Maternal Micronutrient Deficiency, Fetal Development, and the Risk of Chronic Disease

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Abstract

Early life nutritional exposures, combined with changes in lifestyle in adult life, can result in increased risk of chronic diseases. Although much of the focus on the developmental origins of disease has been on birth size and growth in postnatal life and the availability of energy and protein during these critical developmental periods, micronutrient deficiencies may also play an important role in fetal growth and development. Micronutrient status in fetal and early life may alter metabolism, vasculature, and organ growth and function, leading to increased risk of cardiometabolic disorders, adiposity, altered kidney function, and, ultimately, to type 2 diabetes and cardiovascular diseases. This review elucidates pathways through which micronutrient deficiencies lead to developmental impairment and describes the research to date on the evidence that micronutrient deficiencies in utero influence the development of chronic disease risk. Animal studies, observational human studies examining maternal diet or micronutrient status, and limited data from intervention studies are reviewed. Where data are lacking, plausible mechanisms and pathways of action have been derived from the existing animal and in vitro models. This review fills a critical gap in the literature related to the seminal role of micronutrients in early life and extends the discussion on the developmental origins of health and disease beyond birth size and energy and protein deficiency. J. Nutr. doi: 10.3945/jn.109.116327.

Introduction

Vitamins and minerals are essential for human health and development. It has been estimated that 2 billion people worldwide suffer from at least 1 form of micronutrient deficiency (1). Although micronutrient deficiencies during pregnancy have been associated with adverse pregnancy outcomes (2), their effects on the long-term health of the offspring are not well understood.

For a number of reasons, it is plausible to hypothesize that deficiency of vitamins and minerals during critical stages of development will have long lasting health consequences. First, the field of developmental origins of health and disease has now established the link between small size at birth and chronic disease risk in adulthood and old age (3). Birth weight has an inverse association with high blood pressure (4) and type 2 diabetes among adults (5), and natural experiments of exposure to famine during gestation have been associated with a greater risk of chronic disease (6). These studies demonstrate that maternal nutrition during pregnancy may predispose one to a greater risk of chronic disease later in life (7). Animal studies of protein-calorie restriction during pregnancy provide supportive evidence for this (8). Second, several reviews and meta-analyses have described the effects of micronutrients on fetal growth (2,9–13). Third, vitamins and minerals continue to play critical roles in later-life cardiovascular, renal, and pulmonary functioning. For example, increased calcium intake may reduce blood pressure among adults (14) and children (15) and can prevent preeclampsia/eclampsia in women among deficient populations (16). In addition, magnesium and zinc are important for insulin sensitivity, storage, and secretion (17,18) and altered zinc metabolism has been implicated in the development of type 2 diabetes and its complications (19). Vitamin A, in the form of retinoic acid (RA), is important in cardiovascular function and regulation of blood pressure (20,21).

The purpose of this critical review is to fill a gap in the literature on the role of pre-/periconceptional and prenatal maternal micronutrient deficiency in influencing the growth and development of the heart, kidney, lung, and pancreas, and the mechanisms involved, which may then lead to an increased risk of chronic disease later in life. Existing evidence on the effects of micronutrient deficiencies during fetal life on the risk of chronic diseases and related biomarkers in later life, especially using data from intervention studies when available, is also examined. Given the high prevalence of micronutrient deficiencies globally and the growing epidemic of chronic disease, this topic warrants a closer examination.
Plausible pathways
In their description of the “thrifty phenotype” hypothesis, Hales and Barker (7) proposed that maternal or fetal malnutrition could affect fetal growth, metabolism, and vascular development. These changes could, in turn, affect the development of the kidneys; pancreatic β-cells; muscle, liver, or adipose tissue; or the hypothalamic-pituitary-adrenal (HPA) axis. This conceptual framework has been expanded to describe associations between maternal micronutrient status, the role and mechanism for organ systems development, and the consequent functional outcomes in the offspring based on available evidence (Fig. 1). Much work has been done to elucidate the effects of global food restriction or protein restriction on developmental outcomes in the offspring (8), although only recently has micronutrient nutrition come into focus. We have focused on 3 general pathways through which micronutrient deficiency during gestation may affect fetal development: hormonal changes in both the mother and the fetus, epigenetic gene regulation, and restricted fetal growth and development.

