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Maternal Nutritional Status and Development of Atopic Dermatitis in Their Offspring

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Abstract

Atopic dermatitis (AD) is the leading chronic skin inflammatory disease and the initial manifestation of atopic march. Available evidence supports the notion that primary prevention early in life leads to a decreased incidence of AD, thus possibly decreasing the subsequent occurrence of atopic march. Nutritional status is essential to a proper functioning immune system and is valued for its important role in AD. Essential nutrients, which include carbohydrates, proteins, lipids, vitamins, and minerals, are transferred from the mother to the fetus through the placenta during gestation. Various nutrients, such as polyunsaturated fatty acids (PUFAs) and vitamin D, were studied in relation to maternal status and offspring allergy. However, no strong evidence indicates that a single nutrient or food in mothers' diet significantly affects the risk of childhood AD. In the light of current evidence, mothers should not either increase nor avoid consuming these nutrients to prevent or ameliorate allergic diseases in their offspring. Each essential nutrient has an important role in fetal development, and current government recommendations suggest specific intake amounts for pregnant women. This review discusses evidence on how various nutrients, including lipids (monounsaturated fatty acids, PUFAs, saturated fatty acids, and short-chain fatty acids), carbohydrates (oligosaccharides and polysaccharides), proteins, vitamins (A, B, C, D, and E), and trace minerals (magnesium, iron, zinc, copper, selenium, and strontium) in maternal status are associated with the development of AD and their possible mechanisms.

Keywords Atopic dermatitis · Carbohydrate · Lipid · Maternal status · Mineral · Protein · Vitamin

Introduction

Atopic dermatitis (AD) or atopic eczema, similar to other atopic disorders such as asthma and allergic rhinoconjunctivitis, is a growing problem worldwide, affecting approximately 10–20% of young children globally. AD is an inflammatory disease characterized by pruritic skin lesions, immunodysregulation, disrupted epidermal barrier function, and immunoglobulin E (IgE)–mediated sensitization to food and environmental allergens [1]. AD is a complex inflammatory process in which innate and adaptive immune cells contribute to the complex immune network underlying cutaneous inflammation. The imbalance between T helper (Th) 1 and Th2 cells results in an increased secretion of interleukin (IL)-4, IL-5, and IL-13 by Th2-expressing cells [2]. The damage to and dysfunction of the epidermal barrier and the lack of antimicrobial peptides on the skin surface lead to a significantly increased risk of skin infections in AD patients [3]. The chronic relapsing inflammation of skin and the disrupted skin barrier cause severe itchiness and wound infection, largely impairing the quality of life [4, 5]. As a multifactorial disease and given that approximately 60% of the onset of childhood AD occurs before the age of 1 year, a variety of factors in the early years of life are being studied [5]. AD commonly develops as the initial manifestation of atopic march, and sensitization through the skin is likely an important initial step in the development of other allergic diseases [6]. Evidence indicates that primary prevention through the application of emollients early in life leads to a decreased incidence of AD [7], thus possibly decreasing the subsequent development of atopic march. Nutrition, as a major environmental factor, is valued for its important role in AD. Maternal diet and antenatal/perinatal nutrition have gained interest because of their

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considerable influence on the nutrition status during the first year of life, which may in turn alter the immune response, thus manipulating the chances of developing future atopy [8–10].

Essential nutrients, which include carbohydrates, proteins, lipids, vitamins, and minerals, are transferred from the mother to fetus through the placenta during gestation. Maternal nutrition status could thus substantially affect fetal development by altering fetal genome expression and consequently give rise to diseases after birth or later in adulthood, a phenomenon termed "developmental programming" or "fetal programming" [11]. Various food categories, including vegetables, fruits, dairy products, nuts, fish, oil, and antioxidants, were studied for the associations between maternal intake and offspring atopy in the past few decades [8, 12–18]. However, clinicians only recently focused more attention to the effect of individual nutrients. Maternal diet may also affect the content of breast milk, in which certain food allergens such as peanut could be detected [19]. The intake of dietary supplements in large amounts, for example, vitamin D, may also elevate its level in breast milk [20]. However, whether the changes in breast milk content may alter the incidence of AD development among breastfed children remains controversial [21, 22]. In this article, we will review individual nutrients in maternal diet during pregnancy and/or breastfeeding and their effect on the development of AD in the offspring.

Lipids

Lipids are main constituents of human body cells and play an important part in physiological functions; thus, they are critically required for fetal development [23]. Given the natural deficiency of certain fatty acid desaturases in human beings, we cannot synthesize specific crucial fatty acids, that is, essential fatty acids, and must acquire them from dietary sources. Fatty acids directly influence the behavior of a number of proteins involved in immune cell activation, including those associated with T cell responses, antigen presentation, and fatty acid–derived inflammatory mediator production [24]. Fatty acids can have powerful antiinflammatory and immunomodulatory activities in a wide array of diseases (e.g., autoimmunity, arthritis, and infection) [25]. Studies reported the relation of fatty acids and development of allergies. Saturated, unsaturated, and short-chain fatty acids (SCFAs) will be discussed here.

Saturated Fatty Acids

Saturated fatty acids (SFAs) refer to the fatty acids without double bonds. These molecules are mostly present in animal fat products and certain plant oils. The modern Western dietary pattern is rich in foods of animal origin, such as red meat and dairy products, which contain abundant SFAs. In contrast to polyunsaturated fatty acids (PUFAs), SFAs are usually considered "bad fats" because their high intake is associated with a variety of diseases, including cardiovascular diseases, metabolic syndrome, or cancer [26]. Palmitic acid (PA) is the most common SFA in the human body [27], accounting for around 65% of SFAs and 28–32% of the total fatty acids in serum [28]. PA can posttranslationally modify proteins in a process called palmitoylation, in which PA is covalently linked to proteins through a thioester bond, thus regulating protein function and performing pathogenic roles in metabolic syndrome, cardiovascular diseases, cancer, neurodegenerative diseases, and inflammation [29]. PA also promotes cell apoptosis and autophagy through stimulation of phosphorylation of mitogen-activated protein kinases and AMP-activated protein kinase, inhibition of the phosphorylation of Akt and mammalian target of rapamycin [30], and stimulation of NO production through the production of superoxide, nuclear factor (NF)-κB activation, and increase in inducible NO synthase protein content [31]. PA can stimulate an inflammatory response through the Toll-like receptor (TLR) 4 signaling pathway [32].

The quantification of SFA intake is difficult, although several serum markers, such as myristic acid, have been determined as good reflectors of dietary intake [33]. Most studies approximate the amount of SFA intake by detailed record of daily diet with further calculation. Other research relates the consumption of SFAs to atopic diseases, but the findings are inconsistent [34, 35]. A study on adolescents showed a positive association between SFA intake and asthma [36]. Hoppu et al. in Finland used a software to quantify different nutrient proportions in breastfeeding mothers [37]. They observed that atopic mothers had higher percentage of fat and SFAs and lower percentage of carbohydrates of total energy intake than non-atopic mothers; a higher SFA intake during breastfeeding was associated with higher atopic sensitization of infants in terms of skin-prick test (odds ratio (OR) 1.16; 95% confidence interval (CI) 1.001–1.36; $p = 0.048$) [37]. Saito et al. conducted a questionnaire-based study on 771 Japanese mother–infant pairs and observed that maternal intake of either PUFAs, SFAs, or monounsaturated fatty acids (MUFAs) showed no association with atopic eczema in infants aged 3–4 months [38]. Barman et al. demonstrated that children with atopic eczema or other allergic diseases had significantly higher cord blood PUFAs levels, whereas those who remained non-allergic at the age of 13 had lower cord blood PUFAs levels and higher SFA and MUFA levels [39]. The authors also reported no correlation in most fatty acid levels between mothers' and children's sera except for one in the long-chain (LC) PUFA species. The result agrees with the assumption of previous studies indicating that SFAs and MUFAs mainly enter the fetal circulation by passive diffusion [40]. No conclusion could be made for the role of dietary SFAs in childhood AD based on the current evidence. Nevertheless, daily SFA

intake per person, whether pregnant or not, is designated to a limited amount by many health authorities because of its evident association with other health problems [41].

Monounsaturated Fatty Acids

Oleic acid is the most abundant MUFA in the human diet (C18:1 n-9). In Mediterranean countries, olive oil is the main source of MUFAs. Other oil sources of MUFAs include canola, peanut, sunflower, corn, soybean, and safflower oil [42]. MUFAs are associated with atopy development. A European ecological study [43] showed that a high MUFA intake (palmitoleic and oleic acids) was positively associated with sensitization prevalence in 20–44-year-old adults (OR 1.59; $p = 0.035$). In a German prospective study, Nagel et al. [44] revealed a significantly positive association between the dietary intake of oleic acid (C18:1) and hay fever in adulthood (OR 2.86; 95% CI 1.22–6.70; $p = 0.04$). However, the mechanism of MUFAs has not been studied, and the association between maternal MUFA intake and offspring atopy has not been well studied.

Polyunsaturated Fatty Acids

The main categories of PUFAs are ω-3 LC PUFAs and ω-6 LC PUFAs, and both are characterized by multiple double bonds in the long hydrocarbon chain, with the first double bond located between the third and fourth carbons or between the sixth and seventh carbons, respectively. Both classes of PUFAs are important (Fig. 1). Omega-6 PUFAs are subject to consumption for energy and the major ingredients for proinflammatory eicosanoids [45]. The metabolites of ω-6 PUFAs include the eicosanoids prostaglandin (PG)E_2 and leukotriene (LT)B_4, which are proinflammatory and neutrophil chemotactic agents [46]. The modern Western diet often provides more than the necessary amount of ω-6 PUFAs, and excessive ω-6 PUFAs are associated with a variety of health problems, including obesity, cardiovascular diseases, and proinflammation status [45, 47]. Omega-3 PUFAs, on the other

