Role of nutrients in the development of neonatal immune response
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ABSTRACT

Nutrients exert unique regulatory effects in the perinatal period that mold the developing immune system. The interactions of micronutrients and microbial and environmental antigens condition the post-birth maturation of the immune system, influencing reactions to allergens, fostering tolerance towards the emerging gastrointestinal flora and ingested antigens, and defining patterns of host defense against potential pathogens. The shared molecular structures that are present on microbes or certain plants, but not expressed by human cells, are recognized by neonatal innate immune receptors. Exposure to these activators in the environment through dietary intake in early life can modify the immune response to allergens and prime the adaptive immune response towards pathogens that express the corresponding molecular structures.
INTRODUCTION

The neonatal immune response is rapidly modulated at birth through encounters with environmental antigens, immune activators, and biological response modifiers, including those present in colonizing microorganisms and dietary substances. Developmental programming in the context of these interactions leads to characteristic growth patterns in early life that are associated with altered risk of cardiovascular disease, type 2 diabetes, and cancer. Recent studies indicate that perinatal nutrient deficiency is associated with reduced thymic function in later life. The underlying mechanisms involve the interaction of genetic imprinting, the fetal neuroendocrine system, maternal factors, the neonatal microbial flora, and antigen exposure after birth.

Nutrients regulate the priming of immune response postnatally through effects on innate immune signal transduction pathways and immune cell development, thereby affecting early sensitivity to allergens, tolerance towards the emerging gastrointestinal flora and ingested antigens, and host defense against potential pathogens. Micronutrients, such as vitamin A, are critical for the early development of lymphoid cells in the gastrointestinal tract-associated lymphoid tissue (GALT) including Peyer’s patches, the mesenteric lymph nodes, lamina propria, and gut epithelium.

Neonates rely on the innate immune system. The weaker response of their monocytes and macrophages to Toll-like receptor (TLR) ligands is associated with increased risk of infection. Nutrients and growth factors present in human milk are specific regulators and inducers of innate immune response. The fatty acid composition of milk has been found to alter the balance of circulating immune cell subpopulations and cytokine responses in early life. Adequate levels of vitamin A and vitamin D promote gut integrity and mucosal immune function in the neonate, while deficiencies of these micronutrients can cause impaired immune response. Maternal micronutrient deficiencies in selenium, and iron have direct effects on infant T lymphocyte and natural killer (NK) cell populations. Maternal vitamin E levels appear to influence allergic sensitivity. Replacement of critical micronutrients, such as zinc or vitamin A, when these are depleted during infection can substantially enhance recovery from specific infections through effects on host defense mechanisms. The activities of certain ingested plant and environmental microbial components, which present pattern recognition structures to the neonate, are also relevant to the early development of immune response. Molecular structures present on microbes and certain plants, but not expressed by human cells, are recognized by innate immune receptors analogous to the TLRs. For example, edible plants and their products, such as tea, mushrooms, and apples, express alkylamines that are recognized by human gamma delta T cells and trigger an immune response. Others, such as beta glucans, which are present in yeast and fungi as well as mushrooms, seaweed, and barley, stimulate hematopoiesis and innate immune response, modify response to allergens, and may prime the adaptive immune response towards the corresponding pathogens.
PERINATAL MALNUTRITION

Perinatal malnutrition has long-term effects on postnatal development. This concept, which was advanced by Barker as the "developmental origins of health and disease" hypothesis, is relevant to postnatal maturation of the immune response. McDade et al. reported that adolescents who were small for gestational age (SGA) at birth had lower thymopoietin levels when compared to adolescents who were appropriate for gestational age (AGA) at birth. The thymopoietin levels during adolescence correlated with growth in length during the first year of life in both groups. The probability of mounting a positive antibody response for adolescents who were SGA and also undernourished at the time of immunization was lower compared to adolescents who were AGA. Moore et al. have reported similar findings in adults using the same purified Vi surface polysaccharide extracted from Salmonella typhi. Interestingly, while they found a correlation for both the IgG and IgM antibody responses to Vi vaccine with birth weight, they did not find these responses to rabies or typhoid vaccine. The studies suggest that polysaccharide T-independent immune response may be specifically compromised by fetal growth retardation.