Maternal micronutrient status has been posited to influence hormonal regulatory pathways in the developing fetus and neonate. For example, iron or zinc deficiency may reduce the activity of insulin-like growth factor-1 and its receptors (22,23), thus inhibiting fetal growth (24). The regulation of appetite itself appears to have prenatal origins (25). In animal models of prenatal overnutrition, offspring exhibit hyperphagia and rapid weight gain and offspring of protein- or energy-restricted dams display preferences for high-fat foods (26). There are few data on maternal micronutrient status, however. Early postnatal zinc deficiency has been found to reduce appetite (27), although the effect of prenatal deficiency is less clear. Moreover, the HPA axis has an important role in the developmental programming of chronic disease (28) and a pathway to which micronutrient deficiencies may contribute. Under conditions of iron deficiency or hypoxia, circulating norepinephrine levels may increase, serving as a strong stimulus for the release of cortisol and corticotrophin-releasing hormone (22). Under normal conditions, the fetus is buffered from excessive cortisol exposure through the activity of a crucial barrier enzyme on the placenta, 11β-hydroxysteroid dehydrogenase-type 2, which converts active cortisol to inactive cortisone. This enzyme may be sensitive to maternal nutritional status (29). One study using a Swiss albino mouse model of maternal dietary restriction of copper, zinc, and vitamin E reported that the activity of placental 11β-hydroxysteroid dehydrogenase-type 2 was reduced (30), allowing more cortisol to cross the placenta to enter fetal circulation. Fetal exposure to glucocorticoids has been associated with intrauterine growth restriction, impaired nephrogenesis, elevated blood pressure, altered fat metabolism, and insulin resistance in later life (28). Further, fetal cortisol exposure may alter the set-point of the functioning of the postnatal HPA axis (28).

**FIGURE 1** Conceptual framework for how maternal diet and micronutrient status may affect the development of chronic disease in the offspring. Gray boxes represent hypothesized pathways through which various micronutrient deficiencies may influence the growth, development, or function of the indicated systems. Vitamins and minerals that have been investigated with each of these pathways are shown in italics. GFR, Glomerular filtration rate.
The growing field of epigenetic research has highlighted the role of 1-carbon metabolites, including folate and vitamin B-12, on the developmental programming of chronic disease (31). In brief, alterations in DNA methylation patterns have resulted in adult offspring being heavier, with higher percent body fat, increased insulin resistance, and elevated blood pressure (32). Prenatal protein restriction in rodents can induce alterations in hepatic glucocorticoid receptor and PPAR gene methylation, which was prevented by adding folic acid to the diet (33). Finally, in a novel experiment, Waterland et al. (34) found that a diet supplemented with additional folic acid, vitamin B-12, betaine, and choline could prevent the transgenerational amplification of obesity among agouti mice, suggesting that a diet rich in methyl donors may be protective in animals with a genetic tendency for obesity.

Lastly, micronutrient restriction may cause defects in developing organs. Severe micronutrient deficiencies or excesses can have teratogenic effects on the developing fetus. Moderate nutritional deficiencies or excesses during critical periods of fetal development may cause more subtle damage, potentially due to reduced tissue oxygenation as a result of anemia (35), increased oxidative stress (36), or impaired organ development. Maternal zinc restriction, for example, results in renal oxidative damage, as indicated by an increase in lipid peroxidation, reduction in glutathione levels, and glutathione peroxidase and catalase activities within the kidney (37). The specific developmental defects associated with these changes are detailed below.