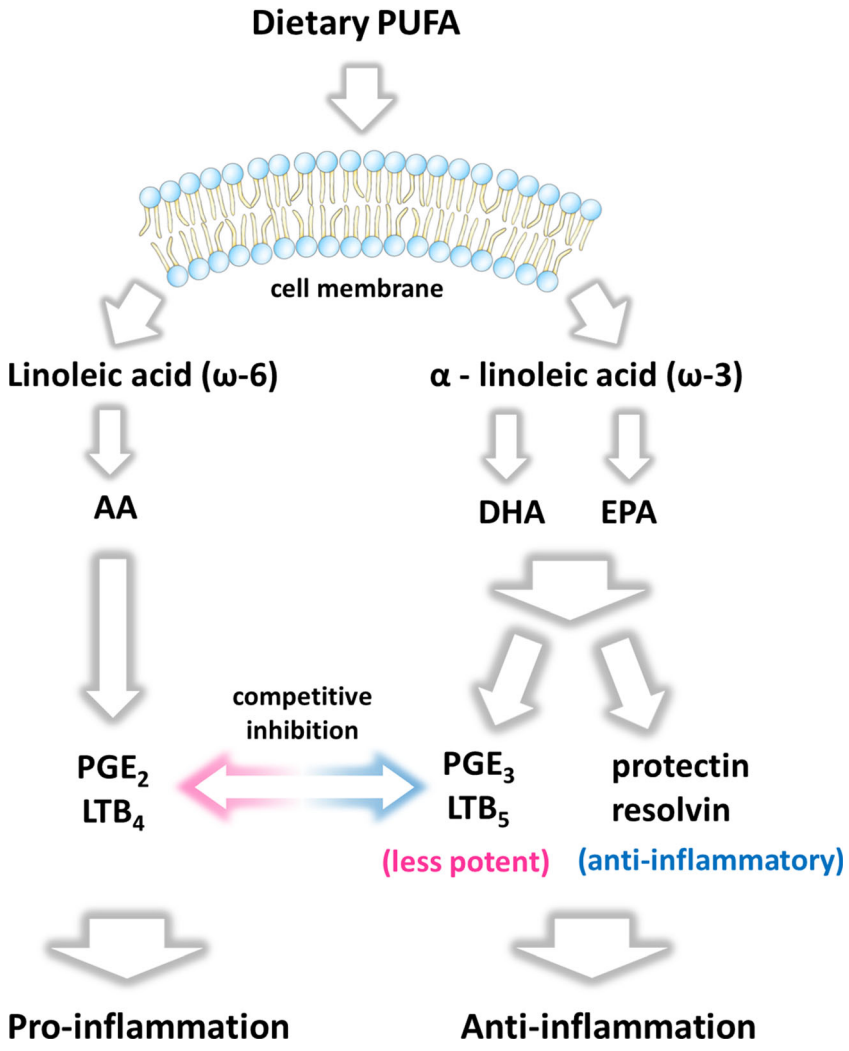

Fig. 1 Mechanism of PUFAs. The ω-6 PUFAs, such as AA, are precursors for PGE_2 and LTB_4, which are proinflammatory mediators and chemoattractants. The ω-3 PUFAs, such as EPA and DHA, are precursors for PGE_3 and LTB_5, which compete with AA in the synthesis of PGE_2 and LTB_4, respectively. The less potent eicosanoids and antiinflammatory mediators, such as protectin and resolvin, reduce the inflammatory process and exert a protective role in various diseases

hand, have gained vast interests over the years because of their multiple health benefits [48]. The incorporation of ω-3 PUFAs into the lipid bilayer increases the membrane fluidity, thereby enhancing membrane-mediated processes, such as phagocytosis and endosome/exosome formation, which regulates the function of immune cells [49]. Omega-3 PUFAs might inhibit the production of PGE_2, which is derived from arachidonic acid (AA), and Th2 responses [50], affect the TLRs, and decrease the transcription of proinflammatory genes, influencing the immunologic response [51–54]. Given that ω-3 and ω-6 fatty acids are metabolized by the same enzymatic pathway in a competitive manner, an imbalanced ω-6 PUFA-to-ω-3 PUFA ratio in the diet is implicated in various diseases [55, 56]. A high proportion of ω-3 LC PUFAs in diet lowers the incidence of cancer, cardiovascular, and neurological diseases [47, 48] and possibly alleviates the inflammatory process and allergic reaction [57–59].

The most well-known members of the ω-3 LC PUFA family are the 20-carbon eicosapentaenoic acid (EPA) and the 22-carbon docosahexaenoic acid (DHA). Oily fish (salmon, tuna, mackerel, sardines, herring, etc.) or commercial fish oil are abundant sources of EPA and DHA. The intake of fish oil had been proven to alter the composition of cell membrane lipids. In a study by Yaqoob et al. in 2000, regular supplementation with fish oil capsule (2.1 g EPA + 1.1 g DHA) significantly increased the percentage of EPA in the plasma membrane in 4 weeks (from 0.5 to 3.7%), replacing the relatively abundant 20-carbon AA (2.0 to 1.3%), which belongs the ω-6 PUFA family and is also the main ingredient of pro-allergic eicosanoids, namely, PGs and LTs [60]. The substitution of AA to EPA dampens the prostanoid signaling pathway, most significantly the PG endoperoxide H synthase-1, which is responsible for downstream products that finally convert into PGDs, PGEs, and PGFs [61]. EPA is also a substrate to 5-lipoxygenase which competes with AA in the pathway of transforming AA into LTB_4 [62]. When supplemented to healthy pregnant women, ω-3 LC PUFAs not only increase EPA and DHA levels in serum or plasma, lowering the levels of the ω-6 LC PUFA family, but also significantly decrease the PGE_2 level. Prenatal supplementation of ω-3 LC PUFAs is recommended in health programs of several countries based on proofs of their multiple health benefits. The European Food Safety Authority has recommended in their 2010 report the supplementation of 100–200 mg preformed DHA in addition to the daily adequate intake (250 mg EPA + DHA daily) for mothers during pregnancy and lactation [63]. Guidelines from the UK government (Scientific Advisory Committee on Nutrition & Committee on Toxicity) also recommend that pregnant and lactating women should consume 1–2 portions (around 140 g each) of fish per week, with at least one being an oily fish. One to two portions of oily fish per week will provide ω-3 LC PUFAs approximately equal to 450 mg EPA and DHA daily [64]. However, an amount exceeding the upper limit of two portions of oily fish per week leads to the intake of additional contaminants, particularly methylmercury [65].

Scientific evidence shows that alteration of PUFA ratio in maternal diet changes the serum fatty acid profile and cytokine/chemokine profiles of the fetus and the offspring risk of AD (Table 1). Dunstan et al. first examined in 2003 the effect of fish oil supplements in Australian pregnant mothers on their children [66]. In this double-blind, placebo-controlled, randomized clinical trial (DBPCRCT), 40 atopic mothers received fish oil capsules, and 43 in the control group received olive oil capsules from 20 weeks of gestation until delivery. As a result, the fatty acid composition of neonate red blood cell showed significantly increased ω-3 PUFAs in the fish oil group compared with the control group; the plasma IL-13 level of the fish oil group was significantly lower, whereas no differences were observed in other cytokines (IL-4, IL-5, IL-6, IL-10, IL-12, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ) or IgE levels between groups [66]. On the other hand, in a later German multicenter, DBPCRCT in 2008, Krauss-Etschmann et al. studied Th1 and Th2-related molecules in the cord blood and observed the increased mRNA for transforming growth factor (TGF)-β, a cytokine associated with induction of tolerance, and decreased mRNA for Th2-related cytokines IL-4 and IL-13 in the fish oil-supplemented group ($p < 0.01$) [71]. Other studies showed the correlation of oily fish intake/supplementary fish oil with decreased inflammation- or allergy-associated cytokine PGE_2 and LTB_4 and increased T cell protein kinase C ζ (PKCζ), a kinase isoform which exists in significantly low levels in neonates with allergic diseases, particularly eczema [67, 68, 72, 95]. The changes in cytokine profile by maternal supplementation of EPA or DHA are implicative of the antiallergic role of prenatally administered ω-3 LC PUFAs.

Several studies investigated the direct association of clinically diagnosed childhood AD with modification of maternal dietary fatty acid composition during prenatal stage or lactation. However, the results were inconsistent. Furuhjelm et al. conducted a DBPCRCT in Sweden involving 145 pregnant women (70 supplied with daily 1.6 g EPA + 1.1 g DHA and 75 with placebo) and followed up their 117 children up to 3 years old [74]. A lower incidence of IgE-associated eczema was detected in the ω-3 LC PUFA supplement group ($p < 0.05$). Interestingly, the ω-6/ω-3 LC PUFA ratio of the mothers' serum showed no statistically significant difference in the study [74]. Other clinical trials, including a larger trial by Palmer et al. involving 706 mother–infant pairs, had failed to find clinical differences in the incidence of offspring AD between intervention and placebo groups [69, 72, 75]. The results of observational studies also varied. Many studies generated promising, statistically significant results, indicating that maternal ω-3 LC PUFA supplement reduces the risk of childhood AD [8, 14, 17, 77, 79–81, 83]. A recent

Table 1 Studies on maternal PUFAs and offspring AD

Interventional study

Study group	Study design/intervention/population	Significant results about AD in intervention group compared to placebo/control
"The Infant Fish Oil Supplementation Study (IFOS)" in Perth, Australia [66–70]	Study design: DBPCRCT Intervention: fish oil capsule vs placebo Duration: GA 20 weeks until delivery Population and size: atopic pregnant mothers ($n = 98$)	↑ ω-3 PUFA level in erythrocyte membrane [66] ↓ Plasma IL-13 [66] ↓ IL-6, IL-10 production in neutrophils [67] ↓ LTB_4 (only trend) production in neutrophils [67] ↑ PKCζ expression in neonatal T cells [68] ↓ AD severity [69] ↔ No difference in frequency of AD [69]
In Neuherberg, Germany [71]	Study design: DBPCRCT, multicenter Intervention: fish oil (DHA + EPA) vs placebo Duration: GA 22 weeks until delivery Population and size: pregnant women ($n = 311$)	↑ mRNA of TGF-β in maternal and cord blood ↓ IFN-γ in mothers' blood ↓ mRNA of IL-4, IL-13, and CCR4 in cord blood ↓ Natural killer cell and $CD8^+$ T cells in cord blood
"The Salmon in Pregnancy Study (SiPS)" in Southampton, UK [72, 73]	Study design: randomized, single-blind controlled trial Intervention: 2 portions of oily fish/week vs habitual diet Duration: GA 20 weeks until delivery Population and size: pregnant women ($n = 123$)	↑ DHA and EPA intake [73] ↑ Percentage of DHA and EPA in maternal and cord plasma phosphatidylcholine [73] ↓ IL-2, IL-4, IL-5, IL-10, TNF-α, and PGE_2 production in cord blood mononuclear cell [72] ↔ No differences in IgE and skin prick tests [72]
In Linköping, Sweden [74]	Study design: randomized placebo-controlled trial Intervention: DHA + EPA vs placebo Duration: GA 25 weeks to 3–4 months of breastfeeding Population and size: pregnant women ($n = 145$) with positive family history of atopic diseases	↓ Prevalence of food allergy at 1 year old (2% vs 15%) ↓ Incidence of IgE-associated eczema (8% vs 24%)
"The Docosahexaenoic Acid to Optimize Mother Infant Outcome (DOMInO) Trial" in Adelaide, Australia [75, 76]	Study design: randomized controlled trial Intervention: fish oil capsule vs vegetable oil capsule Duration: GA 21 weeks until delivery Population and size: mother-infant dyads ($n = 706$) at high risk of atopic diseases	↓ Percentage of atopic eczema (7% vs 12%), not significant after adjustment ↓ Sensitization to egg (9% vs 15%) ↔ No difference in IgE associated allergies

