahamas	70 (12, 188)	791 (2, 1856)	154 (0, 439)	137 (0, 412)		318 (2, 710)	28 (0, 64)	0 (0, 0)
Bahrain	133 (0, 392)	222 (0, 613)	38 (0, 133)	30 (0, 106)		12 (0, 32)	3 (-2, 13)	0 (0, 0)
Bangladesh	7 (3, 12)	72 (26, 135)	7 (-6, 23)	3 (0, 9)		91 (66, 120)	9 (5, 14)	51 (34, 72)
Barbados	80 (24, 185)	794 (166, 1781)	143 (5, 371)	131 (12, 369)		320 (62, 703)	9 (-10, 36)	-1 (-62, 60)
Belize	31 (11, 62)	593 (197, 1120)	116 (28, 266)	88 (11, 214)		142 (81, 226)	14 (4, 30)	38 (16, 71)
Benin	3 (1, 5)	53 (19, 101)	5 (-7, 17)	2 (0, 6)	0 (0, 0)	93 (66, 124)	8 (4, 15)	24 (15, 35)

Appendix Table 1.4 (Continued)

Country name	Child-hood zinc deficiency	Childhood diarrhea	Non-exclusive breastfeeding	Discontinued breast-feeding	Late HAART initiation for childhood HIV*	Unimproved sanitation	Unimproved water	Use of biomass fuels
Bhutan	27 (11, 47)	246 (89, 448)	26 (-14, 77)	24 (3, 66)		358 (266, 466)	10 (2, 20)	45 (22, 74)
Bolivia	8 (3, 14)	299 (127, 508)	27 (-32, 88)	24 (3, 64)		238 (174, 313)	16 (9, 26)	12 (7, 20)
Botswana	142 (56, 264)	1108 (341, 2195)	185 (14, 465)	149 (18, 394)	32 (13, 73)	1080 (674, 1547)	25 (10, 46)	255 (141, 407)
Brazil	53 (11, 140)	1028 (57, 2367)	175 (0, 502)	183 (2, 528)		350 (24, 693)	15 (1, 33)	18 (-7, 59)
Burkina Faso	5 (2, 8)	49 (17, 91)	6 (-1, 15)	1 (0, 4)	0 (0, 0)	74 (53, 99)	6 (3, 9)	14 (9, 21)
Burundi	4 (2, 7)	59 (20, 107)	3 (-9, 14)	1 (0, 4)	0 (0, 0)	59 (39, 84)	7 (3, 13)	19 (12, 27)
Cambodia	2 (1, 4)	49 (20, 84)	4 (-5, 15)	3 (0, 9)		76 (57, 94)	11 (7, 17)	14 (9, 20)
Cameroon	11 (4, 20)	122 (45, 233)	15 (-7, 44)	8 (0, 24)	0 (0, 0)	132 (88, 188)	18 (9, 30)	34 (21, 51)
Cape Verde	12 (4, 27)	108 (17, 277)	14 (-3, 45)	9 (0, 32)	0 (0, 1)	193 (50, 348)	11 (2, 23)	12 (3, 24)
Central African Republic	2 (1, 4)	59 (19, 116)	8 (-2, 21)	2 (0, 6)	0 (0, 0)	74 (47, 103)	9 (4, 15)	21 (13, 32)
Chad	6 (3, 11)	109 (37, 211)	14 (0, 36)	5 (0, 16)	0 (0, 0)	146 (87, 205)	23 (12, 39)	48 (26, 75)
Chile	10 (0, 73)	29 (0, 214)	2 (-3, 20)	4 (0, 31)		2 (0, 14)	0 (0, 2)	1 (0, 4)
China	10 (2, 25)	118 (20, 275)	20 (0, 60)	17 (1, 51)		140 (24, 286)	7 (1, 17)	8 (1, 16)
Colombia	32 (12, 68)	749 (302, 1296)	103 (-30, 267)	87 (13, 219)		289 (196, 412)	23 (8, 41)	36 (11, 67)

Appendix Table 1.4 (Continued)

Country name	Child-hood zinc deficiency	Childhood diarrhea	Non-exclusive breastfeeding	Discontinued breast-feeding	Late HAART initiation for childhood HIV*	Unimproved sanitation	Unimproved water	Use of biomass fuels
Comoros	10 (4, 18)	96 (32, 197)	16 (1, 43)	9 (1, 25)	0 (0, 0)	149 (89, 221)	5 (1, 11)	59 (33, 92)
Congo	18 (7, 34)	213 (70, 437)	30 (-5, 85)	16 (1, 45)	1 (0, 2)	326 (174, 487)	31 (14, 56)	71 (35, 115)
Costa Rica	67 (10, 236)	400 (23, 936)	67 (0, 211)	56 (1, 169)		52 (4, 111)	6 (0, 16)	6 (0, 15)
Cote d'Ivoire	11 (5, 19)	133 (46, 252)	18 (0, 46)	6 (0, 20)	0 (0, 0)	204 (137, 288)	15 (7, 27)	54 (32, 84)
Cuba	64 (8, 194)	335 (0, 797)	55 (0, 170)	58 (0, 181)		66 (0, 151)	11 (0, 25)	5 (-8, 21)
Democratic People's Republic of Korea	4 (2, 7)	30 (10, 56)	4 (-1, 12)	2 (0, 5)		22 (12, 33)	0 (-1, 1)	9 (6, 13)
Democratic Republic of the Congo	5 (2, 8)	38 (13, 71)	4 (-2, 13)	2 (0, 5)	0 (0, 0)	48 (34, 64)	10 (6, 16)	10 (7, 14)
Djibouti	10 (4, 25)	113 (28, 245)	21 (3, 57)	15 (1, 43)		107 (36, 198)	7 (2, 16)	12 (-1, 32)
Dominica	36 (10, 77)	733 (163, 1647)	130 (9, 371)	111 (8, 298)		305 (82, 579)	16 (3, 38)	19 (-16, 66)
Dominican Republic	64 (16, 214)	357 (121, 701)	72 (15, 170)	60 (10, 146)		117 (52, 191)	21 (4, 44)	8 (1, 18)
Ecuador	14 (6, 26)	633 (225, 1145)	60 (-54, 184)	60 (7, 167)		129 (62, 215)	28 (8, 56)	6 (-3, 18)
Egypt	9 (3, 19)	136 (36, 289)	14 (-12, 46)	7 (0, 21)		17 (7, 30)	2 (1, 4)	0 (-2, 2)
El Salvador	47 (19, 88)	566 (229, 949)	91 (-4, 206)	54 (7, 132)		296 (203, 401)	25 (10, 44)	40 (17, 71)

Appendix Table 1.4 (Continued)

Country name	Child-hood zinc deficiency	Childhood diarrhea	Non-exclusive breastfeeding	Discontinued breast-feeding	Late HAART initiation for childhood HIV*	Unimproved sanitation	Unimproved water	Use of biomass fuels
Equatorial Guinea	135 (55, 251)	1943 (571, 3934)	252 (-103, 732)	200 (19, 581)	3 (1, 6)	1407 (823, 2157)	305 (134, 533)	482 (257, 775)
Eritrea	4 (2, 7)	88 (29, 170)	7 (-11, 25)	4 (0, 13)	0 (0, 0)	167 (111, 226)	20 (10, 32)	30 (18, 48)
Ethiopia	2 (1, 3)	78 (28, 146)	7 (-8, 25)	5 (0, 14)	0 (0, 0)	122 (87, 166)	25 (14, 39)	44 (28, 64)
Fiji	7 (-7, 31)	11 (0, 131)	1 (0, 15)	1 (0, 11)		5 (0, 72)	0 (0, 5)	2 (0, 28)
Gabon	35 (12, 71)	517 (141, 1106)	91 (12, 227)	69 (7, 192)	3 (1, 12)	750 (354, 1205)	45 (15, 89)	72 (23, 139)
Gambia	7 (3, 13)	60 (20, 117)	5 (-8, 19)	1 (0, 4)	0 (0, 0)	56 (34, 81)	5 (2, 9)	36 (21, 53)
Georgia	15 (0, 63)	46 (0, 123)	9 (0, 29)	7 (0, 24)		6 (0, 14)	1 (0, 3)	5 (0, 12)
Ghana	7 (3, 13)	93 (31, 175)	8 (-8, 27)	4 (0, 11)	0 (0, 0)	175 (124, 237)	9 (5, 16)	38 (24, 57)
Grenada	41 (13, 85)	988 (244, 2038)	175 (7, 450)	147 (15, 396)		168 (51, 296)	20 (5, 45)	0 (-30, 27)
Guatemala	41 (16, 75)	805 (318, 1423)	70 (-95, 229)	74 (8, 191)		289 (172, 427)	27 (11, 50)	124 (70, 193)
Guinea	2 (1, 3)	42 (14, 80)	4 (-3, 14)	2 (0, 5)	0 (0, 0)	62 (43, 84)	6 (3, 10)	14 (9, 21)
Guinea-Bissau	3 (1, 5)	55 (19, 105)	7 (-1, 19)	2 (0, 5)	0 (0, 0)	72 (47, 98)	8 (4, 13)	28 (16, 42)
Guyana	21 (7, 42)	408 (159, 712)	69 (3, 165)	45 (6, 114)		122 (77, 179)	11 (6, 20)	11 (0, 24)
Haiti	12 (5, 21)	183 (68, 331)	24 (-9, 68)	16 (2, 42)		148 (90, 218)	18 (8, 32)	66 (42, 99)
Honduras	37 (15, 68)	651 (250, 1115)	92 (-17, 237)	62 (7, 167)		255 (173, 356)	35 (19, 55)	102 (63, 152)

Appendix Table 1.4 (Continued)

Country name	Child-hood zinc deficiency	Childhood diarrhea	Non-exclusive breastfeeding	Discontinued breast-feeding	Late HAART initiation for childhood HIV*	Unimproved sanitation	Unimproved water	Use of biomass fuels
India	18 (7, 32)	177 (63, 322)	18 (-16, 55)	13 (2, 37)	0 (0, 0)	299 (196, 413)	14 (7, 23)	111 (64, 170)
Indonesia	30 (11, 57)	208 (68, 428)	28 (-9, 81)	14 (1, 44)		253 (146, 386)	26 (13, 47)	57 (29, 99)
Iran (Islamic Republic of)	65 (18, 175)	319 (56, 727)	31 (-33, 122)	18 (1, 61)		59 (12, 124)	9 (2, 21)	0 (-5, 4)
Iraq	2 (1, 6)	30 (9, 58)	4 (-1, 12)	3 (0, 8)		10 (3, 17)	3 (1, 5)	0 (0, 1)
Jamaica	16 (0, 89)	45 (0, 251)	7 (0, 45)	6 (0, 38)		15 (0, 76)	1 (0, 7)	2 (-2, 16)
Jordan	23 (5, 80)	99 (23, 232)	15 (0, 49)	13 (1, 39)		7 (2, 13)	2 (1, 5)	0 (-1, 1)
Kazakhstan	20 (7, 50)	871 (255, 1684)	123 (-3, 330)	100 (12, 270)		52 (19, 90)	12 (0, 30)	22 (-1, 56)
Kenya	11 (4, 19)	136 (50, 250)	19 (-3, 51)	9 (1, 25)	1 (0, 1)	214 (165, 269)	33 (20, 51)	35 (23, 48)
Kiribati	20 (6, 48)	134 (35, 274)	16 (-14, 52)	10 (1, 29)		208 (76, 357)	25 (7, 51)	25 (9, 45)
Kuwait	152 (0, 353)	780 (0, 2920)	184 (0, 774)	144 (0, 600)		0 (0, 0)	10 (0, 45)	0 (0, 0)
Kyrgyzstan	1 (0, 2)	43 (12, 86)	4 (-3, 15)	4 (0, 10)		5 (2, 9)	2 (1, 5)	3 (1, 6)
Lao People's Democratic Republic	3 (1, 5)	77 (28, 141)	12 (-1, 30)	5 (0, 13)		75 (47, 108)	16 (8, 25)	29 (18, 41)
Lebanon	34 (0, 135)	81 (0, 308)	16 (0, 64)	13 (0, 57)		14 (0, 44)	0 (0, 0)	0 (-1, 1)
Lesotho	30 (12, 52)	282 (100, 522)	35 (-15, 98)	21 (2, 55)	3 (2, 5)	408 (301, 527)	31 (16, 50)	70 (44, 104)
Liberia	2 (1, 4)	27 (9, 52)	3 (-2, 10)	2 (0, 5)	0 (0, 0)	47 (34, 63)	4 (2, 7)	12 (8, 17)

Appendix Table 1.4 (Continued)

Country name	Child-hood zinc deficiency	Childhood diarrhea	Non-exclusive breastfeeding	Discontinued breast-feeding	Late HAART initiation for childhood HIV*	Unimproved sanitation	Unimproved water	Use of biomass fuels
Libyan Arab Jamahiriya	81 (21, 225)	400 (86, 910)	63 (0, 177)	47 (4, 145)		66 (22, 114)	51 (13, 107)	0 (-3, 3)
Madagascar	3 (1, 5)	67 (24, 126)	6 (-6, 19)	3 (0, 9)	0 (0, 0)	129 (95, 170)	23 (13, 34)	35 (23, 50)
Malawi	10 (4, 17)	97 (34, 181)	10 (-9, 32)	3 (0, 11)	1 (0, 1)	113 (84, 148)	11 (6, 17)	39 (26, 55)
Malaysia	22 (4, 70)	135 (19, 314)	20 (-4, 63)	17 (1, 48)		29 (1, 70)	2 (-2, 9)	0 (-4, 4)
Maldives	17 (6, 33)	178 (54, 365)	19 (-16, 63)	13 (1, 38)		49 (1, 103)	2 (-6, 9)	8 (-17, 32)
Mali	3 (1, 5)	58 (21, 109)	5 (-5, 18)	3 (0, 8)	0 (0, 0)	71 (46, 97)	10 (5, 17)	25 (15, 37)
Marshall Islands	22 (6, 62)	209 (32, 453)	31 (-10, 95)	16 (1, 44)		147 (25, 282)	6 (-7, 25)	48 (7, 106)
Mauritania	2 (1, 5)	66 (23, 128)	10 (0, 25)	3 (0, 10)	0 (0, 0)	109 (71, 153)	19 (10, 31)	36 (22, 57)
Mauritius	25 (5, 74)	131 (0, 369)	20 (-3, 68)	18 (0, 57)	0 (0, 1)	39 (0, 85)	0 (-1, 1)	0 (-6, 6)
Mexico	120 (36, 289)	1404 (465, 2896)	321 (80, 767)	227 (35, 616)		427 (191, 751)	36 (13, 71)	46 (15, 92)
Micronesia (Federated States of)	21 (7, 49)	241 (67, 508)	28 (-22, 91)	19 (1, 52)		360 (127, 620)	13 (2, 31)	56 (19, 105)
Mongolia	3 (1, 5)	132 (43, 251)	9 (-17, 35)	7 (1, 22)		106 (56, 163)	17 (8, 31)	17 (10, 27)
Morocco	22 (8, 44)	241 (59, 552)	37 (-5, 107)	29 (3, 84)		124 (45, 229)	26 (8, 53)	2 (-1, 6)

Appendix Table 1.4 (Continued)

Country name	Child-hood zinc deficiency	Childhood diarrhea	Non-exclusive breastfeeding	Discontinued breast-feeding	Late HAART initiation for childhood HIV*	Unimproved sanitation	Unimproved water	Use of biomass fuels
Mozambique	6 (2, 10)	82 (30, 153)	9 (-6, 26)	6 (0, 16)	0 (0, 1)	121 (93, 154)	21 (13, 33)	33 (22, 47)
Myanmar	3 (1, 5)	43 (17, 81)	6 (-1, 15)	2 (0, 6)		28 (16, 45)	6 (3, 11)	24 (14, 36)
Namibia	79 (32, 137)	1056 (352, 2101)	171 (-6, 476)	113 (13, 310)	25 (13, 47)	1725 (1127, 2362)	72 (27, 135)	387 (230, 583)
Nepal	5 (2, 9)	80 (31, 146)	6 (-9, 23)	3 (0, 9)		141 (106, 177)	8 (4, 13)	53 (35, 75)
Nicaragua	17 (7, 30)	208 (83, 368)	30 (-7, 77)	27 (4, 64)		152 (97, 219)	13 (6, 21)	30 (19, 46)
Niger	3 (1, 5)	106 (35, 196)	13 (-2, 35)	4 (0, 11)	0 (0, 0)	150 (103, 204)	24 (13, 38)	56 (35, 83)
Nigeria	10 (4, 17)	201 (65, 399)	28 (-4, 71)	11 (1, 31)	0 (0, 0)	232 (157, 314)	36 (20, 57)	49 (30, 75)
Oman	123 (37, 295)	397 (142, 751)	39 (-39, 132)	29 (3, 82)		79 (4, 168)	38 (13, 73)	0 (0, 0)
Pakistan	9 (4, 15)	188 (66, 345)	29 (0, 71)	17 (2, 44)		210 (151, 278)	9 (4, 15)	86 (56, 125)
Panama	76 (22, 193)	878 (221, 1758)	135 (-19, 377)	119 (12, 332)		415 (149, 773)	27 (8, 56)	46 (14, 97)
Papua New Guinea	9 (4, 16)	352 (128, 641)	24 (-56, 97)	20 (0, 60)		564 (353, 779)	103 (48, 178)	91 (51, 135)
Paraguay	14 (5, 28)	411 (133, 841)	65 (0, 178)	59 (7, 147)		175 (70, 304)	24 (8, 49)	39 (16, 71)
Peru	23 (9, 43)	462 (180, 760)	37 (-58, 121)	36 (4, 90)		239 (177, 307)	32 (15, 51)	40 (25, 58)
Philippines	9 (3, 15)	234 (88, 400)	36 (-2, 86)	29 (4, 71)		168 (120, 223)	13 (7, 21)	96 (51, 147)

Appendix Table 1.4 (Continued)

Country name	Child-hood zinc deficiency	Childhood diarrhea	Non-exclusive breastfeeding	Discontinued breast-feeding	Late HAART initiation for childhood HIV*	Unimproved sanitation	Unimproved water	Use of biomass fuels
Qatar	548 (0, 2180)	537 (0, 1926)	167 (0, 622)	115 (0, 453)		0 (0, 0)	0 (0, 0)	0 (-17, 20)
Rwanda	18 (7, 31)	218 (83, 386)	11 (-20, 43)	8 (0, 25)	0 (0, 0)	185 (120, 257)	38 (21, 60)	48 (32, 67)
Samoa	15 (0, 60)	121 (0, 384)	15 (-5, 62)	11 (0, 50)		37 (0, 105)	2 (0, 7)	5 (0, 14)
Sao Tome and Principe	7 (3, 13)	65 (21, 122)	7 (-5, 20)	3 (0, 9)	0 (0, 0)	112 (78, 150)	4 (1, 9)	16 (10, 24)
Saudi Arabia	95 (0, 260)	280 (0, 753)	44 (-2, 153)	38 (0, 137)		13 (-25, 67)	10 (0, 30)	0 (-10, 9)
Senegal	5 (2, 9)	52 (18, 102)	6 (-3, 16)	2 (0, 7)	0 (0, 0)	61 (43, 83)	9 (5, 15)	20 (11, 30)
Seychelles	27 (0, 97)	137 (0, 432)	22 (-1, 85)	20 (0, 74)		46 (0, 118)	5 (0, 14)	0 (-4, 4)
Sierra Leone	2 (1, 4)	35 (12, 68)	5 (0, 13)	2 (0, 6)	0 (0, 0)	53 (35, 73)	7 (4, 12)	13 (8, 19)
Solomon Islands	19 (7, 36)	154 (62, 278)	10 (-23, 38)	10 (1, 26)		287 (210, 375)	19 (9, 34)	73 (47, 106)
Somalia	6 (3, 11)	129 (41, 254)	23 (3, 60)	15 (2, 40)		163 (95, 240)	41 (22, 68)	39 (22, 61)
South Africa	107 (40, 200)	1042 (332, 2052)	204 (42, 525)	118 (12, 350)	27 (9, 76)	696 (443, 1021)	65 (32, 109)	102 (47, 180)
Sri Lanka	13 (5, 24)	44 (14, 85)	3 (-6, 13)	2 (0, 7)		19 (8, 31)	4 (2, 7)	23 (14, 34)
St. Lucia	19 (7, 40)	969 (248, 2014)	174 (17, 474)	145 (16, 362)		561 (170, 996)	25 (5, 57)	4 (-32, 40)
St. Vincent	36 (12, 76)	800 (183, 1691)	140 (3, 397)	119 (11, 341)		354 (89, 669)	16 (3, 35)	0 (-64, 54)