**Cardiovascular function**

**Cardiovascular development.** Cardiac and vascular morphogenesis is guided by a complex series of events in early gestation. Risk factors for cardiovascular disease, including endothelial dysfunction, intima-media thickness, microvascular density, arterial dimensions, and arterial compliance, have been studied in relation to their association with size at birth (38), yet few have examined how micronutrients may influence these risk factors. Some research, however, exists for vitamins A and D, folate, calcium, iron, and zinc.

There is strong evidence that maternal vitamin A status during the embryonic and fetal periods is important for normal cardiac development as recently reviewed by Pan and Baker (21). RA, the biologically active form of vitamin A, is an important signaling molecule during fetal cardiovascular development (21). A state of both deficiency and excess has been associated with congenital malformations in both human and animal studies (39).

As described previously, maternal folate status may attenuate some of the adverse effects of protein restriction. Specifically, in a model of protein restriction using Wistar rats, offspring experienced attenuated vasodilatation to vascular endothelial growth factor (VEGF), raised systolic blood pressure (SBP), and reduced endothelial nitric oxide (NO) synthase mRNA (40). Folic acid supplementation restored vasodilatation response to VEGF and reduced SBP but did not affect NO synthase mRNA levels. Yet, in the nonprotein–restricted group, folic acid supplementation had no such effect (40). It has also been postulated that folate levels in human pregnancies are associated with endothelial function in the neonate, maybe through oxidative inactivation and reduced synthesis of NO (41).

Beyond vitamin A and folate, there are few data on other vitamins. In a model of vitamin D deficiency where female Sprague-Dawley rats were deficient during lactation, offspring had 15% lower myofibrillar protein, suggesting that maternal deficiency may have slowed the metabolic and contractile development of the heart (42). In contrast, data from 1 human study did not show a strong effect of maternal vitamin D status on offspring cardiovascular function, including SBP or diastolic blood pressure (DBP), carotid intima-media thickness, pulse wave velocity, or various aspects of cardiac structure (43), although losses to follow-up in the study were high.

Maternal calcium consumption during pregnancy may also be associated with cardiovascular development. A study of Wistar-Kyoto rats demonstrated that both deficient and excessive consumption was associated with progressively increasing blood pressure in the offspring (44). Blood pressure-lowering effects of calcium in the mothers may be one pathway, although precise mechanisms remain unknown. Calcium supplementation lowers the risk of preeclampsia and other hypertensive disorders during pregnancy (16) and maternal preeclampsia is a risk factor for elevated SBP among offspring adolescents (45,46), although effect sizes are largely attenuated after controlling for maternal pregnancy or child BMI. Alternatively, prenatal calcium restriction may affect cellular ion transport systems that in turn generate an altered metabolic set-point for calcium-regulating hormones influencing blood pressure, such as 1,25dihydroxy vitamin D, parathyroid hormone, and parathyroid hypertensive factor (44,47).

Severe zinc deficiency can cause developmental impairments to the heart, among other organs (48–50). A study from Peru suggested that prenatal zinc status may also influence fetal cardiovascular autonomic function (51), although the mechanisms are unclear. Women with moderate zinc deficiency were supplemented during pregnancy and their fetuses were monitored. The zinc-supplemented group had a lower mean heart rate at 20 wk of gestation and greater heart rate variability and accelerations beginning at 28 wk of gestation, all suggestive of greater parasympathetic control of the heart (51).

Moderate iron deficiency during gestation in various murine models has been found to be associated with elevations in blood pressure in the offspring (35,52–55). Hypoxia as a result of maternal iron deficiency increases cardiac size and decreases the number of cardiomyocytes and capillaries (56). Iron deficiency during the embryonic period resulted in reduced embryonic growth, increased heart size, and delayed vascular development, but culturing the embryos in control serum was found to reverse the changes in vascularization (57). Embryonic hypertension, with an increase in vascular resistance due to decreased angiogenesis (32), may also partially explain the observed increase in heart size (57).

