### Title

Micronutrient deficiencies in pregnancy worldwide: health effects and prevention




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# Micronutrient deficiencies in pregnancy worldwide: health effects and prevention

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Abstract | Micronutrients, vitamins and minerals accessible from the diet, are essential for biologic activity. Micronutrient status varies widely throughout pregnancy and across populations. Women in low-income countries often enter pregnancy malnourished, and the demands of gestation can exacerbate micronutrient deficiencies with health consequences for the fetus. Examples of efficacious single micronutrient interventions include folic acid to prevent neural tube defects, iodine to prevent cretinism, zinc to reduce risk of preterm birth, and iron to reduce the risk of low birth weight. Folic acid and vitamin D might also increase birth weight. While extensive mechanistic and association research links multiple antenatal micronutrients with plausible materno–fetal health advantages, hypothesized benefits have often been absent, minimal or unexpected in trials. These findings suggest a role for population context in determining health responses and filling extensive gaps in knowledge. Multiple micronutrient supplements reduce the risks of being born with low birth weight, small for gestational age or stillborn in undernourished settings, and justify micronutrient interventions with antenatal care. Measurable health effects of gestational micronutrient exposure might persist into childhood but few data exists on potential long-term benefits. In this Review, we discuss micronutrient intake recommendations, risks and consequences of deficiencies, and the effects of interventions with a particular emphasis on offspring.

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Essential vitamins and minerals are dietary components required in small quantities to support virtually all metabolic activity, including cell signalling, motility, proliferation, differentiation and apoptosis, which regulate tissue growth, function and homeostasis. These fundamental biological roles, in early life, enable the fetus to develop and mature into a healthy neonate. Vitamins and minerals support every stage of maternal, placental and fetal interaction to enable a healthy gestation. Most vitamins and trace minerals are referred to as 'micronutrients'. Some essential nutrients, such as calcium, magnesium and phosphorus are considered 'macro' minerals because they are required in greater than trace quantities and will not be discussed in this Review; nor will semi-essential or conditionally required nutrients, such as arginine, choline and taurine. Micronutrients receiving most attention in pregnancy, and commonly provided as supplements, include vitamins A, D, E, folate, $B_{12}$, $B_6$, and C, iron, zinc, iodine, copper and selenium. Although other B-complex vitamins (such as niacin, riboflavin and thiamine) are nearly always also included in dietary supplements, their individual metabolic roles are less well-specified in pregnancy. Consequently, to illustrate the B vitamin contributions, we focus on folate and vitamin $B_{12}$, for which there is considerable interest and human data available supporting their functions in pregnancy.

In this Review, we discuss the metabolic roles of micronutrients that are known to contribute to an optimal pregnancy outcome. We illustrate their importance in regulating selected materno–fetal processes, and summarize the effects of antenatal micronutrient supplement use on fetal, infant and childhood health, and emerging development outcomes of public health importance. Supplementation can be used in research to investigate causality of nutritional exposure in affecting health outcomes and as a public health approach to increase nutrient intake specifically during pregnancy. Other strategies to improve micronutrient status during pregnancy are discussed, as are

**Key points**

- Micronutrient deficiencies during pregnancy are a global public health concern, yet the full extent of their burden and health consequences are unclear due to infrequent and inadequate assessment
- Micronutrient deficiencies have been linked to compromised conception, length of gestation, and fetal development and growth, which can lead to pregnancy loss, preterm delivery, small birth size, birth defects and long-term metabolic disturbances
- Antenatal supplementation with multiple micronutrients can improve birth outcomes and merits policy and program consideration in low-income settings
- Preconception and periconception intervention research is needed to further assess the full public health effect of micronutrient adequacy on pregnancy outcomes

gaps in current methods of assessment and knowledge of the function of micronutrients in enhancing reproductive health.

## Recommended intakes during pregnancy

Micronutrient intake recommendations are determined by assessing the normal physiological requirements of nutrients to support a healthy pregnancy. These requirements might be determined, in part, by a woman's diet and nutritional status before pregnancy, as well as environmental stressors that can lead to inflammation of body tissues and therefore deplete, or divert the use of, micronutrients. Dietary recommendations determined by panels of nutrition experts are specific in guiding intakes for normally nourished populations to remain healthy[1,2]. However, setting appropriate recommendations for vitamin and mineral intakes during pregnancy is challenging. Micronutrient concentrations, which are often biomarkers that guide estimation of status and, therefore, physiological need, can be affected by plasma volume expansion and other adaptations to the pregnant state. As such, recommendations for pregnancy are often extrapolations from estimates of adult or adolescent (as appropriate) intake requirements, adjusted to account for fetal nutrient accumulation, additional maternal demands to support tissue accretion and metabolism, and changes in efficiency of nutrient absorption that can occur during pregnancy[3] (TABLE 1).

The Recommended Dietary Allowances (RDAs; BOX 1)[1] or Recommended Nutrient Intakes (RNIs)[2] are most often used to guide usual population nutrient intakes in many countries. The RDAs were developed nutrient-by-nutrient over the period of more than a decade by groups of expert nutritionists convened by the Institute of Medicine in the USA. The RDA is one of several dietary reference intakes established for the diets of healthy populations in the USA and Canada. The expert groups examined the literature regarding functional tests or health outcome responses to nutrient intakes to derive requirement distributions for each nutrient. The median represented an intake that should be adequate for half of the population, a value termed the Estimated Average Requirement (EAR). With the requirement distribution assumed as normal, an RDA was set at 2 standard deviations above the EAR, or a level that would meet nutrient intake requirements for 97.5% of a population. Consequently, the EAR rather than RDA should be used to estimate prevalences of inadequate nutrient intake[1].

The RNIs were compiled by expert consultative processes under the auspices of the WHO, which followed a more empirical approach for each nutrient, including considering intake distributions required to maintain normal status, to estimate an EAR[2]. Consequently, while comparable in estimated values, the two sources are not identical in their approaches to derivation. Efforts are also underway to harmonize recommendations across Europe through the European micronutrient Recommendations Aligned (known as EURRECA) network[4]. Despite these attempts to align recommendations, national adaptations can vary widely (for example, for folate[5]), reflecting differences in the purpose of the estimates and national expert interpretation of requirements across dietary, cultural and environmental contexts in different countries. As a result, even with increasingly evidence-based recommendations, practical and reliable translation of micronutrient recommendations into dietary intakes remains a global challenge.

TABLE 1 provides RDAs for selected nutrients along with criteria for setting levels in pregnancy and explanations for why they might differ from an RDA for nonpregnant, nonlactating women. Although RDAs (and RNIs) for pregnancy might not differ from those set for the nonpregnant, nonlactating state, as seen with vitamin D and vitamin E, recommendations for some nutrients are set to intakes that are up to ~50% higher during pregnancy, as is the case for iron, folate, iodine and vitamin $B_6$ to accommodate expected increased maternal, placental and fetal requirements.

Although representing the best possible estimates, micronutrient intake recommendations during pregnancy should be interpreted in context. For example, the RDAs are not applicable to individuals, and by extension to populations, who are malnourished and whose dietary needs to nutritionally recover and mitigate health risks of pre-existing micronutrient deficiencies might be greater than those who are well-fed. For this reason, and given accruing findings of health benefits, TABLE 2 illustrates supplemental micronutrients that the WHO considers essential in low-income settings, and provides a joint WHO/UNICEF/World Food Programme guideline for micronutrient supplementation under complex emergencies that might markedly increase malnutrition due to conflict, natural disasters, or general failures in markets that could lead to famine. These WHO guidelines, intended for programmatic planning, have essentially been adopted as recommendations for healthcare workers by the International Federation of Gynecology and Obstetrics[6]. Furthermore, the WHO/UNICEF/World Food Programme multiple micronutrient formulation has also become a *de facto* global recommendation[7]. Specifically, the supplement that emerged from these guidelines for distribution to pregnant women in undernourished settings — called the United Nations Multiple Micronutrient Antenatal Preparation

