Scaling up prenatal nutrition could reduce the global burden of noncommunicable diseases in the next generation: a modeling analysis

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ABSTRACT

Background: Nutritional conditions during pregnancy may influence the epigenetic development of an individual and consequently their later-life risk of noncommunicable disease (NCD). Improving nutrition for pregnant females may therefore serve the dual purpose of directly improving pregnancy outcomes and preventing NCDs in the next generation.

Objectives: We estimated the impact of prenatal supplementation with iron and folic acid (IFA), multiple micronutrients (MMS), or calcium at 50%, 75%, or 90% coverage on future NCDs by age and sex in 2015.

Methods: We used secondary data sources from 132 countries to quantify the cases of diabetes and hypertension and the deaths from selected NCDs that could be averted or delayed by scaling up prenatal micronutrient supplementation.

Results: Globally, >51,000 NCD deaths, 6 million cases of hypertension, and 3 million cases of diabetes could be prevented per offspring birth cohort if mothers were prenatally supplemented with MMS at 90% coverage. For IFA these numbers would be roughly half. Calcium supplementation at 90% could delay 51,000 deaths per birth cohort. Our model suggests that substantial numbers of NCD deaths and cases of hypertension and diabetes could be prevented in future generations by scaling up micronutrient supplementation for mothers during pregnancy.

Conclusions: Highlighting the additional benefits of proven nutrition interventions is critical in ensuring adequate and sustained investments, and programmatic integration. As the double burden of disease continues to grow, population-wide efforts to scale up micronutrient supplementation to pregnant females could help prevent both undernutrition and chronic disease. Am J Clin Nutr 2022;116:1291–1302.

Keywords: prenatal nutrition, supplementation, intergenerational, noncommunicable disease, double burden of malnutrition

Introduction

Noncommunicable diseases (NCDs) currently lay claim to 64% of all deaths in low- and middle-income countries (LMICs) (1). According to the Developmental Origins of Health and Disease hypothesis, environmental exposures such as nutritional deficits during pregnancy can influence the later-life risk of NCD in an individual (2). Evidence from randomized controlled trials provides plausible causal estimates of the effects of maternal nutrition during preconception or gestation on fetal growth and birth weight (3–5). At the same time, a sizable body of epidemiologic evidence supports associations between adverse birth outcomes and NCD in adulthood (6, 7). Strategies to improve nutrition for pregnant females in LMICs may therefore serve the dual purpose of directly improving pregnancy outcomes as well as reducing the risks of NCDs in the offspring.
Although the WHO Global Action Plan for the Prevention and Control of Noncommunicable Diseases highlights nutrition and nutrition-related outcomes as key targets for the prevention of NCDs, evidence on the intergenerational impact of maternal nutrition on later-life NCD in the offspring is lacking (8–10). The biological plausibility of this relation has been extensively studied and demonstrated in animal models (11–15), and is also documented in the epigenetic literature (16–18). We conducted a scoping review of the association between maternal micronutrient supplementation and offspring cardiovascular health in LMICs. The available evidence for this link is based on prospective follow-up of children born to mothers enrolled in early supplementation trials. However, in these trials, loss to follow-up is a big source of bias and the children born to the study participants are still too young to experience NCDs (19–27). One recent review and meta-analysis summarized the evidence on early-life nutrition interventions and their long-term association with cardiometabolic diseases and found no significant effects (28). However, participants of the offspring cohort in all trials were younger than 17 y at follow-up. The onset of NCDs is typically after age 30 y and therefore the burden of NCD has yet to materialize for these children and any impacts on NCD risk are therefore difficult to ascertain.

To our knowledge, no study has quantified the intergenerational impact on NCD risk, and the case for action against malnutrition in LMICs through this pathway remains limited accordingly. Given the high global prevalence of micronutrient deficiencies and the growing burden of NCDs, we cannot wait for the offspring of participants of supplementation trials to age into higher risk of NCDs over the next few decades to fill this knowledge gap. The role of addressing maternal nutrition in tackling the double burden of disease warrants immediate examination. Therefore, we estimated the annual deaths from NCDs in the offspring generation that could be delayed by scaling up key prenatal micronutrient supplementation in LMICs, by combining evidence from trials on birth outcomes with meta-analyses of observational studies of birth outcomes and NCD risk factors.

