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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.

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Supplemental Tables 1–3, Supplemental Figures 1–4, Supplemental Country Profiles, and Supplemental Text 1 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

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Abbreviations used: FPG, fasting plasma glucose; GBD, Global Burden of Disease; IFA, iron and folic acid; IHD, ischemic heart disease; LBW, low birth weight; LMIC, low- and middle-income country; MMS, multiple micronutrients; NCD, noncommunicable disease; NCD-RisC, NCD Risk Collaboration; PTB, preterm birth; SBP, systolic blood pressure; SGA, small for gestational age; TC, total cholesterol.

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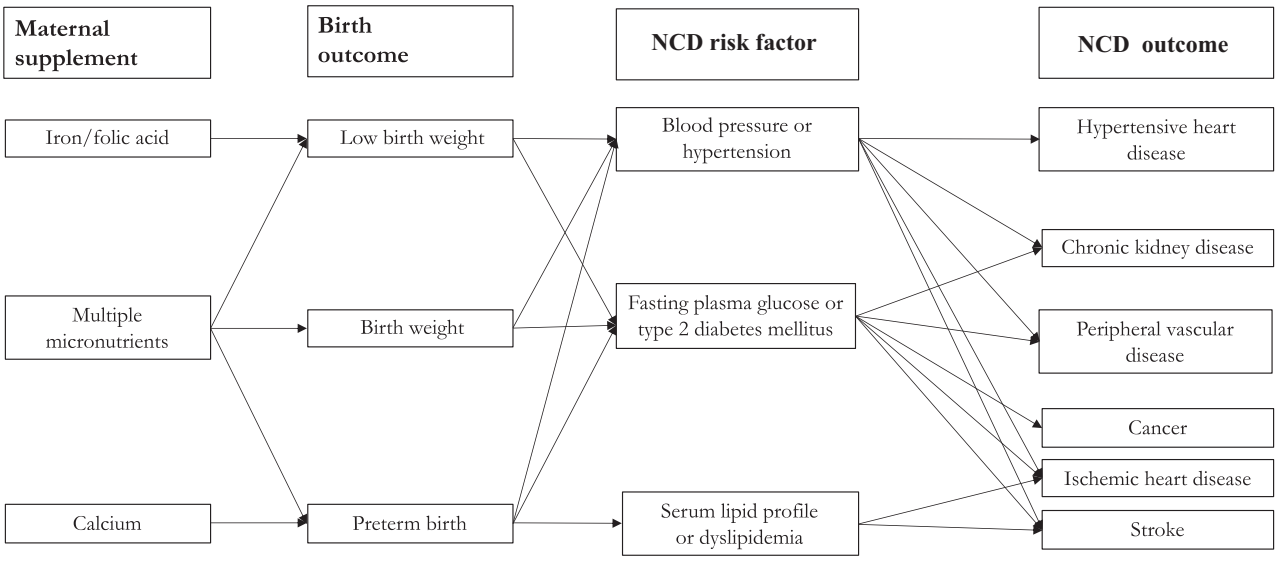

FIGURE 1 Analysis pathways for the relation between prenatal supplementation and NCD. Cancers included colorectal, breast, intrahepatic cholangiocarcinoma, or endometrial cancer. NCD, noncommunicable disease.

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 birth weight (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 $<10^{th}$ 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	
			Meta-analysis	WHO supplementation guidelines
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 At least 3 micronutrients, any gestational age at randomization Anemic vs. not anemic at baseline	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
	LBW[2]	RR: 0.81 (0.74, 0.89) vs. IFA for anemic mothers RR: 0.91 (0.82, 0.98) vs. IFA for nonanemic mothers		
	PTB[3]	RR: 0.93 (0.87, 0.98) vs. IFA (regardless of maternal anemia)		
IFA	BW	MD: 23.75 (−3.02, 50.51) vs. control[4]	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
	LBW[2]	RR: 0.84 (0.69, 1.03) vs. control[4]		
	PTB[3]	RR: 0.93 (0.84, 1.03) vs. control[4]		
Calcium	BW	MD: 85.75 g (37.91, 133.58 g) vs. control[4]	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
	LBW[2]	RR: 0.85 (0.72, 1.01) vs. control[4]	Hofmeyr et al. (5) 13 RCTs and cluster-RCTs	
	PTB[3]	RR: 0.76 (0.60, 0.97) vs. control[4]		
Association between birth outcome and NCD risk factor				
BW	TC	No recent high-quality meta-analysis availableKnop et al. (6)	Knop et al. (6) 36 cohorts, 3–8 case-control, 5–15 cross-sectional	
	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		
LBW[2]	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		
PTB[3]	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		

[1]BW, 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.