Observational study

Study group	Study design/methods/population	Significant results about AD
In Aberdeen, UK [17]	Study design: population-based study, single center Methods: questionnaire, skin prick tests and blood tests since GA 12 weeks until 5 years after birth Population and size: mother-children dyads ($n = 1924$)	↓ Doctor-confirmed eczema for maternal fish consumption
"The Kyushu Okinawa Maternal and Child Health Study (KOMCHS)" in Fukuoka, Japan [77, 78]	Study design: prospective prebirth cohort study Methods: self-administered questionnaire Population and size: Japanese mother–child pairs ($n = 1354$)	For maternal intake of EPA and EPA + DHA: ↓ Infantile wheeze ↔ No relation with infantile eczema
In Krakow, Poland [79]	Study design: prospective birth cohort study Methods: detailed, standardized, face-to-face interview every 3 months after delivery to 1 year Population and size: mothers giving birth to term babies ($n = 469$)	↓ Risk of infantile eczema[a] for maternal fish consumption
In Sabadell, Spain [80]	Study design: population-based birth cohort study, single center Methods: blood sampling at GA 12 weeks and questionnaire when the child is 6–14 years old Population and size: non-atopic mothers ($n = 211$) and children	↓ Atopic eczema for maternal LC PUFA ↓ Atopic eczema for cord blood DHA, total ω-3 and ω-3 LC PUFAs
"The Generation R Study" in Rotterdam, the Netherlands [81, 82]	Study design: prospective population-based cohort study	

Table 1 (continued)

	Methods: questionnaire, blood tests and lung function tests Population and size: mothers from early pregnancy to post-delivery, in pairs with children ($n = 4976$)	↑ Risk of childhood eczema for maternal total PUFA (OR 1.16) and total ω-6 PUFA (OR 1.21) ↔ No association with total ω-3 PUFA or ω-6: ω-3 PUFA ratio
"The Urban Child Institute CANDLE Study" in Memphis, TN, USA [83]	Study design: prospective prenatal cohort study, single center Population and size: racially diverse mother–infant dyads ($n = 1131$)	↑ AD in children of maternal atopy for higher 2nd trimester ω-6 PUFAs ↔ No association with prenatal ω-3 PUFAs and ω-6: ω-3 PUFAs
"The Finnish Type 1 Diabetes Prediction and Prevention (DIPP) Nutrition Study" in Finland [84, 85]	Study design: multidisciplinary population-based prospective birth cohort study, multicenter Methods: questionnaire (181 item FFQ) Population and size: newborn infants with HLA-conferred susceptibility to type 1 diabetes ($n = 2441$)	↔ No association with atopic eczema in dietary fats and fatty acids after adjustment for confounders
"The Avon Longitudinal Study of Parents and Children (ALSPAC)" in Avon, UK [86, 87]	Study design: prospective population-based cohort study, multicenter Methods: questionnaire and blood tests, including cord blood Population and size: 14,541 pregnancies resulting in 14,062 live births (born to 13,866 mothers). $n = 1238$ and $n = 2945$ for cord and maternal analyses, respectively	↑ Eczema at 18–30 months old for the ratio of AA: EPA in cord blood RBC (OR 1.14) ↔ No longer significant after adjustment
"The Growing Up in Singapore Toward healthy Outcome (GUSTO) birth cohort" in Singapore [88, 89]	Study design: prospective population-based cohort study Methods: detailed interview and blood tests Population and size: mother–infant pairs, $n = 1162$; $n = 883$ analyzed for eczema outcome.	↔ No association with offspring rhinitis, eczema, wheezing in maternal total ω-3, ω-6 PUFA status and the ω-6: ω-3 PUFA ratio after adjustment
"Life-style Related Factors on the Immune System and the Development of Allergies in Childhood PLUS the influence of traffic emissions and genetics (LISAplus) study" in Munich, Germany [90, 91]	Study design: prospective population-based birth cohort study Methods: questionnaires completed at 2, 6, and 10 years old. Cord blood and blood tests. Population and size: children ($n = 436$) from the Munich LISAplus birth cohort	↔ No association with eczema or other allergic diseases in ω-3 LC PUFA, ω-6 LC PUFA, or the ω-6: ω-3 ratio in cord blood
"Child, Parent and health: Lifestyle and Genetic constitution (KOALA) cohort" in the Netherlands [92, 93]	Study design: prospective population-based birth cohort study Methods: blood tests for mother at GA 34–36 weeks and for children at age 24 months. Repeated parental questionnaires. Home-visit by trained nurse for atopic dermatitis at age 24 months Population and size: mothers ($n = 1275$) and children ($n = 807$ for home visit and $n = 951$ for follow-up at 6–7 years) from the KOALA cohort	↓ Risk of eczema in the child with high ratio of maternal ω-6: ω-3 LC PUFAs ↓ Risk of eczema in the first 7 months of life with AA
"Perturbateurs endocriniens: Étude Longitudinale sur les Anomalies de la Grossesse, l'Infertilité et l'Enfance (PELAGIE) cohort" in Brittany, France [94]	Study design: prospective population-based birth cohort study Methods: questionnaires (FFQ) at 2 years old Population and size: mothers ($n = 1500$) from the PELAGIE cohort	↔ No association with childhood eczema in maternal seafood consumption

[a] The results also showed that exposure to air pollutants prenatally and postnatally positively correlates with the occurrence of infantile eczema

DBPCRCT double-blind, placebo-controlled, randomized clinical trial, *GA* gestational age, *IL* interleukin, LTB_4 leukotriene B_4, *PKCζ* protein kinase C ζ, *DHA* docosahexaenoic acid, *EPA* eicosapentaenoic acid, *TGF-β* transforming growth factor-β, *IFN-γ* interferon-γ, *CCR4* C-C chemokine receptor 4, *TNF-α* tumor necrosis factor-α, PGE_2 prostaglandin E_2, *LC PUFA* long-chain PUFA, *FFQ* food frequency questionnaire, *AA* arachidonic acid

observational study published in 2019 by Gardner et al. based on a racially diverse cohort suggested an increased OR (OR 1.25; 95% CI 1.01–1.54) of childhood AD in mothers with increased ω-6 PUFA intake, but no association was found with ω-3 PUFA intake alone nor with ω-6/ω-3 PUFA ratio [83]. Other studies either reported no significant differences in the clinical outcomes [84, 86, 88, 90, 123] or inverse findings (that is, ω-3 LC PUFA supplement increased the risk of childhood eczema) [92, 124].

In general, several studies suggest the protective role of low ω-6/ω-3 PUFA ratio (low ω-6 and/or high ω-3) in maternal diet, whereas other research showed no effect. Meanwhile, several studies obtained the opposite results. Carefully designed large-scale studies with longer follow-up periods may be required to generate more solid results. Ethnic and environmental diversity and different risk stratifications of mothers giving birth to babies with atopic diseases should also be considered in future studies.

Short-Chain Fatty Acids

SCFAs contain less than six carbon atoms, with acetate, propionate, and butyrate being the most common. SCFAs are the main energy sources for enterocyte regeneration; they modulate the enteric microbial community and contribute to increasing host health [125]. SCFAs have antiinflammatory properties, including the reduction in expression and signaling of different proinflammatory cytokines, induction of nitric oxide synthesis and metalloproteinases, reduction and activation of lymphocyte proliferation [126], promotion of regulatory T cell (Treg) generation in the colon of mice [127, 128], increase in intestinal IgA secretion, and improvement of Th1/Th2 ratio [129]. Supplementation of SCFAs at high concentration reduces inflammation through altered cytokine expression and enhances tissue repair and mucus secretion [125], affecting the abundance of bacterial populations in intestines [130].

The potential role of SCFAs in eczema has been addressed recently. One study noted the lower levels of different SCFAs compared with non-allergic controls in 1-year old allergic children [131]. Another study noted the inverse correlation of severity of eczema with the amount of butyrate-producing bacteria ($r = -0.52$, $p = 0.005$) in 6-month-old infants [132]. Kim et al. noted the lower amounts of SCFAs in fecal samples of children with later developing eczema in a DBPCRCT of probiotics supplement in pregnant mothers and infants in the first year of life [133]. The intestinal SCFAs may play an important role in the development of eczema in early life, but direct maternal supplementation has not been studied.

Carbohydrates

Carbohydrates are the main energy source of humans. Different sources of carbohydrates have variable digestion rates. Thus, their effects on blood glucose and insulin levels also vary. High glycemic index foods, including rice, white bread, and potatoes, cause a sharp rise in blood glucose levels which declines rapidly, whereas low glycemic index foods, such as fruits or dairy, have slowly digestible carbohydrates that result in a lower postprandial glucose response [134]. Immune cells have various demands for nutrients, including glucose, glutamine, and fatty acids, which are metabolized to generate adenosine triphosphate for energy expenditure; competition for nutrients of different immune cells may regulate immune responses [135]. Dietary fiber describes a variety of plant-based carbohydrates that are resistant to digestion by human gastrointestinal enzymes. They include soluble fiber (fruits, vegetables, and legumes), insoluble fiber (nuts, wholegrain bread, or cereals), or resistant starch (cooked potato and rice). Diets high in fiber and with a low glycemic index can promote laxation, reduce blood cholesterol, and modulate blood glucose and hence may be beneficial in pregnancy [134]. Saccharides, especially oligosaccharides as prebiotics, will be discussed here.

Monosaccharides/Disaccharides

Free sugars consisting mostly of mono- or disaccharides are frequently added by manufacturers in foods or drinks to sweeten the taste. Additionally, high consumption of sugar had been linked to increased risk of atopic diseases, particularly asthma [136]. However, the correlation between sugar-rich foods and the severity of AD lacks clarity [137]. Bedard et al. studied the association between maternal sugar consumption and atopic diseases, suggesting the increased risk of asthma and overall atopy with high sugar intake. However, no significant association was observed between maternal sugar intake and offspring atopic eczema [138].

Oligosaccharides

Prebiotics are a group of food ingredients that are degraded by gut microorganisms and may induce their growth and activity, thus changing the composition of gut microflora. Non-digestible oligosaccharides, most commonly fructo-oligosaccharides (FOS), galacto-oligosaccharides (GOS), and trans-GOS, comprise mostly of known prebiotics, whereas specific resistant starch or non-carbohydrates could also serve as prebiotics [139]. Prebiotics are non-digestible food ingredients that beneficially influence host health by indirect (acting as a fermentable substrate for specific commensal host bacteria, leading to the release of SCFAs in the gut intestinal tract and influencing various molecular and cellular processes) and direct effects (acting directly on several compartments and specifically on different arrangements of cells (epithelial and immune cells)) [140]. SCFAs, as previously stated, play a role in the immunomodulation of gut mucosa [129]. Prebiotics also directly promote barrier integrity to prevent pathogen-induced barrier disruptions [141]. Absorbed prebiotics may be in direct contact with circulating immune cells. For example, inulin and FOS induce the secretion of IL-10, IL-1β, and TNF-α by blood monocytes [142]. In murine models, prebiotics reinforce gut barrier function and reduce allergic reactions [143, 144]. Compared with the more established effects of probiotics in improving symptoms of AD, however, studies

on postnatal prebiotics administration in human yielded inconclusive results [145]. Prenatal administration of prebiotics was studied in a murine model in 2009 by Fujiwara et al., who demonstrated the beneficial effect of supplementation during pregnancy on reducing severity of AD-like skin lesions in mice offspring [146]. A prior study conducted by the same group demonstrated that by supplementing FOS in female mice during pregnancy and lactation, the gut microbiota composition of suckling mice was altered. The result possibly links maternal intake of prebiotics to a preventive role against allergic disease development later in life.