Prenatal stress can program the hypothalamic-pituitary-adrenocortical (HPA) axis and may cause imprinting effects on the immune response; this has led to reduced thymic function in animal models that are analogous to humans undergoing postnatal maturation of the immune response. Maternal psychological stress is associated with a shorter length of gestation and consequent lower birth weight, and has recently been shown to affect cytokine secretion patterns in adult life. Increased cortisol levels after stress in pregnant rats led to altered gene expression of the placental glucose transporter, suggesting a potential impact on transplacental glucose transport to the fetus.

Experimental undernutrition alone has recently been reported to program the HPA axis, leading to increased placental transfer of glucocorticoids to the fetus and increased glucocorticoid response after birth in response to stimulus. Activation of the HPA axis is also central to the etiology of immunodeficiency in malnutrition, where hypercortisolemia is a common finding. Cortisol binds to the glucocorticoid receptor in the cytosol, translocates to the nucleus, and promotes gene transcription. Some of the interactions are presented in Figure 1. A recent study reported by Manary et al. of protein-deficient, marasmic children with or without acute infection showed that an increase in free cortisol was found only in infected children and the level was equivalent in both marasmic and well-nourished children. This may indicate that hypercortisolemia in malnutrition is due to subclinical infection. Marasmic children did have greater amounts of glucocorticoid receptors translocated to the nucleus compared to well-nourished control groups, regardless of infection. However, the expected effect of hypercortisolemia on proteolysis was lacking in marasmic, infected children, suggesting either that intracellular cortisol was not secreted or that the cortisol-binding receptor was inactive.
Figure 1 Interactive effects of malnutrition and infection on immune response. Illustration of some of the ways in which malnutrition and infection modulate immune response and central involvement of the hypothalamic pituitary axis, as described in the text. Abbreviations: APR, acute-phase response; IR, immune response; lymphs, lymphocytes; grans, granulocytes; pre T,B, early uncommitted T and B lymphocytes in bone marrow; Pro T,B early committed T and B lymphocytes in bone marrow; TLR, Toll-like receptor.

Malnutrition leads to reduced production of thymic hormones. Lowered levels of thymulin were observed in malnourished children\(^3\) and in children with zinc deficiency alone.\(^4\) Leptin, the adipocyte-secreted hormone that regulates weight centrally, also has cytokine-like activities. Leptin regulates the thymus by increasing thymopoiesis and inhibiting apoptosis when thymic activity is induced by other activators.\(^5\) While leptin is decreased in malnutrition, glucocorticoid hormone levels are increased, and the combination has been identified as the key mechanism involved in the loss of thymocytes and thymic atrophy.\(^6\) Malnutrition-associated immune deficiency enhances susceptibility to infections and cytokine activation.\(^7\) Tumor necrosis factor and interleukins 1, 6, and 8 induce fever and the hepatic synthesis of acute-phase reactant proteins, such as C-reactive protein (CRP); they also inhibit production of serum albumin and transthyretin.\(^8\) Shifts in storage pools of micronutrients occur during the acute-phase response and cause transient alterations in circulating levels of iron, zinc, and copper. This is due to transport by newly synthesized micronutrient-binding proteins such as ferritin, metallothionein, and ceruloplasmin.\(^9\) A recent study showed that genome-level alterations of zinc homeostasis is prevalent in clinical pediatric septic shock.\(^10\) Neonatal response to infection or "sterile infection" elicited by bacterial lipopolysaccharide (LPS), the main component of the outer membrane of gram-negative bacteria, has a potential impact on both the programming of immune response and brain development.\(^11\) Although malnutrition is associated with reduced cytokine response to antigen in vitro, the levels of circulating pro-inflammatory cytokines in vivo are increased.\(^12,13\) Importantly, neonates appear to have a reduced compensatory anti-inflammatory response and may, therefore, be at greater risk for inflammatory damage.\(^14\) In recent studies, we reported that, compared to adults, the neonatal cytokine response is specifically deregulated in response to bacteria and has a tendency towards an uncompensated pro-inflammatory response. We observed that a lower percentage of monocytes produced cytokine responses to a panel of microbes but that the levels of cytokines IL-6 and IL-8 secreted in response to the same microbes were actually higher than those of adults.\(^15,16\)