[2]Defined as birth weight < 2500 g.

[3]Defined as <37 weeks of gestation.

[4]Control: placebo or usual care.

TABLE 2 Effect sizes for association between NCD risk factors and NCD deaths by age in years[1]

		Effect size by age, y											
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 mm Hg)	IHD	1.68		1.56		1.45		1.33		1.26		1.14	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	1.15	1.14	1.10	1.10	Forouzanfar et al. (48)
	Chronic kidney disease						1.28						
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						1.39						
	Colorectal cancer						1.20						Tsilidis et al. (49)
	Breast cancer						1.20						
	Intrahepatic cholangiocarcinoma						1.97						
	Endometrial cancer						1.97						

[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 "Growth Disorders"[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 of prenatal supplementation through being born SGA (birth weight $<10^{th}$ percentile of gestational age and sex relative to the standard reference population). All relevant meta-analyses' quality was assessed using a modified version of the AMSTAR-2 (A MeaSurement Tool to Assess systematic Reviews-2) tool (29), accounting for total sample size, LMIC representation, assessment of heterogeneity and/or publication bias, confounder adjustments, and subgroup analyses for exposure and outcome measurements (**Supplemental Figure 1**, **Supplemental Table 1**) to ensure that the associations in the meta-analyses are not prone to the most common sources of bias and can be used in lieu of experimental or causal effect estimates. **Supplemental Figures 2** and **3** present forest and funnel plots for the meta-analyses not excluded.

We assumed no coverage of supplementation for MMS and CA because these interventions have not been scaled up in LMICs. Baseline coverage of IFA was derived from the most recent Demographic and Health Surveys in each country. The effect of MMS on the risk of LBW was allowed to vary between anemic and nonanemic mothers (3). Prevalence of LBW and PTB in 2015 were extracted from global pooling models (30, 31). For 36 countries, 2015 LBW prevalence was unavailable and 2010 estimates were used instead (32). For 5 countries (Equatorial Guinea, Fiji, Georgia, Palestine, and South Sudan), prevalence of LBW was not available, and was imputed using the GBD subregion average (**Supplemental Country Profiles**). The numbers of annual deaths from NCDs by country, age (5-y age groups starting at age 35 y), and sex were derived from the GBD project for the most recent year available (2017) (1). Prevalence of diabetes (2014) and hypertension (2015) were derived from the NCD Risk Collaboration (NCD-RisC) (33, 34). All input data are provided in Table 1 and in each Supplemental Country Profile.

Statistical analysis.

First, we quantified the proportional reduction in the prevalence of LBW and PTB using the current coverage, target coverage, and RRs for the effect of prenatal supplements on LBW or PTB using the following PIF estimator:

$$\text{PIF} = \frac{\sum P_i \text{RR}_i - \sum P_i' \text{RR}'}{\sum P_i \text{RR}_i} \quad (1)$$

where PIF is the proportion of an outcome 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, for each country-age-sex group, we estimated the proportional reduction (i.e., PIF) in NCD deaths due to estimated reductions in diabetes/fasting plasma glucose (FPG), hypertension/systolic blood pressure (SBP), or total cholesterol (TC) using age-specific RRs for each outcome separately. When risk ratios or ORs were only available for a dichotomous definition of an NCD risk factor (e.g., diabetes compared with not diabetes), 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 (35).

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:

$$\text{PIF}_{\text{joint}} = 1 - (1 - \text{PIF}_{\text{SBP}})(1 - \text{PIF}_{\text{TC}})(1 - \text{PIF}_{\text{FPG}}) \quad (2)$$

where $\text{PIF}_{\text{joint}}$ 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 through IFA supplementation scaled to 90%, compared with 630,000 for MMS and 673,000 for calcium for the 127,446,400 children born in 2015. The magnitude of estimated impact was approximately proportional to the target coverage with estimates at 50% being nearly half of those at a target level of 90% coverage (see Supplemental Country Profiles for results at each coverage level). The impact estimates were similar by sex.