In humans, several clinical trials used prebiotics as an allergy prevention strategy by intervening in infancy by supplementation of infant formula. In World Allergy Organization Guideline for Allergic Disease Prevention, Cuello-Garcia et al. conducted a systematic review including 22 randomized trials with a minimum follow-up of 4 weeks, comparing any type of prebiotics against placebo or no prebiotics [147]. They concluded the high uncertainty of reducing the risk of developing allergies using the currently available evidence on prebiotics supplementation in infancy. To date, no human studies in which prebiotics have been given to mothers during pregnancy and/or breastfeeding have been published; however, two clinical studies are currently being conducted: SYMBA is a DBPCRCT investigating the effects of maternal prebiotics supplementation (GOS:FOS at a ratio of 9:1) from 18 to 20 weeks of gestation during pregnancy until 6 months of lactation on the development of infant allergic disease [148]; PREGRALL is a multicenter DBPCRCT that aims to evaluate the effectiveness of gestational prebiotics supplementation (from 20th week of gestation until delivery, 11.8 g 9:1 GOS/inulin powder per day) versus placebo on the occurrence of AD at 1 year of age in high-risk children (defined as having a maternal history of atopic disease) [149]. The outcomes of these trials might further verify the effect of maternal prebiotics supplementation on allergic diseases in offspring.

Polysaccharides

Dietary fibers are non-starch polysaccharides consisting of subtypes, including soluble fiber, insoluble fiber, and resistant starch [150, 151]. These polysaccharides are subject to fermentation of gut microbiome [152], leading to the generation of SCFAs which deliver antiinflammatory and immunomodulatory effects in a manner similar to prebiotics. Maternal diet rich in vegetables (especially green- and yellow-leaf vegetables) and fruits during pregnancy is beneficial to offspring with eczema [12, 16]. However, these information do not imply the effect of dietary fibers given that they are inevitably confounded by other coexisting nutrients and antioxidants such as β-carotene. A study conducted by Pretorius et al. [153] followed up over 600 mother–infant pairs and analyzed the relationship between eczema or wheezes, both physician-diagnosed or parent-reported, and the amount of dietary fiber in different subtypes taken by mothers during gestation. Of all different subtypes, statistical significance was observed in resistant starch, which had a negative correlation with clinical wheezes but a positive correlation with atopic eczema. Thus, high maternal intake of resistant starch is associated with a high risk of parent-reported eczema (adjusted OR (aOR) 1.27; 95% CI 1.09–1.49; $p < 0.01$) and physician-diagnosed eczema (aOR 1.19; 95% CI 1.01–1.41; $p = 0.04$). The result was contrary to the hypothesis that AD may be reduced by immunomodulatory effects of SCFAs, which are generated by fermentation of dietary fibers.

Proteins

Proteins are involved in both structural (keratin and collagen) and functional (enzymes, protein transport, and hormones) biological roles [134]. Proteins, out of all kinds of nutrients, are the major allergens for food allergy [154]. Childhood AD is strongly associated with food allergy, with at least 30% of children with moderate to severe AD documented for food allergies [155, 156]. The association between protein intake and AD has long been discussed, and questions have also been raised about whether maternal intake of protein food allergen could possibly cause food allergy in children. Given their importance in fetal development, proteins digested by mothers are generally transferred through the placenta in the form of amino acids by specific amino acid transport proteins [157]. Nevertheless, certain food component proteins, namely, β-lactoglobulin (BLG) and ovalbumin (OVA), are detectable in cord blood and placenta tissues of mothers ingesting milk and eggs, indicating their capability to cross the placenta and be delivered directly to the fetus, thereby mediating fetal T cell priming [158–160]. Other studies showed that component proteins, including BLG [161], OVA [162–164], and peanut antigen [19, 165], are also present in breast milk.

Despite proofs of maternal–fetal passage of food proteins, whether maternal intake of certain food proteins is associated with increased childhood allergic diseases remains controversial. Two aspects are being discussed: maternal diet modification during pregnancy and breastfeeding. An exclusion diet (excluding common food allergens, such as cow's milk, egg, nuts, or fish, in several studies) during lactation decreased the level of related component protein levels in breast milk in several studies [166] but caused no difference in antigen-specific antibody production in infants [166, 167]. No difference in antibody profile was found in the fetal cord blood in the comparison of mothers with and without diet restriction during pregnancy [167]. In their 2008 report, American Academy of Pediatrics (AAP) had concluded that data are lacking to affirm the role of maternal exclusion diet during pregnancy and lactation on childhood food allergy, and by

far, no new clinical trial is being conducted to change this conclusion [168]. A 2012 meta-analysis of Cochrane library by Kramer et al. included five articles, with two studies directly addressing the outcomes of offspring atopic eczema, had also drawn a similar conclusion, that is, the exclusion of common food allergen protein in the mother's diet causes no effect on the incidence of childhood allergic reactions, including AD [166, 169, 170]. A systemic review by Netting et al. in 2014 listed seven interventional studies (five RCTs and two non-randomized comparisons) and sixteen observational studies examining in part the correlation between maternal diet and eczema in children [13]. In the five reviewed RCTs [171–175], including the Isle of Wight prevention study [174], two eliminated cow's milk during pregnancy and lactation in the intervention group and followed up the children's outcomes until 18 months old [172, 175]; one had the intervention group restricted from cow's milk and egg during pregnancy and lactation and followed up the offspring until 5 years of age [171]; one excluded cow's milk, egg, and peanut from diet and limited soy and wheat intake in the intervention group during pregnancy and lactation and followed up the children until 7 years of age [173]; the Isle of Wight study restricted cow's milk, egg, nut, and fish intake in the intervention group during lactation only and followed up the children until 12 months old, with controlled dust mite concentration in the environment and delayed introduction of allergenic food [174]. Overall, these RCTs found no differences in the outcomes in offspring AD between two groups, except for the Isle of Wight study, which addressed a significantly greater prevalence of eczema (OR 3.6; 95% CI 1.0–12.5) in the control group. The two non-randomized studies showed no evidence of maternal restriction diet to improve the outcome on childhood atopic eczema [176, 177]. The results of observational studies were inconsistent. One study suggested that excessive meat consumption by the mother increases the risk of eczema [38]; however, another study failed to reach the same conclusion [123]. Dairy product also causes no effect on the increased risk of eczema [8, 15]. Several studies suggested a possible protective role for maternal fish intake, which echoes the conclusive result of this systemic review, that is, maternal diets rich in fish, fruits, vegetables, vitamin D, and Mediterranean dietary patterns are associated with a low risk for allergic disease in children [8, 13]. However, fish is a source of ω-3 PUFAs and proteins [9, 48]; thus, the causality may very well be that from lipids rather than proteins themselves.

Meanwhile, evidence supporting the protective role of eliminating common protein allergens from maternal diet is lacking. Both AAP and European Academy of Allergy and Clinical Immunology advise a normal diet without restriction for allergenic foods for mothers who are pregnant or breastfeeding [168, 178]. An RCT with large sample size and long follow-up period may be needed to make further suggestions.

Vitamins

Vitamin A and β-Carotene (Provitamin A)

The vitamin A group consists of retinol (the usually called vitamin A) and more than 600 carotenoids [179]. β-Carotene is abundant in plants and fruits and can be converted into vitamin A by dioxygenase in the intestinal mucosa. This compound is a member of the carotenoid group which exhibits a strong antioxidant activity. Vitamin A can influence the immune system by converting into retinoic acid (RA). RA can inhibit Th1 cells to become pathogenic Th17 cells and block the development of innate lymphoid cell (ILC) 2s while promoting the differentiation and expansion of ILC3s and imprinting dendritic cells (DCs) with the ability to produce RA. In the mesenteric lymph node, RA-producing DCs can induce gut tropism on T and B cells and promote the differentiation of Treg. Furthermore, vitamin A can promote Tr1 and Treg differentiation and inhibit NF-κB signaling in macrophages [180].

Many studies surveyed the effect of antioxidants on AD, because oxidative stress takes part in the pathogenesis of AD [181, 182]. However, studies for vitamin A or β-carotene are limited (Table 2). Serum vitamin A levels were reported to be significantly lower in adults AD patients compared with the controls [183]. An Australian study by West et al. [100] investigated the association between maternal intake of β-carotene, vitamin C, vitamin E, zinc, and copper during pregnancy and the risk of offspring atopic diseases, including eczema, wheezing, and food allergy (sample size 300). For β-carotene, the result suggested no association between maternal intake and childhood atopy. Another study based in the UK (sample size 1942) also found no relation in the prenatal intake of β-carotene and childhood eczema [101]. Our study with a small sample size also showed that retinol levels were not significantly different in breast milk for 2–4-month-old AD infants and healthy controls [122]. Therefore, further observational studies for vitamin A intake in pregnant and breastfeeding mothers and RCTs with vitamin A supplementation may be needed to clarify the role of maternal vitamin A in offspring AD.