Appendix Table 1.4 (Continued)

Country name	Child-hood zinc deficiency	Childhood diarrhea	Non-exclusive breastfeeding	Discontinued breast-feeding	Late HAART initiation for childhood HIV*	Unimproved sanitation	Unimproved water	Use of biomass fuels
State of Palestine	5 (1, 16)	32 (4, 71)	5 (-1, 14)	3 (0, 9)		5 (1, 9)	1 (0, 2)	0 (0, 0)
Sudan	4 (2, 8)	191 (63, 363)	28 (-3, 71)	18 (2, 48)		276 (184, 379)	38 (17, 67)	106 (63, 162)
Suriname	87 (31, 192)	1115 (429, 2019)	253 (73, 537)	170 (27, 401)		316 (169, 508)	32 (11, 63)	44 (14, 91)
Swaziland	39 (16, 69)	737 (258, 1369)	108 (-15, 284)	60 (5, 157)	22 (11, 40)	681 (514, 879)	130 (74, 207)	158 (100, 228)
Syrian Arab Republic	12 (4, 25)	122 (32, 265)	17 (-5, 49)	12 (1, 35)		24 (10, 45)	8 (3, 15)	0 (-2, 2)
Taiwan	103 (15, 248)	599 (0, 1567)	106 (0, 362)	65 (0, 209)		588 (0, 1434)	18 (0, 50)	102 (0, 232)
Tajikistan	2 (1, 4)	55 (18, 110)	6 (-4, 18)	4 (0, 12)		5 (1, 11)	7 (3, 12)	4 (1, 9)
Thailand	60 (18, 157)	245 (63, 518)	54 (11, 125)	40 (4, 105)		30 (9, 58)	12 (4, 22)	35 (2, 85)
Timore Leste	4 (1, 8)	84 (15, 206)	9 (-7, 33)	9 (0, 27)		127 (25, 255)	18 (3, 37)	38 (8, 77)
Togo	3 (1, 5)	31 (11, 60)	3 (-3, 11)	1 (0, 3)	0 (0, 0)	56 (40, 74)	7 (4, 12)	12 (7, 17)
Tonga	25 (0, 82)	169 (0, 501)	21 (-15, 91)	14 (0, 57)		94 (0, 249)	1 (0, 4)	13 (0, 36)
Trinidad and Tobago	130 (0, 635)	122 (0, 418)	24 (0, 92)	21 (0, 84)		44 (0, 146)	7 (0, 28)	0 (-6, 6)
Tunisia	23 (0, 85)	74 (0, 221)	13 (0, 43)	10 (0, 36)		24 (0, 63)	3 (0, 8)	0 (-1, 1)
Turkey	101 (25, 297)	774 (91, 1790)	93 (-43, 299)	99 (1, 271)		139 (19, 289)	11 (0, 30)	12 (-4, 38)
Turkmenistan	6 (2, 11)	320 (66, 693)	57 (6, 148)	44 (4, 123)		33 (9, 60)	23 (3, 55)	0 (-2, 2)

Appendix Table 1.4 (Continued)

Country name	Child-hood zinc deficiency	Childhood diarrhea	Non-exclusive breastfeeding	Discontinued breast-feeding	Late HAART initiation for childhood HIV*	Unimproved sanitation	Unimproved water	Use of biomass fuels
Uganda	8 (3, 14)	171 (63, 320)	16 (-14, 54)	11 (1, 31)	0 (0, 1)	217 (156, 291)	26 (15, 42)	69 (44, 101)
United Arab Emirates	195 (0, 755)	355 (0, 1208)	70 (0, 275)	58 (0, 204)		36 (0, 103)	0 (-3, 3)	0 (-4, 4)
United Republic of Tanzania	10 (4, 17)	121 (45, 218)	14 (-10, 43)	6 (0, 17)	0 (0, 0)	214 (172, 258)	33 (21, 48)	38 (26, 52)
Uruguay	51 (0, 198)	545 (0, 1475)	51 (-60, 240)	68 (0, 223)		12 (0, 32)	0 (-2, 2)	0 (-13, 12)
Uzbekistan	3 (1, 6)	96 (25, 192)	12 (-3, 36)	7 (0, 20)		9 (1, 20)	3 (1, 8)	2 (0, 4)
Vanuatu	24 (10, 43)	435 (159, 811)	50 (-52, 156)	24 (1, 71)		516 (305, 792)	39 (17, 67)	171 (97, 269)
Venezuela	111 (9, 363)	837 (0, 2021)	166 (0, 486)	117 (0, 368)		239 (0, 565)	22 (0, 59)	0 (-10, 8)
Viet Nam	4 (1, 7)	79 (29, 144)	10 (-4, 26)	5 (0, 13)		65 (43, 93)	5 (3, 9)	12 (7, 19)
Yemen	8 (3, 14)	170 (53, 338)	30 (6, 75)	17 (2, 46)		163 (102, 235)	32 (9, 61)	46 (26, 76)
Zambia	36 (14, 63)	370 (136, 692)	37 (-40, 124)	15 (1, 46)	3 (1, 4)	423 (302, 575)	77 (41, 125)	111 (70, 160)
Zimbabwe	7 (2, 15)	44 (11, 93)	6 (-1, 18)	2 (0, 6)	1 (0, 2)	57 (22, 94)	6 (2, 11)	14 (5, 25)

* Only estimated for 45 countries due to data availability

Paper 2: The impact of parsimonious versus comprehensive cost estimation in cost-effectiveness analysis: Economic evaluation of a kangaroo mother care program in Mali

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Abstract

Background

Cost-effectiveness analyses (CEAs) can provide valuable evidence to inform resource allocation, but their usefulness depends on their comprehensiveness and validity. While differences between efficacy and effectiveness (representing measures of effect in ideal versus real-world circumstances) have been well-defined, similar distinctions in costing have not been made. This paper highlights three important ways in which costs are commonly underestimated. Using a case study of a kangaroo mother care (KMC) program in Mali, we illustrate how omitting administrative, demand-creation, and patient/family-incurred costs may result in a substantial underestimation of true costs and overestimation of the cost-effectiveness of interventions. In so doing, we also produce the first cost effectiveness analysis of KMC based on empirically-derived cost estimates.

Methods and Findings

We used detailed expenditure records from a KMC program launched in a district hospital in Mali in 2010, adjusting for the lifespan of goods and trainings, inflation, and discounting to produce an annualized program cost. Cost estimates included equipment, provider trainings, patient demand creation, medical supplies, and cost of mothers' time. As no health impact estimates were available from the program, a 33% reduction in neonatal mortality was assumed based on the most recent literature review.

The total cost per infant in the KMC program was an estimated $670, which included $410 per infant in demand-creation. We used these cost estimates to compute the cost-effectiveness of KMC across a range of alternative choices commonly used in CEAs, reflecting the spectrum from highly parsimonious costing assumptions to comprehensive assumptions leveraging the empirically-estimated cost elements. When we employed the idealized cost assumptions used in the only prior CEA of KMC, this resulted in a cost-effectiveness ratio of $11 per death averted. Including the costs of medical staff training, the cost per death averted increased to $3,600; accounting for demand creation costs increased the cost to $12,700, and incorporating mothers' time and out-of-pocket expenditures increased the cost to $13,400 per death averted. While the range of ratios highlight the substantial bias that may result from omitting specific costs relating to implementation of programs in real-world settings, KMC remains highly cost-effective in this setting based on typical benchmarks.

Conclusions

Failing to account for implementation-based administrative costs, demand creation, and costs to patients and families leads to substantial underestimation of costs and overestimation of the cost-effectiveness of health interventions. Our study demonstrates the importance of a shared understanding of what costs should be included. Future CEAs will need to focus on comprehensive costing data collection, and existing CEA estimates should be reviewed carefully in order to increase their utility in resource allocation.

Background

Cost-effectiveness analyses

Cost-effectiveness analyses (CEAs) can provide valuable evidence to inform allocation of limited resources to maximize health gain. However, the usefulness of CEAs depends highly on how comprehensive and valid they are, which in turn depend on the key data inputs, analytic choices, assumptions and values that are incorporated into estimates of intervention effects and costs. Nearly all CEAs, including those attached to intervention trials, involve some amount of modeling in data analysis, evidence synthesis and extrapolation; analyses typically involve curation of data from potentially disparate sources, and default to assumptions where needed data are absent.

The distinction between efficacy and effectiveness has been well-defined in the literature.[1–5] Estimates of the efficacy of an intervention are generally based on explanatory studies (such as randomized control trials) that examine impacts in a highly-controlled ideal environment. In contrast, effectiveness is typically estimated through pragmatic trials that account for factors that generally reduce the impact of the intervention (such as lower compliance and heterogeneous populations).[6] The differences between explanatory and pragmatic trials and their results have been discussed since 1967,[7] and A.L. Cochrane drew distinctions in the 1970s between evidence on efficacy ("can it work?"), evidence on effectiveness ("does it work in practice?"), and finally, on cost-effectiveness ("is it worth it?")[8–11] (Appendix Table 2.1). Cochrane's ladder of evidence highlights important differences in estimating effect sizes between ideal and real-world circumstances, and some authors have considered the potential bias that might result from use of efficacy estimates as effect sizes in cost-effectiveness analyses,[2,3,12] but similar differences with respect to estimates of costs have not been examined.

In fact, the estimated cost of an intervention under certain study circumstances may be quite different than real-world costs when an intervention is implemented outside of a controlled environment and/or brought to scale. For example, costs in a trial-based setting may reflect high efficiency, expertise, compliance, and a small scale, but real-world implementation costs may require large-scale training, overhead costs, costs

to create demand for the intervention, costs of increasing the supply of medical providers, and even costs associated with gaining government support or creating policy change (referred to as costs of supporting change in the Reference Case for Global Health Costing[13]). While in some cases trial-based costs may be greater than those associated with real-world program implementation (for example, if incentives for participation in the study are large, or if trials include more intensive or more comprehensive activities or resources than are used when interventions are scaled in populations), here we highlight three important ways in which costs based on parsimonious assumptions are likely to underestimate the actual cost of implementing these activities.

First, administrative costs are often omitted from CEAs, despite the fact that some interventions may require significant resources relating to planning, advocacy, training, research, and overhead. These costs can be challenging to quantify, often requiring detailed facility-level accounts that accommodate top-down costing approaches. One review examining the inclusion of administrative costs in CEAs of tuberculosis treatment strategies found that only one of the nine studies examined incorporated these elements.[14] Of three other tuberculosis intervention CEAs identified that did include administrative costs, these costs accounted for 16 to 34% of the overall costs of the examined strategies, indicating that these costs can be substantial and variable across settings.[14]

A second set of costs that are sometimes excluded from analyses, even where relevant, are those relating to demand creation. Costs estimated under ideal scenarios, such as randomized control trials (RCTs) where the intervention is administered to a small sample of the relevant population, do not account for the costs of generating or increasing demand, which might be needed to attain high levels of intervention coverage. For interventions that are unfamiliar, inconvenient, stigmatized, or require significant patient or caregiver buy-in or time cost, the cost of generating demand in a broad community, as opposed to in a narrower study population, can be important. The need for demand generation is likely to vary widely by intervention, which suggests that the ranking of interventions may change if these costs are included in CEAs. The tendency to omit or underestimate the cost of demand creation in CEAs is exemplified by the

World Health Organization's approach to standardized cost-effectiveness methods (WHO-CHOICE),[15] which encourages researchers to estimate cost-effectiveness ratios assuming 80% capacity utilization. WHO-CHOICE argues that doing so will generate ratios that are comparable across interventions with different levels of usage.[16] While this analytic choice may reduce one source of inconsistency, it also typically implies 80% capacity utilization is achieved without cost. For interventions with low baseline demand, this assumption will result in overestimation of real-world intervention cost-effectiveness.

Third, costs are often underestimated by omitting costs incurred by patients and families. Only 11% and 12% of cost per disability-adjusted life year (DALY) studies included costs associated with patient and informal caregiver time, respectively,[17] and despite recommendations from the Panel on Cost Effectiveness in Health and Medicine,[18] reiterated in a recent update,[19] only 30% present CEAs using a societal perspective that includes all costs.[17] Likewise, CEAs often exclude caregiver time, underscoring a broader phenomenon discussed in *The Lancet Commission on Women and Health*, which estimated the monetary value of women's unpaid contributions to health care alone to be more than two percent of GDP.[20] Interventions with large out-of-pocket or time costs for users may be burdensome for patients in a way that should be captured in a comprehensive analysis, or may contribute to low demand, which can impact overall cost-effectiveness conclusions.

In short, whereas the distinction between efficacy and effectiveness has been widely recognized, an analogous distinction on the cost side may be equally important, yet has only recently been discussed.[13,21] The goal of this study was to highlight the extent to which common parsimonious and idealized cost assumptions, in contrast to more comprehensive implementation-based costing, may result in underestimation of true costs and overestimation of the cost-effectiveness of interventions. Using the case example of a hospital-based kangaroo mother care (KMC) program implemented in Mali, we conducted an implementation-based economic evaluation to produce the first empirical cost analysis of KMC and to assess the implications of using such implementation-based cost estimates on conclusions about cost-effectiveness.

Kangaroo mother care

Kangaroo mother care, originally developed in 1978 to care for low birthweight infants given inadequate resources for neonatal intensive care units (NICUs),[22] is now widely recognized as an effective intervention for preterm and low birthweight babies in a variety of settings.[23] The definition of KMC varies, but the World Health Organization (WHO) defines it as continuous skin-to-skin contact between mother and infant, exclusive breastfeeding, early discharge from the health facility, and vigilant follow-up care.[23,24] KMC is often practiced in a KMC-specific unit or ward, where infants and mothers stay together until the infant is stable enough and the mother is confident enough to provide KMC at home.[24] KMC has been shown to reduce rates of mortality among low birthweight babies, sepsis, hypothermia, hypoglycemia, hospital readmission, and to improve exclusive breastfeeding, pain measures, respiratory rate, oxygen saturation, and growth.[23] Specifically, the most recent review finds a reduction in mortality among low birthweight babies of 33%.[25] Despite these benefits and WHO's endorsement since 2003, KMC utilization worldwide remains low due to a variety of health system and caregiver-level barriers.[26,27] These barriers include maternal need for physical recovery following delivery, emotional challenges associated with remaining in a hospital ward (loneliness, stigma associated with having a preterm baby, lack of family support), norms of carrying babies on the back (as opposed to the front), financial challenges posed by transport costs and neglect of other responsibilities, limited health provider time to educate mothers on KMC, lack of space for a KMC ward in the health facility, and provider perspectives that KMC is inferior to more technology-intensive infant care.[26,27] Maternal participation is imperative for KMC, yet there is limited evidence on how to increase demand for and utilization of the intervention.[26,27]

Cost-effectiveness of KMC

Because of KMC's seeming simplicity and low technological requirements, it is often cited as requiring minimal cost and as being highly cost-effective.[28–31] To date, there is little empirical data on the costs of implementing and scaling up KMC, and perceptions of cost-effectiveness rely on the assumption that KMC requires minimal health system resources. KMC has been reported to be cost-saving at the facility-

level compared to conventional care (defined differently in different studies, but often involving use of incubators).[32–34] Another study found cost-savings for parents because of shortened infant hospital stay.[35] The one analysis to date reporting on the cost-effectiveness of KMC used the Lives Saved Tool (LiST)[36] and concluded that KMC was highly cost-effective in South Africa, costing only $26 per life-year gained, but provided limited information on the methods and assumptions used to arrive at this result.[37] LiST is a model-based platform used to estimate cost and impact (in terms of "lives saved") of scaling up any combination of 75 maternal and child health interventions, and has been used in hundreds of publications and policy reports.[38] The cost-effectiveness study using LiST assumed that KMC reduces neonatal mortality from preterm birth by 51%, citing an earlier estimate based on three studies,[39] and that the only costs associated with KMC are wages for 30 minutes of midwife time per preterm baby.[36] The study assigned no costs to training health providers; creating, furnishing, and staffing a KMC ward; generating interest in and knowledge of the intervention among mothers; and mothers' time to provide the care.

Kangaroo mother care program in Bougouni District Hospital, Mali

Save the Children's Saving Newborn Lives program (SNL), with local partners, worked with the national Ministry of Health and local health providers to introduce a KMC program in Bougouni District Hospital in Bougouni, Mali, between 2009 and 2010.[40] Prior to the program, no formal neonatal care was available at the hospital, meaning that high-risk infants were either briefly kept with the mother in the labor and delivery unit until transfer to the referral hospital in the capital or were discharged home. KMC had been introduced in a hospital in the capital city, Bamako, but was a new intervention in the region of Sikasso, where Bougouni is located.[40]

The KMC program converted a small underused hospital unit into a KMC room where mothers could stay, and infants could receive KMC from their mothers and receive care from health staff. In addition to furnishing a wing with infant care equipment and beds for mothers, establishment of the program required health provider training at both the district and lower administrative levels, and creation of KMC manuals and education and promotion materials, including posters and radio promotion. In addition to kangaroo

care from their mothers, infants received care from doctors, nurses, and midwives, and administration of various medications and laboratory tests (full lists available in Appendix Table 2.2) as part of their inpatient neonatal care. Figure 2.1 visualizes a summary of the program components and our analysis of their theoretical pathway to impact.

In the year following the launch of the Bougouni District Hospital KMC program, 31 mothers and their infants stayed in the KMC ward for an average of five days (range one to 67). Of the 31 infants, three died during their stay. Information on mothers' and babies' characteristics, frequency and duration of skin-to-skin contact provided, breastfeeding patterns, and morbidity (or mortality after discharge from the hospital) among the 31 infants were not available. Program administrators estimated that among all infants born in Bougouni District Hospital during 2010, only 15% of mothers elected to use the KMC program.