**Kidney.** An alteration in the maternal environment may result in irreversible nephron deficits determined before birth (58). Mild vitamin A deficiency in utero is linked to a reduction in nephron endowment (59–61). In addition, retinol administration can prevent nephron deficits induced by protein deficiency (61,62). RA and aldosterone plus cholecalciferol, as well as VEGF, may have a role in the stimulation of renal endothelial cells (63). RA is critical in the branching growth of the ureteric bud through the maintenance of C-Ret expression (59,64,65). Other potential retinoid target genes, including midkine, sonic hedgehog, Hox d-11, matrix metalloproteinases, and tissue inhibitors of metalloproteinases, may also play a role in renal development (65,66).

Although animal models show the development of hypertension in adult life as a result of in utero exposure to vitamin A deficiency (67), the data are sparse among humans. A small study among pregnant women in Montreal, Canada and Bangalore, India showed that although there was no correlation between maternal serum retinol (55% were <0.9 μmol/L) and renal size...
of the Indian newborns, renal volume was higher in the Montreal than in the Bangalore newborns, after adjusting for body surface area (68). In a 9- to 13-y-old cohort in Nepal whose mothers participated in a randomized controlled trial (RCT) of vitamin A or β-carotene (7000 retinol equivalents/wk) supplementation before, during, and after pregnancy, the rates of hypertension or microalbuminuria did not differ by supplement group (69), although the prevalence of these conditions was only ~5%.

Limited evidence exists for the role of other vitamins in influencing kidney function. In 1 experiment using female Sprague-Dawley rats, vitamin D deficiency before and during pregnancy and throughout lactation resulted in a 20% increase in nephron number accompanied by a decrease in renal corpuscle size in the offspring (70). It is likely that rats exposed to vitamin D deficiency may first undergo an adaptation resulting in prolonged nephrogenesis but without the switch to nephron maturation, suggestive of functional impairment not studied in this experiment (70). Prenatal folic acid supplementation in Nepal resulted in a signification reduction in microalbuminuria (≥3.4 mg/mmol creatinine; relative risk: 0.56, 95% CI: 0.33–0.92) (71). However, the effect was attenuated in a multiple micronutrient supplement containing the same amount of folic acid.

Maternal iron or zinc deficiency results in an increase in the relative weight of the kidneys (35,53) and a reduction in nephron number in the offspring (37,72). Greater sodium sensitivity may explain some of the effects on blood pressure among offspring of iron-restricted dams, who had a 2-fold greater response to sodium intake on mean arterial pressure at 36 wk of age (73). Moderate maternal zinc restriction in Wistar rats resulted in a largely irreversible reduction in the glomerular filtration rate, an increase in SBP, and fibrosis in a number of the structures within the renal cortex (37).

**Blood pressure.** Function and development of both the cardiovascular system and the kidney, as well as a number of other regulatory pathways, are critical in maintaining normal blood pressure. Several studies in humans have examined blood pressure as an outcome in relation to maternal micronutrient status. These studies are described together below.

Maternal iron deficiency or anemia has been studied in a variety of settings for its association with blood pressure in the offspring, although few studies have found a significant relationship. Notably, there was no significant association between maternal hemoglobin (Hb) during pregnancy and offspring blood pressure in a number of studies, after controlling for potential confounding factors (74–77). An exception to this is a study of 5- to 9-y-old children from Argentina who experienced an increase of 1.3 mm Hg (95% CI: 0.4, 2.3) in SBP with each SD increase in maternal Hb concentration during pregnancy after adjustment for a range of child factors (78). This would suggest that lower maternal Hb was protective against higher blood pressure. Hb, however, is a nonspecific indicator of iron deficiency. Yet findings from the Project Viva study supported a positive association with maternal iron status (76). Every 10-mg increase in maternal dietary iron intake during the first, but not second, trimester was associated with an increase in SBP of 0.4 mm Hg (95% CI: 0.1, 0.7) among 3-y-old offspring. The effect was primarily due to iron consumed as supplements, rather than in food, and suggested that iron supplementation may increase the risk of high blood pressure. In contrast, in the Avon Longitudinal Study, 7-y-old children whose mothers consumed iron supplements during pregnancy had a lower blood pressure, but this relationship was confounded by other factors (75). In Nepal, in an iron-deficient setting, supplementation during pregnancy with iron-folic acid or with added zinc had no impact on blood pressure in offspring at 6–8 y of age (71). More studies focusing specifically on maternal iron status are needed to clarify this relationship.