The thymus is selectively sensitive to nutritional injury and specifically important to the formative phases of immune development. Programmed involution of the thymus develops gradually over the first decades of life, and recent studies show that functionally active peripheral perivascular space thymic components predominate in adult life.\(^17,18\) However, this tissue continues to be responsive to nutrients, suggesting that the regulatory effects governing
neuroendocrine-thymus interactions continue to be effective. Healthy neonates have higher levels of plasma zinc and bioactive thymulin compared to their mothers, and emerging studies of change over the first weeks of life in relationship to growth hormone levels and immune cell populations suggest that programmed interactions with the developing immune system evolve rapidly in the postnatal period.

Malnutrition is a major cause of immune deficiency leading to greater frequency and severity of common infections. Primary malnutrition is common among children of all socioeconomic strata in wealthy industrialized societies due to poverty, lack of education, food allergies, inappropriate or limited diet, or eating disorders. Inadequate intake of micronutrients, including vitamins A and E, calcium, iron, and zinc, are prevalent among children under the age of 10 years, and they often go unrecognized. Children comprise a significant part of increasingly large immigrant populations in industrialized urban settings, where they may live in impoverished circumstances and have less access to health care. Such children are especially vulnerable to the effects of nutrient deficiency.

EFFECTS OF SPECIFIC MICRONUTRIENTS

Micronutrients have a major impact on immune response, through antioxidant activities and modulation of cytokine expression. Antioxidant enzymes, such as copper, zinc, and manganese superoxide dismutases, require trace metals for biological activity, and these enzyme reactions protect against oxidative damage caused by free radical formation during immune response and other biological reactions. Intracellular redox balance has a signaling role in immune cell development and function, and the antioxidant effects of micronutrients regulate cytokine production. Table 1 summarizes some of the main findings described in the following sections.

Table 1 Effects of micronutrients on neonatal immune response.

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Target cells</th>
<th>Effect on development of immune system</th>
<th>Interactions in infection</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zinc</td>
<td>T cells, NK cells, B cells</td>
<td>Deficiency impairs immune response, ↓ hematopoiesis</td>
<td>Levels are rapidly depleted</td>
<td>Deficiency ↑ glucocorticoid ↓ pre T cell and B cells via Bcl-2 → apoptosis</td>
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<tr>
<td></td>
<td></td>
<td>Lymphopenia, dermatitis, enteritis</td>
<td>Repletion ↑ recovery</td>
<td>Required for thymic hormone function</td>
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<td></td>
<td></td>
<td>↓ T thymus, bone marrow</td>
<td>Deficiency promotes infection</td>
<td>Required for activity of &gt;100 enzymes</td>
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<tr>
<td>Vitamin</td>
<td>Cell Types</td>
<td>Function/Effect</td>
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<tr>
<td>Vitamin A</td>
<td>T cells, NK cells, B cells</td>
<td>Deficiency ↓ NK activity&lt;br&gt;Repletion improves gut integrity at weaning&lt;br&gt;Deficiency ↑ infections and mortality from infections&lt;br&gt;Levels depleted in infection&lt;br&gt;Repletion ↑ recovery, reduces infection morbidity, mortality&lt;br&gt;IL-2 receptor beta, interferon regulatory factor, transcription factor mRNA</td>
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<td></td>
<td></td>
<td>Inducer for gut-homing of T cells&lt;br&gt;Affects IL-12 and IL-10 production</td>
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<tr>
<td>Selenium</td>
<td>Monocytes, T cells, NK cells</td>
<td>Deficiency affects T and NK cell development&lt;br&gt;Deficiency suppresses antigen presentation&lt;br&gt;May enhance maternal HIV transmission&lt;br&gt;Antioxidant&lt;br&gt;Affects IL-2 response, regulates NF kappa B</td>
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<tr>
<td>Vitamin C</td>
<td>Phagocytes</td>
<td>Promotes phagocytic and NK activity&lt;br&gt;↑ response to strep infection&lt;br&gt;↑ response to LPS&lt;br&gt;Decreases monocyte response to LPS</td>
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<td></td>
</tr>
<tr>
<td>Vitamin D, 1,25-dihydroxy-vitamin D3</td>
<td>T cells, B cells, monocytes, macrophages, dendritic cells</td>
<td>Reduces stress IL-6 response</td>
<td>Promotes gut integrity</td>
<td>Reduces growth of H. pylori</td>
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<tr>
<td>Vitamin D₃ affects differentiation, maturation, and function of cells</td>
<td>Vitamin D₃ suppresses autoimmune disease in animal models</td>
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<tr>
<td>VDR polymorphisms regulate response to mycobacteria, hepatitis B, inflammatory bowel disease through TLR signaling</td>
<td></td>
<td>Affects differentiation of monocytes and dendritic cells</td>
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<tr>
<td>Vitamin E</td>
<td>T cells, B cells, monocytes</td>
<td>Maternal levels provide allergic protection</td>
<td>Deficiency may promote viral virulence</td>
<td>Modulates cyclic AMP response element binding proteins</td>
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### Zinc