Table 1 | **Recommendations for micronutrient intake for women in the USA and Canada**

| Nutrient | Recommended dietary allowance* | | Criterion for setting level in pregnancy | Physiological changes underlying pregnancy-specific recommendations |
|---|---|---|---|---|
| | Pregnant | Nonpregnant/ nonlactating | | |
| Vitamin A | 770 µg RAE | 700 µg RAE | Assure adequate vitamin A stores | Fetal liver and placenta acquire and store vitamin A; mother's stores might be mobilized as needed |
| Vitamin $B_6$ | 1.9 mg | 1.3 mg | Maintain adequate plasma pyridoxal phosphate and meet increased needs of pregnancy | Fetal and utero–placental accumulation with increased maternal weight and metabolism with no gains in maternal absorption compared to non-pregnant state |
| Vitamin $B_{12}$ | 2.6 µg | 2.4 µg | Maintain haematological status and serum $B_{12}$ levels and meet fetal needs | Fetal accumulation; maternal absorption improves and levels of transcobalamin I and III increase in second and third trimesters |
| Folate | 600 µg DFE | 400 µg DFE | Maintain red blood cell folate levels | Enhanced single-carbon metabolism to support materno–placental tissue expansion and fetal growth; active materno–fetal folate transfer, but no gains in maternal absorption compared to non-pregnant state |
| Vitamin C | 85 mg | 75 mg | Maintain adequate maternal neutrophil ascorbate levels (as indicator) and theoretical transfer to fetus | Additional amount of vitamin C required for materno–fetal transfer is unknown; increment is theoretical |
| Vitamin D | 600 IU | 600 IU | Maintain 25(OH)D concentrations necessary to support bone health | No known increased requirement for pregnancy to increase calcium absorption |
| Vitamin E¶ | 15 mg | 15 mg | Maintain plasma levels of α-tocopherol and prevent hydrogen peroxide-induced haemolysis (based on non-pregnancy data) | Nutrient transfers to the fetus but intakes presumed adequate in high-income countries because plasma α-tocopherol concentrations increase across gestation |
| Copper | 1000 µg | 900 µg | Maintain adequate indicators: plasma levels of copper and ceruloplasmin, erythrocyte superoxide dismutase activity or platelet levels of copper | Recommendation based on estimated amount needed for expanded maternal, placental and fetal tissues |
| Iodine | 220 µg | 150 µg | Maintain positive iodine balance, prevent goiter, and meet estimated daily thyroid iodine uptake by the fetus | Additional fetal requirement |
| Iron | 27 mg | 18 mg | Meet physiological requirement for normal function assuming high absorption rate in second and third trimester | Increase of red blood cells; basal losses; fetal iron uptake, iron deposition in fetal and placenta tissues; increased maternal absorption |
| Selenium | 60 µg | 55 µg | Maximize the synthesis of the plasma selenoprotein glutathione peroxidase and meet fetal needs | Additional fetal requirement for saturation of fetal selenoproteins |
| Zinc | 11 mg | 8 mg | Factorial analysis of zinc absorption plus additional needs in late pregnancy | Maternal and fetal tissue accumulation |

DFE, dietary folate equivalents; RAE, retinol activity equivalents; 25(OH)D, 25-hydroxyvitamin D. *From the Institute of Medicine report on Dietary Reference Intakes for each nutrient (http://fnic.nal.usda.gov/dietary-guidance/dietary-reference-intakes/dri-nutrient-reports); for 19–30 year old female individuals, if recommendations differed by age of pregnant woman. ¶As α-tocopherol.

— contains 15 micronutrients at dosages approximating an RDA for pregnancy[8], and has been tested in trials in South Asia and Africa[9].

## Micronutrient deficiencies

Women living in low-income countries are often unable to meet the micronutrient demands of pregnancy due to a chronically poor diet[10]. At the same time, the costs of assessing biochemical indicators of individual micronutrients have led to few population estimates of deficiencies during pregnancy. This situation has given rise to the term 'hidden hunger' (REF. 11), referring to a lack of knowledge as to the extent and consequences of this nutritional burden.

Population data have been used to estimate the global prevalence of certain nutrient deficiencies during pregnancy[12], albeit without delineation by age, parity, socioeconomic status and other factors that might influence nutrition during gestation. Worldwide, the estimated prevalence of prenatal iron deficiency anaemia is 15–20%, calculated as half of women with anaemia, defined as haemoglobin <110 g/l (because half respond to supplementation with iron based on data from population-based intervention trials)[12]. Vitamin A deficiency, classified by a low serum level of retinol (<0.70 µmol/l), affects an estimated 15% of pregnant women in low-income countries[13]. Eight percent of pregnant women have vitamin A deficiency high enough to lead to night blindness[13], an ocular consequence of the deficiency. Iodine deficiency ranges from 17% in Oceania to 40% in Africa[12]. These estimates are based on a median urinary iodine concentration falling below 150 µmol/l in population assessments of children aged 6–12 years, an age group regarded as

Box 1 | **Dietary reference terms**

**Dietary reference intakes for the USA and Canada**

- Estimated Average Requirement (EAR)
  - Average daily intake level estimated to meet the needs of 50% of healthy individuals
  - Used to estimate insufficiency prevalence in populations
- Recommended dietary allowance (RDA)
  - Intake level estimated to meet the needs of 97.5% of healthy individuals
  - Calculated from the distribution used to estimate the EAR
  - Used as a goal for individual intake
  - Amount most often provided in supplements

**Recommended Nutrient Intakes (RNIs) from the WHO**

- Definition is equivalent to RDA above (although actual amounts can differ)

For details on dietary reference intakes and RNI see elsewhere[2,160].

'sentinel' in reflecting geographic and population-level risk, although one that might underestimate iodine deficiency in pregnancy[14]. Although global estimates of other deficiencies are unavailable, population-based studies in South Asia, including India, Bangladesh and Nepal, have reported deficiencies of zinc (15–74%), vitamin $B_{12}$ (19–74%), vitamin E (as α-tocopherol, 50–70%) and folate (0–26%) in pregnant women[15–21]. In a few instances, where a larger number of nutrients have been assessed in the same population, multiple deficiencies appear, although unequal in burden. For example, in Côte d'Ivoire in West Africa, the prevalence of deficiencies among women of reproductive age varied widely for vitamin A (1%), iron (17%), vitamin $B_{12}$ (18%) and folate (86%)[21]. In the plains of southern Nepal, the percentage of pregnant women varied in deficiencies of vitamins A (7%), D (14%), E (moderate-to-severe, 25%), $B_{12}$ (28%), $B_2$ (33%) and $B_6$ (40%), folate (12%), iron (40%) and zinc (61%), and only 4% were normal in status for all nutrients[14]. Deficiencies in the surveyed area of southern Nepal varied by season, which is likely to be the result of seasonal shortages in available food sources and consequent diet, characteristic of rural agrarian societies[22]. Although not well estimated during pregnancy, vitamin D deficiency (defined as 25-hydroxyvitamin D <30 nmol/l) is high in many countries including Turkey (50%), India (60%), and Pakistan (45%)[23], and women and infants (reflective of maternal status) have lower vitamin D status in the Asia/Pacific region[24].

In the absence of adequate data on biochemical status, quantitative dietary data in pregnant women can be used to estimate the prevalence of inadequate intake, based on the percentage of population intakes below the EAR (BOX 1). With few exceptions, most estimates of average intake are below the EAR in low-income and middle-income countries for folate, iron and zinc; vitamin A intake is low particularly in Asia and Africa[25].

In high-income countries, few clinical micronutrient deficiencies exist during pregnancy, a situation that has been attributed to year-round dietary diversity, dietary counselling during pregnancy, widespread intake of fortified foods (such as in the USA)[26] and antenatal micronutrient supplement use[27]. Nonetheless, mild deficiencies remain and dietary micronutrient inadequacy might be emerging as diets of higher fat and sugar and lower nutrient density are increasingly consumed[28]. In a 2013 review of diets among pregnant women in high-income countries, intakes of folate, iron and vitamin D were found to be below recommended intakes in each geographic region examined[29]. Where diets are typically diverse and generally considered adequate, such as the UK, elsewhere in Europe and the USA, national surveys suggest that intrinsic (that is, nonfortified) intakes are low for vitamins A, D, C and folate, which increases the risk of antenatal deficiencies[30]. Mild gestational iodine deficiency also remains endemic in parts of Europe, presumably due to inadequate use of iodized salt[31], and daily iodine intake in pregnant women in the USA might be low based on a borderline median urinary iodine excretion, an indicator that reflects recent dietary intake[32]. A public health success in the USA has been the markedly reduced prevalence of folate deficiency in the first trimester of pregnancy (based on low serum or red blood cell folate), from 55% in the early 1990s to ≤1% by 2010 (REF. 33), owing to folic acid fortification of flour[34]. Poor vitamin D status has been a re-emerging issue, with documented insufficiency in pregnancy in the USA (28%)[35] and the Mediterranean region (50–65%)[36]. Causes of deficiency are complicated to determine due to the dual sources of diet and skin production, but lack of sun exposure is a contributor. Iron deficiency persists. In the USA, the National Health and Nutrition Examination Study (1999–2006) estimated 18% of American gravida to be affected, based on nondetectable total body iron[37].