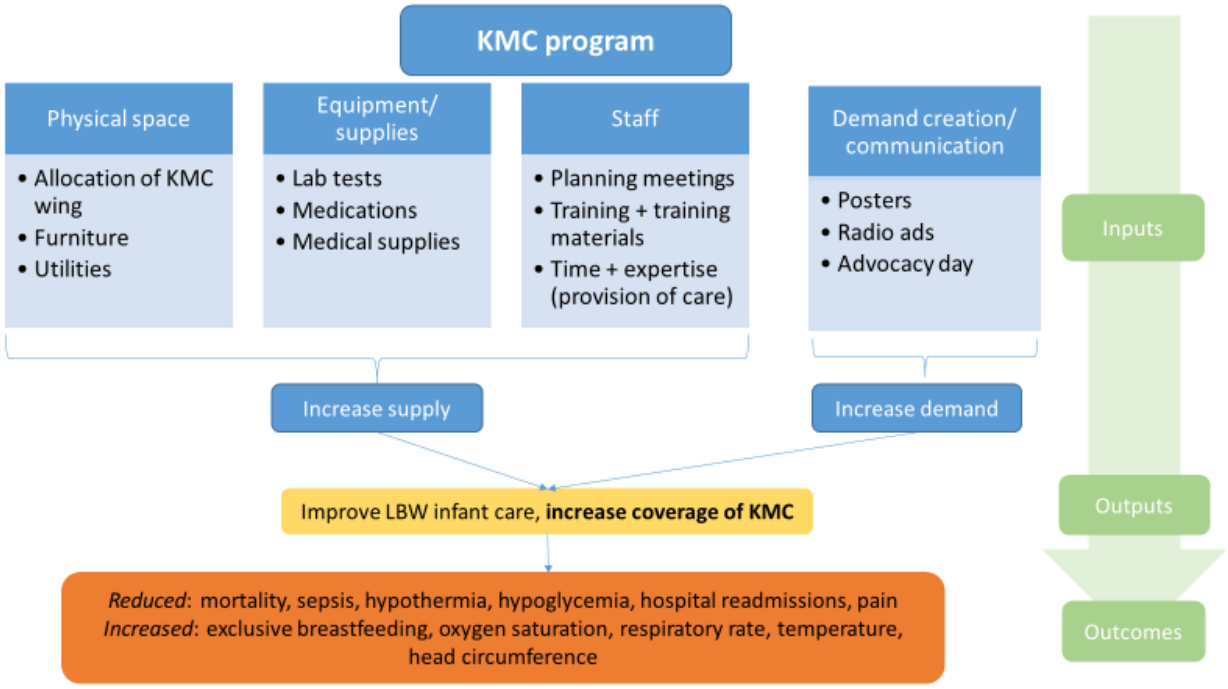

Figure 2.1: Conceptual model displaying program components and theory of change

Methods

Cost analysis

We produced empirically-based estimates of the cost-effectiveness of the Bougouni District Hospital KMC program by combining data inputs from several sources. We used detailed expenditure records from the Save the Children program to determine costs of durable goods and consumable supplies purchased for the KMC wing. Cost of utilities and space was unknown, but assumed to be negligible by the Save the Children program given the small size of the space. The lifespan of durable goods was based on WHO-CHOICE estimates of useful lives of capital items,[41] and for goods without a known lifespan, the lifespan of similar goods was used. The lifespan of provider trainings and advocacy days was assumed to be two years (meaning that these types of activities would likely need to be repeated after two years), while the lifespan of training or informational materials was assumed to be five years. All Save the

Children cost records reported the year items were purchased and their costs in West African francs (CFA). To estimate annualized costs of goods and trainings, we amortized the costs using a three percent discount rate and assumed no residual value at the end of the lifespan.

No additional medical staff members were hired by the program to work in the KMC wing; rather, staff from the maternity ward also supported the KMC wing. Medical staff time required for provision of care to infants in the ward was quantified by a 14-day time and motion study, which found that the average minutes spent per infant per day were 21, 17, and eight for doctors, nurses, and midwives, respectively. The cost associated with provider time was estimated using provider annual salaries from program documents (which were similar to the salaries in LiST, from the OneHealth Tool[42]), and assuming 220 eight-hour work days per year.

Information was available on the kilometers driven, insurance costs, and gasoline costs for the five vehicles used for the project. The vehicles were on loan to (not purchased by) the program, and no information on the wear and tear or lifespan of the vehicles was available to allow us to more fully estimate the vehicle costs. These costs are therefore underestimated as they are limited to the costs of gas and insurance, and are divided based on usage measured in kilometers driven for program setup and running, as it was recorded in program documents.

Costs incurred by infants' families consisted of laboratory test and medication costs. The numbers of each purchased by families were from program records, and prices were from pharmacy records. The cost of mothers' time spent providing skin-to-skin care and breastfeeding in the ward was based on wages, following the Human Capital Method.[43] As data on average wages in Mali in 2010 were not available, we estimated wages as two-thirds of average GNI per capita, as has been done elsewhere.[44] Specifically, this quantity was calculated based on an average duration of stay in the ward of five days, Mali's GNI per capita in 2010 (US$626;[45] based on GNI per capita in 2015, and using a CPI deflator[46]), and an assumed 220 working days per year (based on Save the Children program records).

Finally, we used the 2010 currency exchange rate of US$1 = 497.97 CFA[47] to express costs in 2010 US$. We used the World Bank consumer price index (CPI)[46] to adjust for inflation and translate costs of goods purchased prior to 2010 into 2010 CFA. The annualized cost of the program per infant was calculated by dividing the total annualized costs by 31, which was the total number of infants that stayed in the ward over the course of 2010. We characterized all costs as relating to start-up or implementation,[13] and further divided them into broad categories.

Estimated health impact

Neonatal mortality rate estimates among low birthweight infants in the study area were not available, so we combined several sources to estimate the baseline mortality from low birthweight in Bougouni. We used the neonatal mortality rate from the Sikasso region in which Bougouni is located (aggregated over 2004 to 2013), which was 44 per 1000 live births.[48] We used the national-level prevalence of low birthweight in Mali in 2010 (18.7%),[49] and approximated the relative risk of neonatal death among low birthweight infants compared to normal weight infants using an odds ratio of 7.64 from a systematic review of studies in sub-Saharan Africa.[50] Combining these data sources, we estimated that the neonatal mortality rate among low birthweight infants was 150.0 per 1000 live births in Bougouni district in 2010. This value is the estimated status quo mortality rate prior to the KMC program.

We used an effect size from the literature because the Bougouni program was not designed or implemented to monitor the impact of the program on mortality or morbidity. We therefore followed the standard[16] of employing the effect size from the most recent meta-analysis of KMC compared to conventional care, which was a 33% reduction in mortality among low birthweight infants (relative risk 0.67, 95% confidence intervals 0.39-0.92).[25] This effect size was from 12 RCTs examined in the most recent Cochrane Review and was based on mortality differences observed at the studies' last follow up point, which was roughly within the neonatal period. In Appendix Figure 2.1, we also present results using the effect size from a similar meta-analysis based on 15 studies, nine of which were RCTs and six of which were observational studies (relative risk 0.64, 95% confidence intervals 0.46-0.89).[23] We also

conducted sensitivity analyses using a larger effect size (66%) from a single study in a similar setting to Mali[51] (Appendix Figure 2.2). We then used the baseline estimate of mortality from low birthweight with the estimate of the intervention effect size in the cost effectiveness calculation below.

Cost-effectiveness analysis

We combined the three inputs of costs, effect size, and mortality risk among LBW infants to produce estimates of cost per death averted using the following formula:

$$Incremental\ \$\ per\ death\ averted = \frac{counterfactual\ \$\ per\ infant - KMC\ \$\ per\ infant}{counterfactual\ mortality\ among\ LBW - KMC\ mortality\ among\ LBW}$$

Given that we are comparing the KMC scenario (with its associated costs and reduced mortality) to a counterfactual status quo comparator that has zero costs and the baseline mortality rate described above, this formula simplifies to:

$$\$\ per\ death\ averted = \frac{KMC\ \$\ per\ infant}{counterfactual\ mortality\ probability\ among\ LBW\ *\ effect\ size}$$

We calculated costs per death averted starting with highly parsimonious costing assumptions from the literature and incrementally included costs until arriving at an empirically-based estimate that reflects a comprehensive accounting of costs. We incrementally include costs that are often omitted or oversimplified, such as program costs (administrative costs including trainings), demand creation costs, and costs incurred by patients and their families. The resulting changes in cost-effectiveness estimates demonstrate the impact of using parsimonious or idealized assumptions in comparison to comprehensive, real-world costs.

We also estimated the cost per death averted under the WHO-CHOICE assumption of 80% capacity utilization[16] by calculating the cost-effectiveness ratio had the KMC ward housed 165 low birthweight infants during 2010, rather than the 31 observed, and assuming that observed variable costs (e.g. number

of kangaroo sacks, medications) would scale linearly while holding constant the observed fixed costs (health provider trainings, demand creation costs, etc.).

Using three percent discounting and the Mali life expectancy of 58 years,[52] one death averted shortly after birth translates to 27 discounted years of life lost (YLLs). Following commonly used standards in global health CEA,[53] we benchmarked cost effectiveness ratios against thresholds of either one or three times GNI per capita per life year gained, signifying "highly cost-effective" or "cost-effective" interventions, respectively. Based on Mali's GNI per capita in 2010 (US$626), these standards implied thresholds of $17,100 or $51,300 per death averted.

All analyses were conducted in Microsoft Excel 2013. This study was exempt from Institutional Review Board review.

Results

The results of our costing analysis indicate that the total annualized cost per infant in the KMC program was $666.48, which we parsed into start-up ($594.29) and running costs ($72.19). The annualized cost of training of medical providers per infant amounted to $154.54, and another $6.93 was required per infant for medical staff provision of care. The cost of the activities to create demand among mothers to use the KMC program was $406.40 per infant, and the combination of out-of-pocket spending and time cost amounted to $33.45 for each mother. Table 2.1 shows the breakdown of costs, and detailed costing data by line item are available in Appendix Table 2.2.

Table 2.1: Annualized costs of the KMC program per infant who stayed in the unit in 2010 (in $US 2010)

Start-up or implementation cost	Category	Item	Annualized cost per baby
Start-up	Changing standard of care to prepare for KMC in hospital	Equipment	$21.24
		Provider training (room rental, hotel, transport, food)	$154.54
		Vehicle usage	$12.11
	Creating demand for KMC among mothers	Radio air time & personnel training	$160.60
		Advocacy days	$66.42
		Development of communication and education tools, manuals	$179.38
Implementation	Vehicle usage	For program implementation	$16.99
	Provision of medical care	Staff time	$6.93
		Consumable medical supplies	$10.08
	Time cost and out-of-pocket expenditures for families (societal perspective)	Medications	$23.58
		Lab tests	$0.39
		Mother time	$9.48

We used these cost estimates to compute the cost-effectiveness of KMC across a range of alternative choices reflecting the spectrum from highly parsimonious costing assumptions to comprehensive assumptions leveraging the empirically estimated cost elements. As a starting point for comparison, we first estimated the cost per death averted using only the highly parsimonious costs assumed in the only prior cost-effectiveness analysis on KMC, which used the LiST tool.[37] LiST assumed that costs comprised only the value of 30 minutes of midwife time per low birthweight infant receiving KMC, which amounted to $0.56 per child. Combined with our baseline assumptions about effectiveness of KMC, the resulting cost-effectiveness ratio for KMC was $11 per death averted.

When we replaced the LiST assumption about staff time with the empirically observed staff times from the Bougouni KMC program (21, 17, and eight minutes per infant per hospital day of doctor, nurse, and

midwife time, respectively), the cost per death averted increased to $140. When we further included the costs of training medical staff who were unfamiliar with KMC practice, the cost per death averted increased to $3,606. Including the additional costs of consumable medical supplies and equipment used in the KMC ward furnished by Save the Children increased the cost to $4,239 per death averted.

Given that KMC was unfamiliar to the community and in-facility delivery rates were low, measures to raise awareness of and create demand for KMC were part of the Bougouni KMC program. Accounting for those costs resulted in a cost per death averted of $12,696 (an increase of $8,457). This cost per death averted represents the real-world cost-effectiveness of the KMC program from a health system perspective.

Including the cost of the time spent by mothers in the KMC ward caring for their infants and the out-of-pocket expenditures for medical costs paid by families, the cost per death averted was $13,372. This constitutes the cost-effectiveness ratio from the societal perspective. The notable increases in the cost per death averted as each previously-omitted cost was added signals the magnitude of bias in studies that fail to account for these real-world costs.

The results reported thus far are based on the observed capacity utilization of 15%. Using the WHO-CHOICE assumption of 80% capacity utilization as an alternative, the cost-effectiveness ratio declined from the final empirical estimate of $13,372 to $3,340 per death averted.

Figure 2.2 summarizes the range of cost-effectiveness results produced by incrementally accumulating the empirically-based costs observed in the Bougouni KMC program. Based on a cost-effectiveness threshold of one times GNI per capita, all the cost-effectiveness ratios presented in Figure 2.2 are considered "highly cost-effective."

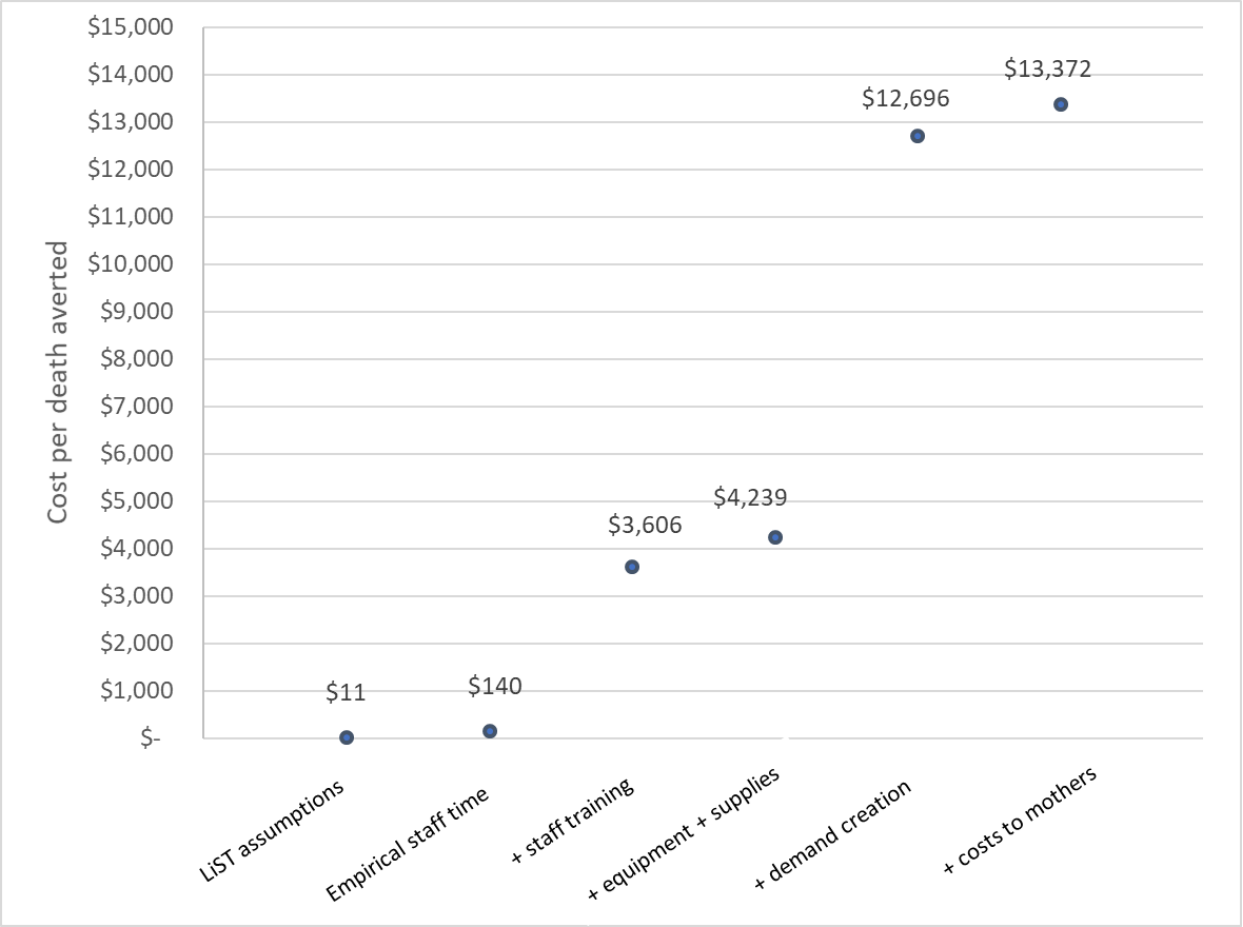

Figure 2.2: Cost (2010 $US) per death averted including empirical costs incrementally,* and using empirical utilization (31 infants; approximately 15% capacity)

*Notes: The "LiST assumptions" scenario refers to the value of 30 minutes of midwife time per LBW infant receiving KMC. The "empirical staff time" scenario refers to the value of 21, 17, and eight minutes per infant per hospital day of doctor, nurse, and midwife time, respectively. The "+ staff training" scenario refers to the value of KMC trainings in addition to empirical staff time. The "+ equipment and supplies" scenario refers to the value of consumable medical supplies and equipment used in the KMC ward, in addition to the cost of staff training and empirical staff time. The "+ demand creation" scenario refers to the value of demand creation activities, including radio advertisements, in addition to the cost of equipment and supplies, staff training, and empirical staff time. The "+ costs to mothers" scenario refers to the value of time spent by mothers in the KMC ward and the out-of-pocket expenditures paid by families, in addition to the cost of demand creation, equipment and supplies, staff training, and empirical staff time.

Discussion

Based on our economic evaluation, the cost per infant in the Bougouni KMC program was an estimated $670, which included $410 per infant in demand-creation activities, and $40 of costs to mothers. Using

these costs, we found that the comprehensive estimate of cost per death averted in 2010 by the program was approximately $13,400 from the societal perspective, and $12,700 from the health system perspective. These estimates are several orders of magnitude larger than the estimates produced using the parsimonious costing assumptions employed in the only previously-published CEA on KMC.[37] The ratios we estimated, ranging from $11 to over $13,000 per death averted highlight the substantial bias that may result from omitting specific costs relating to implementation of programs in real-world settings, including administrative costs (especially training), demand creation costs, and costs incurred by users. Our results also highlight that the 80% capacity utilization assumption that is recommended by WHO-CHOICE can lead to significant under-estimation of cost-effectiveness ratios under conditions where demand constraints are present.

It is important to note that our results do not overturn the conventional wisdom that KMC is highly cost-effective. Even after adjusting for an evidently pronounced bias in prior estimates of the cost-effectiveness of KMC, we found that the Bougouni program provided very good value for money based on typical benchmarks for cost-effectiveness in reference to per-capita income. On the other hand, these results do challenge the misconception that KMC requires little investment of health system resources, and highlight that the benefits of KMC at population level will likely require deliberate deployment of societal resources. Furthermore, the low observed utilization of the KMC ward (approximately 15%) despite significant spending on demand creation for this program further suggests that additional research is required on how to boost demand for KMC. It is important to acknowledge that the experience of this one program does not allow us to discern the direct causal effect or efficiency of the specific demand-generating activities on the utilization of KMC.