Vitamin B9 (Folate)

Folate, or vitamin B9, is essential for cell metabolism by acting as methyl donor for DNA methylation, an important process carried out by DNA methyl transferases [184]. Folate is abundant in a variety of foods, including dark green vegetables, fruits, nuts, beans, grains, eggs, dairy products, and meat. Folic acid, on the other hand, is an oxidized synthetic form of folate and is usually used as supplement given that it is more stable and better absorbed than folate [9]. The requirement for folate or folic acid increases in pregnant women given the

Table 2 Studies about maternal vitamins and offspring AD

Interventional study

Study group	Study design/intervention/population	Significant results about AD in intervention group compared to placebo/control
"The Copenhagen Prospective Studies on Asthma in Childhood 2010 cohort" in Denmark [96]	Study design: DBPCRCT Intervention: vitamin D_3 (2400 IU/day) vs placebo; all with a prenatal 400 IU vitamin D_3 Duration: GA 24 weeks until 1 week after delivery Population and size: mother–child pairs ($n = 623$)	↓ Risk of persistent wheeze through age 3 years ↔ No difference for eczema
"The Vitamin D Antenatal Asthma Reduction Trial" in USA [97]	Study design: DBPCRCT, multicenter Intervention: daily 4000 IU vitamin D vs placebo; all with a prenatal vitamin containing 400 IU vitamin D Duration: GA 10–18 weeks until delivery Population and size: high-risk mothers for offspring asthma ($n = 881$)	↔ Lower the incidence of asthma and recurrent wheezing at age 3 years, but not significant ↔ No difference for eczema
In London, UK [98]	Study design: randomized controlled trial Intervention: no vitamin D, 800 IU ergocalciferol daily until delivery or single oral bolus of 200,000 IU cholecalciferol Duration: GA 27 weeks until delivery Population and size: mother–child pairs ($n = 180$)	↔ No difference for atopy and eczema risk at age 3
In Japan [99]	Study design: DBPCRCT, multicenter Intervention: vitamin D_3 supplements (800 IU/day) vs placebo Duration: 6 months Population and size: mothers with exclusively breastfed infants of facial eczema at 1 month ($n = 164$)	↔ No difference in SCORAD at age 3 month ↑ Doctor-diagnosed food allergy at age 2 years

Observational study

Study group	Study design/methods/population	Study targets	Significant results about AD
"The Infant Fish Oil Supplementation Study (IFOS)" in Perth, Australia [70, 100]	Study design: prospective observational study based on cohort from an associated clinical trial (IFOS) Methods: semi-quantitative FFQ and interview since GA 28 weeks Population and size: atopic mothers paired with infants ($n = 300$)	β-Carotene Vitamin C Vitamin E (Copper) (Zinc)	↓ Risk of any diagnosed infant allergic disease and wheeze for higher maternal dietary vitamin C intake. ↔ No relationships between vitamin C and eczema. ↔ No relationships between β-carotene, vitamin E or zinc and any allergic outcomes. (↓ Risk of eczema for higher dietary copper)
In Aberdeen, UK [101]	Study design: prospective population-based cohort study, single center Methods: semi-quantitative FFQ at GA 34 weeks, 6, 12, 24 months after birth and cord blood sample Population and size: mother-children pairs ($n = 1924$)	β-Carotene Vitamin C Vitamin E	↔ No association of eczema and wheezing in the 1st year ↓ Childhood eczema born to atopic mothers during the 2nd year for maternal vitamin E intake

Table 2 (continued)

			↑ "Ever wheeze" and eczema during the 2nd year for maternal vitamin C intake
In Turku, Finland [102]	Study design: prospective observational study, single center Methods: questionnaire and personal interview at GA 35–36 weeks; skin prick test; breast milk collection at 1 month of age; clinical examination for infants at 1, 3, 6, 12 months of age Population and size: breast milk from atopic mothers ($n = 34$)	β-Carotene Vitamin C Vitamin E (α-tocopherol)	↓ Risk of atopy in the infant (OR 0.30) for higher concentration of vitamin C in breast milk ↔ No consistent relationship of α-tocopherol and atopy.
"The Generation R Study" in Rotterdam, the Netherlands [103]	Study design: prospective population-based cohort study Methods: questionnaire and blood tests from early pregnancy to child age of 48 months Population and size: mother-infant pairs ($n = 8742$)	Vitamin B9 (folate) Vitamin B12	↑ The development of AD (aOR 1.18) for high maternal folate ↑ The development of AD (aOR 1.30) for high maternal vitamin B12
In Perth, Australia [104]	Study design: prospective population-based cohort study Methods: FFQ and blood tests; pregnant mother recruited in third trimester; Children followed-up to 1 year old Population and size: pregnant women ($n = 628$) and their infants ($n = 484$) (partially overlap with IFOS cohort [70])	Vitamin B9 (folate)	↑ Subsequent eczema for folate supplements (especially > 500 μg folic acid/day) ↑ Sensitization risk for cord blood folate levels < 50 nmol/l and > 75 nmol/l
"Child, Parent and health: Lifestyle and Genetic constitution (KOALA) cohort" in the Netherlands [93, 105]	Study design: prospective population-based birth cohort study Methods: questionnaires and blood tests Population and size: mother-child pairs ($n = 2834$)	Folic acid	↔ No association with any of the atopic outcomes
"Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study" in the Netherlands [106]	Study design: prospective population-based birth cohort study Methods: questionnaires and blood tests; mothers recruited during pregnancy; children followed up to 8 years old Population and size: mother-child pairs ($n = 3786$)	Folic acid	↔ No association with eczema or other respiratory allergic outcomes
"The Osaka Maternal and Child Health Study (OMCHS)" in Neyagawa City, Osaka, Japan [107, 108]	Study design: prospective population-based birth cohort study Methods: diet history questionnaire; Mothers recruited during pregnancy; Children followed up to 8 years old Population and size: mother-child pairs ($n = 763$)	Vitamin B2 Vitamin B6 Vitamin B9 (folate) Vitamin B12	↔ No association with the risk of wheeze or eczema in the offspring for maternal consumption of folate, vitamins B12, B6, and B2 during pregnancy after adjustment
"The Mothers and Children's Environ-mental Health (MOCEH) study" in Seoul, South Korea [109, 110]	Study design: prospective population-based birth cohort study Methods: questionnaires and blood tests; mothers recruited at mid- or late- pregnancy; children followed up to 24 months old Population and size: mother-child pairs ($n = 917$)	Vitamin B9 (folate)	↓ Cord blood eosinophil count ↑ Cord blood IL-10 ↓ Risk for offspring lower respiratory tract infections at 6 months of age (aOR 0.50) and AD at 24 months (aOR 0.52)
		Vitamin B9 (folate)	↔ No association with childhood AD

Table 2 (continued)

"The Conditions Affecting Neurocognitive Development and Learning in Early Childhood (CANDLE) Study" in Memphis, TN, USA [111, 112]	Study design: prospective population-based birth cohort study Methods: blood tests and clinical diagnosis of atopic diseases; Serum folate measured at 2nd and 3rd trimester; Diagnosis of atopic diseases made at 3 years of age. Population and size: mother-child dyads ($n = 858$)		↓ Odds of current wheeze at age 3
"The Generation R Study" in Rotterdam, the Netherlands [113]	Study design: prospective population-based cohort study Methods: questionnaire and blood tests; data collection at birth (cord blood), 4 years old (eczema), and 6 years old (FeNO and Rint) Population and size: Caucasian children ($n = 2001$)	Vitamin B9 (folate) Vitamin B12 (homocysteine) (*MTHFR* gene SNP C677T and A1298C)	↔ No association with any of the outcome (eczema, wheezing) at any age for cord blood folate, B12 and homocysteine ↑ Risk of eczema for folate in children carrying C677T mutations in MTHFR
"The Southampton Women's Survey (SWS)" in Southampton, UK [114]	Study design: prospective population-based cohort study Methods: blood tests, questionnaire and examination by trained nurse Population and size: mother-infant pairs ($n = 497$)	Nicotinamide (metabolites: kynurenine, kynurenic acid, anthranilic acid, tryptophan, N1-methylnicotinamide)	↔ No association with offspring atopic eczema at age 6 months for maternal nicotinamide and related metabolite ↓ Risk of eczema at age 12 months for nicotinamide and anthranilic acid
"The Finnish type 1 Diabetes Prediction and Prevention Nutrition Study" in Finland [115]	Study design: prospective population-based cohort study, multicenter Methods: maternal pregnancy FFQ; allergen specific IgE at 5 years of age Population and size: newborn infants with HLA-conferred susceptibility to type 1 diabetes ($n = 931$)	Citrus fruits Vitamin D	↑ Sensitization to inhalant allergen for citrus fruits intake (OR 1.14) ↓ Sensitization to food allergen for vitamin D intake (OR 0.56)
"The Etude des Déterminants pré et post natals du développement et de la santé de l'Enfant (EDEN) birth cohort" in France [116]	Study design: prospective birth cohort Methods: cord blood 25(OH)D; International Study of Asthma and allergies in childhood-based symptom questionnaires at 1, 2, 3, and 5 years Population and size: newborn ($n = 239$)	25(OH)D	↓ Risk of transient early wheezing and early- and late-onset AD, as well as AD, by the ages of 1, 2, 3, and 5 years ↔ No association with asthma and allergic rhinitis at age 5 years
In Perth, Australia [117]	Study design: prospective birth cohort Methods: cord blood 25-hydroxyvitamin D_3 [$25(OH)D_3$] concentration; allergic outcomes in the first year of life Population and size: high-risk mother–infant pairs ($n = 669$)	$25(OH)D_3$	↓ Risk of eczema for high cord blood $25(OH)D_3$ ↔ No association with allergen sensitization, IgE-mediated food allergy, and eczema severity
In Southampton, UK [118]	Study design: prospective cohort study Methods: maternal blood tests at late pregnancy; atopic eczema assessed at 9 months old; asthma at age 9 years Population and size: mother-infant pairs ($n = 466$)	25(OH)D	↑ Risk of eczema at age 9 months (OR 3.26) ↑ Risk of asthma at age 9 years (OR 5.40)
"The Avon Longitudinal Study of Parents and Children (ALSPAC) study" in UK [119]	Study design: prospective population-based cohort study, multicenter Methods: maternal blood 25(OH)D; allergic outcome at age 7.5 years Population and size: mother–infant pairs ($n = 5513$)	25(OH)D	↔ No association with wheeze, asthma, eczema, atopy and hay fever at age 7.5 years.

Table 2 (continued)

"The KOMCHS prebirth cohort" in Japan [120]	Study design: prospective prebirth cohort Methods: maternal diet history questionnaire; offspring allergic outcome by questionnaires at age 23–29 months. Population and size: mother–infant pairs ($n = 1354$)	Vitamin D	↑ Risk of infantile eczema (aOR 1.63)
"The Prediction of Allergies in Taiwanese Children (PATCH) study" in Taiwan [121]	Study design: prospective birth cohort Methods: maternal and cord blood 25(OH)D; allergic outcome at age 4 Population and size: mother–infant pairs ($n = 164$)	25(OH)D	↓ Risk of eczema (OR 0.12) and asthma (OR 0.22) at age 4 for high maternal 25(OH)D
In Taiwan [122]	Study design: prospective observational cohort Methods: breast milk retinol and $25(OH)D_3$; objective SCORAD in infants Population and size: breast milk for exclusively breastfed AD and healthy infants ($n = 90$)	Retinol $25(OH)D_3$	↔ No association with AD for retinol ↑ objective SCORAD for lower $25(OH)D_3$ ↔ No association with persistent AD till age 3–4 years for $25(OH)D_3$

DBPCRCT double-blind, placebo-controlled, randomized clinical trial, *SCORAD* SCORing Atopic Dermatitis index, *GA* gestational age, *FFQ* food frequency questionnaire, *FeNO* fractional exhaled nitric oxide, *Rint* interrupter resistance, *SNP* single-nucleotide polymorphism, *MTHFR* methylenetetrahydrofolate reductase, *OR* odds ratio, *HLA* human leukocyte antigen

needs of the developing fetus for processing DNA synthesis and rapid cell division. An inadequate periconceptional maternal folate status may lead to defects in fetal development, most notably neural tube defects, such as spinal bifida, meningocele, or anencephaly [184]. Hence, the importance of folic acid status and supplementation during pregnancy has been addressed in prenatal care programs of various countries [185]. In January 1992, the UK government first suggested that pregnant women should consume 400 mg folic acid per day for the first 12 weeks of pregnancy and preferably before conception. Later the same year in September, the US government made similar recommendations with same dosage (400 mg daily) for all women of childbearing age [186]. In Asia, the Ministry of Health and Welfare in Taiwan recommends a 400-mg folic acid intake before conception and an increased amount to 600 mg daily during pregnancy.