## Micronutrient function during pregnancy

Micronutrients support maternal health and fetal development throughout gestation through processes that are integrated across maternal, placental and fetal compartments (FIG. 1). Micronutrient function in human pregnancy is typically inferred from *in vitro* studies and experimental animal models, observational data in human studies, and a limited number of human trials that have explored metabolic mechanisms and outcomes. Overall, we have limited *in vivo* understanding of specific, causal mechanisms by which micronutrients act through the materno–placental fetal axis to influence human pregnancy outcomes[38].

### *Mother*

Micronutrient nutriture affects the maternal capacity to conceive and support pregnancy through to birth. Deficiencies in micronutrients involved in one-carbon metabolism, including folate and vitamins $B_6$ and $B_{12}$, might contribute to disturbances in gametogenesis, fertilization and development of the embryo before implantation, which have been associated with elevated systemic and follicular levels of homocysteine[39]. These nutrient deficiencies might also adversely affect DNA and histone methylation of the oocyte (and sperm in the male partner), with long-term consequences[40]. Reductions within normal dietary ranges in periconceptional (8 weeks before to

Table 2 | **Micronutrient supplement recommendations for pregnant women in low-income settings**

| Nutrient | WHO* | Joint WHO, UNICEF & WFP for emergencies: multiple vitamin and mineral supplement‡ |
|---|---|---|
| Vitamin A | Up to 10,000 IU per day for ≥12 weeks to prevent night blindness in deficient settings | 800 µg RAE |
| Vitamin $B_6$ | None | 1.9 mg |
| Vitamin $B_{12}$ | None | 2.6 mg |
| Folate | 400 µg daily or 2.8 mg weekly as folic acid, all settings § | 600 µg as folic acid |
| Vitamin C | None | 55 mg |
| Vitamin D | None | 200 IU |
| Vitamin E‖ | None | 15 mg |
| Copper | None | 1150 µg |
| Iodine | 250 µg daily or 400 mg annually where iodized salt coverage is <20% | 250 µg |
| Iron | Daily 30–60 mg or weekly 120 mg elemental iron supplement, all settings§ | 27 mg |
| Selenium | None | 30 µg |
| Zinc | None | 10 mg |

UNICEF, United Nations Children's Fund; WFP, World Food Programme *WHO. Essential Nutrition Actions: improving maternal, newborn, infant and young child health and nutrition (World Health Organization, Geneva, 2013) http://www.who.int/nutrition/publications/infantfeeding/essential_nutrition_actions/en/. ‡WHO/UNICEF/WFP. Preventing and controlling micronutrient deficiencies in populations affected by an emergency: Multiple vitamin and mineral supplements for pregnant and lactating women, and for children aged 6 to 59 months. http://www.who.int/nutrition/publications/WHO_WFP_UNICEFstatement.pdf. §Combined iron and folic acid supplement is recommended. ‖As α-tocopherol.

6 days post-conception) consumption of vitamin $B_{12}$ and folate in sheep dams were associated with epigenetic changes in offspring DNA methylation and increased susceptibility to obesity, insulin resistance and hypertension in adulthood[40]. In a randomized, placebo-controlled trial in a nutritionally-compromised population, data from cord blood and infants aged 9 months living in the Gambia revealed differential patterns of DNA methylation, particularly of genes affecting immune response, following maternal multiple micronutrient supplementation[41]. These results demonstrated the potential for epigenetic responses to micronutrient interventions in humans[41]. Beyond the periconceptional period, because folate and vitamin $B_{12}$ are required for nucleotide and DNA synthesis to support cell division, deficiencies in these nutrients also increase the risk of miscarriage and fetal malformations, including neural tube defects[39].

Other micronutrient deficiencies have also been associated with early reproductive failure. Vitamin E (as α-tocopherol) is required to protect essential fatty acids from oxidative degradation during embryogenesis based on animal and *in vitro* studies[42]. Antioxidant roles, as well as roles in promoting enzyme induction, cell signalling and lipid membrane integrity could be mechanisms underlying the nearly doubled risk of miscarriage associated with early pregnancy vitamin E deficiency observed in women in rural Bangladesh[21]. Severe selenium, zinc and copper[43] and iodine deficiencies[44], while now less common in human populations, have also been associated with miscarriage. Important maternal haemodynamic, cardiovascular, renal and gastrointestinal adaptations occur throughout pregnancy, but little is known about specific micronutrient functions that might support or respond to these changes. Pregnancy-associated haemodilution reduces circulating concentrations of many micronutrient indicators during the second and third trimesters of pregnancy. This phenomenon is well established, for example, for iron status[45], while hormonal changes increase concentrations of nutrients such as vitamin E and copper[43]. These changes limit our ability to accurately assess micronutrient status during pregnancy with conventional cutoffs for micronutrient status indicators, although lower cutoffs for second trimester haemoglobin concentrations are advocated for assessing anaemia to account for this issue[45].

### *Placenta*

Vascularization of placental tissue requires invasion of the external trophoblast cells from the embryo into the maternal decidua, a process eliciting oxidative stress and thereby requiring modulation by antioxidant nutrients[43]. The placenta is rich in micronutrient-requiring antioxidant enzymes, including glutathione peroxidases (selenium) and superoxide dismutases (copper, zinc and manganese), essential for protecting the embryo and placenta from oxidative stress as maternal spiral arteries are invaded to initiate maternal–fetal circulation[43]. Insufficient antioxidant activity has been posited to be associated with reductions in placental vascularization, potentially limiting blood flow to the fetus, which results in hypoxia and ischaemia and is likely to contribute to preeclampsia and poor fetal growth[43].

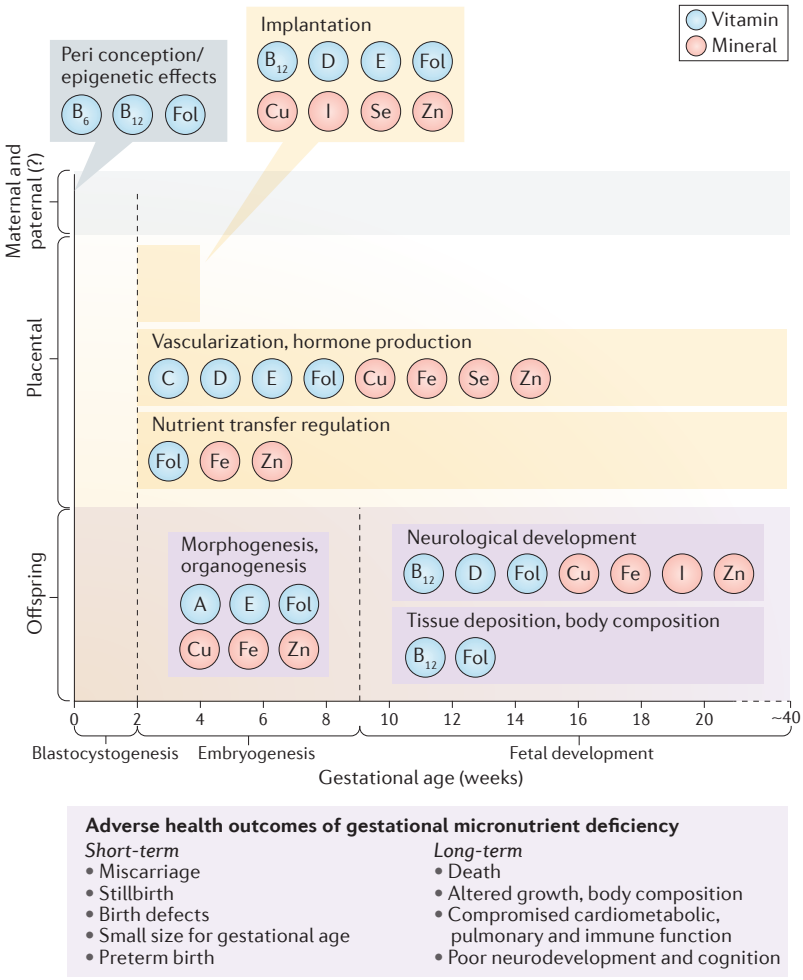


Figure 1 | **The function and timing of micronutrients that affect outcomes in offspring.** Insights on micronutrient function are primarily derived from reviews of data from *in vitro* studies, experimental animal models, observational data in human studies and a limited number of trials that have explored metabolic mechanisms and outcomes. The relevant time of action and the function of micronutrients is depicted, but the accumulation of fetal micronutrient stores, generally dependent on the status of the mother, is not. Availability of fetal micronutrient stores to support growth and developmental processes into infancy and beyond is, therefore, an implied pathway. Fol, folate.