More generally, these findings demonstrate that the results of cost-effectiveness analyses are heavily impacted by researcher-selected assumptions and the incorporation of high-quality and comprehensive real-world costing data. For interventions that require high levels of user involvement, estimates based on ideal as opposed to real-world, comprehensive costing assumptions may be particularly different given

that demand-side constraints (and the associated costs of attempts to mitigate them) may be large when an intervention is taken to scale. As most of the financial burden was incurred prior to actual provision of infant care, this work implicitly highlights the importance of detailed costing data collection at all stages of program development, and adherence to and further development of guidelines such as those provided by the Global Health Cost Consortium.[13]

Limitations

In this paper, we have focused on a few parsimonious or idealized costing assumptions that result in underestimates of real-world cost-effectiveness ratios (failure to account for administrative costs, patient perspective, and demand constraints), but have left unexplored many other areas. For example, we did not explore the ways in which costs may be *overestimated* (such as the fact that well-funded programs may have higher salaries for their employees or other benefits resulting in higher spending in a way that does not necessarily lead directly to health impact). We also did not explore the ways in which bias in estimated *effect sizes* may contribute to over- or underestimated cost-effectiveness ratios.

This paper also has limitations with respect to the comprehensiveness and accuracy of the numerical values of the CEA estimates. The cost of the physical space and associated utilities for the ward were not captured in this analysis, but were likely small. The cost of transport, both in terms of time cost and mode of transport, of the mothers between home and the KMC ward was not included; the administrative program information suggests that some mothers came and went with some regularity[40] but further details are unavailable. Program information also suggests that many mothers were cared for by other family members who visited the KMC ward to bring food (food is not typically provided as a hospital service), and the time cost and transport cost of these family members, in addition to the cost of food, were not accounted for. While mothers' time cost was included in the cost estimation, the cost of the burden potentially placed on other caregivers at home in the mother's absence was not estimated.

While these omitted costs suggest that this analysis produced an underestimate of the cost-effectiveness ratio, several other omitted aspects may work in the opposite direction. Specifically, it is possible that the impact of the demand creation techniques employed in this program may have been larger in subsequent years, meaning that the low utilization (and high per infant costs) observed in 2010 was not representative of the rates overall, but information on use of the program beyond the first year is not available. In addition, while information about them is more limited, KMC wards were subsequently opened in other districts of Mali, and would have benefited from the existing training and demand-creation materials produced for Bougouni. This means that the fixed costs per death averted are likely lower than estimated here.

In addition, the 33% effect size used in this analysis may be an underestimate of the true impact of the program even if fidelity to the actual KMC intervention was at times low, as suggested by program reports. This is because the incremental improvement in newborn care provided by the Bougouni KMC program was more than just KMC (also included provision of essential medicines, laboratory tests, monitoring, etc.). In addition, the impact on outcomes other than mortality was not estimated, including the KMC program's assumed resulting reduction in morbidity or delays in child development, which also come with their own averted, or potentially added, costs.

In estimating the health impact of the KMC program, we assumed that the regional-level neonatal mortality and national-level low birthweight prevalence values were relevant in the Bougouni hospital setting. These estimates could in fact be an overestimate if mothers with access to a health facility for delivery also have access to other health-promoting and mortality-reducing interventions, or they could be an underestimate if those who deliver in-facility do so because of a complicated or high-risk birth. Finally, using an odds ratio as a proxy for a relative risk results in an over-estimate of the relative risk,[54] which biases our estimate of the health impact upward (and therefore the cost-effectiveness ratio downward). Appendix Tables 2.3 and 2.4 show what is included/omitted in this analysis in relation to the

Impact Inventory from the Second Panel on Cost-Effectiveness in Health and Medicine[19] and Global Health Cost Consortium Reporting Checklist,[13] respectively.

Despite these limitations, our analysis provides a KMC CEA with enhanced comprehensiveness compared to previous studies. Our study is the first to use detailed high-quality costing data from a real-world KMC program, and underscores the importance of comprehensive costing data collection in order to avoid over-estimating the cost-effectiveness of interventions.

Conclusions

While previous research has extensively documented the difference between efficacy and effectiveness, we demonstrate that an analogous distinction can be important to recognize in costing analyses. Our study demonstrates that the results of cost-effectiveness analyses are highly dependent on the chosen assumptions and underscores the importance of comprehensive costing data collection and guidelines in order to increase the utility of CEAs in resource allocation.

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Appendices

Appendix Table 2.1: Cochrane's ladder of evidence[8–11] (table reproduced from James 2017[9])

Type of evidence	Question	Description
Efficacy	Can it work?	Extent to which an intervention does more good than harm under *ideal* circumstances
Effectiveness	Does it work in practice?	Extent to which an intervention does more good than harm under *usual* circumstances
Cost-effectiveness	Is it worth it?	The effect of an intervention in relation to the resources it consumes

Appendix Table 2.2: Detailed cost breakdown of the Bougouni KMC program (2010 $US)

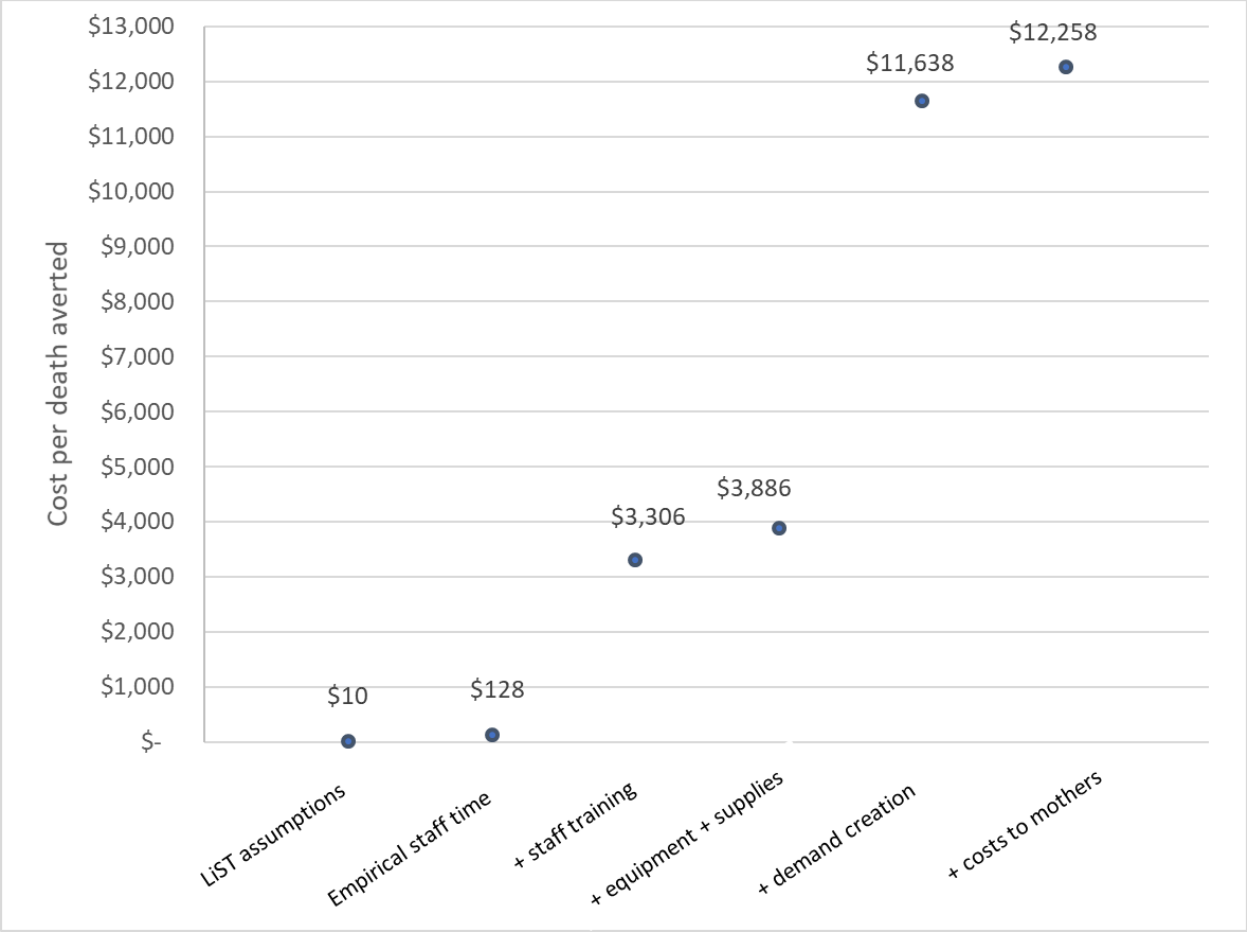
Start-up or implementation cost	Category	Item	Total annualized cost
Start-up	**Durable equipment**	TV	$ 30.47
		Voltage stabilizer	$ 27.06
		DVD Video Kit	$ 5.60
		Metal beds with adjustable backrests	$ 83.63
		Mattresses	$ 41.82
		Pillows	$ 4.18
		Medical consult tables	$ 40.95
		Pediatric sphygmomanometer	$ 18.46
		Electronic baby scale	$ 110.76
		Manual aspirator	$ 77.53
		Folding 3-panel screens	$ 48.79
		Vertical refrigerator	$ 69.26
		Small bench with backrest (has 4 seats)	$ 41.82
		Plastic bin with lid	$ 4.18
		Cabinets	$ 32.17
		Electronic thermometer	$ 8.31
		10m extension cord	$ 2.32
		Manual breast pump	$ 11.08
	Training	Training of nurses, doctors at regional hospital (including per diems, transport)	$ 1,309.01
		Training of nurses, doctors, midwives at outpatient clinic (including per diems, transport)	$ 3,481.75
	Vehicle use	For program set up	$ 375.53

Appendix Table 2.2 (Continued)

Start-up or implementation cost	Category	Item	Total annualized cost
Start-up	**Demand creation**	Training of radio personnel (room rental, food & drink, per diems, hotels, transport, materials)	$ 2,119.04
		Radio contracts for air time	$ 2,859.72
		Development/scale-up of behavior change communication materials (non-research = 15.8%)	$ 668.27
		Development/scale-up of behavior change communication materials (research)	$ 3,561.30
		Advocacy Day in the district (room rental, food & drink, per diem, transport)	$ 886.12
		International Day of the African Child (room rental, food & drink, per diem, transport)	$ 1,172.78
		Working session with regional health directorate of Sikasso and Bougouni referral health center staff (per diems, transport)	$ 982.60
		Working session with Bougouni referral health center team (per diems, transport)	$ 179.46
		Adaptation of KMC manual for Bougouni	$ 169.06
Implementation	**Consumable supplies**	CH6 feeding tubes	$ 27.41
		CH8 feeding tubes	$ 3.05
		CH6 aspiration probe	$ 3.25
		Aspiration probe	$ 3.21
		Gloves	$ 62.25
		Kangaroo sacks	$ 213.19

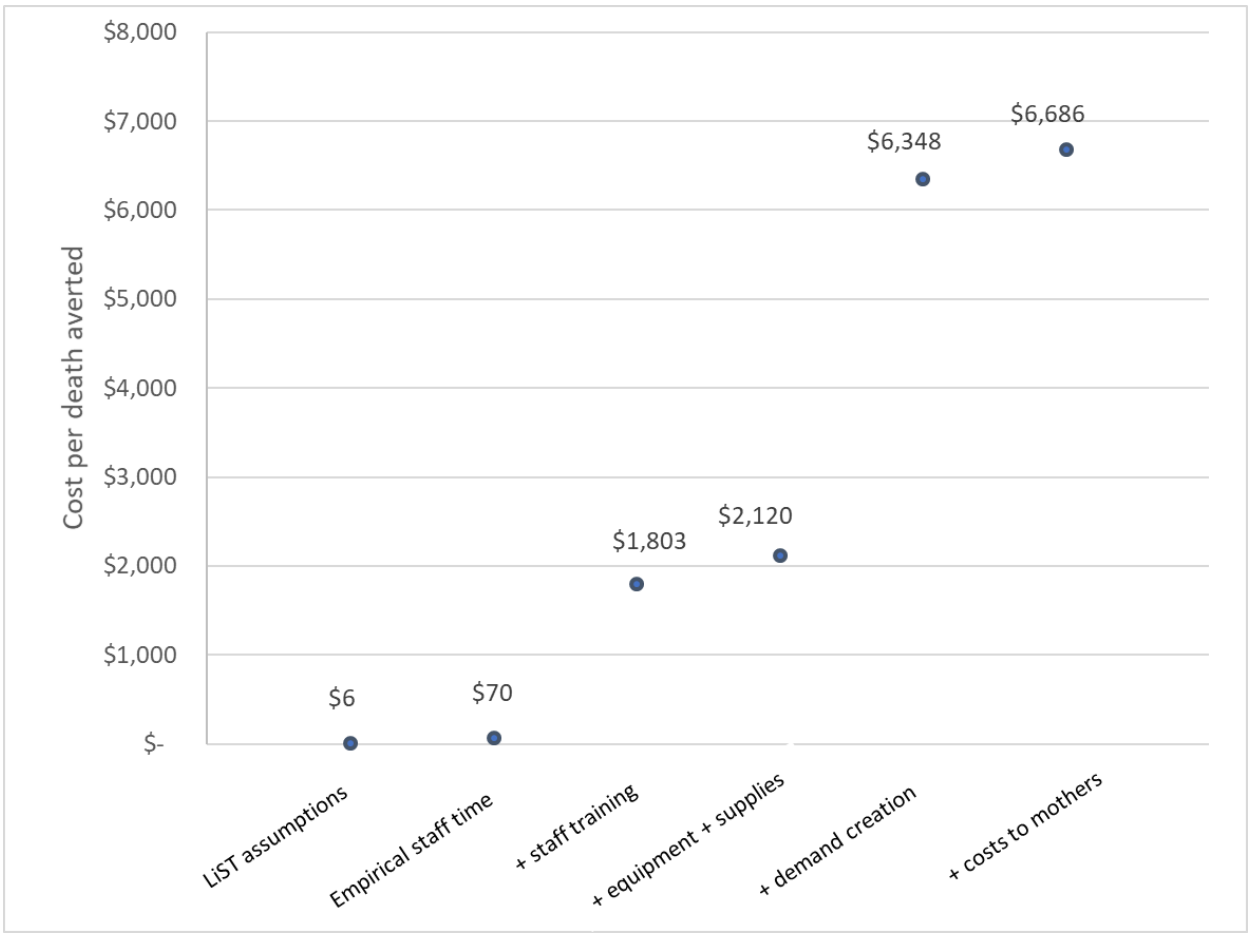
Appendix Table 2.2 (Continued)

Start-up or implementation cost	Category	Item	Total annualized cost
Implementation	**Medications**	Alvityl	$ 7.65
		Amoxicillin 500mg injection	$ 72.29
		Biodroxyl 125 mg suspension	$ 6.75
		Ceftriaxone 250 mg injection	$ 145.39
		Cotrimoxazole	$ 0.84
		Dakin antimicrobial solution	$ 12.25
		Debridat	$ 4.39
		Dexametazone	$ 0.20
		Erythromycin 125 mg	$ 74.08
		Gentalline eyedrops	$ 37.35
		Gentamicine 80 mg injection	$ 3.21
		Metronidazole	$ 0.96
		Nystatin oral suspension	$ 21.53
		Paracetamol syrup	$ 0.96
		Perfalgan	$ 17.51
		Oral rehydration solution	$ 0.17
		Ferceferol 50 mg	$ 96.49
		Multivitamin 800 IU	$ 73.15
		Peridys 1mg	$ 155.94
	Lab tests	Hemoglobin testing	$ 12.05
	Vehicle use	For program running	$ 526.82
	Staff time	Doctor time (based on wages for 21 minutes per baby per day for an average infant stay of five days)	$ 142.99
		Nurse time (based on wages for 17 minutes per baby per day for an average infant stay of five days)	$ 48.86
		Midwife time (based on wages for eight minutes per baby per day for an average infant stay of five days)	$ 22.99
	Mother time	Based on GNI per capita & 220 working days per year	$ 293.81



Appendix Figure 2.1: Cost (2010 $US) per death averted for each scenario* when assuming an effect size of 36% mortality reduction[23] (instead of 33%)

*Notes: The "LiST assumptions" scenario refers to the value of 30 minutes of midwife time per LBW infant receiving KMC. The "empirical staff time" scenario refers to the value of 21, 17, and eight minutes per infant per hospital day of doctor, nurse, and midwife time, respectively. The "+ staff training" scenario refers to the value of KMC trainings in addition to empirical staff time. The "+ equipment and supplies" scenario refers to the value of consumable medical supplies and equipment used in the KMC ward, in addition to the cost of staff training and empirical staff time. The "+ demand creation" scenario refers to the value of demand creation activities, including radio advertisements, in addition to the cost of equipment and supplies, staff training, and empirical staff time. The "+ costs to mothers" scenario refers to the value of time spent by mothers in the KMC ward and the out-of-pocket expenditures paid by families, in addition to the cost of demand creation, equipment and supplies, staff training, and empirical staff time.



Appendix Figure 2.2: Cost (2010 $US) per death averted for each scenario* when assuming an effect size of 66% mortality reduction[51] (instead of 33%)[§]

*Notes: The "LiST assumptions" scenario refers to the value of 30 minutes of midwife time per LBW infant receiving KMC. The "empirical staff time" scenario refers to the value of 21, 17, and eight minutes per infant per hospital day of doctor, nurse, and midwife time, respectively. The "+ staff training" scenario refers to the value of KMC trainings in addition to empirical staff time. The "+ equipment and supplies" scenario refers to the value of consumable medical supplies and equipment used in the KMC ward, in addition to the cost of staff training and empirical staff time. The "+ demand creation" scenario refers to the value of demand creation activities, including radio advertisements, in addition to the cost of equipment and supplies, staff training, and empirical staff time. The "+ costs to mothers" scenario refers to the value of time spent by mothers in the KMC ward and the out-of-pocket expenditures paid by families, in addition to the cost of demand creation, equipment and supplies, staff training, and empirical staff time.

[§] The context (rural Mozambique) from which the effect size from Lincetto et al (66% reduction in neonatal mortality attributable to KMC; not statistically significant) was estimated may more closely approximate the low-resource setting of Bougouni District Hospital. We therefore also present results (above) using this effect size. The main point of this analysis is to highlight the large increase in cost per death averted when accounting for empirically-based costs, which is still clear regardless of the effect size used.