**Methods**

We estimated the number of deaths from NCDs that could be delayed in the offspring generation by scaling up prenatal supplementation with iron and folic acid (IFA), multiple micronutrients (MMS), or calcium to target coverages of 50%, 75%, and 90% or a 25-percentage-point increase in prevailing coverage. We estimated the impact of each supplement-coverage scenario on the following outcomes: 1) reductions in low birthweight (LBW) and preterm birth (PTB); 2) reductions in prevalence and cases of hypertension and diabetes, or reductions in mean blood pressure, blood glucose, or serum cholesterol; and 3) reductions in cause-specific NCD and all-cause mortality (Figure 1).

The analysis included all countries designated as low- or middle-income by the Global Burden of Disease (GBD) Study for which necessary data were available (n = 132). We included all maternal nutrition interventions for which high-quality evidence of the impact on birth outcomes was available. We quantified the effect through adverse birth outcomes with available high-quality, nationally representative data (i.e., LBW, defined as birth weight < 2500 g; and PTB, defined as <37 weeks of gestation), and with strong evidence of association with selected NCD risk factors (i.e., blood pressure, plasma glucose, and total serum cholesterol) (Table 1, Supplemental Table 1). We did not quantify the impact of calcium on reductions in LBW, because most of the impact of calcium supplementation is through reductions in PTB due to lower risk of pre-eclampsia. No meta-analyses on the relation between being born small for gestational age (SGA; birth weight <10th percentile of gestational age and sex relative to the standard reference population) and NCD risk factors were identified, and our analysis therefore did not include this pathway. We estimated impacts on 6 NCDs that are
TABLE 1  Effect sizes used in estimations for paths between supplements and NCD risk factors.1

| Exposure | Outcome | Effect size (95% CI) | Source |
|----------|---------|---------------------|--------|
| **Effect of supplementation on birth outcome** | | | |
| Multiple micronutrients | BW | MD (grams): 61 (43, 79) vs. IFA for anemic mothers MD: 38 (21, 56) vs. IFA for nonanemic mothers | Smith et al. (3) 17 RCTs | Antenatal multiple micronutrient supplements that include iron and folic acid are recommended in the context of rigorous research. Rigorous research includes implementation research using high-quality methods appropriate to the specific research questions |
| | LBW2 | RR: 0.81 (0.74, 0.89) vs. IFA for anemic mothers RR: 0.91 (0.82, 0.98) vs. IFA for nonanemic mothers | Peña-Rosas et al. (4) 44 RCTs or quasi-RCTs Anemic vs. not anemic at baseline | Daily oral iron and folic acid supplementation with 30 mg to 60 mg of elemental iron and 400 μg (0.4 mg) folic acid |
| | PTB3 | RR: 0.93 (0.87, 0.98) vs. IFA (regardless of maternal anemia) | Imdad and Bhutta (46) 15 RCTs | In populations with low dietary calcium intake, daily calcium supplementation (1.5 g–2.0 g oral elemental calcium) is recommended for pregnant females |
| IFA | BW | MD: 23.75 (−3.02, 50.51) vs. control4 | Knop et al. (6) 36 cohorts, 3–8 case-control, 5–15 cross-sectional | Association between birth outcome and NCD risk factor |
| Calcium | BW | MD: 85.75 g (37.91, 133.58 g) vs. control4 | | |
| | LBW2 | RR: 0.84 (0.69, 1.03) vs. control4 | Hofmeyr et al. (5) 13 RCTs and cluster-RCTs | |
| | PTB3 | RR: 0.93 (0.84, 1.03) vs. control4 | | |
| Association between birth outcome and NCD risk factor | BW | TC | No recent high-quality meta-analysis availableKnop et al. (6) | |
| | SBP, hypertension | MD: −1.36 (−1.62, −1.09) per 1 kg BW HR: 0.77 (0.68, 0.88) per 1 kg BW | | |
| | Type 2 diabetes | HR: 0.78 (0.70, 0.87) per 1 kg BW | | |
| | LBW2 | TC | No recent high-quality meta-analysis available | | |
| | Hypertension | OR: 1.30 (1.16, 1.46) vs. not LBW | | |
| | Type 2 diabetes | OR: 1.45 (1.33, 1.59) vs. not LBW | | |
| | PTB3 | SBP | MD: 4.22 mm Hg (2.98, 5.45 mm Hg) vs. term | Markopoulou et al. (7) 8 retrospective, 29 longitudinal, 6 population-based studies |
| | Fasting plasma glucose | MD: 0.07 mmol/L (0.02, 0.13 mmol/L) vs. term |
| | TC | MD: 0.17 mmol/L (0.00, 0.34 mmol/L) vs. term |

1BW, birth weight; IFA, iron and folic acid; LBW, low birth weight; MD, mean difference; NCD, noncommunicable disease; PTB, preterm birth; RCT, randomized controlled trial; RD, risk difference; SBP, systolic blood pressure; TC, total cholesterol.