The evidence that maternal calcium status may have an impact on offspring blood pressure has also been equivocal. For example, calcium intake during pregnancy was inversely associated with SBP in children at 1 mo and DBP at 6 and 12 mo of age (79). In Project Viva, dietary calcium intake during pregnancy was also inversely associated with offspring SBP at 6 mo of age (~1.1 mm Hg/500 mg calcium consumed) (80), but not at 3 y (81), suggesting that the effect did not persist beyond infancy. However, in a study of 147 Tasmanian twins, blood pressure of 9-y-old children did not differ by maternal calcium intake in pregnancy (82).

Data are available from 4 RCT studies of antenatal calcium supplementation where blood pressure in the offspring was examined (83–86). In Argentina, 7-y-old children had a modest reduction in mean blood pressure (~1.4 mm Hg; 95% CI: 3.3, 0.5) and a significant reduction in the risk of high SBP due to maternal calcium supplementation (11.4%) relative to the control group (19.3%) (83). In Portland, Oregon, offspring of a maternal calcium-supplemented group had a 2.2- and 4.8-mm Hg reduction in SBP at 3 mo and 2 y of age, respectively, compared with the controls (84), yet the losses to follow-up were substantial. In contrast, in Australia and The Gambia, there was no evidence that antenatal calcium supplementation caused any change in the blood pressure of 4- to 10-y-old offspring (85,86).

RCT at 2 sites in Nepal provide additional data on the effect of maternal micronutrient interventions on offspring blood pressure. One study providing a daily multiple micronutrient supplement to pregnant women showed decreases in mean SBP and DBP of offspring at 2.5 y of age (87). In contrast, at a different site, no effects on blood pressure were observed with maternal multiple micronutrient supplementation among 6–8 y old offspring (71).

In 1 RCT of maternal vitamin A or β-carotene in rural Nepal, neither supplement had an impact on blood pressure of children followed at 11–13 y of age (69).

**The pancreas and β-cells**

There is limited evidence that deficiencies in vitamin A, folate, zinc, and iron may have an effect on pancreatic development or the pathogenesis of insulin resistance. The importance of retinoids in the development of the pancreas and islet cells is not well established, although vitamin A-dependent proteins found in progenitor ductal and duct-derived islet cells is suggestive (88,89), as is the role of vitamin A in the expression of sonic hedgehog and fibroblast growth factor among other regulators that may influence α and β-cell neogenesis and replication (90,91). In an experiment using Sprague-Dawley rats, low to marginal deficiency of vitamin A before and during pregnancy and in the offspring during the postweaning period, caused reductions in β-cell area and number per islet by ~50% and a reduction in β-cell replication in the offspring (92). The 35- and 65-d-old offspring of rats fed the deficient diet had a 55% lower plasma insulin concentration and a 76% higher serum glucose concentration compared with rats fed a vitamin A-sufficient diet, suggesting that fetal vitamin A deficiency may have caused glucose intolerance later in adult life. Unfortunately, few if any human studies have examined the association between fetal vitamin A deficiency and the risk of insulin resistance.
Gestational folate or vitamin B-12 status may be predictors of insulin resistance via epigenetic mechanisms. One observational study conducted in India found higher maternal erythrocyte folate concentrations at 28 wk and low vitamin B-12 status at 18 wk of gestation to be associated with higher adiposity and insulin resistance, measured by the homeostasis model assessment (HOMA), among children at 6 y of age (93), although the observational design of the study makes it hard to interpret these findings. In a RCT in Nepal, folic acid supplementation during pregnancy did not affect fasting glucose, HbA1c (glycated hemoglobin), or HOMA among 6- to 8-y-old offspring (71).