Gestational zinc deficiency, caused by an imbalance between intake and increased requirement, is a common problem worldwide. Experimental models of zinc deficiency show a teratogenic effect on fetal development that also occurs due to "sequestration-induced deficiency" in individuals with borderline zinc status or an infection. Fetal malformations or loss have been observed in women with the genetic zinc deficiency, acrodermatitis enteropathica (AE), caused by an autosomal recessive defect of zinc absorption, who had inadequate, compensatory zinc intake during pregnancy; the loss or malformation of a fetus was also more common in mothers without AE who had low dietary intake. Circulating zinc levels decline during pregnancy due to hemodilution, decreased levels of zinc binding protein, hormonal changes, and the active transport of zinc from the mother to the fetus. While zinc status is difficult to assess accurately, the consensus is that deficiency is common in
pregnancy, particularly in women consuming all-vegetarian diets with high levels of dietary phytate, which blocks zinc absorption. Neonatal zinc can be acquired through maternal milk. A recent study found that higher levels of expression of the CD4 T-cell receptor correlated with increased thymulin and zinc levels in healthy infants. While maternal defects in zinc transport into milk can be a cause of zinc deficiency in infants, premature infants have both a higher requirement and a reduced ability to conserve absorbed zinc. AE presents in infancy as skin lesions (acute dermatitis or hyperkeratotic plaques), diarrhea, alopecia, and is associated with increased incidence of infections caused by severe immune deficiency. Immune defects range from severe thymic atrophy and profound lymphopenia to skin test anergy and loss of NK cell activity. All symptoms resolve with adequate zinc supplementation. Zinc-fortified formulae improved linear growth in infants with protein calorie malnutrition and also improved delayed-type hypersensitivity, as shown by improved skin test reactivity, enhanced lymphoproliferative responses, and increased salivary IgA. Shah et al. reported that prenatal maternal zinc supplementation improved infants’ immune function and neurobehavioral development.

Animal model studies have demonstrated that perinatal zinc deficiency causes decreases in helper T-lymphocytes and NK cells and causes reduced cytokine responses that persist after zinc repletion. Zinc deficiency induces increased glucocorticoid production and reprogramming of the immune system at the level of bone marrow and is characterized by thymic atrophy, lymphopenia, and compromised cell- and antibody-mediated responses. Although few human studies have been performed, investigators have observed that antenatal zinc supplementation is beneficial for low-birth-weight-infant responses to BCG vaccination post birth, while zinc supplementation of infants after birth enhanced the response to one serotype of heptavalent pneumococcal protein conjugate vaccine.

Iron

Iron deficiency anemia in children is associated with impaired immune response, as shown by reduced phagocytic activity and immunoglobulin levels. Prenatal stress in a nonhuman primate model led to iron-deficiency anemia and reduced NK cell activity in early infancy. Acute infection in iron-deficient children modulates proinflammatory cytokine responses and correlates with increased IL-6 and decreased IL-8 responses. Compared to adults, a lower level of CRP increase is associated with nutritional compromise in children, suggesting that the impact of infection on micronutrient balance is greater. Thus, among apparently healthy children at 1 year of age, CRP levels greater than 0.6 mg/L were associated with significantly reduced levels of transthyretin, iron, retinol, and beta-carotene. The relevance of iron status to postnatal immune development has been addressed in a few studies. Collins et al. demonstrated that experimental iron deficiency led to upregulation of apical iron transport-related proteins, transferrin receptor and heme oxygenase, and copper loading genes; it also decreased the expression of genes involved in the oxidative stress response.