As a key participant in DNA methylation, folate/folic acid can therefore regulate transcriptional activity by facilitating in the methylation of specific regulatory regions of genes, thereby silencing their expression [9]. Given that mammals are highly dependent on dietary methyl donors and cofactors for the methyl groups to convey all biological methylation reactions, early administration of methyl donors, such as folic acid, in diet could cause significant epigenetic alterations [187]. This epigenetic function may influence the Th1/Th2 polarization of the immune system. Animal studies showed that methylation of Th1-related genes caused by in utero exposure drives the Th1/Th2 balance toward Th2 reactions, thus making the host more prone to developing atopic diseases [188]. The reduced expression of typical Th1 cytokine IFN-γ by methylation of the promoter region, for example, increases the risk of AD [189, 190]. However, whether early folic acid supplementation specifically facilitates hypermethylation of cytokine expressions in a certain T helper pathway is unclear. Further studies may be required to clarify the causality.

Although the mechanism remains unclear, clinical studies are being conducted to examine whether folic acid supplementation during pregnancy or lactation influences the risk of developing allergic diseases, whereas most focus on airway allergies rather than eczema or AD. The 2012 Generation R Study in the Netherlands conducted by Kiefte-de Jong et al. is by far the largest in scale, with a population-based birth cohort of 8742 children followed up from fetal life to 48 months old. This study revealed that maternal folate > 16.2 nmol/L was positively associated with the development of AD (aOR 1.18; 95% CI 1.05–1.33) [103]. A high maternal vitamin B12 level > 178 pmol/L demonstrated a similar association with AD (aOR 1.30; 95% CI 1.06–1.60) in the same study [103]. Another study by Dunstan et al. in Australia in 2012 showed that relatively high intake of folate supplement by the mother (> 500 μg/day) increased the probability of infants to develop eczema at the age of one than those whose mother had low levels of folate supplement (< 200 μg/day; OR 1.85; 95% CI 1.14–3.02; $p = 0.013$) [104]. Interestingly, the amount of maternal folate intake from ordinary food causes no difference in the risk of offspring eczema. The folate level in cord blood shows no difference in children with or without eczema, but it is possibly associated with sensitization, indicating a greater risk when the level is either low or high (< 50 or > 75 nmol/L, respectively) [104]. Other studies, however, showed different trends. Two separate studies in the Netherlands [105, 106],

including one based on the KOALA cohort [105] and a Japanese study [107] investigating outcomes on both airway allergy and eczema, found no association between maternal intake of folate and eczema. Two studies reported that a high folate level in the middle of gestation possibly demonstrates a protective rather than harmful effect on the risk of offspring atopy. A South Korean study with a prospective cohort of 917 mother–child pairs showed that a high maternal serum folate level (≥ 9.5 ng/mL) during gestational age (GA) of 12–28 weeks was associated with the reduced risk of maternal-reported AD at 24 months; however, no relationship was observed for the high folate level in late pregnancy (29–42 weeks) or AD in other ages [109]. Another recent study based in the USA found decreased odds of wheezing in children whose mothers had 2nd trimester folate ≥ 20 ng/mL, but no association was noted for AD [111].

Overall, current studies focusing on the relationship between maternal folic acid/folate supplement and childhood AD had shown inconsistent results. All research about maternal folic acid status and childhood atopic diseases are observational cohort studies, partly due to the difficulties and infeasibility of conducting clinical trials and given that deficiency or overdosing of folic acid during the gestation stage could be harmful [191]. A meta-analysis investigated the effect of prenatal folic acid supplement on childhood risk of asthma and discovered no association [192]. However, in the case of AD, thus far, neither meta-analysis nor systemic review is available to generate a conclusive result. The role of maternal folic acid supplement on offspring AD remains unclear. A larger cohort study with detailed documentation of maternal folic acid status and prolonged follow-up period of the children might be needed to gain deeper insights into this topic.

Vitamins B2, B6, and B12

Vitamins B2, B6, and B12 participate in the DNA methylation pathway, which is carried out mainly by folate. Deficiency in vitamin B2, B6, or B12 may impair folate metabolism [193]. For pregnant women, these group B vitamins, including folate (B9), are often supplemented in combination. Little is known regarding the roles of vitamin B2 and B6 in association with atopic diseases. A Japanese study conducted by Miyake et al. analyzed the maternal consumption of vitamin B2, B6, folate, and B12 and its effects on childhood atopic diseases including AD [107]. None of the vitamins analyzed in the study affected the risk of AD.

Vitamin B12 (cobalamin) is a group of cobalt-containing vitamins. Although this vitamin can be synthesized by microorganisms in human gut, most of the vitamin B12 in our body comes from food sources, especially those of animal origins, such as milk, cheese, and eggs [194]. Vitamin B12 facilitates normal physiological function in humans by multiple metabolic functions. One member of B12, methylcobalamin, acts as a co-enzyme that methylates homocysteine into methionine, which is an important step to convert folate (B9) into metabolically active form to perform its function as methyl group donor [194]. Methylcobalamin can also suppress cytokine production by T cells in vitro and modulate lymphocyte function through augmenting Treg activities, although the mechanism is not fully understood. Topical vitamin B12 is effective in treating AD in both adults and children [195, 196].

Vitamin B12 is often supplemented together with folate for pregnant women. Despite the claimed effect of improving AD, current studies, including a Japanese study on vitamin B group and the Generation R Study mentioned above, found no beneficial role for vitamin B12 in childhood AD when supplemented to mothers during pregnancy [103, 107]. The Generation R Study identified an increased risk with maternal supplementation of vitamin B12. One study investigated the relation between cord blood folate, homocysteine, and vitamin B12 levels and childhood asthma and eczema and found no association [113].

A polymorphism in the gene encoding methylenetetrahydrofolate reductase, the MTHFR gene, is also being studied for its role in manipulating folate and vitamin B12 status, which could render susceptibility to atopic diseases. With a prevalence of 5–15% in the general population, the single-nucleotide polymorphism C677T in MTHFR gene reduces the activity of the enzyme, causes decreased re-methylation of homocysteine to methionine by vitamin B12, and subsequently alters folate distribution [197, 198]. The presence of homozygous MTHFR C677T may further augment the effect of low folate or vitamin B12 status on DNA methylation in lymphocytes and affect the risk of developing allergic diseases. Several studies investigated maternal and/or fetus MTHFR C677T polymorphism, along with maternal folate and vitamin B12 status, and their association with offspring AD [199]. However, of all the genetic combinations analyzed, no difference was found in the outcomes of the studies [103, 200].

Vitamin B3 (Niacin)

Niacin (vitamin B3) is found in a variety of food sources, including fish, poultry, meat, mushroom, and nuts. Nicotinamide is the amide form of niacin, which could be supplemented by niacin intake and shares similar physiological functions with niacin. Niacin can be converted from tryptophan, an essential amino acid, by the kynurenine pathway. An increased intake of tryptophan-containing foods or supplemental niacin can increase the serum level of nicotinamide; topical and oral forms of nicotinamide are effective in the treatment of dermatitis by reducing transdermal water loss [201, 202].

One study carried out in the UK by El-Heis et al. examined the relation of maternal serum concentrations of

nicotinamide and tryptophan metabolites in the kynurenine pathway to the risk of atopic eczema in offspring [114]. The study included 497 mother–infant pairs, and the outcomes were analyzed at 6 and 12 months of age. The results showed that high concentrations of nicotinamide and anthranilic acid were associated with a low risk of eczema at age 12 months but not at 6 months [114]. The other metabolites showed no association with AD. However, given the limited number of studies and their relatively small sample size, the relationship between maternal niacin intake and childhood AD remains to be concluded.

Vitamin C

Vitamin C, or ascorbic acid, is a water-soluble vitamin with well-known antioxidant properties and is abundant in fruits and vegetables [203]. The rationale of the effect of vitamins C on AD originates from two aspects: vitamin C plays a role in maintaining the integrity of skin by aiding in the synthesis of ceramides in the epidermis [204], and as an antioxidant, vitamin C reduces the oxidative stress that plays a part in the pathogenesis of AD [205]. Adult studies with small sample sizes had demonstrated that serum vitamin C level is low in patients with AD and is inversely correlated with severity in terms of SCORing Atopic Dermatitis index (SCORAD) [183, 204].

Despite several proven rationales, however, the results of mother–infant studies showed inconsistencies. The Australian study by West et al. investigated the maternal intake of multiple antioxidants during pregnancy; a high dietary vitamin C was correlated with reduced offspring wheezes but not eczema [100]. A breast milk analysis by Hoppu et al. measured the antioxidant composition based on vitamin C and E levels of 34 mothers and revealed that high concentrations of vitamin C in breast milk reduced the risk of atopy in infants ($p = 0.038$), which is defined by the presence of AD during the first year of life and a positive skin-prick test reaction at 12 months [37]. By contrast, a prospective questionnaire-based UK study of 1924 mother–infant pairs revealed that a high maternal intake of vitamin C was associated with weak but positive risk of AD in infants in their second year of life [101]. Results of other studies based specifically on children population are also inconsistent [205]. Evidence is still inadequate to make suggestions for vitamin C intake of pregnant or breastfeeding mothers.