Inconsistent effects on insulin resistance have been reported for iron and zinc in animal studies and data from human pregnancies are scarce. In studies of Wistar rats, glucose tolerance was improved among 3-mo-old (52) but not 14-mo-old (53) offspring of iron-restricted dams. In contrast, a separate study found no effect of maternal iron deficiency on glucose tolerance among 10-wk-old offspring (54). Maternal zinc restriction was found to cause irreversible changes in offspring fasting insulin levels and a muting of the insulin response to an oral glucose challenge (94). Yet there was no effect on glucose tolerance, perhaps reflective of greater insulin sensitivity. In Nepal, fasting insulin, glucose, or HOMA did not differ among 6- to 8-y-old children whose mothers had received antenatal iron+folic acid relative to those in the control group (71). Further, zinc supplementation (when added with iron+folic acid) was also not associated with insulin resistance in these children (71).

**Body composition and adiposity**

Developmental programming may influence body composition through appetite regulation, a propensity for increased sedentary behavior, epigenetic modification of key regulatory genes, and altered fat deposition and adipocyte metabolism (Fig. 1) (8,25).

Animal studies of maternal dietary restriction in multiple vitamins (95) or minerals (96) have been found to cause elevations in offspring percent body fat and triglycerides. Maternal dietary restriction in iron, zinc, calcium, and magnesium, individually or in combination, was found to result in increased percent body fat (96) and some varying effects on insulin resistance in the offspring. For example, the offspring of magnesium-deficient WNIN rat dams had greater percent body fat and lower lean body mass and fat free mass at 3, 6 (97), and 18 mo of age (98) despite having lower body weight and BMI than controls. At 3 mo of age, the rats also had elevated triglycerides and by the age of 6 mo they became insulin resistant (98). The offspring of iron- (73) or zinc- (94) deficient animals were found to have greater visceral adipose tissue or percent body fat despite having a lower overall body weight. This was partially explained by lower locomotor activity in the offspring in the iron-restricted model (73).

One longitudinal study in England found that maternal folate intake at 18 or 32 wk of gestation was not associated with any measures of body composition in children at 9 y of age (99). However, supplementation studies showing this are lacking. In Nepal, maternal supplementation during pregnancy with iron+folic acid+zinc, but not folic acid alone or with iron, resulted in a slight increase in height and decreased adiposity as reflected by lower skinfold thicknesses in children at 6–8 y of age relative to controls (100). In parallel, a study from Peru found evidence of increased lean body mass among infants whose mothers had received a daily zinc+iron+folic acid vs. iron+folic acid supplement during pregnancy (101).

**The lung.** Many respiratory pathologies in adulthood appear to have their origins in impaired growth and maturation of the lung in utero (102). It is well established that uptake and storage of retinyl esters occurs in the lungs (103). The lungs are sensitive to maternal vitamin A deficiency (104). In particular, deficiency results in immature lungs with reduced bronchial branching and reduced elastin (important for maturation of alveoli both in the number and size, which in turn influences lung capacity in the neonate) (105). Such effects may, however, persist into perinatal life such as decreases in the expression of elastin and growth arrest specific gene 6 in lungs of vitamin A-deficient fetuses. Respiratory failure among vitamin A-deficient rat pups is a common cause of perinatal mortality (106) and pups have lower lung capacity, smaller sacculi, and fewer elastic fibers. Interestingly, prenatal RA administration to Merino sheep did not improve alveolization or postnatal lung function in either preterm or term animals despite increases in liver retinol at birth (107).