Animals have developed various methods to sequester iron as a means of host defense. These methods are designed to deprive invading organisms of iron by depleting plasma during the acute-phase response; however, pathogens have simultaneously evolved systems to acquire iron even in highly iron-depleted environments. The anemia resulting from chronic disease is
a contributing cause of faltering growth in children and is common in infants with congenital HIV infection. The controversy about iron supplementation has continued over several decades because of concern that excess, or inappropriate timing of, iron repletion would promote bacterial growth. The current consensus is that iron supplementation has a high probability of adversely affecting outcome in individuals who present with concurrent infection or who carry genes predisposing to iron overload. Studies of nutrient-gene interactions involving polymorphisms in haptaglobin, the hemoglobin-binding acute-phase protein, and the iron transporter NRAMP1 (natural-resistance-associated macrophage protein-1, or SLC11A1) have addressed the critical question of how iron affects the host response to HIV and Mycobacterium tuberculosis infections. Both infections are characterized by altered iron handling and the interactions have greater potential effects in infancy.

Selenium

Selenium is a critical component of the antioxidant enzyme glutathione peroxidase, and it has independent antioxidant activity that is linked to decreased transcription and expression of manganese superoxide dismutase and uncoupling protein 2. Selenoproteins are an important component of the antioxidant host defense system affecting leukocyte and NK cell function. Selenium affects TLR signaling by inhibiting NF-kappa B activation by some agonists including LPS. Deficiency can be a critical component of protein calorie malnutrition and is associated with congestive heart failure in this setting. Juvenile cardiomyopathy (Keshan) appears to involve both selenium deficiency and enteroviral infection. Selenium and vitamin E deficiency can enhance the virulence of two RNA viruses, coxsackie B and influenza, through variant selection and possibly by direct effects on viral phenotype; this could have important implications for human transmission. One experimental study suggests that selenium deficiency could be protective against influenza A in certain circumstances. Selenium may protect against cell death caused by some viral infections. Selenium supplementation in HIV infection enhances child survival without having direct effects on HIV progression. However, maternal selenium supplementation has been observed to enhance HIV viral shedding and may increase maternal infant transmission.

Vitamin A

The value of vitamin A supplementation in the first few days of life for reducing early infant mortality from infections in populations with endemic vitamin A deficiency is well established. Vitamin A enhanced newborn immune response to hepatitis B vaccine and, when given in combination with zinc supplementation to children in Africa, it reduced the risk of fever and clinical episodes of malaria. Retinoic acid (RA), the vitamin A metabolite, is an inducer for the gut-homing specificity of T cells that enhances the expression of the integrin alpha4beta7 and CCR9 on T cells upon activation. Retinoic acid has also been shown to synergize with GALT-dendritic cell (DC) production of IL-6 or IL-5 and to induce IgA secretion. Current studies show that specific DCs in the GALT, which induce the development of Foxp3+Treg cells from CD4+ T cells, require the dietary metabolite retinoic acid (RA) and that RA directs Treg cell homing to the gut. Therefore, dietary vitamin A may be critical for the postnatal development of tolerance outside the thymus in
response to antigen presentation under subimmunogenic conditions. Since impaired gut immune response in early infancy could contribute to the development of atopic sensitization, Pesonen et al. looked for an association between plasma retinol concentrations and the subsequent development of allergic symptoms in healthy infants. They found that retinol concentration at 2 months correlated inversely with a positive skin prick test at 5 and 20 years, and with allergic symptoms at 20 years. Others have shown that intestinal barrier function in mildly malnourished children was inversely correlated with serum retinol concentrations.