Appendix Table 2.3: Impact Inventory from the Second Panel on Cost-Effectiveness in Health and Medicine[19] completed with information for this study

Sector	Type of Impact	Included in This Reference Case Analysis From… Perspective?		Notes on Sources of Evidence
		Health Care Sector	Societal	
Formal Health Care Sector				
Health	**Health outcomes (effects)**			
	Longevity effects	Yes	Yes	Conde-Agudelo et al 2016
	Health-related quality-of-life effects	No	No	
	Other health effects (eg, adverse events and secondary transmissions of infections)	No	No	
	Medical costs			
	Paid for by third-party payers	Yes	Yes	Program documentation
	Paid for by patients out-of-pocket	Yes	Yes	Program documentation
	Future related medical costs (payers and patients)	No	No	
	Future unrelated medical costs (payers and patients)	No	No	
Informal Health Care Sector				
Health	Patient-time costs	NA	NA	
	Unpaid caregiver-time costs	NA	Yes	Estimated wages from GNI per capita
	Transportation costs	NA	No	
Non-Health Care Sectors (with examples of possible items)				
Productivity	Labor market earnings lost	NA	No	
	Cost of unpaid lost productivity due to illness	NA	No	
	Cost of uncompensated household production	NA	No	
Consumption	Future consumption unrelated to health	NA	No	

Appendix Table 2.3 (Continued)

Sector	Type of Impact	Included in This Reference Case Analysis From… Perspective?		Notes on Sources of Evidence
		Health Care Sector	Societal	
Social Services	Cost of social services as part of intervention	NA	No	
Legal or Criminal Justice	Number of crimes related to intervention	NA	NA	
	Cost of crimes related to intervention	NA	NA	
Education	Impact of intervention on educational achievement of population	NA	No	
Housing	Cost of intervention on home improvements (eg, removing lead paint)	NA	NA	
Environment	Production of toxic waste pollution by intervention	NA	NA	
Other (specify)	Other impacts	NA	No	

Appendix Table 2.4: Global Health Cost Consortium Reporting Checklist[13] completed with information for this study

Reference Case Checklist Items	**Options**
STUDY DESIGN AND SCOPE	
Principle 1 - The purpose of the study, the population, and the intervention and/or service/output being costed should be clearly defined.	
Purpose	
Purpose type:	Economic evaluation
Relevance for health practice and/or policy decisions:	This analysis highlights areas where CEAs may underestimate cost-effectiveness when certain common costing assumptions are made, and makes the case for improved costing data collection. This analysis also puts forth an empirically-based estimate of the cost-effectiveness of KMC, which highlights the resources required to implement a KMC program.
Aim of the cost analysis:	Examine discrepancies between ideal/parsimonious and real-world/comprehensive cost estimates/assumptions, produce empirical estimates of KMC cost-effectiveness
Intended user(s) of the cost estimate:	CEA researchers, governments/NGOs intending to roll out KMC programs
Intervention	
Main activities/technologies involved:	Creation of a KMC ward, generation of demand for KMC, provision of KMC over the course of one year
Target population:	KMC is provided to LBW infants by their mothers, so the target population benefitting from the intervention is LBW infants but the population requiring demand creation are their mothers (who provide the care)
Coverage level:	The KMC program aimed to reach all LBW infants in the district
Delivery mechanism (e.g. health system level, facility type, ownership, etc.):	The intervention of KMC is delivered at the hospital by mothers
Epidemiological context (i.e. incidence/prevalence of disease)	Incidence of LBW births
Intervention	The details of the intervention are described in the main text

Appendix Table 2.4 (Continued)

Reference Case Checklist Items	Options
Principle 2 - The perspective (extent of the resource use captured) of the cost estimation should be stated and justified relevant to purpose	
Study perspective (e.g. provider, health system, societal, household):	Societal (health system perspective also presented)
Principle 3 - The type of cost being estimated should be clearly defined, in terms of economic vs financial, real world vs guideline, and incremental vs full cost, and whether the cost is 'net of future cost', should be justified relevant to purpose.	
Defining the cost	
Economic vs. financial cost	Economic
Real world' vs. guideline cost	Real world cost
Full vs. incremental cost	incremental cost
Net of future cost	No
Principle 4 - The 'units' in the unit costs for strategies, services and interventions should be defined, relevant for the costing purpose and generalizable	
List the unit costs used:	No standardized unit costs were used
Describe any adjustments made to reflect the quality of service output:	None

Appendix Table 2.4 (Continued)

Reference Case Checklist Items	Options
Principle 5 - The time horizon should be of sufficient length to capture all costs relevant to the purpose, and consideration should be given to disaggregating costs into separate time periods where appropriate.	
Time period	
Period type (start-up vs implementation):	Both
Time period:	one year of start-up, one year of implementation (2009, 2010, respectively)
SERVICE AND RESOURCE USE MEASUREMENT	
Principle 6 - The scope of the inputs to include in the cost estimation should be defined and justified relevant to purpose	
Defining the scope	
Above service delivery costs included:	Yes: trainings, materials development, demand creation, education materials
Costs of supporting change included:	No
Research costs included:	No
Unrelated costs included:	No
If incremental costs, assumptions made for existing capacity	No assumptions made; empirical existing capacity was a fully-staffed district hospital in Mali with no neonatal intensive care capacity
Any exclusions other to scope:	This analysis is limited to one hospital in Bougouni, Mali, and the 31 infants cared for in the KMC wing there during 2010, and estimation of costs and impact is limited to the time these infants were in the unit

Appendix Table 2.4 (Continued)

Reference Case Checklist Items	Options
Principle 7 - The methods for estimating the quantity of inputs should be described, including methods, data sources and criteria for allocating resources	
Describe the measurement of each input as either top-down or bottom up	Bottom up
Describe method to allocate human resources inputs	Time and motion study for 14 consecutive days to quantify health provider time required per infant
Describe methods to allocated above site/ overhead inputs	All equipment and training costs accounted for, including vehicle usage; value of space, utilities, and other overhead not accounted for/assumed negligible
Describe the methods for excluding research costs:	N/A: materials development was included in the cost of the program, but no other research costs
Describe the methods for measuring other resources	All resource use was captured through record keeping; maternal time was valued based on estimated wages
Principle 8 - The sampling strategy used should be determined by the precision demanded by the costing purpose and designed to minimise bias	
Site/client selection process/criteria	
Describe geographic sampling (if applicable):	Selected based on available costing data (one site in a Mali hospital)
Describe site sampling (if applicable):	Selected based on available costing data (one site in a Mali hospital)
Describe patient sampling (if applicable):	All LWB infants/mothers who spent time in KMC ward
Describe methods to calculate sample size:	N/A

Appendix Table 2.4 (Continued)

Reference Case Checklist Items	Options
Principle 9 - The selection of the data source(s) and methods for estimating service use should be described, and potential biases reported in the study limitations.	
Identify the data source used to measure the units:	Routine hospital information systems were used to track patient stays and supply utilization; medical provider time was tracked using a time monitor (timer)
Where relevant describe the sampling frame, method and size:	N/A
Describe any method used to fill missing data	The only data that were not empirical were the effect size and baseline mortality estimates; the methods used are described in the main text
Principle 10 - Consideration should be given to the timing of data collection to minimise recall bias and, where relevant, the impact of seasonality and other differences over time	
The timing of data collection should be specified in the following ways:	
Timing of data collection (resource and service use)	Costing data were collected by hospital record reviews (for lab tests and medicine use, etc.) and reviews of program costs based on Save the Children program documents, looking back at activities that took place between 2009 and 2010
Prospective or retrospective	Retrospective
Longitudinal vs. cross-sectional data:	cross-sectional
Where relevant recall period:	N/A
VALUATION AND PRICING	
Principle 11 - The sources for price data should be listed by input, and clear delineation should be made between local and international price data sources, and tradeable, non-tradeable goods.	
Report the sources of price data by input:	Medication costs were based on pharmacy prices in the study hospital (local market). Cost of capital goods based on records of their purchase. Health staff salaries based on administrative records.

Appendix Table 2.4 (Continued)

Reference Case Checklist Items	Options
Report inputs where local and international prices were used:	Goods and time costed in Mali CFA; goods purchased before 2010 were adjusted to 2010 values using World Bank CPI. All prices were then converted to 2010 US$
Principle 12 - Capital costs should be appropriately annuitized or depreciated to reflect the expected life of capital inputs	
Describe the depreciation approach:	Amortization, assuming 3% discounting, taking lifespan of goods into account, and assuming all goods depreciate to value of $0 at end of lifespan ($0 salvage value)
Describe any discount rate used for capital goods:	3%
Report the expected life years of capital goods, and data sources:	Expected life years based WHO-CHOICE estimates of useful lives of capital items[41]
Principle 13 - Where relevant an appropriate discount rate, inflation and exchange rates should be used, and clearly stated.	
Describe any discount rate used for future costs:	N/A
Describe the reported currency year:	World Bank CPI[46] was used to adjust costs of goods purchased prior to 2010 to account for inflation such that all costs were expressed in 2010 CFA. 2010 CFA were converted to 2010 US$ based on exchange rate record of exchange rate between these two currencies in 2010
Describe any conversions made:	2010 CFA converted to 2010 US$
Report the inflation type and rate used:	World Bank CPI[46]

Appendix Table 2.4 (Continued)

Reference Case Checklist Items	Options
Principle 14 - The use and source of shadow prices for goods and for the opportunity cost of time should be reported	
Methods for valuing the following should be reported:	
Report methods for valuing volunteer time:	N/A (maternal care time was valued using hourly wages based on GNI per capita for Mali in 2010)
Report adjustments for input prices (donated or subsidised goods):	N/A
ANALYSING AND PRESENTING RESULTS	
Principle 15 - Variation in the cost of the intervention by site size/ organisation, sub-populations, or by other drivers of heterogeneity should be explored and reported.	
Describe any sub-groups or populations analysed	None
Describe any statistical methods used to establish differences in unit costs by sub-group	None
Describe any determinants of cost (model specification)	None
Describe any multivariate statistical methods used to analyse cost functions	None
Principle 16 - The uncertainty associated with cost estimates should be appropriately characterised.	
Describe sensitivity analyses conducted	The results are presented such that common alternative assumptions are presented in the main analysis
List possible sources of bias	Described in full in the main text

Appendix Table 2.4 (Continued)

Reference Case Checklist Items	Options
Principle 17 - Cost estimates should be communicated clearly and transparently to enable decision-maker(s) to interpret and use the results.	
Limitations	
Limitations in the design, analysis, and results:	Described in full in the main text
Aspects of the cost estimates that would limit generalizability of results to other constituencies:	The results of this analysis are not meant to be generalizable to other settings; this case study was a purely empirical examination of one specific KMC program in one particular hospital in Mali. These results are not generalizable to settings with different epidemiologic profiles, standard of care, and KMC program design.
Conflicts of Interest	
All pecuniary and non-pecuniary interests of the study contributors:	None
All sources of funding that supported conduct of the costing:	None
Non-monetary sources of support for conduct of the costing:	None
Open access	
Dataset available	Yes: detailed information available in Appendix Table 2.2

Paper 3: Can placental characteristics predict child development delays? Findings from São Paulo Western Region Cohort Study

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Abstract

Background

Delays in early childhood growth and development are common in low- and middle-income countries and have substantial impact on health, wealth, and human capital. Interventions during early childhood have been shown to have particularly high returns, especially if targeting children at highest risk. Placental pathology exams are increasingly used to assess the most likely drivers for adverse birth outcomes. We use data from a Brazilian cohort to assess the degree to which placental characteristics can predict developmental adversity and to target early childhood development programs more generally.

Methods and Findings

We followed up 290 infants with placental pathology exams born at the University Hospital in São Paolo's Western Region, and conducted a developmental assessment of the children at age three years. We used C-statistics to assess the predictive accuracy of three sets of factors to predict developmental

delays. These were: birth record data (anthropometric measures, gestational age, etc.), maternal risk factor information collected via survey (report of smoking, alcohol consumption, education, income, maternal height and weight, etc.), and placental characteristics from pathology exams.

A total of 64 children (22%) with developmental delay were identified. Using data from hospital birth records alone resulted in 72% predictive accuracy (C-statistic of 0.72) and adding survey-based maternal risk factors increased the C-statistic to 0.78. Including placental characteristics in addition to birth-record based measures resulted in a C-statistic of 0.82, while including all three sets of factors resulted in a C-statistic of 0.87. Survey-based predictors and placental predictors both resulted in significantly increased predictive ability beyond birth record information but did not differ from each other in this ability.

Conclusions

Placental characteristics may be effective predictors of developmental delay, as are survey-based measures of maternal risks. In some clinical settings, using placental exam results that are part of routine hospital care may provide a novel opportunity to better identify infants at high risk of developmental delays.

Background

Nearly half of all children ages three and four years in low- and middle-income countries fail to meet their developmental potential in the physical, cognitive, and/or socioemotional domains.[1] This has serious human capital consequences in terms of lower cognitive ability, educational attainment, and work capacity.[2–6] In fact, an estimated US$177 billion in lifetime wage earnings is lost each year in developing countries due to early childhood growth faltering alone.[7]

The first 1000 days (from conception to age two years) have been highlighted as a crucial developmental period during which interventions can have long-term benefits,[2] and be cost-effective with high returns on investments.[8–11] This suggests that there is the potential for large improvements in child development in the short run, and for large improvements in health and human capital outcomes in the long run if at-risk infants can be supported early on.

Targeting early childhood interventions requires identification of markers/predictors at birth of later developmental delay. A large number of risk factors have been identified, such as socioeconomic status, maternal education, maternal depression, exposure to violence, teenage motherhood, advanced maternal age, and marital status.[12–17] Other maternal risks include prenatal iodine deficiency, maternal underweight and short stature, short birth intervals, prenatal alcohol exposure, maternal smoking during pregnancy, fertility assistance, and high parity.[18–27]

In addition to maternal predictors of developmental delay, adverse birth outcomes, such as being born preterm (prior to 37 weeks of gestation) or low birthweight (LBW; birthweight less than 2,500 grams) are predictive of later life stunted growth and poor developmental outcomes,[14,28,29] and medical complications at birth can even predict neurodevelopment at preschool age.[30] Novel techniques using biomarkers such as testosterone and cortisol levels, or brain event-related potentials measured at birth, have also been suggested as predictors cognitive, motor, and/or language development.[31,32]

However, most studies, including those described above, examine the relationships between single risks/predictors and developmental delay. Only recently has the notion of multivariable risk prediction, a methodology used in cardiovascular literature for decades,[33] been applied to child development. Specifically, Chittleborough et al used 22 perinatal predictors together to identify children at risk for poor health and development in an Australian sample.[34] If risk prediction is to be widely-used in ensuring child development interventions reach children most in-need, it is important to identify easy-to-measure and widely-collected predictors and develop risk prediction models that use multiple factors to identify at-risk children.

The placenta, a temporary organ that develops during pregnancy, has the potential to provide novel information on child development. The placenta provides nutrition to the developing fetus and serves as the intermediary between it and the mother during gestation.[35] It has been called a "diary" for gestational processes,[36] serving as a record of development and adversity, yet it remains one of the most poorly understood organs.[37,38] Placental pathology is often a standard part of postnatal care in high-income countries and/or in academic clinics and hospitals with a laboratory. In these settings, after birth, placentas may be submitted for pathological examination based on a set of guidelines. These guidelines may vary by setting, but those set forth in 1997 by the College of American Pathologists (CAP)[39] are commonly used even outside of the United States. Placental pathology results are used to identify an undiagnosed condition requiring immediate attention, identify placenta-related conditions that may also pose a risk in future pregnancies, provide information that can guide management of subsequent pregnancies or care of mother/child, or explain a particular fetal outcome (such as preterm birth or stillbirth).[40] Based on these guidelines, some studies imply that an estimated 50% of deliveries should receive a placental pathology exam, but adherence to these guidelines varies substantially.[41,42]

To date, most placental pathology research focuses on relationships between placental characteristics and adverse birth outcomes.[43–46] For example, previous studies have examined the relationship between single risks and single birth outcomes, such as altered placental gene expression and low birthweight;[47]

indications of bacteria in the placenta among extremely low gestational age newborns;[48] or the impact of individual placental abnormalities such as chorioamnionitis, placental insufficiency, or calcifications, on preterm birth or low birthweight.[45,49,50] While much of the currently available literature focuses on birth outcomes, there is some evidence that individual placental characteristics may be able to predict later disease and developmental delay. Placental exam records are not traditionally utilized beyond their function in providing relevant information for the care of mother and infant, meaning that using them in risk prediction for child development is a novel undertaking. The only study that we were able to identify used data collected between 1959 and 1976 from a cohort study in the US and identified between 20 and 40 placental morphological and histopathological measures that predict a composite metric of child disease with sensitivity between 53% and 68%, and specificity between 34% and 53%, depending on the number of placental measures used.[51] The predictive ability of placental characteristics was examined in isolation rather than in addition to other potentially important predictors, such as maternal or environmental risk factors.

Therefore, the objective of this analysis was to assess the extent to which placental characteristics can provide additional information in predicting child development delays. Specifically, we examined whether novel information gained from placental pathology exam records can provide predictive ability above and beyond what is gained from traditionally-considered birth outcomes and maternal risk factors.

Methods

Data

Western Region Cohort

We used data from the Western Region Cohort (WRC), which is a cohort of infants residing in São Paulo's Butantã-Jaguaré region who were born in the Hospital Universitário (HU) of São Paulo, Brazil between April 1, 2012 and March 31, 2014. This large teaching hospital is one of two hospitals where births occur in the region (the other being a private hospital primarily used by middle- and upper-class

families). Previous research has documented that approximately 80% of the urban poor residents of the Butantã-Jaguaré region deliver in HU,[52] meaning that birth records from this hospital represent high coverage of our population of interest (urban poor). There were 6,207 children born into the cohort, and efforts were made to include them in every subsequent follow-up survey up to three years, regardless of participation in the previous round. There were several data collection points for this cohort study, including hospital-based birth records, pathology records, a postpartum survey of mothers, and an in-home follow-up survey and developmental assessment when the children were three years of age. We included only singleton births (which excluded eight infants) because twins have importantly distinct placental characteristics that would have complicated the analysis. Creating a sample with non-missing values for all of the measurements used in this analysis resulted in a reduced sample size of 290 (Figure 3.1).

Birth records

Birth records were available for all cohort members, and included information on maternal date of birth and birth characteristics. Specifically, the records contained information on child date of birth and sex; type of delivery (non-instrumental vaginal, caesarean, forceps); Apgar score at one minute; gestational age category (preterm, <37 weeks gestation; full-term, 37-41 weeks; or post-term, >41 weeks gestation, based on the New Ballard method[53]); weight for gestational age category (small for gestational age, normal for gestational age, or large for gestational age, based INTERGROWTH standards[54,55]); length, weight, head circumference, chest circumference, abdominal perimeter at birth; and whether the birth was a singleton or multiple birth. No information was available in these records on birth complications such as preeclampsia or hemorrhage.

Placental exam records

Pathology records from placental exams (including umbilical cord exams) were retained in a computerized medical record system that was linked to infants' birth records. There was no clear or

systematic documentation available on why certain placentas were sent for pathological examination and others were not. However, as is standard, each delivering clinician decided whether to send the placenta to the hospital's pathology laboratory based on guidelines. Commonly-used guidelines suggest that infants with prematurity, growth restriction, infection, seizures, anemia, low birthweight, Apgar score less than 7, and multiple gestation, among others, should be examined. Indications of infection or unexplained bleeding, and unusual placental or cord size/shape, or fragmentation, should also merit a placental exam.[39] The criteria from the College of American Pathologists is listed in Appendix Table 3.1.[39] No such guidelines for Hospital Universitário of São Paulo were available, but a review of the listed reasons for placental submission to the laboratory suggests that they were similar to the ones described above. In addition, in this hospital, the placentas of mothers who present for delivery without any antenatal care records were also sent for exam, and healthy control placentas were also periodically sent.

The placental records were extracted from the hospital system after enrollment for the cohort was complete, meaning that the records reflect the natural recording process of the pathology laboratory. The records were not created for the purposes of this research nor were pathologists aware at the time that the records would be used for any study purposes. We therefore refer to the placentas in this sample as a "clinical practice" sample, rather than one derived for research.

Placental exam records from HU contained information on both macroscopic and histologic characteristics. We coded the presence or absence of each of these characteristics for every placental record, resulting in 122 coded characteristics (full list available in Appendix Table 3.2), which were translated into English from Portuguese. These 122 characteristics included both normal and abnormal placental features.

Postpartum survey

Shortly after giving birth, mothers whose infants were enrolled in the cohort were approached for an in-person postpartum survey administered by a trained interviewer. 3,810 mothers participated in this

survey, which collected detailed self-reported information on sociodemographic characteristics and risk factors, particularly related to experiences during pregnancy. Specifically, information was collected on maternal self-reported pre-pregnancy anthropometrics, parity, pregnancy planning, antenatal care, educational attainment, income, violence experienced during pregnancy, depression, and marital status, among others.