Vitamin E, probably via phosphorylated α-tocopherol, might promote vascularization of the placenta, presumably by enhancing expression of angiogenic factors like vascular endothelial growth factor (VEGF)[46]. The placenta expresses vitamin D receptors and can convert 25-hydroxyvitamin D (25(OH) D) to active calcitriol — which is probably utilized for localized paracrine/autocrine functions as calcitriol is not transferred to the fetus[47]. Vitamin D promotes placental VEGF production[48], modulates immune function[49,50], and is thought to support implantation and placental metabolism[47], providing plausible mechanisms for positive associations between vitamin D status and birth outcomes. Maternal iron levels have also been associated with pregnancy health. Placental size is inversely associated with maternal haemoglobin concentration, and maternal or fetal stress induced by hypoxia or iron deficiency might trigger release of placental corticotropin-releasing hormone, which induces changes in signals for parturition and/or fetal macronutrient metabolism, respectively[51]. Among a variety of roles for zinc in supporting pregnancy[52], zinc deficiency can impede placental development, including trophoblast differentiation, placental size, weight and protein expression in a mouse model of periconceptional zinc deficiency[53].

Human placental lactogen (hPL), placental growth hormone (GH-2), and insulin-like growth factor-1 (IGF-1) released by the placenta into the maternal circulation increase insulin resistance to ensure a supply of glucose to the fetus[54]. However, growth-restricting maternal cortisol might be transferred to the fetus more efficiently in malnourished mothers whose placental production of 11 β-hydroxysteroid dehydrogenase type 2 is reduced[54]. In two trials in which multiple micronutrient effects on maternal (hPL, GH-2)[55] and cord blood endocrine factors (insulin, IGF-1, and IGF binding protein-1 [REF. 55] or IGF-1, insulin, free tetraiodothyronine, and cortisol[56]) were studied, no differences were found between multiple micronutrient and iron–folic acid supplemented groups. While levels of maternal or cord blood zinc have been examined in relation to cord blood or placental expression of IGF-1 in human pregnancies, associations between zinc and IGF-1 have been mixed despite the persistent association of IGF-1 with fetal growth[57,58] and evidence linking zinc with the IGF-1 axis and fetal growth in experimental animals[59].

The mature placenta can adapt to maternal supply of, and fetal demand for, nutrients by altering the surface area across which nutrients are exchanged, the thickness of the barrier between the maternal and the fetal circulation, the number and type of nutrient transporters, blood flow, metabolic rate and hormone production[60,61]. For several nutrients transported against concentration gradients (for example, folate, iron, zinc), nutrient-specific transporters are upregulated when availability is limited to maintain fetal supply[45,61–63]. This is perhaps most clearly demonstrated with respect to iron status, where levels of placental transferrin receptor and natural resistance-associated macrophage protein 2 (also known as divalent metal transporter 1) have been shown to be upregulated in response to fetal iron status[45,61]. Other water soluble vitamins (such as, vitamins $B_6$, $B_{12}$ and C) are also actively transported to the fetus[64], while fat-soluble vitamins tend to cross the placenta along a gradient that parallels maternal status[46,65,66].

### *Fetus*

Basic organ structures of the offspring are established during embryogenesis (that is, 2–8 weeks of gestation), and micronutrients are required for organogenesis, supporting the structural development of fetal organs. Later in gestation, adequate micronutrient status might have an effect on organ size or function. Division of cells in the neural tube and neural crest during embryogenesis might double every 5 h[62], which is consistent with the high requirement for folate in the embryo at this time.

Vitamin A is also crucial for embryonic development early in fetal life, and roles for retinoic acid via nuclear receptors have been demonstrated in virtually every tissue studied in animal models, including the nervous system, eye, heart, skeleton, respiratory system and pancreas[65], as well as ear structure[67]. Retinoic acid availability and function must be tightly controlled by the developing offspring, as excessive maternal vitamin A has been shown to be teratogenic[65]. Deficiency of micronutrients including vitamin A, iron, zinc, copper, vitamin E and magnesium during fetal development has been postulated to result in structural alterations of the kidney, pancreas and vasculature that might predispose offspring to cardiometabolic disease in later life; this effect has been reviewed elsewhere[68,69].

Nutritional inadequacies of the developing fetal brain and central nervous system might compromise neurological development, function and cognition. The roles of micronutrients including iron, zinc, copper, choline, iodine, folic acid and vitamin D in fetal and neonatal brain development have been extensively reviewed elsewhere[70–73]. Briefly, micronutrient deficiencies *in utero* can affect specific brain structures, function and neurochemistry, and have differential effects depending on timing of brain development[70]. For example, gestational iron deficiency can affect the developing hippocampus and alters brain energy metabolism, neurotransmitter systems and myelination[74]. Zinc and many B vitamins contribute to DNA and RNA synthesis and energy metabolism within the brain and to neural synapse formation and function[75]. Iodine deficiency is considered the most common cause of preventable mental deficits globally. Maternal tetraiodothyronine, an iodine containing thyroid hormone, crosses the placenta and is required for fetal brain development in the first and second trimester, before the independent function of the fetal thyroid gland, after which thyroid hormone of both maternal and fetal origin supports brain development and function[71].

During the second and third trimesters of pregnancy, the fetus grows and accumulates nutrient stores. Iron stores, for example, accumulate in proportion to the length of gestation and are the major source of this nutrient for the growing infant during the first 6 months of life[76]. For many vitamins and minerals, neonatal stores reflect both duration of gestation and maternal micronutrient status, and infants born either prematurely or to mothers with micronutrient deficiency might have insufficient stores to support rapid postnatal growth and development. Pregnancy is also crucial for ensuring optimal neonatal micronutrients when breast milk, as the primary source of infant postnatal nutrition, does not compensate for poor status at birth due to low nutrient content (such as vitamin D, iron and zinc), regardless of maternal status[77]. Iron and vitamin D provide two classic examples. Transfer of iron to the fetus is greatest during the third trimester of pregnancy, such that preterm infants are born with limited iron stores and are at high risk of anaemia by 1 year of age[45,78]. Another example is that the risk of developing rickets among infants of vitamin D-deficient mothers is associated with suboptimal infant nutrient status related to low transfer of 25(OH)D to the fetus in pregnancy and the limited contribution of breast milk. However, placental calcium transfer for fetal bone mineralization is preserved over a range of maternal vitamin D and calcium states during pregnancy[66].

Micronutrients are likely to contribute to the biological processes that support fetal growth, resulting in enhanced birth weights; however, the specific mechanisms by which *in utero* micronutrient exposure elicits this effect are not yet established[38,79]. An example of micronutrient deficiencies implicated in alterations in tissue deposition include folate and vitamin $B_{12}$, which increased the amount of visceral body fat, inflammation and dyslipidaemia among offspring of deficient rat dams[80]. Deficiencies in a variety of micronutrients (folate, vitamin $B_{12}$, zinc) potentially predispose offspring to chronic disease outcomes, including obesity, insulin resistance and dyslipidemia, later in life[81], although data from human populations are limited.