Vitamin A deficiency is associated with severity of many infections, including measles, rotavirus, HIV, and bacterial infections. Reduced levels of serum transretinol are common in infants of HIV-1-infected mothers, and this is independent of whether their own HIV status is positive. As shown in Figure 2, we found that the levels of transretinol were reduced in both seroreverters and in HIV-positive children in early life who were born to HIV-positive mothers compared to healthy children. Vitamin A deficiency, as measured by a low maternal serum retinol level, is a risk factor for mother-to-child transmission. Postpartum maternal and neonatal vitamin A supplementation of HIV-positive infants prolongs survival. However, the same supplementation regimen increased progression to death for breastfed children who were initially HIV negative and later infected through breast milk. Subsequent studies reported that mannose-binding lectin (MBL) gene polymorphisms have a regulatory effect on response to vitamin A in HIV infection. MBL is a component of the innate immune system that binds to carbohydrate ligands on the surface of many pathogens and activates the lectin pathway of the complement system. Persons with MBL-2 allele variants have deficiencies in innate immunity and have an increased susceptibility to HIV infection. Evaluation of infants receiving vitamin A plus beta-carotene A supplementation showed that the rates of maternal HIV transmission were higher in infants with MBL-2 variants in the control arm compared to the supplementation arm. Overall, the supplementation trials show that selective vitamin A supplementation of HIV-positive children prolongs their survival, but the trials do not provide evidence to recommend vitamin A supplementation of HIV-infected pregnant women.

Figure 2  Vitamin A levels in congenital HIV exposure. Data show comparison of serum transretinol levels in HIV-positive children (n = 13; mean age 2.2 ± 2.0 years) compared to seroreverter children (n = 9; mean age 1.1 ± 1.2 years) and control healthy children (n = 23; mean age 2.3 ± 1.6 years). Differences in vitamin A levels compared to controls were significant by one-way analysis of variance (P = 0.0003) and pairwise differences using Tukey's multiple comparison test between HIV-positive versus controls and HIV-negative serorevertors compared to controls were significant (P < 0.05).

Vitamin C
Dietary vitamin C intake is specifically associated with preterm birth via premature rupture of membranes, and it may be linked to genetic variants in the vitamin C transporters by enhancing risk of spontaneous preterm birth. Vitamin C is a free radical scavenger that serves as an important antioxidant. Vitamin C concentrations in the plasma and leukocytes decline during infections and stress. Supplementation with antioxidant vitamins, including vitamin C, has been shown to improve immune response to group A streptococcal infection in children compared to penicillin alone. Supplementation may enhance phagocytosis and NK cell activity by increasing levels of the antioxidant plasma glutathione levels. Helicobacter pylori infection is associated with a decrease in gastric juice ascorbic acid concentration, and this effect is greater in children with the CagA-positive strain A. Vitamin C has antimicrobial effects against H. pylori. Children are susceptible to H. pylori infection through household contact, and infection is associated with increased incidence of gastric reflux in childhood and lifetime risk of gastric cancer.

**Vitamin D, 1,25- dihydroxy vitamin D3 [1,25(OH)\(_2\)D3]**

The critical role of vitamin D as a regulator of calcium homeostasis in growing children and the impact of vitamin D deficiency on bone mineral density due to inadequate sun exposure or obesity is emerging as a serious health problem. Experimental vitamin D deficiency promotes the development of autoimmune disease including inflammatory bowel disease and is blocked by the active form of vitamin D. This discovery has led to the hypothesis that vitamin D is an environmental factor that affects the development of immune-mediated diseases. Other studies showed that inflammation in the IL-10 knockout mouse could be suppressed by 1,25(OH)\(_2\)D3. This therapeutic effect was maximized by the addition of high levels of calcium. Overall, blockade of inflammation involved inhibition of the TNF-alpha pathway. Relevant studies in humans suggest that vitamin D receptor variants are linked to the development of asthma and atopic disease. Vitamin D deficiency in children with nutritional rickets is associated with increased infections. Allelic variants of the vitamin D receptor appear to mediate differential susceptibility of children to M. tuberculosis infection and to acute lower respiratory infections. In the case of mycobacterial infection, the mechanism of effect involves TLR activation of human macrophages, upregulated expression of the vitamin D receptor and the vitamin D-1-hydroxylase genes, leading to induction of the antimicrobial peptide cathelicidin and intracellular killing of M. tuberculosis.