Vitamin D

Vitamin D is a fat-soluble vitamin that occurs in two main forms: ergocalciferol (vitamin D_2, produced by plants) and cholecalciferol (vitamin D_3, derived from animals) (Fig. 2) [206]. Humans predominately derive vitamin D by cutaneous synthesis under the influence of sunlight, with limited vitamin D sourced from dietary intake [207]. Therefore, the UK Department of Health recommends that women consume a daily vitamin D supplement of 400 IU throughout pregnancy and lactation, whereas the AAP suggests that all infants and children should have a minimum intake of 400 IU vitamin D per day beginning immediately after birth. Vitamin D potentially modulates allergy outcomes via its multifaceted effects on altered epidermal barrier function, immune dysregulation, and inadequate bacterial defense [208]. Systemically, vitamin D is an immunomodulator that targets innate and adaptive immune cells, including monocytes, macrophages, DCs, T cells, and B cells. Vitamin D decreases excessive inflammation by suppressing TLR production by monocytes, enhancing the mast cell production of IL-10, inhibiting DC activation by lipopolysaccharides, decreasing cytokine secretion from Th1 cells, inducing Treg activities, and inhibiting B lymphocyte function and IgE secretion [209, 210]. Deficiencies in vitamin D levels and/or signaling would favor a predominant Th2 response and IgE elevation. In the skin, vitamin D exhibits pleiotropic effects ranging from keratinocyte proliferation, differentiation, and apoptosis to barrier maintenance and immunoregulatory processes [206]. Vitamin D plays an important role in epidermal differentiation and barrier function through the regulation of calcium, antimicrobial peptides (i.e., cathelicidin), and TLRs [211–213]. Vitamin D prevents skin T cell infiltration by downregulating the expression of cutaneous lymphocyte-associated antigen [214]. Therefore, vitamin D deficiency might lead to the dysfunction of the skin barrier, infiltration of T cells, and increased predisposition of patients with AD to skin superinfection by *Staphylococcus aureus* or its superantigens [213].

Although several studies reported no significant relationship [215], most of the research found a negative correlation between AD severity and vitamin D levels with dose-dependent effects [216–218]. Low serum vitamin D levels were associated with elevated serum IgE levels [218] and increased house dust mite sensitization in AD patients [219]. A specific vitamin D receptor gene polymorphism occurs frequently in patients with severe AD, thus suggesting the important role of vitamin D in the pathogenesis of the disease [217]. Maternal vitamin D intake in pregnancy is associated with the reduced risk of detection of IgE, which is specific to food allergens, in offspring at 5 years of age [115].

Controversies surround the results regarding the association of vitamin D status in utero and AD development. The EDEN prospective birth cohort study in France found a significant inverse association between the cord serum 25-hydroxyvitamin D [25(OH)D] levels and risk of AD by the ages of 1, 2, 3, and 5 years [116]. The prospective study with 669 mother–infant pairs in Australia showed a low cord serum vitamin D in infants that developed eczema ($p = 0.018$); eczema was significantly more likely to occur in those with

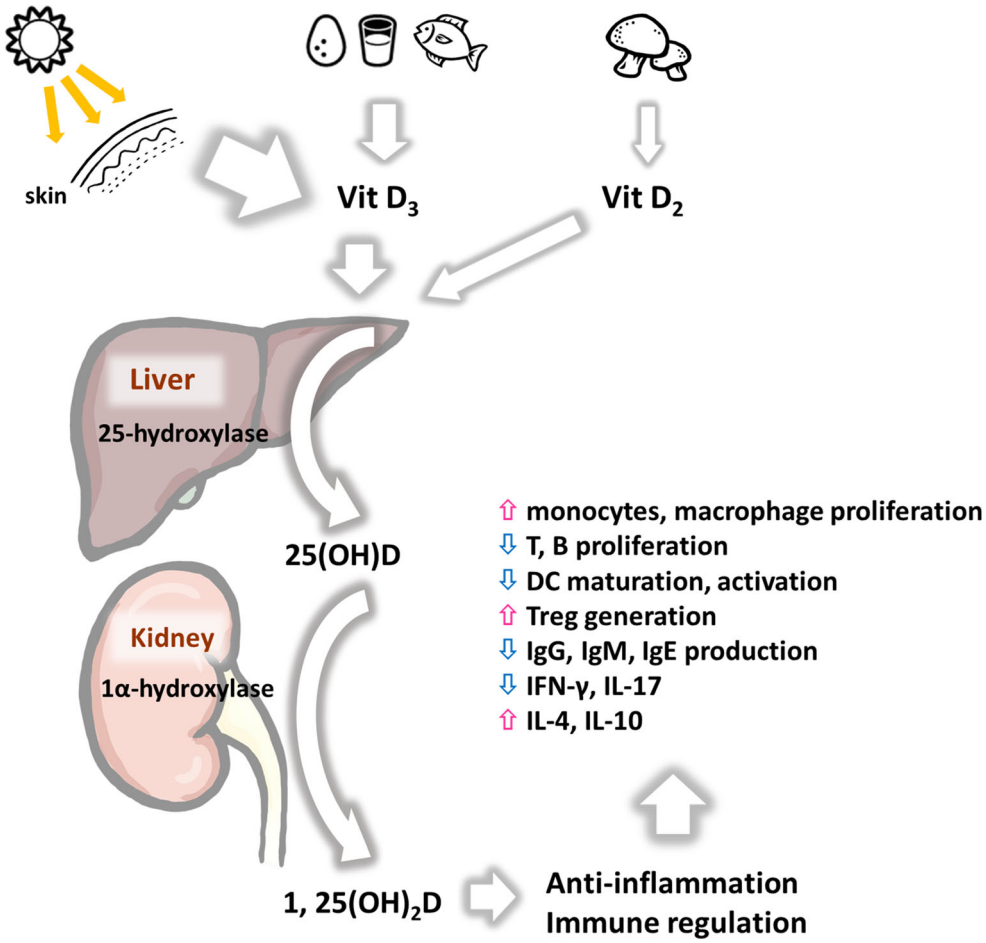

Fig. 2 Vitamin D metabolism. Vitamin D is mainly derived from cutaneous synthesis under the sunlight, with limited vitamin D sourced from dietary intake. The main dietary sources are egg, fish, milk (vitamin D_3 from animals), and mushroom (vitamin D_2 from plants). After metabolized by the liver and kidney, 1,25 $(OH)_2D$ regulates the immune system by various effects, such as inhibition of T and B cell proliferation, decrease in IgE production, inhibition of DC activation and maturation, and increase in Treg generation

vitamin D concentrations < 50 nmol/L in comparison with those with concentrations ≥ 75 nmol/L (OR 2.66; 95% CI 1.24–5.72; $p = 0.012$) [117]. A UK study showed that children born to mothers in the highest quartile of the cohort for maternal serum 25(OH)D concentration in late pregnancy had an increased risk of eczema at 9 months of age and asthma at 9 years of age [118]. Altogether, observational studies support a protective relationship between vitamin D status in utero and the risk of eczema development, whereas others suggest that high levels may be a risk factor. In an Avon Longitudinal Study of Parents and Children (ALSPAC) study, maternal serum 25(OH)D concentration was measured at each stage of pregnancy and showed no association with parentally reported allergic diseases (wheeze, asthma, eczema, or hay fever) or sensitization to three common aeroallergens [119]. These studies measured maternal 25(OH)D levels during pregnancy [116, 119, 220] and/or in cord blood [117, 118, 220] at birth and reported the eczema outcomes in infants. A major limitation of these studies is that 25(OH)D levels were only measured once, thus failing to capture the effects of likely changes in 25(OH)D status and exposure to the fetus over the course of pregnancy [208]. However, limited information is available regarding the primary prevention of allergic diseases after vitamin D supplementation. The two combined independent RCTs of vitamin D supplementation during pregnancy resulted in a significantly reduced risk of asthma/recurrent wheezing, but not eczema, in the offspring [96, 97, 221]. In a UK randomized study, 180 women received no supplement, 800 IU per day ergocalciferol (vitamin D2), or a single bolus dose of 200,000 IU cholecalciferol (vitamin D3) at 27 weeks of gestation [98]. No significant differences were observed between the control group versus the intervention groups for atopic sensitization or risk of eczema. In exclusively breastfed infant, our study showed that vitamin D levels in breast milk were negatively associated with objective SCORAD at age of 2–4 months ($p = 0.003$) [122].

In summary, conflicting evidence is available about the association between maternal vitamin D status and risk for AD development in offspring. However, from the serum status and AD severity in children and adults, vitamin D plays a protective role in AD. Although serum 25(OH)D concentration reflects dietary intake and UVB exposure, a number of other factors influence circulating 25(OH)D. Genetic variation in a number of genes, including the vitamin D binding protein, the carrier molecule that delivers all vitamin D and vitamin D metabolites to tissues, influences serum 25(OH)D [222]. More

double-blind placebo-controlled vitamin D intervention studies are required. These studies need to consider the supplement type (vitamin D3 vs. D2), timing (a highly developed immune system is already present by 20 weeks of pregnancy), and dosage [9].

Vitamin E

Vitamin E is a family of fat-soluble compounds that deliver antiinflammatory properties and act as powerful antioxidants [205]. Two principal classes of vitamin E, tocopherols and tocotrienols, exist, and they can be further divided into four forms: α, β, δ, and γ [223]. These eight forms of vitamin E are naturally present in food sources, most abundantly in plant oils, cereals, and nuts. The strong antioxidative property of vitamin E has inspired studies inspecting its nutrient–disease association with AD. In adult studies including DBPCRCT, vitamin E supplementation has significantly improved AD in terms of symptoms, SCORAD, and serum IgE level [224, 225]. In children, a questionnaire-based study has shown that AD patients have significantly lower dietary vitamin E intake than those without the disease.

In mother–infant studies, however, not all results are in agreement. A UK prospective study investigating 1924 mother–infant pairs in multiple antioxidants showed that maternal intake of vitamine E was inversely associated with the risk of childhood eczema in atopic mothers ($p = 0.024$), but no statistical significance was observed for the whole population [101]. In the Australian study by West et al., no association was found between maternal intake of vitamin E and eczema in offspring [100]. In a Finnish study in which 37 atopic mothers were enrolled, the ratios of infant serum γ- and α-tocopherol to fat were significantly correlated with maternal serum ratios (infant α-tocopherol/fat was higher, and γ-tocopherol/fat ratio was lower than those of mothers), indicating that maternal vitamin E status may affect that of the infants. Nevertheless, the serum tocopherol levels showed no correlation with the clinical presentation of AD or skin-prick test [226]. In general, vitamin E may have a protective role against AD, but its association with offspring AD when supplemented in maternal diet during pregnancy remains unclear.

Minerals and Trace Elements

Magnesium

Magnesium assists in the activation of vitamin D, which in turn regulates serum calcium and phosphate levels and facilitates immune function; this element has thus been widely studied for its relationship with AD [227]. Magnesium itself also exhibits antiinflammatory activity on the skin and improves skin barrier function by participating in cell proliferation and differentiation [228, 229]. In a small-scale children's study, AD patients had significantly lower serum magnesium level compared with the controls ($p = 0.007$). Erythrocyte zinc levels were significantly lower in AD patients in the same study [230]. However, the mechanism is still unclear. Studies on magnesium intake in the mother–fetal or mother–childhood atopy relationship are lacking.