Across all 132 LMICs, a total of 24,000 deaths were estimated to be delayed owing to IFA supplementation, 51,000 deaths delayed owing to MMS, and 51,000 deaths delayed owing to calcium per pregnancy cohort supplemented (127,446,400 children; **Figure 2**). About 50% of deaths delayed were from IHD and ∼30% were from stroke. Cancers made up 1%–2%

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[1]

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
Attributable percentage of relevant NCD deaths delayed														
IFA	0.09	0.11	0.08	0.08	0.09	0.09	0.18	0.16	0.31	0.34	0.25	0.24	0.15	0.16
MMS	0.16	0.19	0.17	0.17	0.18	0.19	0.34	0.29	0.71	0.77	0.51	0.48	0.32	0.34
Calcium	0.23	0.31	0.22	0.25	0.26	0.32	0.38	0.43	0.46	0.52	0.38	0.43	0.30	0.35
Attributable percentage of all-cause deaths delayed														
IFA	0.06	0.06	0.04	0.04	0.03	0.03	0.10	0.08	0.11	0.12	0.08	0.06	0.07	0.07
MMS	0.10	0.10	0.08	0.08	0.07	0.06	0.19	0.15	0.25	0.28	0.16	0.11	0.14	0.14
Calcium	0.15	0.16	0.11	0.12	0.10	0.11	0.22	0.22	0.16	0.19	0.11	0.10	0.13	0.14
Years of life gained														
IFA	9700	10,800	26,700	34,700	6500	6900	10,400	11,100	64,500	86,000	14,000	12,900	131,800	162,300
MMS	16,800	18,800	58,600	76,200	13,700	14,400	19,200	20,700	144,900	193,000	28,200	25,600	281,300	348,700
Calcium	27,300	34,100	85,200	123,000	22,100	26,400	24,900	34,000	103,300	143,800	23,800	25,300	286,600	386,700

[1]Relevant NCD deaths include ischemic heart disease, stroke (any subtype), 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.