2Defined as birth weight < 2500 g.

3Defined as <37 weeks of gestation.

4Control: placebo or usual care.
| NCD risk factor                                      | NCD outcome | 35–39 | 40–44 | 45–49 | 50–54 | 55–59 | 60–64 | 65–69 | 70–74 | 75–79 | 80–84 | 85 or older | Reference          |
|-----------------------------------------------------|-------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|--------|------------------|
| Elevated systolic blood pressure (per 10 mmHg)      | IHD         | 1.68  | 1.56  | 1.45  | 1.33  | 1.26  | 1.14  | 1.26  | 1.14  | 1.10  |       | Singh et al. (47) |
|                                                     | Ischemic stroke | 2.05  | 1.83  | 1.63  | 1.44  | 1.28  | 1.10  |       |       |       |       |        |                   |
|                                                     | Hemorrhagic stroke | 2.11  | 1.89  | 1.66  | 1.46  | 1.29  | 1.10  |       |       |       |       |        |                   |
|                                                     | Hypertensive heart disease | 2.86  | 2.49  | 2.16  | 1.88  | 1.63  | 1.37  |       |       |       |       |        |                   |
|                                                     | Peripheral vascular disease | 1.25  | 1.14  | 1.14  | 1.15  | 1.15  | 1.15  | 1.16  | 1.16  | 1.10  | 1.10  |       | Forouzanfar et al. (48) |
|                                                     | Chronic kidney disease |       |       |       |       |       |       |       |       |       |       |        |                   |
| Elevated total cholesterol (per 1 mmol)             | IHD         | 2.20  | 1.82  | 1.44  | 1.27  | 1.18  | 1.30  |       |       |       |       |        | Singh et al. (47) |
|                                                     | Ischemic stroke | 1.71  | 1.41  | 1.20  | 1.08  | 1.03  | 0.92  |       |       |       |       |        |                   |
| Elevated fasting plasma glucose (per 1 mmol)        | IHD         | 1.21  | 1.19  | 1.18  | 1.16  | 1.16  | 1.14  |       |       |       |       |        |                   |
|                                                     | Stroke (any subtype) | 1.19  | 1.16  | 1.14  | 1.14  | 1.10  | 1.06  |       |       |       |       |        |                   |
| Diabetes (vs. no diabetes)                          | Peripheral vascular disease | 5.04  | 4.14  | 3.95  | 3.76  | 3.57  | 3.37  | 3.18  | 2.99  | 2.80  | 2.32  | 2.32  | Forouzanfar et al. (48) |
|                                                     | Chronic kidney disease |       |       |       |       |       |       |       |       |       |       |        |                   |
|                                                     | Colorectal cancer | 1.39  |       |       |       |       |       |       |       |       |       |        |                   |
|                                                     | Breast cancer | 1.20  |       |       |       |       |       |       |       |       |       |        |                   |
|                                                     | Intrahepatic | 1.97  |       |       |       |       |       |       |       |       |       |        |                   |
|                                                     | Cholangiocarcinoma |       |       |       |       |       |       |       |       |       |       |        |                   |
|                                                     | Endometrial cancer |       |       |       |       |       |       |       |       |       |       |        |                   |

1 IHD, ischemic heart disease; NCD, noncommunicable disease.
caused by the selected NCD risk factors: ischemic heart disease (IHD), stroke, hypertensive heart disease (HHD), chronic kidney disease (CKD), peripheral vascular disease (PVD), and selected cancers (colorectal, breast, intrahepatic cholangiocarcinoma, or endometrial cancer).

**Data sources**

**Scoping review.**

We conducted a scoping review for each pathway (Figure 1) and extracted effect estimates for model parameterization (Tables 1 and 2). The search was conducted on PubMed and restricted to results denoted as meta-analyses. The following search terms were used and returned 947 results.