Iron

Iron supplementation is essential for pregnant women, and the World Health Organization has made recommendations of 400 μg daily iron supplement along with folic acid to prevent maternal anemia, puerperal sepsis, low birth weight, and preterm birth [231]. Iron is often supplemented to infants or toddlers because of possible iron deficiency or anemia associated with exclusive breast milk or formula feeding, as suggested by AAP [232]. The relationship between iron status and the immune system is complicated. Free ferrous ion in the blood can interact with H_2O_2 through a mechanism called Fenton reaction, leading to the production of free radicals and increased oxidative stress within cells [233]. On the other hand, a deficient iron status may also be harmful. Poor iron status at birth may compromise Th1 lymphocytes and bias the immune response toward the Th2 pathway, increasing the risk of development of allergic diseases [234].

An exploratory study by Nwaru et al. investigated the associations between maternal iron status in pregnancy and childhood wheezing and atopy in their first 10 years of life. A reduced maternal serum iron level is significantly associated with childhood wheezes. The risk of "doctor-diagnosed eczema" is high with low maternal iron status, but the association is of borderline significance [235]. In part of the ALSPAC study by Shaheen et al., high iron levels in cord blood are negatively associated with later onset of eczema (OR 0.90), but the cord blood level shows no relation with the maternal intake [236]. Fortes et al. noted that prenatal co-supplementation of iron and folic acid leads to a fourfold decreased risk of AD (OR 0.22; 95% CI 0.06–0.79; $p = 0.02$) after adjusting for possible confounding factors [237]. Although studies with large sample size are lacking, current available evidence indicates a possible protective role of adequate iron supplement in perinatal or infancy against AD.

Zinc

Zinc is an essential micro-nutrient [205] that is related to the integrity and immune status of the skin barrier in multiple functional pathways [238]. Zinc acts as the structural cofactor of zinc-finger motifs, which are present in the proteins involved in the expression of filaggrin, a key component involved in the pathogenesis of AD [239]. Topical zinc oxide application can alter the dermal cytokine profile into an

antiinflammatory pattern (increased IL-10 and decreased IL-1β, IL-6, and TNF-α levels) [239]. An in vitro study has shown a possible antimicrobial activity of zinc oxide against methicillin-resistant *Staphylococcus aureus* [240]. Although the mechanism between zinc and AD is still not fully known, several pilot studies have suggested the protective role of high serum, hair, and erythrocyte zinc level against the development of AD [238].

Dietary zinc is most abundant in meat, shellfish, nuts, and certain vegetables. A Mediterranean diet pattern may generally satisfy the zinc requirement [241, 242]; maternal Mediterranean diet pattern may be beneficial for childhood atopy [12]. Nevertheless, a limited number of studies focused specifically on zinc in maternal diet and its effect in offspring eczema or AD. Currently existing large-scale studies analyzing antioxidants in maternal diet and offspring atopy discovered no associations between zinc intake and childhood eczema [10, 16, 100]. Whether zinc in maternal diet would influence childhood atopic disease remains unclear.

Copper

The rationale of how copper influences the development of allergic disease is not fully discovered. Copper is suggested to have antioxidant activities and act as a cofactor that participates in cell growth and function [243]. A 1987 study by Di Toro et al. investigated both zinc and copper status in allergic children. However, in contrast to zinc, whose level in hair is negatively correlated with development of AD, a significantly higher hair copper level was found in children with the disease [244]. Similarly, in 1990, el-Kholy et al. observed a significantly high serum ceruloplasmin in children with AD ($p < 0.001$), whereas high serum and hair copper levels were associated with asthma [243].

In spite of these early studies suggesting that high copper levels may induce atopy, recent maternal–infant studies valued copper for its antioxidant role, whereas others reported different results. The Australian study by West et al. showed that a high dietary copper intake is associated with reduced risk of offspring eczema and other allergic diseases [100]. Another cohort study by Martindale et al. found no relationship [101]. Interestingly, maternal intake of copper showed an opposite influence compared with the copper status of the children themselves. Given that the role of copper in allergic diseases is not fully elucidated, additional studies have to be carried out to clarify the related mechanism.

Selenium

Selenium is known for its role as an antioxidant in human health. Environmentally, selenium is ubiquitous and can be found in rock, water, and soil. This element enters the food chain by being taken up by plants from the soil and finally reaches animals through bioaccumulation. The most abundant food sources of selenium include fish, egg, meat, and Brazilian nuts. Biologically, selenium is a key component in several enzymes, such as glutathione peroxidase, thioredoxin reductase, and iodothyronine deiodinases, which carry out antioxidative functions [245]. Sufficient amount of selenium is therefore necessary for maintaining optimal antioxidative capacity in the body [205]. In studies, selenium status is being linked to diseases, including AD, because of the possible role of oxidative stress in their pathogenesis [181, 182, 246]. Limited clinical evidence supports the beneficial role of selenium in improving AD. A DBPCRCT conducted in 1989 by Fairris et al. enrolled 60 adults with AD, who were supplemented with either selenium-enriched yeast plus vitamin E, selenium-enriched yeast only, or placebo. No difference was observed in the severity of eczema or the concentration of cutaneous selenium among groups [247].

For pregnant women, serum selenium concentration decreases significantly during gestation [248]; a deficient selenium status is associated with multiple health problems, such as recurrent miscarriages, preterm delivery, gestational diabetes mellitus, thyroid peroxidase antibody-positive autoimmune thyroiditis, and neural tube defect of the fetus [249]. Adequate selenium intake or supplement is thus suggested by authorities, especially during pregnancy [250, 251]. Regarding the antioxidative property, several studies investigated the association of maternal selenium status or selenium supplementation and the risk of atopic diseases, including eczema, in children. In the ALSPAC study that analyzed trace elements in the umbilical cord, high cord blood selenium level was negatively associated with childhood wheezing, but no association was found with eczema [236]. Another study on UK cohort by Martindale et al. revealed no consistent statistically significant associations between eczema in the first 2 years of life and total maternal intake of selenium [101]. A Japanese cohort study of 1036 mother–infant pairs by Yamada et al. analyzed 32 measurable minerals in the hair of infants and mothers using proton-induced X-ray emission (PIXE); only selenium and strontium demonstrated significant association with childhood dermatitis [252]. Selenium deficiency in either infant or mother increased the risk of AD at the age of 10 months, but for mothers, the result was borderline significant ($p = 0.048$ for infants and $p = 0.062$ for mothers). Compared with childhood asthma or wheezing, of which more evidence is needed for a relatively concrete conclusion, little is known for selenium's role in AD and how mother's selenium status affects children.

Strontium

Strontium is present in seawater and soil. The strontium we obtain mostly originates from seafoods, cereals, and grains. Strontium is scarcely studied for its biological role compared

with other trace elements. Most of the physiological functions currently known for strontium are related to the metabolism of bones [253]. Less is known for its association with atopic diseases. A study by Barneo-Caragol et al. revealed that strontium level rose significantly during the third trimester of pregnancy, possibly to cope up with the oxidative damage that developed physiologically during this period [254]. Yamada et al. discovered that among all 32 minerals tested in infants' and mothers' hair by PIXE in their study, only selenium and strontium had significant association with the risk of childhood AD. In contrast to selenium, whose levels in both infants' and mothers' hair are inversely related to AD risk, the hair strontium level in mother is positively associated with AD risk in children [252]. With the tool, the authors of this study developed a logistic prediction model for childhood AD using the levels of these elements, with a sensitivity of 65.9% and specificity of 70.5% [252].

Discussion

In consideration of children, maternal nutrition status may have substantial effects as one of the most modifiable environmental factors and may play a prominent role in the development of chronic and multifactorial diseases, such as allergy. However, studying the causality of mothers' food intake to offspring disease could be difficult. The nutrients from mothers are delivered through the placenta to the fetus or secreted in breast milk. Thus, the levels of most nutrients in cord blood or breast milk and in mothers' and children's sera must be examined to establish a robust correlation. Several nutrients may be quantified indirectly using other specimens, for example, minerals which can be measured in urine or hair [252]. However, certain obstacles could prevent the acquisition of samples in real clinical settings, especially with vulnerable groups as subjects. Not all nutrients have highly correlated, measurable markers. Most of the available mother–fetal or mother–infant studies utilized well-designed, validated questionnaires to assess the nutrient composition of maternal diet; however, although they are easy to administer, such questionnaires could be affected by recall bias [255]. The often observed inconsistencies in the amounts of specific nutrients from mother's intake, maternal serum concentration to cord blood, and fetal serum concentration also suggest a complicated physiological mechanism involved in the process of nutrition transportation [104, 236].

Compared with childhood asthma and wheezes, studies rarely evaluated the influence of maternal nutrition status to examine the outcome of childhood AD or eczema. The mechanism behind the causality is also less explored in AD, either in animal models or in nutrient–genome interaction. The paucity of studies causes difficulty in developing a solid conclusion. Of all the nutrients that were reviewed, ω-3 PUFA, folic acid, and vitamin D are the most studied. Small-scale RCTs are conducted for ω-3 PUFA and vitamin D, of which commercialized supplementary products are available because of a relative common deficient status in modern Western lifestyle. Other nutrients are mostly investigated in observational studies, of which several use a large sample size and long period follow-up periods, for example, the Generation R Study or the ALSPAC [103, 236]. However, neither solid proof nor concordant results of being beneficial or risky to offspring with AD has been found for any of the nutrients. Systemic reviews or meta-analyses are also lacking due to the highly heterogenous study designs and methodology and inadequate number of studies.

Several studies investigated the influence of maternal diet in terms of specific food category or dietary pattern, instead of focusing on single nutrients. A few research suggested a potentially protective role of maternal Mediterranean diet pattern, which consists of high proportions of vegetables, fruits, nuts, seafoods, and grains, against AD or other atopic diseases [12, 13, 241, 242]. Additional intake of fish [8, 17], vegetables, and fruits [8, 16] is also beneficial [256]. Nevertheless, whether the effect is delivered mainly by a sole key nutrient in certain foods (e.g., ω-3 PUFA in fish or vitamin C in citrus fruits) is unclear. One RCT specifically examined the level of single nutrient (ω-3 PUFA) after increased intake of salmon and detected an increase in EPA in maternal serum and cord blood [73]. A change in the cytokine and Ig profile was also observed in the fetus, but no difference was noted in the outcomes [72]. This condition demonstrates that certain food source modifications in maternal diet can alter the nutrition status of offspring using a measurable nutrient component, although no correlation was observed between the laboratory test results and clinical presentations. Given the complicated mechanisms involved in nutrition physiology, concluding the net effect of individual nutrients would be extremely difficult, especially when certain food or diet is composed of various portions of different nutrients. The interplay of other environmental factors, genetic factors, and microbiota also increases the complexity. More strategically designed, carefully conducted, and less biased studies are required to shed a light on this topic.

To conclude, no strong evidence indicates that a single nutrient or food in maternal diet significantly affects the risk of childhood AD. Nevertheless, a balanced diet is not only always helpful for humans in pregnancy or during lactation but also a key to healthy immune function against allergies and other diseases. A healthy lifestyle with healthy, balanced dietary intake is thus encouraged.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval and Informed Consent Not applicable.

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