## Antenatal effects across the lifespan

Micronutrient levels in the mother at the time of pregnancy can affect immediate, short-term and long-term outcomes for the offspring. Randomized controlled trials (RCTs) of micronutrient supplementation provide the strongest available evidence of causal relationships between micronutrient intake and pregnancy-associated outcomes in human populations. A summary of meta-analyses of RCTs examining single nutrient effects on pregnancy and birth outcomes primarily conducted in low-income, undernourished populations is provided in TABLES 3,4. Evidence of the short-term effect of multiple micronutrient supplements has been published in a 2015 Cochrane review[9]. Supplements tested in humans have comprised single or combined micronutrient formulations, usually starting in the first trimester, or at least the first half, of pregnancy to optimize nutrient exposures and, theoretically, establish their influence on the complex nutrient-regulated mechanisms and pathways discussed earlier in the text. However, only a limited number of studies have examined the benefits of preconception or periconceptional micronutrient supplementation, when placentation and embryogenesis would be expected to benefit most. Systematic trial data on long-term outcomes past infancy from *in utero* exposure to micronutrients are also lacking and greatly needed.

### *Gestational effects*

A number of possible short-term responses exist to changes in materno–placento–fetal nutriture that are attained by maternal improvement in micronutrient status. These can include differences in fetal survival affecting the risk of pregnancy loss due to miscarriage and stillbirth; organ formation affecting the risks of birth defects; duration of gestation affecting the risks of preterm birth, and consequent low birth weight; and rate of fetal growth, affecting birth size and consequent risks of being born small for gestational age and/or having a low birth weight.

Table 3 | **Randomized controlled trials supplementing pregnant women with individual micronutrients included in meta-analyses**

| Micronutrient | No. trials | Total no. of pregnancies (range between studies) | Country income context | Dose (times RDA)* | No. of trails starting during each gestational period (weeks) | | | | | Study |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Prepregnancy | 1–10 | 11–20 | 21–30 | >31 | |
| ***Vitamins*** | | | | | | | | | | |
| Vitamin A‡ | 19 | 169,337 (27–102,952) | Low–Middle | 1–3 | 2 | 1 | 9 | 5 | 2 | McCauley *et al.*[157] |
| Vitamin $B_6$ | 4 | 1623 (22–1532) | Middle–High | 1–53 | – | – | 2 | 1 | 1 | Salam *et al.*[158] |
| Folic acid | 5 | 8357 (218–5502) | Low–High | 1–11 | 5 | – | – | – | – | De-Regil *et al.*[92] |
| Folic acid | 31 | 13,396 (20–2928) | Low–High | 0.3–42 | – | 1 | 16 | 13 | 1 | Lassi *et al.*[103] |
| Vitamin C§ | 8 | 2007 (60–815) | Low–High | 1–12 | – | 1 | 6 | 1 | – | Rumbold *et al.*[159] |
| Vitamin D‖ | 9 | 1271 (40–260) | Low–High | 1–8 | – | – | 1 | 8 | – | De-Regil *et al.*[105] |
| ***Minerals*** | | | | | | | | | | |
| Iodine¶ | 9 | 1521 (35–1047) | Low–High | 436–4364 | 2 | – | 6 | 1 | – | Bougma *et al.*[130]; Zhou *et al.*[129] |
| Iron# | 44 | 22,802 (13–5828) | Low–High | 1–37 | – | 2 | 27 | 12 | 2 | Peña-Rosas *et al.*[102] |
| Iron/IFA | 48 | 17,793 (13–3929) | Low–High | 0.3–33 | – | 3 | 30 | 12 | 2 | Haider *et al.*[101] |
| Zinc | 21 | 11,774 (56–2124) | Low–High | 0.5–8 | 1 | – | 17 | 3 | – | Ota *et al.*[111] |

We did not identify a meta-analysis that met our criteria for vitamin $B_{12}$ or selenium. We identified no individual studies for vitamin E, thiamin, riboflavin, niacin or copper. IFA, iron and folic acid. *RDA used for pregnant women aged 19–30 years as the referent group. ‡One study gave a bolus dose (600,000 IU). §Only includes trials comparing groups with vitamin C to groups without vitamin C (does not include trials of vitamin C and vitamin E tested together). ‖Only includes trials comparing groups with vitamin D to groups without vitamin D; four trials of vitamin D gave participants bolus doses (ranging from 60,000 to 600,000 IU). ¶Three trials of iodine gave bolus injections (96–1600 mg). #Only includes trials comparing groups with iron to groups without iron, does not include trials of iron and folic acid tested together.

***Pregnancy loss.*** Periconceptional deficiencies of vitamin E[21], thiamine[82] and selenium[83] among others have been variably associated with spontaneous or recurrent pregnancy loss. Folate supplementation in an observational USA study of almost 16,000 women has been linked to a 20% lower risk of miscarriage (adjusted risk ratio [RR] 0.80; 95% CI 0.71–0.90)[84]. However, trials that have examined effects of micronutrient supplementation on early pregnancy loss are currently lacking. For example, selenium deficiency has a hypothesized link with miscarriage[43], but no trials have been conducted to test its effect (TABLE 3). Vitamin A and folic acid supplementation have been tested but seem to have no effect on lowering the risk of miscarriage (TABLE 4). Among the few trials conducted to assess vitamin supplementation before pregnancy and/or within the first half of pregnancy, no effect on early or late miscarriage has been identified[85], nor has miscarriage risk been lowered from multiple micronutrient use[9].

By contrast, trial data exist on effects of individual and multiple micronutrient interventions on risk of stillbirth (TABLE 4). However, these studies are often statistically underpowered to measure this outcome, and meta-analyses of combined findings suggest no significant effect of antenatal supplementation with vitamin A, vitamin C, folic acid or zinc on stillbirth, while meta-analyses for this outcome have not been examined or reported for other individual micronutrients[85,86] (TABLE 4). In a trial comparing multiple micronutrient versus iron and folic acid (IFA) in Bangladesh (starting supplementation at ~9 weeks' gestation), which was designed to evaluate stillbirth, multiple micronutrients reduced the incidence of stillbirth by 11% (95% CI 1–19%)[87]. Moreover, in a Cochrane systematic review of all randomized multiple micronutrient supplementation trials that combined effect estimates from 15 studies in low-income and middle-income countries, a 9% reduction in stillbirth (RR 0.91; 95% CI 0.85–0.98) was found compared with iron supplementation both with or without folic acid[9]. Collectively, these data suggest that sustained and adequate antenatal micronutrient supplementation might indeed improve late fetal survival rates.

***Birth defects.*** Periconceptional micronutrient inadequacy might increase the risk of congenital anomalies but folic acid is the only nutrient proven effective at reducing this outcome. Neural tube defects (NTDs), in particular, represent a complex group of multifactorial lesions (including anencephaly and spina bifida) that together affect between 1 and 10 per 1000 births worldwide[88], with undernourished populations, for example, in India, seeming to be at the highest risk[89]. NTDs have been associated with a deficiency in folate since the 1960s[90], which is attributed to the pivotal roles of folate in single-carbon metabolism and DNA synthesis and function, but the mechanisms are still not fully understood[91]. Strong, consistent evidence from trials have established that periconceptional provision of folate markedly reduces the risk of NTDs, by 72% (95% CI 48–85%), as well as recurrent NTDs[92], an effect that has been extended to public health applications through

Table 4 | **Meta-analyses of RCTs supplementing pregnant women with micronutrients: pregnancy and early-life postnatal outcomes**

| Micronutrient | Outcome (quality of evidence: low; moderate; high)* | | | | Study |
|---|---|---|---|---|---|
| | During pregnancy | At birth | <1 month | <5 years | |
| ***Vitamins*** | | | | | |
| Vitamin A | No effect on still birth | No effect on low birth weight or preterm birth | No effect on neonatal mortality | – | McCauley *et al.*[157] |
| Vitamin $B_6$ | No effect on preeclampsia | – | – | – | Salam *et al.*[158] |
| Folic acid | • 72% decrease in risk of neural tube defects (low)<br>• No effect on other birth defects or miscarriage | – | – | – | De-Regil *et al.*[92] |
| | No effect on still birth | • 136 g increase birth weight (high)<br>• No effect on low birth weight | No effect on neonatal mortality | – | Lassi *et al.*[103] |
| Vitamin C‡ | No effect on still birth or preeclampsia | • 36% decrease in risk of preterm PROM (high)<br>• No effect on preterm birth or IUGR | No effect on neonatal mortality | – | Rumbold *et al.*[159] |
| Vitamin D‖ | No effect on still birth or preeclampsia | • 60% decrease in risk of low birth weight (moderate); 64% decrease in risk of preterm birth (moderate)<br>• No effect on birth weight, preterm birth, SGA | No effect on neonatal mortality | – | De-Regil *et al.*[105] |
| ***Minerals*** | | | | | |
| Iodine | – | – | – | Increase of eight IQ points (high); decrease in risk of cretinism | Bougma *et al.*[130]; Zhou *et al.*[129] |
| Iron§ | No effect on birth defects | • No effect on preterm birth, low birth weight, birth weight | No effect on neonatal mortality | – | Peña-Rosas *et al.*[102] |
| Iron/IFA | – | • 41 g increase birth weight (low); 19% decrease in risk of low birth weight (low)<br>• No effect on preterm birth, SGA | – | – | Haider *et al.*[101] |
| Zinc | No effect on still birth, preeclampsia, birth defects | • 14% decrease in risk of preterm birth (moderate)<br>• No effect on birth weight, low birth weight, SGA | No effect on neonatal mortality | – | Ota *et al.*[111] |