("Infant, Low Birth Weight"[Mesh] OR “Birth Weight”[Mesh] OR “Infant, Small for Gestational Age”[Mesh] OR “Infant, Premature”[Mesh] OR “Diarrhea, Infantile”[Mesh] OR “Diarrhea”[Mesh] OR “Low Birth Weight”[tiab] OR “Birth Weight”[tiab] OR “Small for Gestational Age”[tiab] OR “Small-for-Gestational”[tiab] OR “preterm”[tiab] OR “Premature”[tiab] OR “Stunt”[tiab] OR “Diarrhea”[tiab]) AND (“Hypertension”[Mesh] OR “Blood Pressure”[Mesh] OR “Arterial Pressure”[Mesh] OR “Hyperlipidemias”[Mesh] OR “Body Mass Index”[Mesh] OR “Body weight”[Mesh] OR “Obesity”[Mesh] OR “Overweight”[Mesh] OR “Diabetes Mellitus”[Mesh] OR “Hyperglycemia”[Mesh] OR “Hypertension”[tiab] OR “Blood Pressure”[tiab] OR “Arterial Pressure”[tiab] OR “lipid disorder”[tiab] OR “Hyperlipidemia”[tiab] OR cholesterol [tiab] OR hypercholesterolemia[tiab] OR “Body Mass Index”[tiab] OR “Body weight”[tiab] OR “Obesity”[tiab] OR “Overweight”[tiab] OR “Diabetes”[tiab] OR “Hyperglycemia”[tiab] OR “blood sugar”[tiab] OR “blood glucose”[tiab]).

All 947 results were screened for relevancy by title and abstract. The search was also evaluated to make sure it included key seminal meta-analyses independently suggested for inclusion. Where multiple meta-analyses presented effect estimates for the same parameter (link in analytic diagram), the highest-quality meta-analysis was selected. If no meta-analysis of high quality was identified, the pathway was removed from the analytic model and the relation was not quantified in this analysis. An example of this was modeling the impact from the analytic model and the relation was not quantified on each NCD outcome using the following relation, which was used to quantify the proportion of deaths attributable to changes in coverage. $P_i$ is the baseline coverage and $P_i'$ is the counterfactual coverage, and $RR_i$ is the relative risk of LBW or PTB for each supplementation intervention. The percentage point reduction in LBW and PTB in each birth cohort was then estimated as the product of the PIF and the current levels of these birth outcomes in each country.

Second, we estimated the proportion of diabetes and hypertension cases that could be averted owing to the estimated reduction in LBW and PTB using the same PIF formula. Lastly, we converted these to risk ratios or ORs per unit of exposure using mean difference in the continuous risk factor (e.g., FPG) between the 2 comparison groups in a recent large population health survey in the same GBD region (see the list of these regions in Supplemental Table 2). We converted glycated hemoglobin (HbA1c) to FPG where the latter was missing using a regression model developed and validated previously.

We estimated the combined effect of multiple NCD risk factors on each NCD outcome using the following relation, which incorporates multicausality and avoids double-counting deaths delayed owing to improvement in multiple risk factors:

$$\text{PIF}_{joint} = 1 - (1 - \text{PIF}_{SBP})(1 - \text{PIF}_{TC})(1 - \text{PIF}_{FPG})$$

where $\text{PIF}_{joint}$ denotes the proportion of deaths attributable to reductions in blood pressure, TC, and FPG corresponding to
a given supplement-coverage scenario. The absolute reduction in annual NCD deaths was estimated by multiplying the joint impact fraction and the number of deaths observed for each age-sex-cause in each country. This assumes no correlation between risk factors; because a positive correlation between SBP and TC is likely, this assumption may lead to underestimating their joint effect and therefore more conservative estimates. Attributable deaths were summed over all ages and all causes of death. We used PIFs for each age-sex group and the 2015–2020 life tables for each country to calculate years of life gained from supplementation (36). Impacts per 1,000,000 children were estimated by dividing the number of deaths delayed by the average yearly birth cohort size of the period 2015–2020 (36) (Figure 3). Table 3 presents the proportion of all-cause mortality and aggregate deaths delayed, and years of life gained by region. Supplemental Text 1 gives a numerical example of the estimations.

Reduction in cases and prevalence of hypertension and diabetes through the calcium intervention had to be estimated using a semiparametric method, because effect estimates were only available for reductions in mean blood pressure and plasma glucose for children born preterm compared with term. We conducted a sensitivity analysis for the effect of MMS through both continuous birth weight and LBW (Supplemental Table 3), and report results for the more conservative pathway.