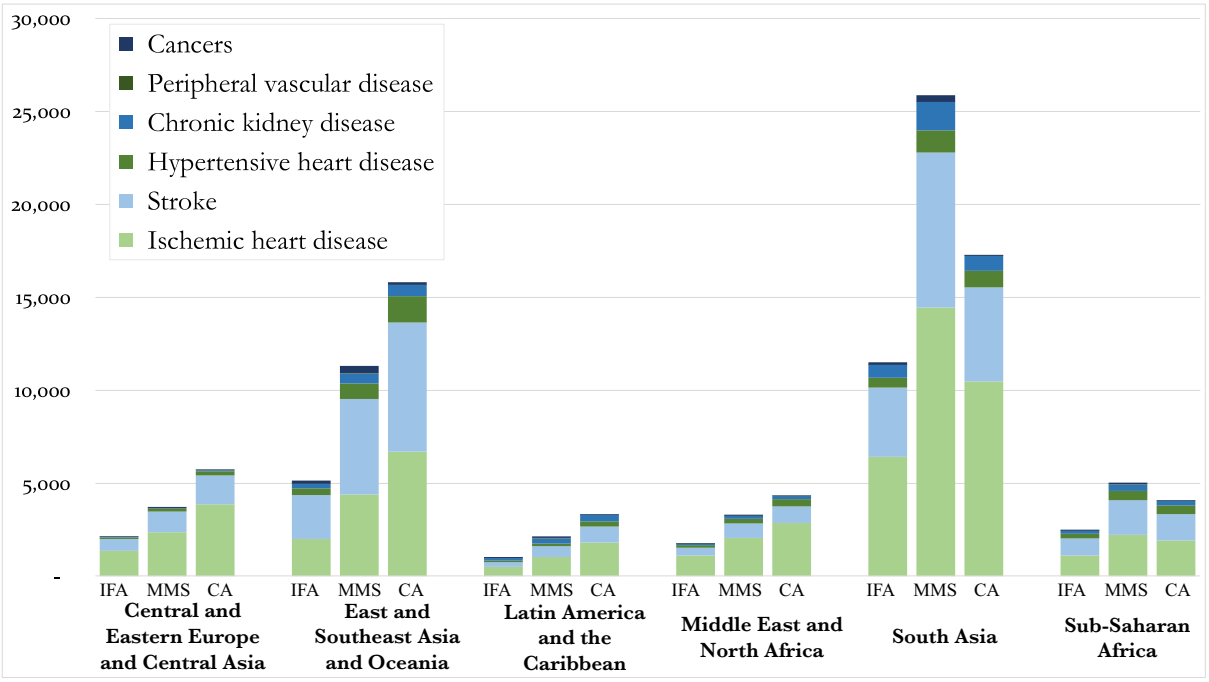

FIGURE 2 Annual relevant deaths delayed in the offspring cohort by scaling up prenatal supplementation coverage to 90% in 132 low- and middle-income countries. Cancers included colorectal, breast, intrahepatic cholangiocarcinoma, or endometrial cancer. CA, calcium; IFA, iron and folic acid; MMS, multiple 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 3.3 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

TABLE 4 Annual sex-specific proportions and cases of hypertension and diabetes averted in the offspring cohort by scaling up prenatal supplementation coverage to 90% in 132 LMICs[1]

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
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	0.13	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.