Most outcomes presented were not assessed in all trials (for example, birth weight was only assessed in five of 31 folic acid trials). Improvements in biochemical status or clinical issues that are not specific to pregnancy (such as nightblindness or anaemia) are not presented. IFA, iron–folic acid; IUGR, intrauterine growth restriction; PROM, premature rupture of the chorioamniotic membrane; RCT, randomized controlled trial; SGA, small for gestational age. *Quality of evidence is defined by the original meta-analysis. ‡Only includes trials comparing groups with vitamin C to groups without vitamin C (does not include trials of vitamin C and vitamin E tested together). ‖Only includes trials comparing groups with vitamin D to groups without vitamin D. §Only includes trials comparing groups with iron to groups without iron, does not include trials of iron and folic acid tested together.

folic acid fortification of grain products in the USA since the late 1990s[93,88]. Other single micronutrients either have not been tested for an effect on birth defects or have not shown an effect (iron and zinc; TABLE 4).

Adequate periconceptional folate nutriture might also reduce the risk of developing heart defects[94], an observation that awaits confirmatory trials[95]. Beyond folate, antenatal vitamin $B_{12}$ deficiency has been associated with a higher risk of NTDs[64] and increased reported periconceptional intakes of thiamine, niacin and vitamin $B_6$ have been associated with lower risks of orofacial cleft[96], although supplementation trials have yet to be done to test causality of these associations (TABLE 3). In several observational studies, antenatal multivitamin supplement use has been associated with lower risks of orofacial, heart, urinary tract, limb and other non-NTD birth defects[97], findings that evoke plausible mechanisms but that also require confirmation. The need for balanced micronutrient nutriture to guide normal fetal development is suggested by a potentially increased risk of neural crest defects with either severe vitamin A deficiency[67] or excessive fetal retinoid exposure[98].

***Fetal growth.*** Low birth weight (LBW, <2.5 kg) can result from decrements in either fetal growth or length of gestation, while small for gestational age (SGA) is due to the former; however, both increase the risk of infant morbidity and mortality[99,100]. Inadequate maternal micronutrient nutriture might compromise birth size via either pathway. A number of antenatal supplement trials have assessed effects of single nutrients, most commonly iron and folic acid, on birth weight (TABLES 3,4). In a meta-analysis published in 2013 comparing antenatal iron (with or without folic acid) to no iron or placebo, an increase in birth weight (of 41 g) and 19% reduction in risk of LBW was found[101], although

an updated estimate in 2015 incorporating more trials has yielded weaker and statistically nonsignificant effects of iron supplementation alone on birth weight (24 g; 95% CI −3 to 51 g) and the risk of LBW (RR 0.84; 95% CI 0.69–1.03)[102]. A pooled analysis of data from four trials with positive effects of antenatal folic acid on birth weight was deemed inconclusive due to low quality evidence (owing to potential selection bias and blinding issues) and a lack of other offspring benefits[103]. At a policy level, IFA remains globally recommended by the WHO for antenatal use to reduce the risks of maternal iron deficiency and consequent anaemia as well as the risk of LBW[104]. Folic acid is included in the WHO recommendation to help maintain maternal haemoglobin levels and reduce birth defects (if started periconceptionally) rather than increase birth weight[104]. In other trials, vitamin A and zinc have each shown no effect on birth weight, SGA or LBW[102,103]. In a meta-analysis of three small but high quality trials ($n = 493$), supplemental vitamin D reduced the risk of LBW by 60% (RR 0.40; 95% CI 0.24–0.67)[105]. The results of randomized trials have consistently shown antenatal, multiple micronutrient supplementation to modestly increase birth weight beyond that achieved with IFA, reducing LBW on average by 12% (95% CI 9–15%)[9], although nothing is known about the composition or tissue contributions to the observed increment. Although the results of meta-analyses suggest the effect is associated with a reduction in SGA (by 10%; 95% CI 3–17%)[9], implying increased intrauterine growth, a comparable reduction in LBW in a large trial in rural Bangladesh (by 12%; 95% CI 9–15%) was associated with prolonged gestation rather than accelerated fetal growth and a lower risk of SGA[87].

***Preterm birth.*** Preterm birth, which occurs before 37 weeks' gestation, is associated with increased risks of neonatal mortality[106,107], poor postnatal growth[108] and impaired cognition[109]. A preterm infant also has less time to accrue adequate, late gestation nutritional reserves, which might contribute to postnatal micronutrient deficiency. However, evidence on whether maternal micronutrient deficiency predisposes a pregnancy to preterm birth is limited[86]. Although antenatal iron or IFA improves fetal growth outcomes, their supplemental use during trials has not reduced the risk of preterm birth[102,110]. Antenatal zinc supplementation can decrease risk of preterm birth, overall by 14%, but perplexingly without affecting birth size[111]. Vitamin D, albeit with evidence from only three trials, reduces risk of preterm birth by a striking 64% (RR 0.36; 95% CI 0.14–0.93), complementing the effect on birth size noted above[105]. Meta-analyses of the effects of multiple micronutrient trials in low-income countries around the world, but largely not powered to test effects of supplement use on preterm birth, have discerned no effect on this outcome[9]. By contrast, in a large, adequately powered trial in Bangladesh investigators reported a 2–3 day longer gestation and 15% reduction in preterm birth (95% CI 9–20%) following daily antenatal multiple micronutrient versus IFA from the first trimester onward[87]. These differing results suggest that pre-existing nutritional, disease and other environmental conditions might modify the public health effect of any given nutritional intervention.

### *Postnatal effects*

Maternal micronutrient adequacy during pregnancy might alter the health and development of offspring during infancy, childhood and even adulthood. Causal inferences can be drawn for effects when plausible biological pathways exist, the nutrient and comparative interventions were randomized, and compliance and follow-up of a cohort is high. The effects are likely to vary by nutrient and their interactions, ages of children when followed, metabolic networks and organ systems investigated, outcome indicators assessed as well as other ambient dietary, disease and contextual factors. Risk of death in the first year after birth is often examined as an endpoint. Outcomes investigated beyond the first year are few but have included child mortality, growth, body composition, cardiometabolic risk, immunity, respiratory function and cognition.

***Infant and child mortality.*** In systematic reviews of iron supplementation both with and without folic acid, no effect on early neonatal (first 7 days)[110] and neonatal (first 28 days) mortality have been reported[102]. In Nepal, daily antenatal IFA with vitamin A ($n = 957$ pregnancies) versus a control (vitamin A alone, $n = 1{,}051$) also did not reduce early infant mortality[112], but when followed up at 6–7 years of age, at which point vital status was obtained on 96% of the cohort, a 34% reduction (Hazard ratio [HR] 0.69; 95% CI 0.49–0.99) in mortality was noted in children born to mothers who received an antenatal IFA supplement[113]. Mechanisms remain unexplained but are likely to be complicated given that a multiple micronutrient supplement also containing iron did not have a similar survival effect[113]. A trial of antenatal selenium supplementation among women who had HIV in Tanzania reported a 57% reduction in post-neonatal mortality (HR 0.43; 95% CI 0.19–0.99), though the effect was attenuated when neonatal and post-neonatal infant deaths were combined (HR 0.64; 95% CI 0.36–1.13)[114]. In trials conducted in other low-income communities no effects on neonatal mortality have been found following randomized maternal supplementation with vitamin A or β-carotene, vitamin C, folic acid or zinc (TABLE 4).