Results

Our model suggests an annual 0.30%–0.35% of deaths caused by NCDs across the 132 LMICs considered could have been delayed through MMS or calcium supplementation at 90% coverage; 0.15%–0.16% of relevant NCD deaths could have been delayed per birth had mothers been supplemented with IFA at 90%. There was noticeable variation in the effect of IFA and MMS across regions, with slightly more than 0.7% of annual NCD deaths delayed from MMS in South Asia compared with only 0.16%–0.19% in Central and Eastern Europe and Central Asia. Regional impact of IFA followed a similar pattern. For calcium, variation across regions was smaller, ranging from 0.22% to 0.52%.

Globally, 0.13%–0.14% of all deaths could have been delayed per birth cohort through MMS or calcium supplementation scaled to 90%; 0.07% of all-cause annual deaths could be delayed per birth cohort by supplementing IFA to their mothers at 90% coverage (Table 3). These translate to 294,000 y of life that would have been gained per birth cohort by scaling up prenatal supplementation coverage to 90% in 132 LMICs.

### Table 3

Annual sex-specific proportions of relevant and all-cause deaths delayed in the offspring cohort by scaling up prenatal supplementation coverage to 90% in 132 LMICs

| Continent                          | IFA  | MMS  | Calcium |
|------------------------------------|------|------|---------|
| Central and Eastern Europe and Central Asia | 0.09 | 0.16 | 0.23 |
| East and Southeast Asia and Oceania | 0.08 | 0.17 | 0.22 |
| Latin America and the Caribbean    | 0.11 | 0.19 | 0.31 |
| Middle East and North Africa       | 0.10 | 0.15 | 0.26 |
| Sub-Saharan Africa                 | 0.08 | 0.17 | 0.32 |
| South Asia                         | 0.07 | 0.25 | 0.40 |
| All 132 LMICs                      | 0.06 | 0.30 | 0.52 |

| Sex   | IFA  | MMS  | Calcium |
|-------|------|------|---------|
| Men   | 0.09 | 0.16 | 0.23   |
| Women | 0.08 | 0.17 | 0.22   |

Relevant NCD deaths include ischemic heart disease, other coronary heart disease, hypertensive heart disease, chronic kidney disease, peripheral vascular disease, and cancer (colorectal, breast, intrahepatic cholangiocarcinoma, or endometrial). IFA, iron and folic acid; LMIC, low- and middle-income country; MMS, multiple micronutrients; NCD, noncommunicable disease.
Intergenerational effects of prenatal nutrition

FIGURE 2  Annual relevant deaths delayed in the offspring cohort by scaling up prenatal supplementation coverage to 90% in 132 low- and middle-income countries. Cancers included colorectal, breast, intrahepatic cholangiocarcinoma, or endometrial cancer. CA, calcium; IFA, iron and folic acid; MMS, multiple micronutrients.

of the deaths delayed (Figure 2). Results were similar across sex except for slightly higher attributable proportions for males than for females in South Asia (Supplemental Figure 4 presents sex-specific results). Owing to population size, the estimated total deaths delayed and the number of years of life saved were highest in South Asia and far outweighed deaths delayed in Sub-Saharan Africa, despite comparable proportions of NCD deaths that could be delayed. In fact, 37% of all years of life gained across LMICs were from South Asia followed by 31% from East and Southeast Asia and Oceania. Regional patterns in percentage point reductions in the prevalence of hypertension and diabetes were similar to that of NCD mortality (Table 4). Here again, the size of the diabetic and hypertensive population in South Asia led to a much higher number of cases of diabetes and hypertension in this region that were estimated to be averted by scaling up the 3 interventions. Indeed, 33% of averted cases of hypertension across all LMICs and 42% of averaged cases of diabetes were estimated to be from South Asia.

Globally, prenatal supplementation with MMS was estimated to reduce the prevalence of hypertension by 1.2 and diabetes by 1.6 percentage points in the offspring, corresponding to 6 million cases of hypertension and 3 million cases of diabetes averted per birth cohort. Impacts of IFA were consistently half of the impacts of MMS: 2.7 million cases of hypertension and 1.5 million cases of diabetes averted per birth cohort (Table 4). Calcium supplementation yielded 4 million cases of hypertension and 0.5 million cases of diabetes averted per birth cohort. The effect of calcium supplementation on reductions in SBP and FPG was small (4.22 mm Hg and 0.07 mmol/L, respectively) and therefore reductions in diabetes and hypertension prevalence were lower than those for IFA and MMS. For prevalence of hypertension, the estimated effect of calcium was similar to that of IFA, and roughly half of the impact of MMS. For prevalence of diabetes, the impact from calcium supplementation was roughly one-tenth of that of MMS.