Three-year survey

The final time point of data collection for the cohort was at 36 months of age, when the outcome of interest was measured. 2,590 mothers participated in this survey round. In addition to various sociodemographic and home environment measures, this survey contained several child growth and development measures. The child development scales collected were the Caregiver-Reported Early Childhood Development Instruments (CREDI),[56] PRIDI,[57] and the Strengths and Difficulties Questionnaire (SDQ).[58] Anthropometric measurements, including height and weight, were also collected, which allowed us to identify stunted children using the WHO Child Growth Standards.[59]

Statistical analyses

Given that all of the measurements described above are widely-accepted metrics of adversity in child growth and development, and delayed child development is challenging to measure,[60,61] we created a composite binary measure. That is, a child was identified as experiencing a developmental delay if he/she fell beneath two standard deviations below the median for HAZ (based on the WHO Child Growth Standards[59]), or beneath two standard deviations below the mean (of the entire sample of children in the three-year survey) of the PRIDI or CREDI assessments, or scored 19 or higher on the SDQ scale (“very high” based on standard scoring). Appendix Table 3.3 shows the relationship between each of these variables with each other and the final composite score.

We assessed the ability of birth record information to predict delayed child development at three years of age as measured by the composite indicator. We used the following variables recorded in hospital birth

records: maternal age, delivery type, child sex, Apgar at one minute; small for gestational age (SGA); preterm; low birthweight; length, weight, abdominal perimeter, head circumference, and chest circumference at birth. Using these variables, we calculated the area under the Receiver Operating Characteristic (ROC) Curve (C-statistic or AUC), which is a measure of the discriminative ability of a model in predicting outcomes.

We then assessed the ability of survey-based maternal risk factor information, in addition to birth record data, to predict poor child development. To determine which maternal risks to include, we conducted a literature review to identify key risk factors for poor child development and triangulated those identified risks with the ones that were measured in our sample. The resulting list of survey-based risks included maternal underweight before pregnancy, maternal short stature, parity, educational attainment, household income, report of cigarette smoking during pregnancy, report of alcohol consumption during pregnancy, report of violence experienced during pregnancy, self-report of depression, and marital status.

We also determined the ability of placental characteristics, in addition to birth record data, to predict poor child development at three years. We calculated summary statistics for each of the 122 placental characteristics from the exam records to examine the prevalence of important characteristics in a clinical practice sample of placentas. For the prediction modeling, however, we only included 37 placental characteristics that were deemed clinically relevant by a placental pathologist (author TB). Those 37 characteristics are listed in Table 3.1. While our focus for this analysis was on the predictive ability of placental characteristics above and beyond what can be learned from birth record information alone (given that in settings where placental records are available, birth record information would also likely be available, the novel contribution of this work is to highlight whether placental characteristics can provide *additional* predictive ability such that using these more complex data might be worthwhile), we also estimated the AUC for placental variables alone.

Finally, we calculated the C-statistic for a model that included birth record variables, maternal survey-based variables, and placental variables. To quantitatively compare the predictive ability of these four

models, we calculated χ^2 statistics testing the equivalence of the C-statistics across pairs of models. As a robustness check, we also assessed the ability of our variables of interest to predict the outcome of developmental delay as defined by stunting alone, and by a very high SDQ score alone (the two most prevalent measures of poor development in the analysis sample) as opposed to the composite measure. We quantified the sensitivity and specificity of all models in identifying children with developmental delay at thresholds of 10%, 30% and 50%.

As a sensitivity analysis, we used inverse probability weights in an effort to account for selection into the final analysis sample (N=290) from the initial cohort (N=6,207). Specifically, we developed weights based on the probability of inclusion in the final sample using variables available for all members of the complete cohort (additional details in the Appendix, with probability model visible in Appendix Table 3.8). We then reran the four sets of models described above using inverse probability weighting and calculated the associated sensitivity and specificity.

All analyses were conducted using STATA SE version 13.1. This study was approved by the IRB at HU in Brazil, and only de-identified data were shared with the authors as part of a research partnership, resulting in a Harvard IRB designation for this study as "non-human subjects research."

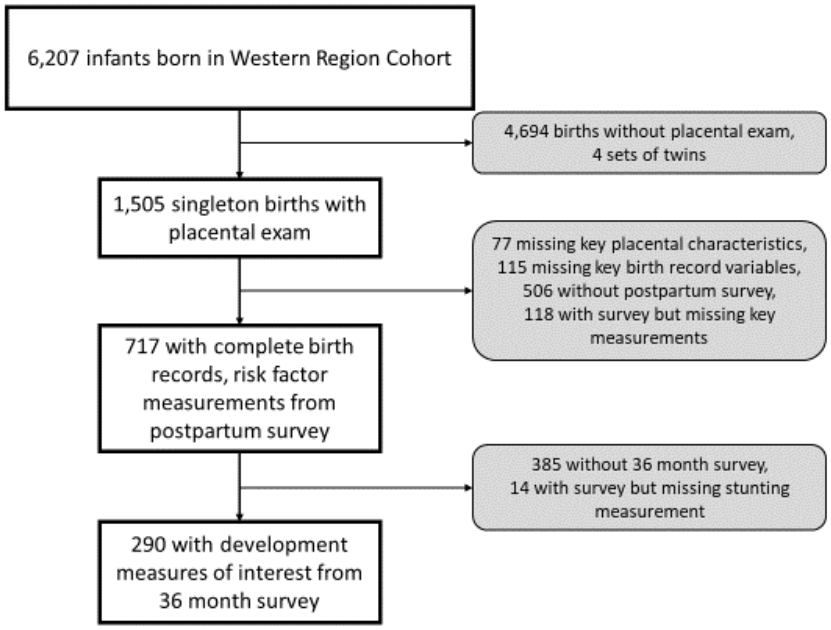


Figure 3.1: Cohort size, culminating in the predictive modeling analysis sample (N=290)

Results

Of the 6,207 infants in the cohort, 1,513 (24%) had a placental exam and of these 1,505 were from singleton births. Table 3.1 shows the prevalence of the 37 placental characteristics used in the predictive modeling, indicating that infarcts were present in 47% of the placentas of the infants in the analysis sample, followed by chorioamnionitis (36%) and cord torsion (29%). The number of placental abnormalities per child ranged from 0 to 9 (of a total of 35 abnormalities), with a mean of 3.5 and a standard deviation of 2.1. Appendix Table 3.2 shows the prevalence, in the entire sample of singleton placentas, of all the 122 placental characteristics that were coded for this analysis.

Table 3.1: Prevalence of placental characteristics (35 abnormal, plus weight and volume) (N=290)

Rank	Characteristic	Prevalence % (N)
1	Infarct	47 (137)
2	Chorioamnionitis	36 (104)
3	Cord torsion	29 (83)
4	Chorangiosis	27 (77)
5	Any indication of meconium	26 (74)
6	Omphalitis	22 (64)
7	Nonspecific mononuclear deciduitis	22 (63)
8	Marginal cord insertion	21 (60)
9	Indication of prolonged meconium exposure from histologic exam	17 (49)
10	Extra syncytial knots	13 (39)
11	Indication of meconium on the fetal face	12 (36)
12	Chronic villitis	10 (28)
13	Diminished villi	9 (25)
14	Edema on cut face of placenta	7 (20)
15	Maternal face of placenta is incomplete	6 (16)
16	Immature villi	6 (16)
17	Retroplacental hematoma	4 (12)
18	Subacute villitis	4 (12)
19	Excess Wharton's Jelly	4 (12)
20	Avascular villitis	3 (10)
21	Intraplacental hematoma	3 (8)
22	Fetal face is diffusely opaque	3 (8)
23	Chronic necrotizing villitis	2 (6)
24	Villous dysmorphia	2 (5)
25	Acute villitis	2 (5)
26	Suspected subcorionic thrombotic fetal vasculopathy	2 (5)
27	Evidence of iron pigment in membranes from histologic exam	2 (5)
28	Decidual vasculopathy	2 (5)
29	Velamentous cord insertion	2 (5)
30	Forked cord	1 (4)
31	Hematoma in cord	1 (3)
32	Obliterant arteriopathy of the vessels of the villous trunks	1 (3)
33	Hypotrophy of tertiary villi	1 (3)
34	White/yellow spots in Wharton's Jelly	1 (2)
35	True knot in cord	1 (2)
	Placental weight: mean g (N):	480.99 (290)
	Placental volume: mean cubic cm (N)	701.17 (290)

22.0% of children aged three years had a developmental delay on one or more domains as measured by the composite metric described above: 12.8% were stunted, 3.8% had a PRIDI score below -2 SD of the mean of all children in the three-year survey, 1.0% had a CREDI score below -2 SD, and 7.9% scored "very high" on the SDQ test. Appendix Table 3.4 shows these values in contrast to the prevalence of developmental delay in the complete three-year survey sample and the full sample of infants with placental exams. While the differences are small, comparison of the three groups indicates that the prevalence of poor developmental outcomes is lowest in the full sample, and highest in the full sample with placental exams, with the analysis sample falling in between. This suggests that those children with placental exams whose mothers completed a postpartum survey may have other characteristics that help support healthy development.

Just over half the sample of children were male, 21% were preterm, and 21% were LBW (Table 3.2). The high rates of adverse birth outcomes (as opposed to the 7% LBW in the overall cohort sample of 6,207 infants, for example) are reflective of the fact that adverse birth outcomes are a common reason for submission of a placenta to the pathology laboratory (Appendix Table. 3.1). Almost 7% of infants had an Apgar score <7 after one minute, and 35% of births were by caesarean section. Maternal age was recorded in the birth record, and 9% mothers were teens, while over 13% were of advanced maternal age. Over half of mothers had at least secondary education, and over 83% had a monthly family income less than R$2,488 (roughly equivalent to US$770, which is an approximate annual income of less than US$10 thousand). The most common marital status was living together (but not married), and 15% of mothers reported drinking alcohol and almost 20% reported smoking tobacco at least once per month during pregnancy.

Table 3.2: Summary statistics of birth record risks, maternal survey-based risks (N=290)

Source of information	Variable	Prevalence % (N)
Birth record	Male	53.79 (156)
	Mother was under age 20 at birth	8.62 (25)
	Mother was age 35+ at birth	13.79 (40)
	Weight at birth (g)	2858.48
	Low birthweight (<2500g)	21.38 (62)
	Length at birth (cm)	47.10
	Abdominal perimeter at birth (cm)	30.70
	Head circumference at birth (cm)	33.52
	Chest circumference at birth (cm)	31.77
	Birth was caesarean	34.83 (101)
	Birth was by forceps	10.34 (30)
	Preterm (<37 weeks gestation)	21.03 (61)
	Small for gestational age (<10th percentile)	24.83 (72)
	Apgar score at 1 minute was 3 (reference is 2)	1.38 (4)
	4	2.07 (6)
	5	0.69 (2)
	6	2.07 (6)
	7	4.83 (14)
	8	17.93 (52)
	9	33.10 (96)
	10	37.24 (108)
Maternal survey	Mother was underweight before pregnancy (BMI < 18 kg/m^3)	6.21 (18)
	Mother was victim of physical violence during pregnancy	3.79 (11)
	Mother has depression (self-report to yes/no question)	1.38 (4)
	Mother has more than 1 child	63.45 (184)
	Mother's schooling is complete primary (reference is incomplete primary)	22.41 (65)
	secondary	54.48 (158)
	tertiary	4.48 (13)
	Family's monthly household income is between R$622 and R$1244 (reference is less than R$622)	36.55 (106)
	between R$1244 and R$2488	37.93 (110)
	between R$2488 and R$6220	14.83 (43)
	between R$6220 and R$12440	1.38 (4)

Table 3.2 (Continued)

Source of information	Variable	Prevalence % (N)
Maternal survey	Mother smoked at least once a month during pregnancy (reference is rarely; <5 times total)	3.01 (9)
	at least once a week	3.10 (9)
	every day	13.45 (39)
	Mother drank alcohol at least once a month during pregnancy (reference is rarely; <5 times total)	10.00 (29)
	at least once a week	2.07 (6)
	every day	2.76 (8)
	Maternal stature is <145cm (reference is at least 160cm)	0.69 (2)
	145 to 150cm	5.86 (17)
	150 to 155cm	17.59 (51)
	155 to 160cm	26.55 (77)
	Mother's marital status is married (reference is single)	20.69 (60)
	divorced	0.34 (1)
	living together	41.03 (119)
	widow	0.34 (1)
	other	14.48 (42)

Birth record variables alone (model 1) had a high predictive accuracy of 72% (C statistic or AUC of 0.72; 95% confidence intervals [CIs] 0.65, 0.79). The values in the cells of Table 3.3, moving diagonally down the table, represent the C-statistics associated with each model (with only birth record variables; with birth record and survey-based variables; and with birth record, survey-based and placental variables). Figure 3.2 displays the associated ROC curves. The model that included only birth record information, using a threshold of 10%, had a sensitivity of 94% but specificity of only 19%. The same model, using a threshold of 30%, had a sensitivity of 42% and specificity of 80%. Using 50% as the threshold, the sensitivity was 2% and specificity 99% (Figure 3.3).

Table 3.3: C-statistics (diagonal, blue cells, with 95% confidence intervals) and results of test of equivalence (off-diagonal) comparing the C-statistics from ROC curves fitted using different sets of variables and the composite development measure as the outcome (N=290)

#	Variables included	Birth record variables	Birth record + Survey variables	Birth record + Placenta variables	Birth record + Survey + Placenta variables
1	**Birth record variables**	0.7179 (0.6504, 0.7855)			
2	**Birth record + Survey variables**	χ^2 = 6.59, p-value = 0.0103	0.7811 (0.7211, 0.8412)		
3	**Birth record + Placenta variables**	χ^2= 15.04 p-value = 0.0001	χ^2= 1.80, p-value = 0.1797	0.8198 (0.7653, 0.8743)	
4	**Birth record + Survey + Placenta variables**	χ^2= 23.65, p-value < 0.0001	χ^2= 15.78, p-value = 0.0001	χ^2 = 6.66, p-value = 0.0099	0.8666 (0.8208, 0.9125)

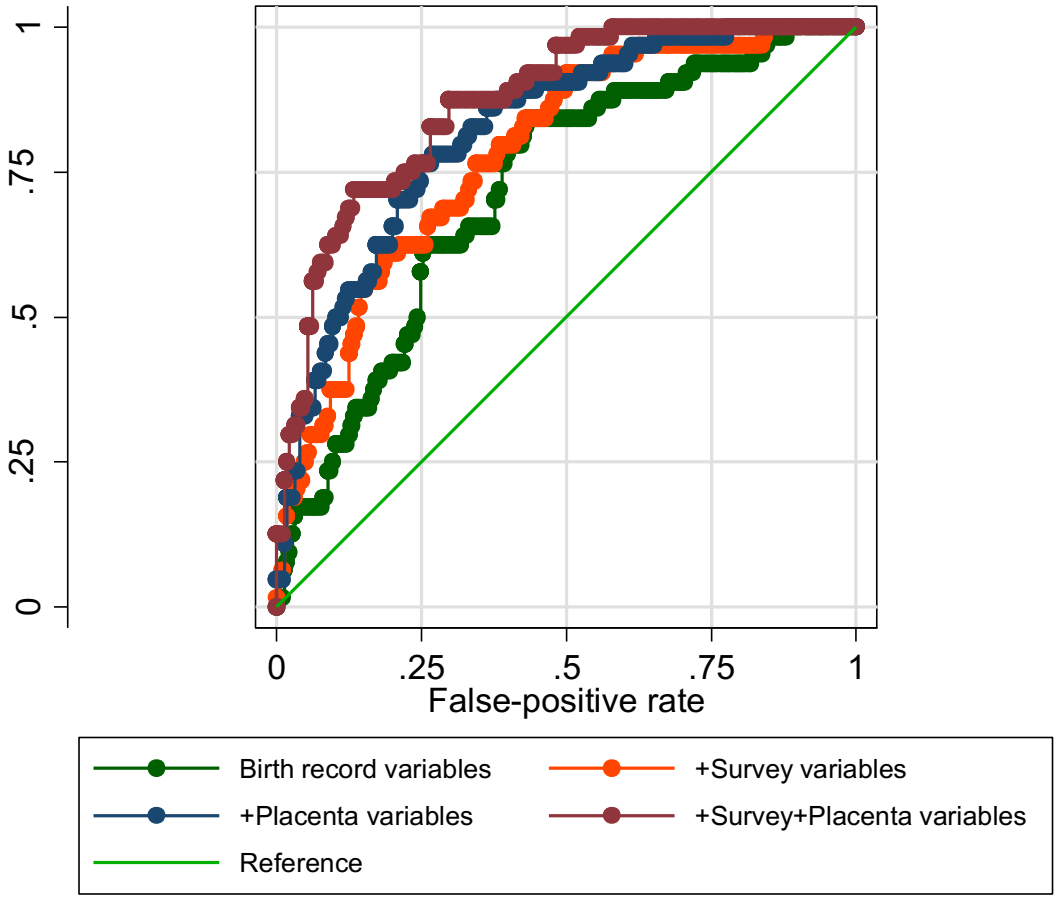
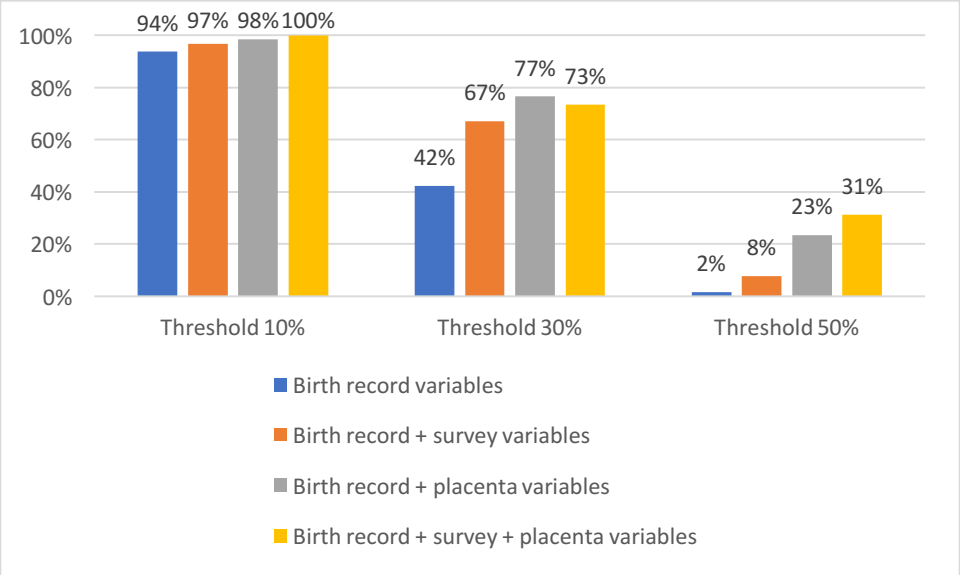
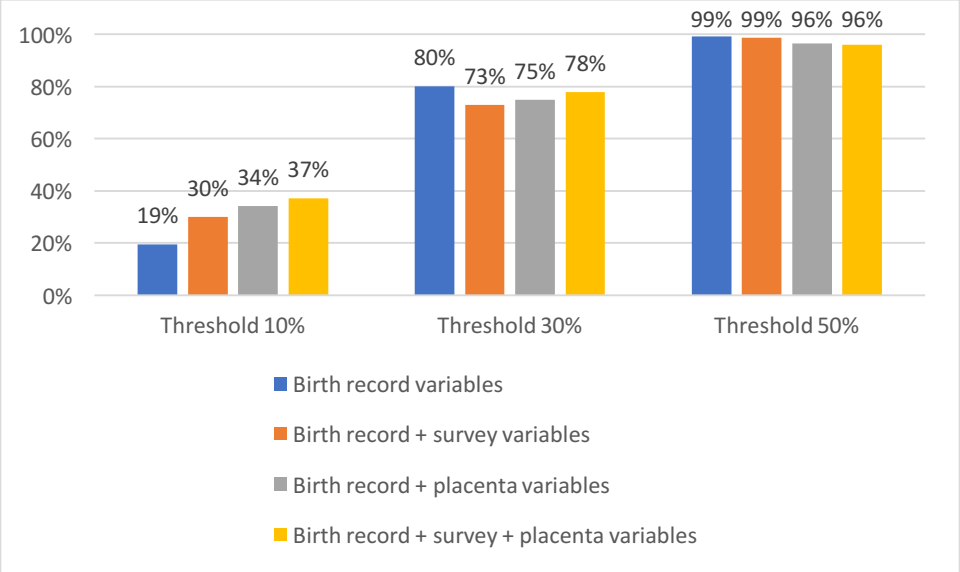


Figure 3.2: ROC curves fitted using different sets of variables and the composite development measure as the outcome (N=290)



A)



B)

Figure 3.3: Sensitivity (A) and specificity (B) of each prediction model, using 10%, 30%, and 50% as thresholds

The C-statistic improved to 78% (95% CIs 72, 84%) when survey-based maternal risk variables were included (model 2). If placental variables were included instead of survey variables (model 3), the predictive accuracy was 82% (95% CIs 77, 87%), with similar sensitivity and specificity.