**Vitamin E**

Vitamin E is a strong antioxidant that enhances monocyte/macrophage-mediated response. Emerging studies suggest improvement in eczema and reduced serum levels of immunoglobulin E in atopic subjects with dermatitis treated with vitamin E. Current studies, as noted above, suggest that vitamin E deficiency may enhance the virulence of viral infections through effects on the virus.

**Beta Glucan**
The neonatal innate immune system provides the initial line of defense against microbial infections through recognition and response to a wide range of microorganisms, and it is based on a germ-line encoded repertoire of invariant TLR receptors. The requirement for post-birth maturation of this system under the influence of dietary factors, including soluble forms of TLRs present in human milk, is now appreciated.\textsuperscript{115} The development of the adaptive immune response post birth initially requires maturation of the innate immune system and, in the absence of such contacts, as formulated in the "hygiene" hypothesis, asthma, allergies, and atopic and autoimmune diseases are more likely to develop in susceptible individuals. Antigen dose affects response and may define the outcome of sensitization. Th-2 (allergic) priming is preferentially favored by low-dose antigen exposure, whereas higher doses favor Th-1 priming. Therefore, enhanced exposure to endotoxin and other microbial components is considered the important protective factor that is prevalent in farm environments. Assessment of the levels and determinants of bacterial endotoxin or LPS, mould beta(1,3)-glucans, and fungal extracellular polysaccharides in the house dust from environments of exposed and reference children recently showed that the levels per gram of house dust in farm homes were 1.2- to 3.2-fold higher than the levels in reference homes.\textsuperscript{116}

Beta 1, 3 D-glucan is a cell-wall component found in several fungal pathogens, including Candida and Aspergillus spp., but also in mushrooms and barley. Children have been shown to have higher levels of beta glucan in blood compared to adults.\textsuperscript{117} Iossifova et al. examined the association between (1-3)-beta-D-glucan exposure and the prevalence of allergen sensitization and wheezing during the first year of life in a large birth cohort of infants born to atopic parents. The results showed that high exposure to beta glucan, but not to endotoxin, was associated with decreased risk of recurrent wheezing among infants born to atopic parents. This effect was more pronounced in the subgroup of allergen-sensitized infants.\textsuperscript{118}

Glucans are hematopoietic and immune system activators. We studied the effects of an extract from the Maitake mushroom beta glucan (MBG), on the proliferation and differentiation of hematopoietic stem cells in the mouse and in human umbilical cord blood. We found that MBG enhanced murine bone marrow cell proliferation and differentiation into granulocyte-monocyte colony forming unit (CFU-GM) in a dose-dependent manner.\textsuperscript{119} MBG enhanced cord blood stem cell proliferation and differentiation into CFU-GM in vitro in a dose-dependent manner. MBG induced granulocyte colony stimulating factor production in cord blood but not in adult monocytes.\textsuperscript{120} This difference could reflect the early stage of development of the cord blood monocyte compared to the adult monocyte or may suggest that adults are less responsive to beta glucans due to tolerance induction.

Experimental studies have shown that orally administered water-soluble glucans translocate from the gastrointestinal tract into the systemic circulation. The glucans are bound by gut epithelial and GALT cells, and they modulate the expression of pattern recognition receptors in the GALT, increase IL-12 expression, and induce protection against infectious challenge with Staphylococcus aureus or Candida albicans.\textsuperscript{121}

In addition to their presence in the environment, beta glucans are found in human milk\textsuperscript{122} and are being introduced into the food supply in yogurts and oat milk.\textsuperscript{123,124} Therefore, the
potential effect of beta glucans in modulating neonatal immune response may provide another approach to enhancing host defense in early life.

CONCLUSION

In summary, nutrients exert unique regulatory effects in the perinatal period that mold the developing immune system. The interactions of micronutrients as well as microbial and environmental antigens condition the post-birth maturation of the immune system, thereby influencing reactions to allergens, fostering tolerance towards the emerging gastrointestinal flora and ingested antigens, and defining patterns of host defense against potential pathogens.

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Declaration of interest. The authors have no relevant interests to declare.

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