The benefit to the individual child in terms of deaths delayed was highest in Eastern Europe and Central Asia, India, and certain sub-Saharan African countries (Figure 3). For example, in Bulgaria and Ukraine prenatal calcium supplementation could delay ~5000 deaths per million children born. Benefits per individual were also moderately high in Latin America and the Caribbean (~1500 deaths per million children born).

Discussion

Globally, we estimated that 51,000 NCD-related deaths (or 0.14% of all-cause mortality) could have been delayed per cohort of 127 million live births and 6 million cases of hypertension and 3 million cases of diabetes could have been averted if 90% of expecting mothers received prenatal MMS; the impact of scaling calcium supplementation to 90% was similar (51,000 deaths delayed per birth cohort), whereas through IFA it was roughly half (24,000 deaths delayed per birth cohort). This corresponds to ~294,000 y of life gained for IFA, compared with 630,000 for MMS and 673,000 for calcium. In comparison, the impact of calcium or MMS supplementation at scale prenatally is equivalent to nearly half of the all-cause mortality attributable to high consumption of sugar-sweetened beverages in LMICs (0.32% of all deaths) estimated by the GBD (1). In sub-Saharan Africa, proportional benefits were twice the global average owing to high prevalence of LBW and PTB; and in South Asia, the benefits were even larger owing to the combination of high prevalence of LBW and PTB combined with higher prevalence of NCD risk factors (1). In comparison, the burden of LBW and...
| Supplement | Central and Eastern Europe and Central Asia | East and Southeast Asia and Oceania | Latin America and the Caribbean | Middle East and North Africa | South Asia | Sub-Saharan Africa | All 132 LMICs |
|------------|------------------------------------------|-----------------------------------|--------------------------------|-----------------------------|------------|------------------|--------------|
| Sex        | F    | M    | F    | M    | F    | M    | F    | M    | F    | M    | F    | M    | F    | M    | F    | M    |
| Attributable reduction in prevalence of hypertension, % | | | | | | | | | | | | | | | | | |
| IFA        | 0.22 | 0.22 | 0.20 | 0.19 | 0.25 | 0.24 | 0.45 | 0.44 | 0.70 | 0.70 | 0.56 | 0.56 | 0.53 | 0.53 |
| MMS        | 0.38 | 0.38 | 0.45 | 0.43 | 0.51 | 0.51 | 0.80 | 0.79 | 1.56 | 1.57 | 1.03 | 1.03 | 1.15 | 1.15 |
| Calcium    | 0.37 | 0.40 | 0.43 | 0.46 | 0.53 | 0.58 | 0.51 | 0.60 | 0.59 | 0.67 | 0.51 | 0.65 | 0.49 | 0.55 |
| Cases of hypertension averted, n | | | | | | | | | | | | | | | | | |
| IFA        | 80,800 | 70,900 | 231,800 | 236,700 | 81,000 | 83,200 | 88,900 | 79,000 | 724,500 | 728,100 | 208,300 | 172,100 | 1,415,200 | 1,370,000 |
| MMS        | 140,300 | 123,200 | 511,800 | 520,200 | 168,000 | 172,500 | 164,800 | 146,600 | 1,638,700 | 1,645,000 | 409,500 | 338,500 | 3,033,100 | 2,946,000 |
| Calcium    | 141,100 | 131,600 | 615,100 | 701,000 | 182,700 | 210,100 | 136,800 | 145,800 | 624,800 | 703,400 | 224,800 | 238,000 | 1,925,200 | 2,129,900 |
| Attributable reduction in prevalence of diabetes, % | | | | | | | | | | | | | | | | | |
| IFA        | 0.33 | 0.33 | 0.28 | 0.26 | 0.36 | 0.36 | 0.57 | 0.60 | 1.02 | 1.02 | 0.79 | 0.80 | 0.73 | 0.75 |
| MMS        | 0.57 | 0.58 | 0.63 | 0.58 | 0.74 | 0.74 | 1.04 | 1.08 | 2.26 | 2.26 | 1.47 | 1.49 | 1.59 | 1.63 |
| Calcium    | 0.14 | 0.15 | 0.13 | 0.13 | 0.14 | 0.15 | 0.12 | 0.14 | 0.30 | 0.28 | 0.11 | 0.08 | 0.17 | 0.17 |
| Cases of diabetes averted, n | | | | | | | | | | | | | | | | | |
| IFA        | 42,700 | 31,600 | 138,000 | 152,300 | 61,200 | 49,900 | 77,000 | 69,900 | 373,400 | 416,400 | 71,200 | 66,100 | 763,400 | 786,100 |
| MMS        | 74,000 | 54,500 | 303,500 | 333,100 | 127,000 | 103,200 | 144,300 | 130,600 | 840,500 | 936,900 | 143,700 | 131,000 | 1,633,000 | 1,690,200 |
| Calcium    | 19,400 | 14,900 | 81,100 | 90,200 | 23,100 | 21,700 | 21,600 | 22,000 | 112,700 | 117,400 | 12,300 | 7600 | 270,200 | 273,900 |