When all three sets of variables were included in the model (model 4), the predictive accuracy rose to 87% (95% CIs 82, 91%). Using a threshold of 30%, the sensitivity and specificity were 73% and 78%, respectively. Comparing models, any incremental addition of a set of variables resulted in a statistically significant increase in predictive accuracy. Including survey variables resulted in a statistically significant improvement in the AUC compared to birth record variables alone (Table 3.3, p-value = 0.01). Similarly, including placental variables in addition to birth record variables resulted in a statistically significant predictive improvement (p-value = 0.0001), as did including all three sets of variables compared with birth record variables alone (p-value < 0.0001). However, there was no statistically significant difference in the predictive accuracy of the placenta variables as opposed to the survey variables when added to the birth record variables (p-value = 0.1797).

As a sensitivity analysis, we present the results of these same four models, except using stunting and SDQ as separate outcomes, instead of the composite measure (Appendix Tables 3.5 and 3.6, and Appendix Figures 3.1 and 3.2). The C-statistics were very similar to the main findings (Table 3.3) and the conclusions are the same, which supports the use of our composite child development measure. In addition, Appendix Table 3.7 displays the predictive ability of the placental characteristics alone (omitting the birth record and survey variables), indicating that placental characteristics in isolation provided approximately the same predictive ability as the birth record variables alone (Appendix Figure 3.3 shows the ROC curve for placental variables alone). Finally, the sensitivity analysis using inverse probability weighting in an effort to account for selection from the initial cohort into the final sample produced no notable difference in the study findings (Appendix Tables 3.9 and 3.10).

Discussion

This study examined the added value of placental exam records to predict child development delay at age three years among a cohort of children in São Paulo, Brazil. Our results demonstrated that overall developmental delays at age three years can be accurately predicted by standard birth outcome measures collected in hospital records. In Brazil this information should be automatically recorded for the 98% of births that take place in a facility.[62]

Collecting additional, non-standard, information on maternal risk factors can significantly increase predictive accuracy. The predictive power (C-statistic of 0.78 for the model including birth record and survey variables) found in our analysis is slightly higher than the results of a prior child development prediction modeling analysis, which estimated a C-statistic of 0.682 for males and 0.724 for females with only 6 (many fewer than our analysis) similar maternal predictors.[34] However, collection of this type of survey-based data may be more resource intensive than simply using birth record information. Specifically, gathering this type of data required additional staff and data management systems that were not already in place in this Brazilian hospital setting, and may require similar additional resources in other contexts. In addition, the response rate to surveys measuring other predictors may be low and responses may be subject to reporting bias. For example, social desirability bias is likely to influence responses to questions on smoking or alcohol consumption during pregnancy, as has been documented elsewhere,[63,64] and stigma surrounding mental health[65] may influence mothers' likelihood of self-reporting depression or of responding to a survey at all.

Placental pathology records had approximately the same predictive value as the survey-based maternal risk factors. Placental exams require a pathology laboratory and associated costly technology and skilled labor, but are a standard part of hospital-based medical care in many settings. It is therefore possible that using placental pathology records to target interventions would require few additional resources in many cases, and may be less prone to the bias and nonresponse seen in surveys.

Including birth record information, maternal risk factor measurements based on surveys, and placental exam record information allowed us to predict developmental delay at age three years with an impressive 87% accuracy in our sample. If resources are available, measuring and including all these sets of characteristics will likely also provide the best predictive accuracy in other applications. However, given constraints on resources to devote to risk factor measurement, birth record information alone is highly predictive, and if only one additional data collection strategy is feasible, including either survey-based maternal risk factors or placental information increased predictive accuracy from 72% accuracy to between 78% and 82% in our sample. Overall, this analysis highlights the ability of placental characteristics to predict later life outcomes, on par with more traditional maternal risk factors.

We also found that among a clinical practice sample (rather than a sample selected for study purposes) of singleton births in a Brazilian hospital, ascending maternal infection, opalescent membranes, and dystrophic calcifications in villous trunks were the most prevalent placental abnormalities (Appendix Table 3.2). Given the large size of this sample, the prevalence of characteristics identified in this analysis adds to the current literature,[43] shedding light on the frequency with which various characteristics are observed in clinical practice. We find remarkably high occurrence of infectious indicators within the placenta sample (over 60%), which highlights the importance of further investigation to understand the cause of these infections within this population.

Limitations

The nature of the data used in this analysis results in several limitations. The first set of limitations are with respect to the analysis outcome. The SDQ and CREDI measures rely on parental report of child development measures, which may be subject to social desirability bias.[66,67] However, we have little reason to believe that this bias would be different in other settings in a way that would influence the external validity of our results in this particular area. While it is a strength of our analysis that we do not restrict our definition of developmental delay to one particular narrow scale or metric, the fact that we use a composite score based on four metrics leads to a heterogeneous group of children being identified as

"delayed" and this group may not be directly comparable to those identified as delayed in other studies. This limitation is mitigated by our sensitivity analysis using stunting and SDQ scores as outcomes, which generated the same conclusions.

The second set of limitations relate to the birth and maternal risks. The New Ballard Score was used to determine whether an infant was preterm; while this method has high validity, it may result in slightly different results than if last menstrual period or ultrasound were used.[53] While most women in the study sample would have likely received an ultrasound during pregnancy (which would have allowed for more accurate estimation of gestational length), these ultrasounds are generally performed at lower-level health facilities, the records of which are not transferred to the study hospital. This means that the hospital must use cruder methods of estimating gestational age, which is a limitation. INTERGROWTH curves were used to assess whether an infant was small for gestational age; while these curves are of high quality, their use relies on our estimates of gestational age, which may be noisy, as described above. Both of these factors may reduce the precision of our models and may influence the external validity of our results. The fact that several of the self-reported maternal risk factors may be subject to reporting bias (such as alcohol and cigarette consumption during pregnancy, or self-report to a yes/no question about depression) does not compromise the internal validity of our results because we are simply using the responses to these survey questions, with their inherent biases, to predict child development outcomes. However, in the unlikely case that reporting bias for these types of survey questions differs in different contexts in a way that influences their relationship with child development outcomes, then this could also influence the external validity of our predictive models.

The third group of limitations are related to the placental characteristics. While a strength of the placental database is that the records were not initially created for the purposes of research (and therefore reflect the natural recording process of the placental pathology laboratory), the associated weakness is that there were no study-related quality control or consistency checks, which could have helped improve data reliability. For example, while placental weight and dimensions were recorded in the exam records, we

have no information on the extent to which the placentas underwent trimming or draining[68] before measurements were taken (which would influence weight and volume). In addition, placental pathology procedures differ in different hospitals. This may mean that predictive models using other placental characteristics from other pathology record systems could produce different results. Also, with respect to the interpretability and generalizability of the characteristics of the placentas, the criteria used to determine which placentas were examined were not precisely documented, meaning that the data included were neither a random sample nor a sample selected based on precisely known characteristics. This means that understanding how this sample might be similar to or different from samples from other settings is difficult, though this is not an uncommon problem; evidence from a hospital in the US suggests that even when clear guidelines for submitting a placenta for examination exist, they are not always followed.[41] However, it is worth noting that the full set of placental exams (N=1,505) remains one of the largest examined in such a comprehensive manner to date.

Finally, the sample itself that we used in our predictive modeling may not be generalizable and may be subject to selection bias. Specifically, the children in the sample were all born in one hospital in one city in Brazil. In addition, they all had a placental exam, mothers who consented to participate in the study, who completed all relevant questions of the postpartum survey, and were successfully followed-up and completed at least one of the developmental assessments at the three-year time point. This means that the relationships observed between various birth, maternal, and placental characteristics with child development at age three may not hold in other settings and populations. Somewhat relatedly, while the process of selection into the placental exam sample (N=1,505) was fairly standard (based on rough clinical guidelines, as opposed to research design or data quality), the subsequent selection process, based on loss-to-follow-up and non-response to survey questions, is less clear. This led to our sensitivity analysis using inverse probability weighting of the prediction models, which found no indication of differences in the findings when accounting for selection. However, this sensitivity analysis was limited by the available variables used to predict inclusion in the final sample, and may have produced different

findings if it had been possible to include variables specifically capturing socioeconomic factors, for example.

Implications

While the relationship between various placental characteristics and later health and developmental outcomes has been examined before,[51] our study uses placental pathology lab results that are over 50 years more recent and are from a middle-income country. Our findings may be more relevant today given technological advances in the field of pathology. Our work uses placental exams that reflect clinical practice placental samples and reporting, therefore reflecting what can be learned from placentas under feasible (non-study) circumstances. Our analysis is also the first to use many placental characteristics together in risk prediction modeling and highlights the utility and feasibility of prediction modeling in child development.

Our novel algorithm has value particularly in Brazil where extensive resources are devoted to early developmental intervention among potentially at-risk children. Specifically, Brazil's Criança Feliz program, which began implementation in the summer of 2017, provides home visiting to children under age three years who are supported by the country's Bolsa Familia program, and to children up to age six years who receive Benefício de Prestação Continuada (a disability pension).[69] Given that 98% of births in Brazil take place in a facility,[62] this suggests that the type of predictive modeling used in our analysis could, after further research, be broadly implemented to refine this system of targeting. It is conceivable that following additional successful research in this area, public hospital records (like the birth and placental records used in this analysis) could be used in country-wide predictive modeling to identify children at risk of poor developmental outcomes who could subsequently be targeted by the Criança Feliz program. Models with high sensitivity, such as those developed in this analysis, could help ensure that nearly all infants at risk are identified. For example, our model including all three sets of predictors and using a threshold of 30% resulted in sensitivity and specificity of approximately 80%, which means that it can correctly identify at-risk infants at a high rate without producing high rates of false-positives that

would impose undue burden on programs administering developmental interventions. Specifically, at present, interventions to support child development are often provided regardless of clear risk for poor development (as in the case of Criança Feliz), which means that even marginal improvements in targeting could be cost-saving. Given that there are no expected adverse effects of providing child development support even to those without risk for poor development, and that intervening early in life has repeatedly been documented to be cost-effective,[8–11] using models like these could improve policy decision-making.

More broadly, the results of this analysis corroborate previous research on the power of information about an infant at birth in predicting later developmental outcomes. The types of data examined here are also widely collected at birth around the world in certain settings, meaning that after further validation, a similar strategy could be used in early detection beyond this context. While other work has documented challenges in bringing child development interventions to scale,[70] future access to a novel and reliable risk prediction algorithm could facilitate such scale-ups. Resource-intensive interventions will be more cost-effective when targeted with high accuracy to support infants at risk of poor developmental outcomes.

Conclusions

Our analysis takes a novel approach to risk prediction modeling by examining the additional predictive accuracy of placental characteristics in identifying children at risk of later developmental delay. This work demonstrates that information from birth records can help predict child development delays at age three years, and that both placental characteristics and survey-based measures of maternal risks provide more predictive accuracy. In cases where survey-based measures are expensive to collect or subject to bias, using placental exam results where they are part of standard hospital care may help identify infants who could benefit from receiving early developmental interventions.

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Appendices

Appendix Table 3.1: Guidelines for submitting a placenta for pathological review[39] (table reproduced from Redline 2014[71])

Maternal
Delivery at <37 weeks or more than 42 weeks (alternative: <34 weeks only)
Unexplained or recurrent pregnancy complications
Systemic disorders, gestational or underlying, including malignancy with concern for mother or infant
Peripartum fever or infection
Excessive third-trimester bleeding
Thick or prolonged meconium
Severe oligohydramnios/polyhydramnios
Fetal/neonatal
Stillbirth or neonatal death
NICU admission
SGA/LGA (birthweight <10th or >90th percentile for gestational age)
Birth depression/pH <7.0 / 5-minute Apgar <7 / assisted ventilation >10min
Neonatal hematocrit <35
Neonatal seizures
Suspected infection or sepsis
Hydrops fetalis of unknown etiology
Multiple pregnancy (alternative: fused placentas, same-sex twins, and/or twins with discordant fetal growth)
Placental
Structural abnormalities or masses involving the placental disc, umbilical cord, or membranes
Abnormal size for gestational age
Fragmented, possibly incomplete placenta

Appendix Table 3.2: Prevalence of all placental characteristics (both normal and abnormal) considered in this analysis, among all singleton births with a placental exam (N=1,505)

Rank	Characteristic	Prevalence % (N)
1	Single placenta	100 (1505)
2	3 vessels in cord	99 (1490)
3	Cut face is wine colored	90 (1352)
4	Marginal membrane insertion	84 (1269)
5	Central cord insertion	72 (1086)
6	Shiny amnion	72 (1083)
7	Ascending maternal infection	63 (942)
8	Opalescent membranes	62 (940)
9	Dystrophic calcifications in villous trunks	56 (837)
10	Paracentral insertion of cord	55 (828)
11	Oval shaped	49 (739)
12	Infarct	49 (732)
13	Placenta is discoid in shape	45 (670)
14	Translucent placental membranes	43 (642)
15	Prominent vessels on the fetal face	42 (628)
16	Chorioamnionitis	38 (576)
17	Discolored with white areas	38 (569)
18	Cord torsion	31 (472)
19	Any indication of meconium	29 (443)
20	Chorangiosis	28 (423)
21	Indications of fetal suffering	24 (361)
22	Marginal cord insertion	23 (349)
23	Nonspecific mononuclear deciduitis	22 (325)
24	Fibrinoid necrosis of villi	21 (323)
25	Omphalitis	18 (277)
26	Maternal blood infection	17 (263)
27	Indication of prolonged meconium exposure from histologic exam	17 (257)
28	Indication of meconium on the fetal face	16 (237)
29	Subchorionic necrosis	16 (236)
30	Extra syncytial knots	15 (219)
31	Subchorionic hematoma	14 (206)
32	Maternal face is red (wine-colored)	13 (198)
33	Opaque nodules on the membranes	13 (191)

Appendix Table 3.2 (Continued)

Rank	Characteristic	Prevalence % (N)
34	Punctate calcifications	12 (187)
35	Thickening of medium	12 (183)
36	Subacute deciduitis	12 (181)
37	Peripheral membrane insertion	12 (178)
38	White nodules on the fetal face	10 (154)
39	Diminished villi	10 (154)
40	Myointimal thickening	10 (149)
41	False knot in cord	10 (143)
42	Chronic villitis	9 (128)
43	Villous fibrosis	8 (125)
44	Edema on cut face	8 (122)
45	Immature villi	6 (92)
46	Dots or crunchy yellow plaques	6 (87)
47	Intervillous fibrinoid necrosis with thrombosis	6 (84)
48	Membrane is brown	5 (78)
49	Maternal face is incomplete	5 (78)
50	Deciduitis with abscess	5 (75)
51	Placenta shape is irregular	5 (74)
52	Green color of membranes	5 (72)
53	Villous edema	5 (70)
54	Subacute villitis	4 (63)
55	Fetal face is opaque	4 (62)
56	Excess Wharton's Jelly	4 (59)
57	Avascular villitis	4 (59)
58	Intervillous edema	4 (59)
59	Fetal face is opalescent	4 (58)
60	Subamniotic hematoma	3 (50)
61	Membrane is yellow	3 (45)
62	Intraplacental hematoma	3 (43)
63	Intervillous fibrin with neutrophils	3 (41)
64	Retroplacental hematoma	3 (38)
65	Hematoma in cord	2 (36)
66	Suspected subcorionic thrombotic fetal vasculopathy	2 (31)
67	Velamentous cord insertion	2 (26)
68	Indications of maternal tobacco use	2 (25)
69	Chronic necrotizing villitis	2 (25)

Appendix Table 3.2 (Continued)

Rank	Characteristic	Prevalence % (N)
70	White/yellow spots in Wharton's Jelly	2 (24)
71	Decidual vasculopathy	2 (23)
72	Acute villitis	1 (22)
73	Suspected thrombotic fetal vasculopathy	1 (19)
74	Hypotrophy of tertiary villi	1 (16)
75	Forked cord	1 (16)
76	Maternal face is intact and complete with all cotyledons	1 (14)
77	Deciduitis with presence of necrosis of the decidua reflexa	1 (13)
78	Evidence of iron pigment	1 (13)
79	Fibrinoid necrosis of the villi	1 (12)
80	Obliterant arteriopathy of the vessels of the villous trunks	1 (12)
81	2 vessels in cord	1 (12)
82	Irregular lobes (bilobed, multilobed, accessory lobes)	1 (12)
83	Placenta is bilobed	1 (11)
84	Sickle cell anemia	1 (10)
85	Acute atherosis	1 (9)
86	Circumvallation	1 (9)
87	Constricted cord	1 (9)
88	Placenta is circumvallate	1 (9)
89	Fibrinoid necrosis of the villous vessels	1 (8)
90	Villous dysmorphia	1 (8)
91	Thrombosis of the spiral artery	0 (7)
92	True knot in cord	0 (6)
93	Reduced Wharton's Jelly	0 (6)
94	Hemorrhagic arteriopathy obliterant	0 (6)
95	Subintimal hemorrhage	0 (6)
96	Placenta accreta	0 (5)
97	Thrombi on cord	0 (5)
98	Multifocial collapse of intervillous space	0 (4)
99	Intervillous abscess	0 (4)
100	Tumors on the cut face	0 (3)
101	Placental abruption	0 (3)
102	Cysts on the fetal face	0 (2)
103	Cysts on the membrane	0 (2)
104	Mesenchymal dysplasia	0 (2)
105	Hematic depletion in the intervillous space	0 (2)

Appendix Table 3.2 (Continued)