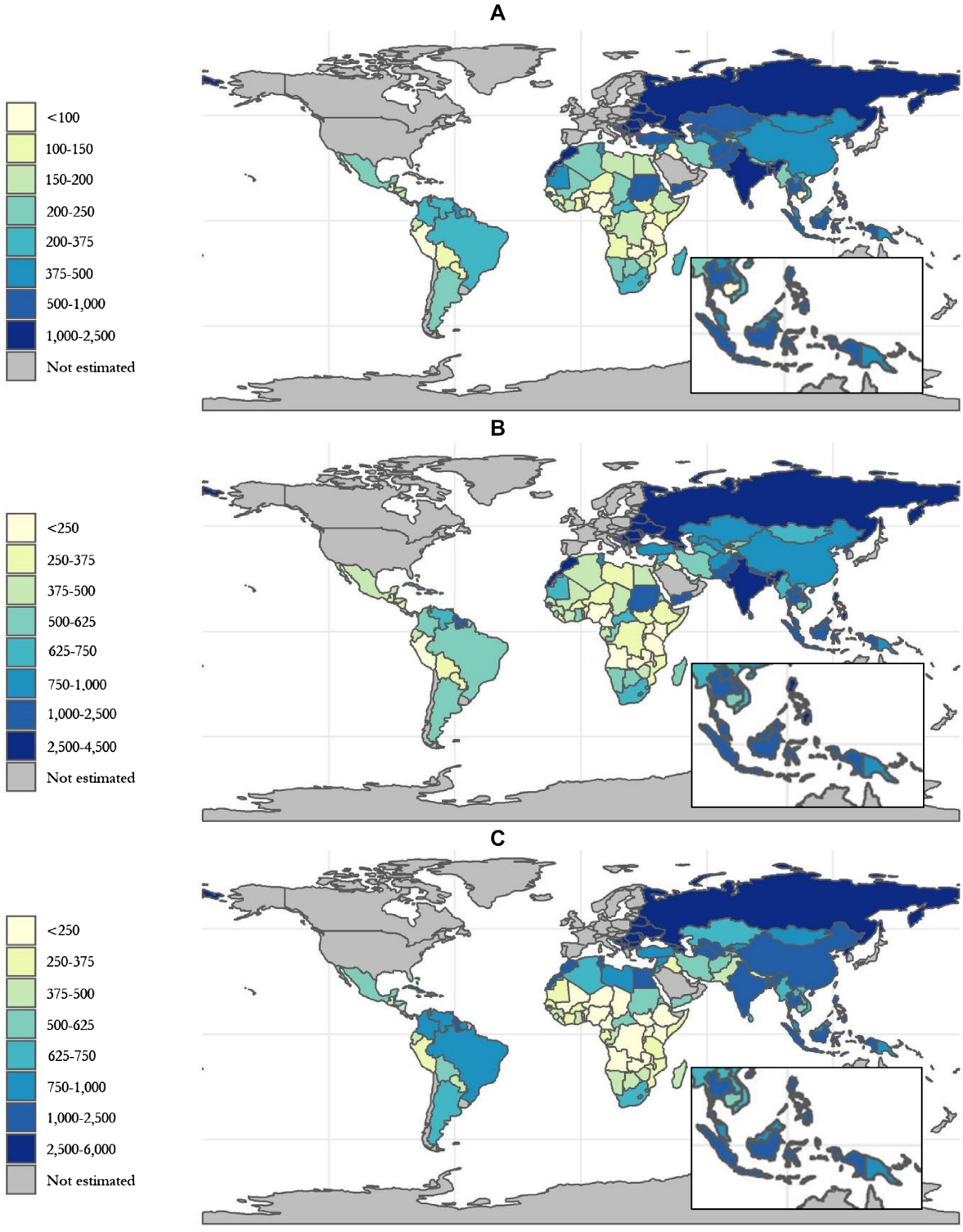

FIGURE 3 Annual deaths delayed per 1,000,000 children born to mothers supplemented at 90% with iron and folic acid (A), multiple micronutrients (B), and calcium (C).

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/m^2 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.

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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 and hypertension were derived from the NCD-RisC (33, 34).