1 Percentage reductions are weighted by number of noncommunicable disease deaths by country/age/sex. Cases are rounded to the nearest 100. IFA, iron and folic acid; LMIC, low- and middle-income country; MMS, multiple micronutrients.
PTB was low in Central and Eastern Europe and Central Asia leading to a small proportional effect for supplements per birth cohort. Estimated benefits per child were generally higher for countries with either a high burden of NCDs, a high burden of maternal anemia and adverse birth outcomes, or a combination of both. When considering the potential benefit per child, we estimated that ≤5 deaths per 1000 children could be delayed by MMS and calcium supplementation in Central and Eastern Europe and Central Asia. However, the reader should note that although this region has small birth cohorts and the absolute
impacts are correspondingly small, this finding illustrates how there are notable impacts of scaling up prenatal supplements even in epidemiologically advanced LMICs with lower burdens of maternal and child mortality. This phenomenon is due to the large proportion of deaths that are due to NCDs [57% in Central and Eastern Europe and Central Asia in 2019 (1)].

Our results likely represent a lower bound of the true intergenerational impact of prenatal micronutrient supplements. We quantified the effect as mediated through reductions in adverse birth outcomes, rather than a longer-term follow-up of a supplementation trial or pregnancy cohort. Our analysis does not factor in that supplementation at higher coverages is likely to have more efficient delivery mechanisms than lower coverages and may provide opportunities for added check-ups at the point of contact. Further, as countries progress through the epidemiologic transition, the burden of NCDs will most likely rise in LMICs, and the proportion of deaths that could have been delayed per birth cohort may rise accordingly. In addition, given that children born to supplemented females are less likely to die from LBW or PTB, more of these children will survive and live to experience the benefits of lower NCD risk. We did not incorporate this survival effect into our estimates. Lastly, there may be additional benefits of prenatal supplements on NCDs for the mother herself which we did not quantify here. For example, calcium has been shown to reduce the risk of pre-eclampsia, and the latter is associated with future risk of systemic hypertension (5).

This is the first study that we know of to quantify the population-level effect of prenatal nutritional supplements on NCDs in adult offspring. Only 1 observational study has addressed this question and it reported that reductions in nutrients available during pregnancy led to higher risk of cardiovascular disease in the offspring, but the dietary estimates were based on recall (37). The intergenerational effects quantified in our work may be explained by a general maladaptation response that occurs when there is a mismatch between the nutritional environment in utero and the environment in which the offspring grows (38). Several pathways have been proposed to explain this maladaptive response: hormonal changes, epigenetic gene regulation, and restricted fetal growth and development (39). For instance, prenatal folate deficiency plays a central role in DNA methylation, which has been linked to insulin resistance and raised blood pressure in adult offspring in animal models (40). Lastly, micronutrient deficiencies may impair organ development, for instance owing to tissue damage from inadequate oxygenation in the case of moderate to severe anemia, leading to increased oxidative stress. In animal models, a notable postnatal rise in SBP was found in offspring exposed to maternal anemia during pregnancy (41).

Our study has several strengths and limitations. We present the first set of consistent and comparable estimates of the effect of prenatal supplements on offspring NCD risk. We used recent and high-quality meta-analyses and included 132 LMICs that had sufficient data. We used data from large-scale global pooling of health surveys for birth outcomes, NCD risk factors, and NCD outcomes. Each of the data sources was the result of a rigorous effort to procure representative data conducted by independent research networks with whom we collaborate. Lastly, we systematically accounted for and incorporated rigorous evidence for potential pathways from supplementation to NCD and conducted sensitivity analyses. Effect estimates for the impact of LBW and PTB on NCD risk factors were obtained from meta-analyses of studies mostly conducted in high-income countries (98%, 92%, and 63%), and the estimates may not be directly transportable to LMICs (e.g., the pattern of confounding may differ from that of the countries of interest in this analysis). However, in our scoping review we found meta-analyses that had higher LMIC representation but were of lower quality, and their effect estimates were of a similar magnitude, suggesting that our extrapolation was reasonable. We did not estimate uncertainty for our model because comparative risk assessment CIs are limited to quantifying parameter uncertainty alone. Parameter uncertainty, however, would be substantially less than the modeling uncertainty, which is unquantifiable. Data on impact of supplements on LBW and PTB prevalence were not available by sex. Therefore, we estimated sex differences through variations in NCD risk factor prevalence and NCD deaths. Previous studies have reported potential sex differences in the effect of supplements on LBW and PTB outcomes (3). Therefore, we may have underestimated sex differentials. We did not project trends in morbidity and mortality for NCDs. However, as the NCD burdens for most of the countries included in our analysis are on the rise, our results are likely conservative estimates of what current birth cohorts stand to gain from prenatal supplementation.