Retinoids are critical in lung development and maturation during the early postnatal period when lung structure is rapidly developing. All-trans RA administration in rodents promotes septation and increases the number of pulmonary alveoli (108–110). Moreover, RA prevents the inhibition of septation caused by glucocorticoid exposure during alveologenesis (111). Although the lung serves as a storage location for retinyl esters (103), levels decrease at birth as they serve as a source of RA needed for lung development (112). Recent animal studies have shown that lipid interstitial cells of the alveolar wall store retinol and also synthesize and secrete RA, thereby suggesting an endogenous source of retinoids for alveolar formation (113). In the pulmonary microvascular endothelial cells, all trans RA has been shown to increase the expression of mRNA of cellular retinol binding protein-1 (113). In an experiment using mice of the ICR strain, antenatal vitamin A administration increased both lung and plasma levels of VEGF collected from fetal and neonatal samples (114). VEGF is a strong mitogenic factor and a mediator of angiogenesis that plays an important role in lung development and maintenance of lung function. The lung presents the highest tissue VEGF gene expression (115,116) and pulmonary VEGF levels are reduced among infants dying from bronchopulmonary dysplasia (117). Treatment with RA has been shown to promote alveolar development via regulation of VEGF and VEGF receptor-2 (118).

Defects in pulmonary development associated with prenatal vitamin A deficiency have been found to be largely reversible with early postnatal vitamin A supplementation. In a Wistar rat model of moderate prenatal vitamin A deficiency, postnatal administration of vitamin A at birth reversed many of the lung abnormalities associated with deficiency (119). Vitamin A-deficient offspring displayed a reduced number and surface area of alveoli, increased thickness of the alveolar septum, reduced elastin fibers, and increased collagen deposits. Supplemental vitamin A improved all of these pulmonary defects by 8 wk of age, bringing some indicators back up to the same level as controls (119). Vitamin A supplementation among preterm neonates has been found to reduce the incidence of broncho-pulmonary dysplasia, decrease the need for oxygen and mechanical ventilation, and reduce the risk of airway infections, indicating the role of vitamin A in prevention/repair of lung injury in the neonate (120–123). RA influences gene production responsible for the synthesis of 3 surfactant proteins (SP) (i.e. SP A, SP B, and SP C) and enzymes producing their lipid components in cultured epithelial cells (124). Nuclear RA receptors are also involved in lung development as indicated in...
by specific localization of certain RA receptor proteins during fetal lung branching and airway growth (112).

Despite the extensive role of retinoids and their receptors in pulmonary function, virtually no data exist to examine the long-term effects of vitamin A metabolites on pulmonary function in childhood or adulthood. In Nepal, children 9–13 y of age whose mothers received weekly vitamin A supplementation during pregnancy had significantly higher forced inspiratory volume in 1 s and forced vital capacity compared with those whose mothers were in the placebo group (125). There are few data on other nutrients in pulmonary development in utero.

In conclusion, the short-term consequences of micronutrient malnutrition during pregnancy on the mother and infant are fairly well understood, but the long-term costs of these deficiencies have yet to be fully elucidated. Although there is evidence from animal experiments and observational studies in humans to suggest a link between intrauterine micronutrient status and the potential risk of chronic diseases, the understanding of molecular mechanisms of these effects for many micronutrients is weak. The roles of vitamin A, folate, iron, and, in some instances, zinc seem to have been the best elucidated both in terms of underlying mechanisms and long-term impacts on chronic disease outcomes (Fig. 1). In addition, few studies have been done to determine nutrient-nutrient interactions that may alter the effects and mechanistic pathways. Both antagonistic and synergistic interactions are likely. More work is needed to better understand underlying mechanisms of action of single and multiple nutrients and interactions between nutrients, using animal models as well as human studies. In the epidemiologic literature, evidence for the longer term health consequences from a few randomized controlled maternal micronutrient intervention trials is emerging, especially those examining antenatal vitamin A, iron, zinc, folic acid, and calcium supplementation, although longer follow-ups beyond childhood are needed. Yet the connection to the basic developmental biology research is lacking. For example, the greatest body of research into cardiac, renal, and pulmonary developmental biology exists for vitamin A, yet there are few long-term studies in humans. Clearly, more work is needed to bridge the developmental biology research to disease outcomes. Much could be gained from longitudinal studies, particularly if mechanistic research could be simultaneously carried out, to further our understanding of how maternal micronutrient deficiency during pregnancy may set the stage for the long-term health of offspring.

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