Meta-analyses of multiple micronutrient supplementation trials, which although individually underpowered to detect differences in survival have, when combined to give adequate power, found no effect on neonatal mortality[9]. However, the results of a few large and adequately powered trials have revealed more nuanced effects. For example, in a trial conducted in Indonesia, daily antenatal multiple micronutrient supplementation with vitamins A, $B_2$, $B_3$, $B_6$, $B_9$, $B_{12}$, C, D and E; iron, zinc, copper, selenium and iodine had no effect on neonatal mortality but significantly reduced mortality by 3 months of age by 18% (RR 0.82; 95% CI 0.70–0.95), which suggests a latent benefit of these nutrients following fetal exposure[115]. In Bangladesh,

antenatal multiple micronutrient with the same formulation as used in Indonesia versus IFA supplementation had no effect on all-cause infant mortality in boys but lowered mortality in girls by 16%[87]. In this study, the investigators suggested that a larger birth size for boys might have increased the risk of dying from asphyxia in the first few days after birth, which was not seen in girls[87]. Consequently, antenatal micronutrient supplementation might improve survival among offspring but the effect is likely to be modulated by local nutrition, disease and health care conditions. Unknown at present is the potential for preconceptional micronutrient interventions to affect survival of offspring during gestation and postnatally, which are effects requiring adequately sized population-based randomized trials with extended postnatal follow-up[86,116].

***Growth and body composition.*** The modest increases in birth size following antenatal multinutrient versus IFA (or placebo) supplement use are generally not sustained during the preschool years. This finding is evident across nine trials that included children aged up to 5 years who had comparable distributions of weight, height and age-standardized indicators (weight-for-age, height-for-age and weight-for-height z-scores)[117]. However, potentially important is a sustained increment of 0.08 cm (95% CI 0.00–0.15) in head circumference that was larger in those exposed to multiple micronutrients than controls[117]. By contrast, in Nepal, children aged 6–8 years and born to mothers who received folic acid, iron and zinc supplementation were taller by 0.64 cm (95% CI 0.04–1.25) than children of mothers who received placebo[118]. The increment was accompanied by smaller skinfold thicknesses, consistent with improved linear growth amidst comparable energy intakes[118]. Inexplicably, a similar growth increment was not seen among children born to mothers supplemented with multiple micronutrients, who received folic acid, iron and zinc as part of their supplement[118], which we think implicates a chance growth effect or unknown nutrient interactions when multiple nutrients are regularly ingested in a single supplement.

***Cardiometabolic, pulmonary and immune function.*** Experimental micronutrient depletion during gestation in multiple animal species has been shown to have cardiovascular consequences[69]. However, evidence from childhood studies remains limited and inconclusive with respect to changes in the cardiometabolic risk indicators of blood pressure, kidney function and insulin resistance[69]. In Nepal, where multiple micronutrient deficiencies coexist[15], the investigators of one study reported a modest decrement in systolic blood pressure by 2.5 mmHg (95% CI 0.5–4.6) at 2 years of age in children whose mothers received a multiple micronutrient versus IFA supplement during pregnancy[119]; however, in two other studies, conducted in Nepal and Bangladesh, no differences in blood pressure were found by 4–8 years of age[120,121]. Neither was there an effect of maternal multi-nutrient supplementation on glomerular filtration rate measured in children aged 4 years[121].

Plausible long-term effects of some individual nutrients, consistent with experimental data, have been discerned when provided as a sole nutrient during pregnancy in populations at high risk of nutrient deficiency. To illustrate, research primarily in mammalian and avian models has established roles of gestational vitamin A deficiency in compromising developing cardiovascular[122], pulmonary[122,123], kidney[124], nervous[122] and immune[125] systems. These findings have guided hypotheses of potential developmental effects among offspring of women supplemented with vitamin A in undernourished settings. For example, in rural Nepal, 9–13 year old children born to mothers who were randomly assigned to receive weekly supplemental vitamin A (equivalent to an RDA) versus placebo before, during and after pregnancy had expanded lung capacity, which was evident by increased forced expiratory volume at 1 s and vital capacity[126]. Innate immunity was also stimulated in children of vitamin A versus placebo-supplemented mothers, as evidenced by higher circulating concentrations of natural antibodies known to be secreted by lymphopoietic B1a cells, whose fetal progenitors have been shown to be sensitive to vitamin A nutriture[127]. No effects were seen on blood pressure or microalbuminuria[128], seeming to reflect specificity in organ response to fetal vitamin A exposure in an endemic, vitamin A-deficient population.

***Neurodevelopment and cognition.*** Maternal micronutrient deficiencies might also affect the cognitive, motor and socio-emotional development of offspring, although data examining these outcomes is inconclusive[60]. A challenge in this area of research is the standardization and validation of methods that enable these outcomes across cultures to be measured comparably. The strongest, consistent evidence for cognitive improvement exists for iodine[129,130], although only two RCTs of maternal supplementation have reported outcomes in children[129]. Supplementing mothers before conception reduces (and possibly eliminates) the risk of cretinism when iodine deficiency is severe[129,131]. Observational studies suggest that mild maternal iodine deficiency is associated with an increased risk of cognitive impairment among offspring and that supplementation with iodine might be beneficial[31], although data from RCTs is lacking. Associations between gestational iron exposure and cognitive function have long been supported by mechanisms possibly involving iron in neuronal proliferation, myelination and metabolism. However, among mothers who are not anaemic and who live mostly in high-income countries, antenatal iron supplementation has had no detectable effects on cognitive or mental development test scores of offspring, although some improvement has been detected in psychomotor tests[132]. In China, antenatal iron supplementation had no effects on the Bayley Scales of Infant Development (BSID) or on the intelligence quotient at 4 years of age[133]. In Nepal, where iron deficiency is endemic, 7–9 year old children born to mothers randomly assigned to receive IFA versus placebo during pregnancy exhibited improved intellectual, executive

and motor test scores, effects that were attenuated in children whose mothers had also received antenatal zinc[134]. While many plausible pathways exist linking zinc to neuronal development and function, trials of antenatal zinc supplementation in Peru, Nepal and Bangladesh have either had no effects[134,135] or, by 13 months of age, a potential negative effect on cognitive development, possibly due to competitive interactions with other nutrients such as iron or copper[136].

A number of randomized, antenatal multiple micronutrient supplementation trials have been performed to assess developmental outcomes in infancy or childhood. For example, in one study from Bangladesh, no overall cognitive or psychomotor developmental improvements were noted in children aged 7 months, although positive effects on motor scores (*z* score 0.28; 95% CI 0.08–0.48) and activity ratings (*z* score 0.24; 95% CI 0.037–0.45) were observed in children born to mothers with a low BMI[137]. In China, there were supplementation benefits on the mental, but not psychomotor, development (measured by BSID) in children reported at 1 year of age, yet no apparent differences between groups when children were evaluated at 7–10 years of age[138]. Similarly, in Indonesia, no overall benefit of antenatal multiple micronutrient supplement use was seen on child development at age 3 years; however, motor or visual attention/spatial abilities were improved compared to iron–folic acid supplement use in children of mothers who were thin (arm circumference <23.5 cm) or had anaemia (haemoglobin <110 g/l)[139]. By contrast, no improvement in performance on tests of working memory, executive function and motor ability was observed among Nepalese children aged 7–9 years whose mothers received a multiple micronutrient supplement versus placebo during pregnancy while positive effects on the same tests were seen following maternal receipt of IFA alone[134]. In Tanzania, 6–18 month old infants born to mothers with HIV-1 infection who received multiple micronutrients during pregnancy scored higher on a psychomotor development index ($\beta = 2.6$; 95% CI 0.1–5.1) and experienced a 60% reduction (RR 0.4; 95% CI 0.2–0.7) in motor developmental delay than those in the placebo group[140]. Taken together, little evidence exists to support the overall benefits of iron, zinc or multiple micronutrients on motor or cognitive development, although though some benefits seem to be observed among high risk groups, such as children of mothers who are poorly nourished or have HIV-1 infection. However, stratified population effects in trials merit caution and future trials are needed to reject or confirm these initial findings.