The 2008 Lancet Nutrition series draws on data from several birth cohorts and suggests that higher birth weights are associated with higher BMI in adults (42), which would go against the hypothesis that increasing birth weight through maternal nutrition interventions would only have a positive impact on NCDs. We did not parameterize this relation in our model because we did not identify any meta-analyses that met our quality criteria (Supplemental Table 1). However, the impact of birth weight on adult BMI has been estimated at a 0.87-kg/m² increase in adult BMI per 1-kg increase in birth weight (42). We have observed that higher birth weight leads to lower SBP, TC, and FPG: 46% of the effect of BMI on IHD and 76% of the effect of BMI on stroke are mediated through SBP, TC, and FPG (43). Therefore, the impact of higher birth weight on adult BMI would be largely offset through the beneficial effects of higher birth weight on SBP, TC, and FPG.

According to the WHO’s Global Action Plan for the Prevention and Control of Noncommunicable Diseases, nutrition and nutrition-related outcomes are key targets for the control and prevention of NCDs (9). Among nutrition interventions, benefits of prenatal micronutrient supplements go beyond improving child survival and human capital and include noticeable improvements in long-term NCD risk in the offspring generation. And, although impacts are small per person, the intergenerational benefits of prenatal supplementation scale up at the population level. Furthermore, micronutrients are not the only form of prenatal supplementation that might affect later health (44). Future work by our research group aims to examine the impact of protein energy supplementation and other nutritional interventions in the first 1000 d. This implies a triple benefit from investing in prenatal supplements in most LMICs, including first-order effects on fetal and infant morbidity and mortality, second-order effects on neurodevelopment and long-term schooling and earning potential, and potential third-order effects on NCD risk factors and NCD mortality in the next generation quantified here.
Nutrition interventions are key contributors to the progress toward the Sustainable Development Goals (SDGs), aiming to end poverty, protect the planet, and improve the lives and prospects of everyone by 2030 (45). Highlighting the additional benefits of proven nutrition interventions, especially those with the potential to address short-, medium-, and long-term nutrition and health outcomes, is critical in ensuring adequate and sustained investments by governments and donors, attention by policy makers, and programmatic integration to improve coverage for those most in need. As the double burdens of disease and malnutrition are on the rise, clinical and public health efforts to scale up prenatal micronutrient supplementation should be prioritized and may be presented as double- or even triple-duty actions. Investments in nutrition and toward addressing NCDs can potentially be one and the same if channeled toward evidence-based, proven, double-duty and triple-duty actions.

We thank Lily Bliznashka for her input on the analysis. The authors’ responsibilities were as follows—MMB and GD: conceptualized and designed the study; MMB: conducted the literature search, data curation, formal analysis, visualization, and data interpretation, wrote the original manuscript, and is responsible for the design, writing, and final content of the manuscript; WWF, MCC, AT, and MA: contributed to the study conceptualization; WWF and MCC: contributed to supervision; WWF, MCC, AT, MA, and GD: reviewed and edited the manuscript; AT and MA: contributed to funding acquisition; AT: contributed to the project administration; GD: supervised the project; and GD: all authors: read and approved the final manuscript.

Data Availability
All data used are publicly available and accessible through the sources referenced in the article, except for the estimates obtained from correspondence with the NCD-RisC. Baseline coverage of IFa was derived from the most recent Demographic and Health Surveys in each country. Impacts of MMS on the risk of LBW were derived from a meta-analysis (3). Prevalence of LBW and PTB were extracted from global pooling models (30–32). The numbers of annual deaths from NCDs by country, age, and sex were derived from the GBD Study (1). Prevalence of diabetes numbers of annual deaths from NCDs by country, age, and sex were derived from the NCD-RisC (33,34).

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