References

1. Global Burden of Disease Collaborative Network. GBD results [Internet]. Seattle, WA: Institute for Health Metrics and Evaluation (IHME); 2020. Available from: http://ghdx.healthdata.org/gbd-results-tool. Last accessed July 1st 2021.
2. Hales CN, Barker DJP. The thrifty phenotype hypothesis. Br Med Bull 2001;60(1):5–20.
3. Smith ER, Shankar AH, Wu LS-F, Aboud S, Adu-Afarwuah S, Ali H, et al. Modifiers of the effect of maternal multiple micronutrient supplementation on stillbirth, birth outcomes, and infant mortality: a meta-analysis of individual patient data from 17 randomised trials in low-income and middle-income countries. Lancet Glob Health 2017;5(11):e1090–100.
4. Peña-Rosas JP, De-Regil LM, Garcia-Casal MN, Dowswell T. Daily oral iron supplementation during pregnancy. Cochrane Database Syst Rev 2015;(7):CD004736.
5. Hofmeyr GJ, Lawrie TA, Atallah ÁN, Torloni MR. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. Cochrane Database Syst Rev 2018;10(10):CD001059.
6. Knop MR, Geng T-T, Gorny AW, Ding R, Li C, Ley SH, et al. Birth weight and risk of type 2 diabetes mellitus, cardiovascular disease, and hypertension in adults: a meta-analysis of 7 646 267 participants from 135 studies. J Am Heart Assoc 2018;7(23):e008870.
7. Markopoulou P, Papanikolaou E, Analytis A, Zoumakis E, Siahanidou T. Preterm birth as a risk factor for metabolic syndrome and cardiovascular disease in adult life: a systematic review and meta-analysis. J Pediatr 2019;210:69–80.e5.
8. Stephenson J, Heslehurst N, Hall J, Schoenaker DAJM, Hutchinson J, Cade JE, et al. Before the beginning: nutrition and lifestyle in the preconception period and its importance for future health. Lancet 2018;391(10132):1830–41.
9. WHO. Global action plan for the prevention and control of noncommunicable diseases 2013–2020. Geneva, Switzerland: World Health Organization; 2013.
10. Pullar J, Wickramasinghe K, Demaio AR, Roberts N, Perez-Blanco K-M, Noonan K, et al. The impact of maternal nutrition on offspring's risk of non-communicable diseases in adulthood: a systematic review. J Glob Health 2019;9(2):020405.
11. Symonds ME, Gardner DS. Experimental evidence for early nutritional programming of later health in animals. Curr Opin Clin Nutr Metab Care 2006;9(3):278–83.
12. Kwong WY, Wild AE, Roberts P, Willis AC, Fleming TP. Maternal undernutrition during the preimplantation period of rat development causes blastocyst abnormalities and programming of postnatal hypertension. Development 2000;127(19):4195–202.
13. Fernandez-Twinn DS, Ekizoglou S, Wayman A, Petry CJ, Ozanne SE. Maternal low-protein diet programs cardiac β-adrenergic response and signaling in 3-mo-old male offspring. Am J Physiol Regul Integr Comp Physiol 2006;291(2):R429–36.
14. Hoppe CC, Evans RG, Moritz KM, Cullen-McEwen LA, Fitzgerald SM, Dowling J, et al. Combined prenatal and postnatal protein restriction influences adult kidney structure, function, and arterial pressure. Am J Physiol Regul Integr Comp Physiol 2007;292(1):R462–9.
15. Brennan KA, Olson DM, Symonds ME. Maternal nutrient restriction alters renal development and blood pressure regulation of the offspring. Proc Nutr Soc 2006;65(1):116–24.
16. Au Yeung SL, Lin SL, Li AM, Schooling CM. Birth weight and risk of ischemic heart disease: a Mendelian randomization study. Sci Rep 2016;6(1):38420.
17. Würtz P, Wang Q, Niironen M, Tynkkynen T, Tiainen M, Drenos F, et al. Metabolic signatures of birthweight in 18 288 adolescents and adults. Int J Epidemiol 2016;45(5):1539–50.
18. Küpers LK, Monnereau C, Sharp GC, Yousefi P, Salas LA, Ghantous A, et al. Meta-analysis of epigenome-wide association studies in neonates reveals widespread differential DNA methylation associated with birthweight. Nat Commun 2019;10(1):1893.
19. Hiller JE, Crowther CA, Moore VA, Willson K,Robinson JS . Calcium supplementation in pregnancy and its impact on blood pressure in children and women: follow up of a randomised controlled trial. Aust N Z J Obstet Gynaecol 2007;47(2):115–21.
20. Belizán JM, Villar J, Bergel E, del Pino A, Di Fulvio S, Galliano SV, et al. Long-term effect of calcium supplementation during pregnancy on the blood pressure of offspring: follow up of a randomised controlled trial. BMJ 1997;315(7103):281–5.
21. Ekström E-C, Lindström E, Raqib R, El Arifeen S, Basu S, Brismar K, et al. Effects of prenatal micronutrient and early food supplementation on metabolic status of the offspring at 4.5 years of age. The MINIMat randomized trial in rural Bangladesh. Int J Epidemiol 2016;45(5):1656–67.
22. Navarro E, Funtikova AN, Fíto M, Schröder H. Prenatal nutrition and the risk of adult obesity: long-term effects of nutrition on epigenetic mechanisms regulating gene expression. J Nutr Biochem 2017;39:1–14.
23. Palmer AC, Schulze KJ, Khatry SK, West KP. Prenatal and childhood exposures are associated with thymulin concentrations in young adolescent children in rural Nepal. J Dev Orig Health Dis 2020;11(2):127–35.
24. Taylor CM, Atkinson C, Penfold C, Bhattacharya S, Campbell D, Davey Smith G, et al. Folic acid in pregnancy and mortality from cancer and cardiovascular disease: further follow-up of the Aberdeen folic acid supplementation trial. J Epidemiol Community Health 2015;69(8):789–94.
25. Kumordzie SM, Adu-Afarwuah S, Arimond M, Young RR, Adom T, Boatin R, et al. Maternal and infant lipid-based nutritional supplementation increases height of Ghanaian children at 4–6 years