Rank	Characteristic	Prevalence % (N)
106	Placental insufficiency	0 (1)
107	Membrane is absent	0 (1)
108	Subchorial hematoma (Breus Mole)	0 (1)
109	Focal diminished Wharton's Jelly	0 (1)
110	Proliferation of citotrophoblastic cells	0 (1)
111	Multilobed shape	0 (1)
112	Cord is lacerated	0 (1)
113	Vascular collapse of the villi	0 (1)
114	Trophoblast inclusions	0 (1)
115	Acute marginal hematoma	0 (1)
116	Placenta previa	0 (1)
117	Accessory lobes in placenta	0 (1)
118	Placenta membranacea	0 (0)
119	Thickening of villous basement membrane	0 (0)
120	Subchorial hematoma	0 (0)
	Placental volume: mean cubic cm (N)	687.8954 (1505)
	Placental weight: mean g (N)	468.2796 (1505)

Appendix Table 3.3: Correlation matrix of child development outcomes with each other and the composite score, in the analysis sample (N=290)

	Stunted	PRIDI < -2SD	CREDI < -2SD	High SDQ	Development composite indicator
Stunted	1				
PRIDI < -2SD	-0.0209	1			
CREDI < -2SD	-0.0488	-0.0414	1		
High SDQ	0.0408	0.2260*	0.1285	1	
Development composite indicator	0.7186*	0.4010*	0.3072*	0.5515*	1

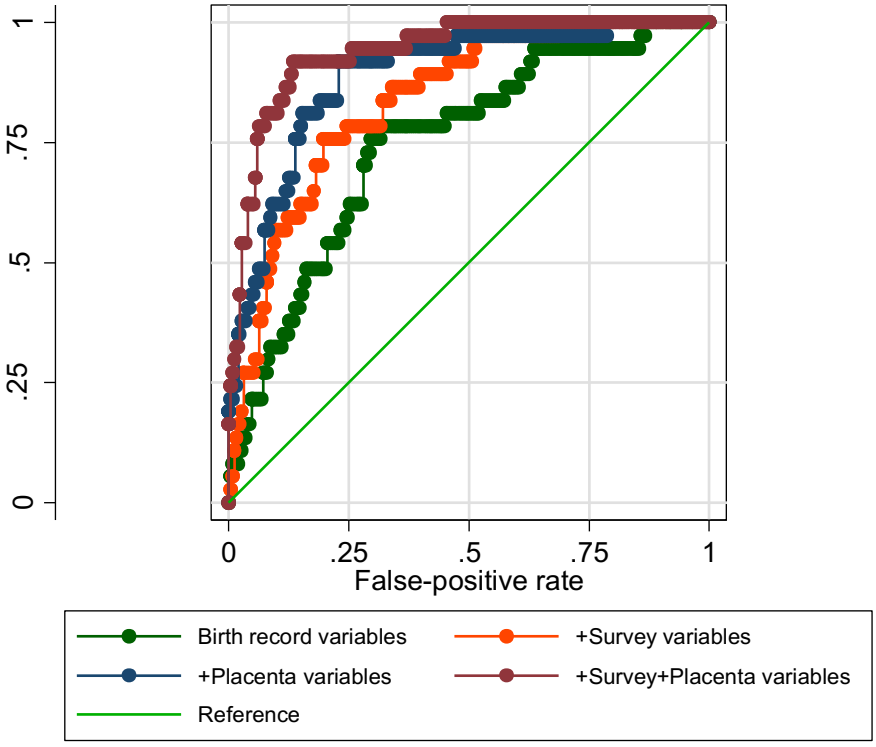
*P-value indicates the correlation coefficient is statistically-significant at the 0.05 level.

Appendix Table 3.4: Prevalence of each developmental outcome at 3 years, and the prevalence of the composite child development measure, in the full three-year sample, in the three-year sample among children who had a placental exam, and in the analysis sample (children who had a placental exam and with non-missing maternal risks measured postpartum)

	Full sample % (N)	**Sample with placental exam % (N)**	**Analysis sample (placental exam, maternal risks) % (N)**
Stunted	10.55 (260)	14.34 (80)	12.76 (37)
PRIDI < -2SD	3.67 (830)	4.28 (21)	3.79 (11)
CREDI < -2SD	2.71 (230)	5.08 (9)	1.03 (3)
High SDQ	8.21 (211)	9.06 (53)	7.93 (23)
Development composite indicator	19.76 (511)	23.60 (139)	22.07 (64)
N	2586	589	290

Appendix Table 3.5: C-statistics (diagonal, blue cells, with 95% confidence intervals) and results of test of equivalence (off-diagonal) comparing the C-statistics from ROC curves fitted using different sets of variables and stunting as the outcome (N=290)

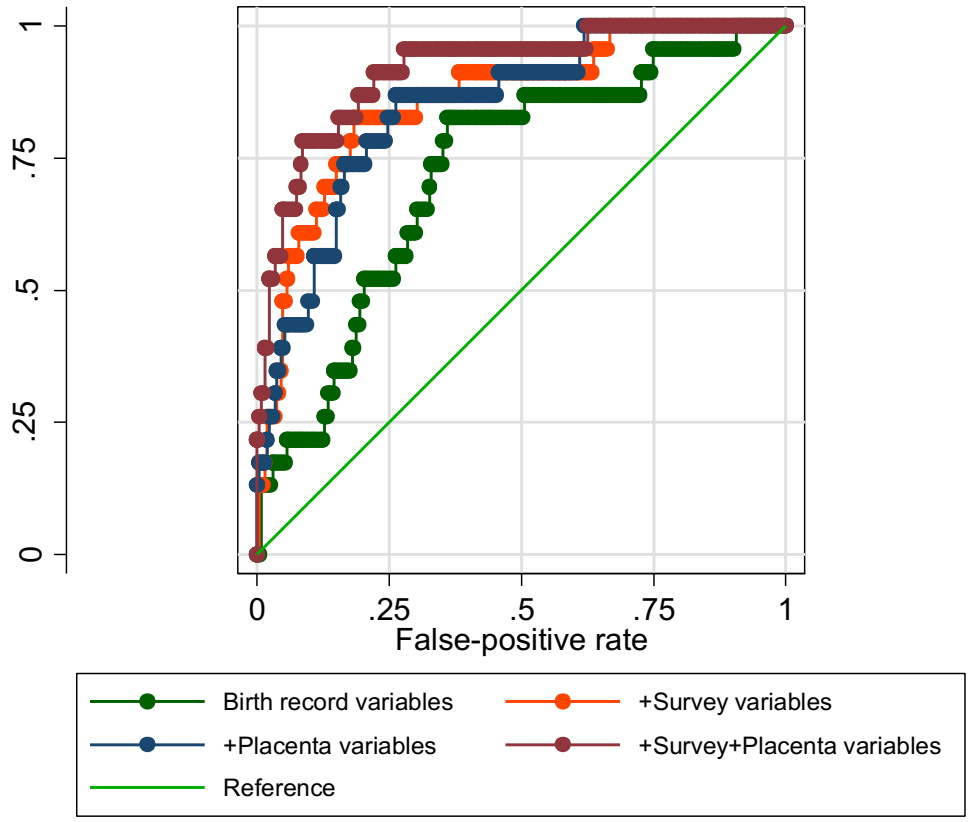
#	**Variables included**	**Birth record variables**	**Birth record + Survey variables**	**Birth record + Placenta variables**	**Birth record + Survey + Placenta variables**
1	**Birth record variables**	0.7455 (0.6631, 0.8280)			
2	**Birth record + Survey variables**	χ^2 = 6.83, p-value = 0.0090	0.8366 (0.7749, 0.8982)		
3	**Birth record + Placenta variables**	χ^2= 21.51 p-value < 0.0001	χ^2= 2.96, p-value = 0.0854	0.8872 (0.8326, 0.9418)	
4	**Birth record + Survey + Placenta variables**	χ^2= 30.47, p-value < 0.0001	χ^2= 18.87, p-value < 0.0001	χ^2 = 10.49, p-value = 0.0012	0.9358 (0.8996, 0.9720)



Appendix Figure 3.1: ROC curves fitted using different sets of variables and stunting as the outcome

Appendix Table 3.6: C-statistics (diagonal, blue cells, with 95% confidence intervals) and results of test of equivalence (off-diagonal) comparing the C-statistics from ROC curves fitted using different sets of variables and SDQ<-2SD as the outcome (N=290)

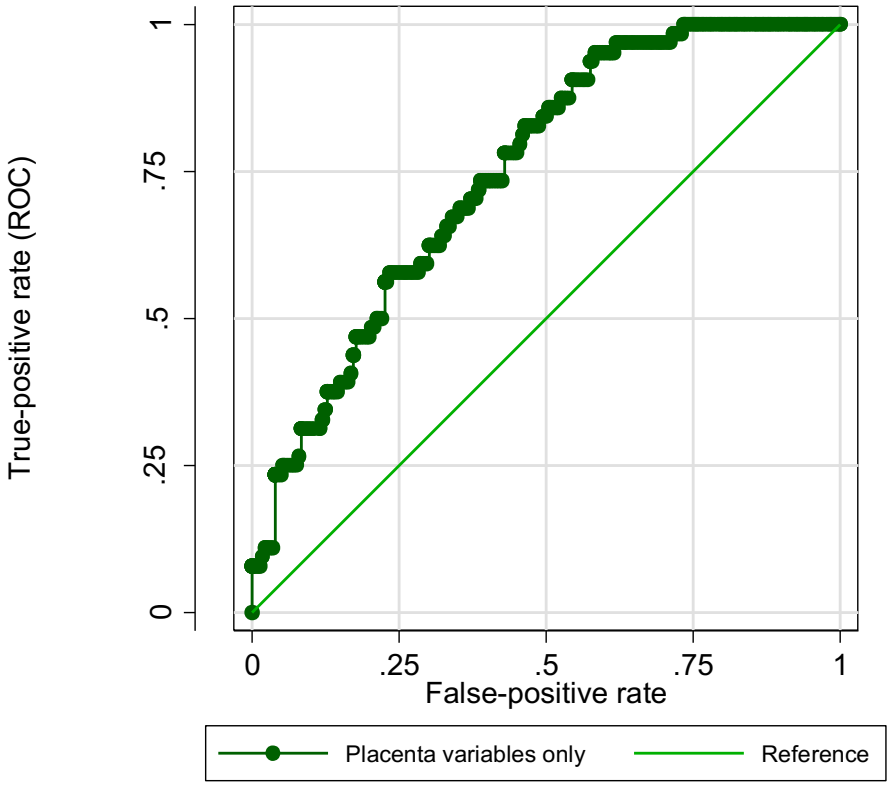
#	Variables included	Birth record variables	Birth record + Survey variables	Birth record + Placenta variables	Birth record + Survey + Placenta variables
1	**Birth record variables**	0.7224 (0.6174, 0.8273)			
2	**Birth record + Survey variables**	χ^2 = 14.16, p-value = 0.0002	0.8598 (0.7798, 0.9398)		
3	**Birth record + Placenta variables**	χ^2= 13.81 p-value = 0.0002	χ^2= 0.17, p-value = 0.6778	0.8456 (0.7674, 0.9238)	
4	**Birth record + Survey + Placenta variables**	χ^2= 22.31, p-value < 0.0001	χ^2= 6.63, p-value = 0.0100	χ^2 = 7.78, p-value = 0.0053	0.9152 (0.8551, 0.9752)



Appendix Figure 3.2: ROC curves fitted using different sets of variables and SDQ<-2SD as the outcome

Appendix Table 3.7: C-statistics (diagonal, blue cells, with 95% confidence intervals) and results of test of equivalence (off-diagonal) comparing the C-statistics from ROC curves fitted using birth record variables alone and placental variables alone with the composite development measure as the outcome (N=290)

Variables included	**Birth record variables**	**Placenta variables**
Birth record variables	0.7179 (0.6504, 0.7855)	
Placenta variables	$\chi^2 = 0.38$, p-value = 0.5395	0.7455 (0.6840, 0.8071)



Appendix Figure 3.3: ROC curve fitted using only the placental variables and the composite development measure as the outcome (N=290)

Appendix Table 3.8: Results of logistic regression to predict the probability of inclusion in the final analysis sample (N=290) among all members of the cohort (N=6,207); the probabilities produced from this regression were used to generate inverse probability weights[§]

Variables	**OR of inclusion in analysis sample (95% CIs)**
Maternal age (continuous)	0.982 (0.951 - 1.015)
Mother was under age 20 at birth	0.359*** (0.217 - 0.594)
Mother was age 35+ at birth	1.411 (0.838 - 2.376)
Birth was caesarean	0.828 (0.637 - 1.077)
Birth was by forceps	0.704* (0.468 - 1.060)
Small for gestational age (<10th percentile)	4.827*** (3.622 - 6.435)
Preterm (<37 weeks gestation)	2.179*** (1.519 - 3.126)
Low birthweight (<2500g)	1.343 (0.907 - 1.991)
Male	1.019 (0.799 - 1.300)
Apgar <7	0.777 (0.473 - 1.274)
Constant	0.0613*** (0.0257 - 0.146)
Observations	6,205

*** p<0.01, ** p<0.05, * p<0.1

[§]The values of the inverse probability weights ranged from 2.5 to 115.7, with mean 32.8 and standard deviation 18.7. Other variables, such as maternal education and income, were not available for all members of the complete cohort, so could not be included. We then used the probability weights in the regression models used to generate the C-statistics (Appendix Table 3.9).

Appendix Table 3.9: C-statistics (with 95% confidence intervals) from ROC curves fitted using different sets of variables with the composite development measure as the outcome, comparing the main results with those generated using inverse probability weighting to account for selection into the final sample (N=290)

#	Variables included	C-statistics, no weighting (95% CIs)	C-statistics, IPW for inclusion in final sample (95% CIs)
1	**Birth record variables**	0.7179 (0.6504, 0.7855)	0.6909 (0.6189, 0.7629)
2	**Birth record + Survey variables**	0.7811 (0.7211, 0.8412)	0.7416 (0.6717, 0.8114)
3	**Birth record + Placenta variables**	0.8198 (0.7653, 0.8743)	0.7846 (0.7246, 0.8446)
4	**Birth record + Survey + Placenta variables**	0.8666 (0.8208, 0.9125)	0.8220 (0.7607, 0.8832)

Appendix Table 3.10: Sensitivity and specificity using a threshold of 30% and the composite development measure as the outcome, comparing the main results with those generated using inverse probability weighting to account for selection into the final sample (N=290)

		Sensitivity, threshold 30%		**Specificity, threshold 30%**	
#	**Variables included**	**C-statistics, no weighting**	**C-statistics, IPW for inclusion in final sample**	**C-statistics, no weighting**	**C-statistics, IPW for inclusion in final sample**
1	**Birth record variables**	42%	44%	80%	80%
2	**Birth record + survey variables**	67%	58%	73%	78%
3	**Birth record + placenta variables**	77%	66%	75%	74%
4	**Birth record + survey + placenta variables**	73%	73%	78%	75%

Conclusion

Summary of dissertation papers

We documented the impact of risk factors for poor child development, highlighted current shortcomings in cost-effectiveness analyses, and examined innovative models to predict later developmental delay. In the first paper, "Human capital loss attributable to stunting risks: A systematic analysis of the impact of risk factors for childhood stunting on schooling and income losses in 137 developing countries", we built on previous research from the risk factor and economics literature.[1,2] We found that risks relating to fetal growth restriction and preterm birth result in the largest educational and income losses, followed by diarrhea and unimproved sanitation, and that the magnitude of these losses makes intervention appealing and potentially cost-saving. More broadly, this work underscored the importance of quantifying the impact of risk factors on human capital, providing policymakers with a comprehensive view of the massive long-term impact of failing to address these risks.

In the second paper, "The impact of parsimonious versus comprehensive cost estimation in cost-effectiveness analysis: Economic evaluation of a kangaroo mother care program in Mali", we highlighted ways in which costs are frequently underestimated in cost-effectiveness analyses. Specifically, examining a kangaroo mother care program, we found that failing to account for administrative costs, demand-creation costs, and costs to patients' families resulted in cost-effectiveness ratios that are underestimated by orders of magnitude. This work suggested that existing cost-effectiveness estimates may need to be carefully reviewed, and future studies will need to increase the comprehensiveness of costing data collection in order to be optimally useful for resource allocation in both child development and beyond.

In the third paper, "Can placental characteristics predict child development delays? Findings from São Paulo Western Region Cohort Study", we examined the predictive ability of several sets of risk factors. Specifically, we tested the ability of birth characteristics from birth records, maternal risk factors measured in surveys, and placental characteristics from placental pathology exam records to predict

developmental delay at age three years. Our findings suggested that placental characteristics can be effective predictors of later developmental adversity, as can survey-based measures of maternal risks. Where survey-based measures are expensive to collect or subject to reporting bias, using placental exam results that are part of standard hospital care may provide a novel and cost-effective opportunity to identify infants who would particularly benefit from developmental intervention, helping to target and maximize the impact of limited resources.

Policy implications and future research

The findings from our quantification of the impact of risks for stunting on education and income highlight the massive human capital effects of these risks. This work implies that a focus on child development should extend beyond the health sector, given that the ramifications for schooling and income are relevant to the education, employment, and finance sectors. While policy efforts to improve human capital have focused on schooling attainment,[3] our work implies that the risk factors driving poor child development outcomes should be at the forefront of human capital policy attention, given that these factors are in play before children even reach school.

The evidence generated from our CEA work suggests that some CEA studies/results may suffer from pronounced underestimation of costs and therefore underestimation of cost-effectiveness ratios, making interventions look more favorable. While this paper reports on a single intervention program in one setting, it can serve as a model for future research exploring the impact of costing assumptions in other environments. This work highlights the importance of comprehensive and consistent data on costs, but moving toward high-quality, detailed costing data collection as a standard part of the roll out of intervention programs will be difficult. Such detailed data collection is arduous and may present a conflict of interest for industry-funded or interest-group funded studies, as better cost accounting is likely to reduce the apparent cost-effectiveness of the program. This creates a perverse incentive scheme that can likely only be overcome by rigorous guidelines for cost reporting (such as those provided by the Global Health Cost Consortium[4]) and incentives to adhere to them. Despite the burden associated with

comprehensive costing data collection, the vast benefits will be in the form of more accurate and useful cost-effectiveness ratios. This discussion adds to the existing literature on CEAs of early childhood development interventions that also identifies barriers to comparability of results. A recent review[5] found that CEAs of interventions in this realm did not report common outcome measures, making it difficult to compare ratios between studies. Moving forward, a shift in the field toward strict adherence to costing and CEA guidelines and reference cases[4,6–8] must be prioritized in order to generate reliable information on the cost-effectiveness of child development interventions, making these results useful in identifying low-cost and high-impact solutions.

Our work examining the predictive ability of birth record information, survey-based maternal risk factor information, and placental exam records demonstrates the power of data collected at birth in predicting developmental adversity as many as three years later. Future research is required to test the generalizability of these findings, and more generally, to test the limits and utility of predictive modeling in child development. If a set of highly-predictive characteristics were measured among all infants at birth, or even before birth, and used to accurately predict risk of future developmental adversity, this could revolutionize the way child development interventions are administered. Early intervention targeting could begin at birth, and resources could be used more effectively by focusing on those with the greatest need. There is ample room for future high-impact research in this area.

As child development is complex and multi-faceted, so too are the research and policy courses ahead. Sustained progress in this area will be imperative in order to support all children in reaching their full potential.

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