## Prevention

The most desirable approach to prevent micronutrient deficiencies in pregnancy is to assure a sustained diet of various micronutrient-dense foods[6]. As such a diet is often difficult or expensive to attain, preventing adverse birth outcomes due to micronutrient deficiencies through supplementation represents a sound and effective strategy[141]. The WHO has developed micronutrient supplement guidelines for pregnant women (TABLE 2). One of the most commonly adopted by many low-income countries is that of daily IFA supplementation as part of routine antenatal care to reduce the risk of low birth weight and maternal anaemia where iron deficiency is a public health problem[104]. The WHO recommended daily dosage of iron is 30–60 g of elemental iron and 400 μg of folic acid beginning as early as possible in pregnancy[104]. For low-income countries where the prevalence of anaemia among women of reproductive age (15–45 years) is ≥20%, intermittent IFA for menstruating women is also recommended[142]. The International Federation of Gynecology and Obstetrics recommends the use of iodized salt to prevent gestational iodine deficiency disorders[6]. However, iodine supplementation (250 μg per day) is recommended for pregnant women in countries where there is limited access to iodized salt[143]. Where the prevalence of vitamin A deficiency is 5% or more among pregnant women or in children aged 2 to under 5 years, the WHO recommends gravida be supplemented with up to 10,000 IU daily or 25,000 IU weekly of vitamin A to prevent maternal night blindness[144]. Even with evidence-based recommendations, implementation of these strategies is extremely challenging due to reasons of low rates of antenatal care, inadequate supply and poor adherence. For example, in one review, only 8% of women reported taking a full course of 180 or more iron-folic acid tablets during pregnancy[145].

A balanced, diverse and nutritious diet is universally recommended to meet nutritional needs and maintain health during pregnancy. Daily antenatal multiple vitamin and mineral supplements are commonly taken prophylactically by women in the USA and other high-income countries, where there are few formal medical society recommendations to do so. More common are recommendations for individual micronutrients, such as in Germany, where pregnant women are advised to take folic acid and iodine supplements[146]. In low-income countries, where evidence of fetal health benefit is increasing in support of multiple micronutrient supplement use during pregnancy, a WHO/UNICEF policy recommends that pregnant and lactating women take a daily multiple micronutrient supplement in emergency settings (such as, refugee settings or natural disasters)[7]. Although the beneficial effects of antenatal multiple micronutrient supplementation on birth outcomes compared with IFA alone support a change in global policy to promote this intervention in low-income and middle-income countries[9], no such broad WHO/UNICEF policy current exists for this purpose. Programmatic platforms, especially antenatal care visits, through which IFA supplements are distributed, already exist although with variable success; Demographic and Health Survey data show that any supplement use during pregnancy varies from ~10% to 90% of women across low-income countries[147]. However, nutritional interventions that successfully increase birth size should be accompanied by adequate intrapartum care, via facility-based delivery or skilled birth attendants, especially where adolescent

pregnancy and maternal stunting are common, to mitigate potential risks of intrapartum constraint and birth asphyxia-related complications[87].

The preconception period is increasingly seen as a period of great influence in the life course, yet intervention efforts at this time are fewer than in pregnancy[86]. In 53 countries worldwide, ranging from low-income to high-income, folic acid fortification of flour is mandatory (although this does not indicate compliance in all those countries)[148]. Other strategies currently being tested but with potential impact on pregnancy outcomes include dual fortified salt (iron and iodine)[149], iron-fortified flour[150] and biofortification of staple crops such as rice and maize[151]. Overall, fortification is a promising strategy for improving micronutrient status during pregnancy, but data on health outcomes is scarce[152]. Improving diets and the adequate and diverse intake of various food groups continues to be a long-term goal for enhancing maternal micronutrient status, regardless of geographical location or income status.

## Knowledge gaps

Although evidence has rapidly accrued about the roles of antenatal micronutrients on the health of offspring, gaps in our knowledge still remain. Ascertaining nutritional risk during pregnancy will require refinement of dietary recommendations and pregnancy-specific tools for nutritional assessment. The dietary reference intake reports for micronutrients all note a lack of pregnancy-specific data to accurately inform recommendations for this life stage[3,153–155]. Moreover, little information exists on the specific requirements for women with pre-existing deficiencies, as the dietary reference intakes are established for healthy individuals. Improving micronutrient intake recommendations for pregnancy will require pregnancy-specific data and harmonized interpretation in order to use dietary recommendations and ascertain the risk of deficiencies in individuals and across populations. Understanding plasma volume in pregnancy and its impact on interpretation of biomarkers also deserves attention[78,156]. Improved global data on the prevalence or prevention of micronutrient deficiencies, beyond folate, iron, iodine and vitamin A, using appropriate functional, biochemical or clinical indicators is also needed.

With better evidence of global deficiencies, more effective micronutrient delivery might be achieved through supplementation, the use of fortified (or biofortified) food, and dietary counselling or behavioural change programs. Current trials are lacking on effective strategies for influencing pregnancy-related diet and nutritional status in pregnancy in low-income contexts. Caveats for influencing dietary behaviour during pregnancy must be better understood given that this period is a life stage in which food aversions are common and cultural dietary practices, including food avoidance, persist, requiring qualitative research to understand barriers to improving micronutrient intakes. This gap in our knowledge needs to be urgently addressed.

Perhaps the most ambitious need is to establish a comprehensive understanding of the biological pathways and effects of single and multiple micronutrient interventions. Key questions for future research include what are the nutrient interactions, optimal timing and dosage of nutrient delivery, and the wide spectrum of metabolic and functional outcomes that are affected. Specifically, a better understanding is needed of the effects of micronutrients on gestational viability, epigenesis, implantation and placental biology, as well as nutrient functions in the pathways of morphogenesis, pattern formation, neurogenesis and cardiovascular development. Micronutrient provision before and just after conception might be important to assure normal placentation and embryogenesis in malnourished populations, as intervening later in pregnancy might not realize the full potential effect. However, most interventions tested to date have begun supplementation only after the first trimester, leaving the confirmatory effects of intervening earlier an unmet research need.

Randomized, controlled trials in pregnancy remain sparse to absent for evaluating vitamin $B_{12}$, vitamin $B_6$, vitamin E, copper and selenium, while other micronutrients of high interest (such as vitamin D) lack trials of adequate size to examine effects on outcomes such as preterm birth and preeclampsia. Although global multiple micronutrient supplement recommendations of approximately one RDA for a variety of nutrients are anticipated, increased amounts of some nutrients might be warranted, for example for iodine, zinc, vitamin $B_{12}$, and vitamin D, if shown to be safe and beneficial.

## Conclusions

Micronutrient deficiencies in pregnancy remain widespread globally. In low-resource settings, although the burden of the so called 'hidden hunger' during pregnancy remains to be fully revealed, diets are inadequate and micronutrient deficiencies are common. Although adequate food intake remains the preferred means for meeting dietary requirements for micronutrients, some nutrient needs are challenging to meet in pregnancy with diet alone. In response, some countries (across all income levels) fortify selected foods and/or recommend the use of dietary supplements. Micronutrient research in pregnancy has made dramatic advances in the past two decades. Antenatal multiple micronutrient supplement use has emerged as an important public health intervention for women in low-income countries and has benefits for birth outcomes over and above IFA, which is currently recommended for pregnant women by the WHO. Some individual micronutrients (for example, iodine, zinc, vitamin $B_{12}$ and vitamin D) deserve more attention for their potential to further improve offspring outcomes beyond the single daily dose provided in a typical multi-supplement. Micronutrient deficiencies might also have consequences for longer term outcomes of survival, cognition and cardiometabolic risk in offspring, further attesting to their importance in early life, but this effect is not yet evident. Multiple micronutrient supplement is an effective strategy during the critically important biological period of pregnancy; however, much more research is warranted during the preconceptional period.

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The authors contributed equally to all aspects of this article

### Competing interests statement
The authors declare no competing interests

### Review criteria
Our main search strategy for this paper was a PubMed search for articles in English using the MeSH terms "female AND humans AND pregnancy AND ("Meta-Analysis" [Publication Type] OR "review" [Publication Type])" plus the MeSH term for each vitamin or mineral of interest.