only if the mother was not overweight before conception. J Nutr 2019;149(5):847–55.
26. Stewart CP, Christian P, Schulze KJ, LeClerq SC, West KP Jr, Khatry SK. Antenatal micronutrient supplementation reduces metabolic syndrome in 6- to 8-year-old children in rural Nepal. J Nutr 2009;139(8):1575–81.
27. Mannan T, Ahmed S, Akhtar E, Roy AK, Haq MA, Roy A, et al. Maternal micronutrient supplementation and long term health impact in children in rural Bangladesh. PLoS One 2016;11(8):e0161294.
28. He S, Stein AD. Early-life nutrition interventions and associated long-term cardiometabolic outcomes: a systematic review and meta-analysis of randomized controlled trials. Adv Nutr 2021;12(2):461–89.
29. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ 2017;358:j4008.
30. Chawanpaiboon S, Vogel JP, Moller A-B, Lumbiganon P, Petzold M, Hogan D, et al. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. Lancet Glob Health 2019;7(1):e37–46.
31. Blencowe H, Krasevec J, de Onis M, Black RE, An X, Stevens GA, et al. National, regional, and worldwide estimates of low birthweight in 2015, with trends from 2000: a systematic analysis. Lancet Glob Health 2019;7(7):e849–60.
32. Lee ACC, Katz J, Blencowe H, Cousens S, Kozuki N, Vogel JP, et al. National and regional estimates of term and preterm babies born small for gestational age in 138 low-income and middle-income countries in 2010. Lancet Glob Health 2013;1(1):e26–36.
33. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19·1 million participants. Lancet 2017;389(10064):37–55.
34. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4·4 million participants. Lancet 2016;387(10027):1513–30.
35. Ito C, Maeda R, Ishida S, Sasaki H, Harada H. Correlation among fasting plasma glucose, two-hour plasma glucose levels in OGTT and HbA1c. Diabetes Res Clin Pract 2000;50(3):225–30.
36. United Nations Department of Economic and Social Affairs Population Division. In: Online Edition. Rev. 1. 2019. United Nations World Population Prospects 2019 Revision. https://population.un.org/wpp/Download/Standard/MostUsed/ last accessed June 2022
37. Bygren LO, Edvinsson S, Broström G. Change in food availability during pregnancy: is it related to adult sudden death from cerebro- and cardiovascular disease in offspring? Am J Hum Biol 2000;12(4):447–53.
38. Gluckman PD, Hanson MA, Low FM. Evolutionary and developmental mismatches are consequences of adaptive developmental plasticity in humans and have implications for later disease risk. Phil Trans R Soc B Biol Sci 2019;374(1770):20180109.
39. Christian P, Stewart C. Maternal micronutrient deficiency, fetal development, and the risk of chronic disease. J Nutr 2010;140(3):437–45.
40. Sinclair KD, Allegrucci C, Singh R, Gardner DS, Sebastian S, Bispham J, et al. DNA methylation, insulin resistance, and blood pressure in offspring determined by maternal periconceptional B vitamin and methionine status. Proc Natl Acad Sci U S A 2007;104(49):19351–6.
41. Crowe C, Dandekar P, Fox M, Dhingra K, Bennet L, Hanson MA. The effects of anaemia on heart, placenta and body weight, and blood pressure in fetal and neonatal rats. J Physiol 1995;488(2):515–19.
42. Victora CG, Adair L, Fall C, Hallal PC, Martorell R, Richter L, et al. Maternal and child undernutrition: consequences for adult health and human capital. Lancet 2008;371(9609):340–57.
43. The Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration (BMI Mediated Effects). Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: a pooled analysis of 97 prospective cohorts with 1·8 million participants. Lancet 2014;383(9921):970–83.
44. Ford ND, Behrman JR, Hoddinott JF, Maluccio JA, Martorell R, Ramirez-Zea M, et al., Exposure to improved nutrition from conception to age 2 years and adult cardiometabolic disease risk: a modelling study. Lancet Glob Health 2018;6(8):e875–84.
45. Lopez de Romaña D, Greig A, Thompson A, Arabi M. Successful delivery of nutrition programs and the sustainable development goals. Curr Opin Biotechnol 2021;70:97–107.
46. Imdad A, Bhutta ZA. Effects of calcium supplementation during pregnancy on maternal, fetal and birth outcomes. Paediatr Perinat Epidemiol 2012;26(s1):138–52.
47. Singh GM, Danaei G, Farzadfar F, Stevens GA, Woodward M, Wormser D, et al. The age-specific quantitative effects of metabolic risk factors on cardiovascular diseases and diabetes: a pooled analysis. PLoS One 2013;8(7):e65174.
48. GBD 2015 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016;388(10053):1659–724.
49. Tsilidis KK, Kasimis JC, Lopez DS, Ntzani EE, Ioannidis JPA. Type 2 diabetes and cancer: umbrella review of meta-analyses of observational studies. BMJ 2015;350:g7607.