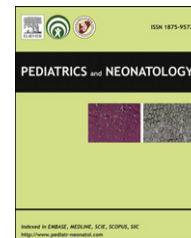


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REVIEW ARTICLE

Influence and Mechanisms of Maternal and Infant Diets on the Development of Childhood Asthma

Su-Boon Yong^a, Chih-Chiang Wu^a, Lin Wang^b, Kuender D. Yang^{c,*}^a Department of Pediatrics, Show Chwan Memorial Hospital, Changhua, Taiwan, ROC^b Department of Pediatrics, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan, ROC^c Department of Medical Research, Show Chwan Health Care System, Changhua, Taiwan, ROC

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Perinatal nutrition has been implicated in the programming of diseases in children and adults. The prevalence of asthma has dramatically increased in the past few decades, particularly in children. This suggests that the perinatal environment, including maternal and infant diets, may be involved in the increase in the prevalence of asthma. Recent studies have demonstrated that certain maternal and infant diets have a protective or augmentative effect on the development of asthma. Maternal diets with higher vitamin D, vitamin E, or /and probiotics are related to asthma prevention. Infants with breast feeding for at least 4 months and/or complementary diets between 4 and 6 months may have regulatory effects on the prevention of asthma. In summary, diets may have epigenetic or immune regulatory effects on the promotion or prevention of asthma. This article analyzes recent reports on the potential mechanism and mechanism-driven early prevention of childhood asthma by modification of maternal and infant diets.

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1. Introduction

Maternal diet and general health during pregnancy have a significant impact on the development of diseases in offspring. The importance of maternal diet and nutrition on the development of metabolic diseases, such as hypertension, diabetes, and insulin resistance has been recognized.¹

* Corresponding author. Department of Medical Research & Development, Show Chwan Health Care System, 6 Lu-Kung Road, Lu-Kong, Changhua 505, Taiwan, ROC.

E-mail address: yangkd.yeh@hotmail.com (K.D. Yang).

This is also called the developmental origins of health and diseases. The prenatal programming of metabolic diseases in childhood and adulthood has been linked to the environmental modulation of epigenetic imprinting.² The prevalence of childhood asthma has increased globally.³ It has been postulated that maternal and infant diets play an important role in the development of childhood asthma.⁴ Observational studies have reported associations between asthma and diets including vitamins C, D, and E, and fruit.⁵ Currently, there is evidence that excessive folate supplementation during pregnancy is associated with childhood asthma.⁶ The associations of vitamin D, vitamin E, and polyunsaturated fatty acid (PUFA) levels during pregnancy with childhood asthma remain controversial.⁵ Traditional natural products such as garlic, curcumin, and broccoli that could modify the epigenetic program, such as DNA methylation and histone acetylation, may prevent allergic disease in the perinatal stage.^{7,8} This article provides a review of recent reports regarding the roles of maternal and infant diets on the promotion of or protection against asthma. We also summarize the mechanism-driven early prevention of asthma by various modifications of the maternal diet.

2. Influence of Maternal Diets on the Development of Asthma

2.1. Maternal folic acid

Folate plays an important role in nucleic acid and protein synthesis by donating methyl groups. Pregnant women usually have diets supplemented with folate. Supplemental maternal folate can protect the fetus from neural tube defects and cardiac defects. A Norwegian mother and child cohort study (a questionnaire analysis) of 32,077 children reported that higher maternal folate levels are associated with a high risk of developing asthma by the age of 3 years.^{6,9} In a further analysis in the case-control design nested within this cohort, Håberg et al demonstrated that supplementation with maternal folate during pregnancy increases respiratory infection in childhood and that folate supplementation during the first trimester is associated with an increased risk of wheeze.¹⁰

In animal studies, methyl donors such as methionine enhanced DNA methylation and suppressed gene expression.¹¹ Similarly, Hollingsworth et al showed that dietary methyl donor supplementation to mice *in utero* enhanced DNA methylation at specific CpG motifs associated with hypermethylation (silencing) of regulatory genes in lung tissue and was associated with allergic disease.¹² It was further demonstrated that *runx-related transcription factor 3* (*Runx3*) is a specific gene that negatively regulates allergic airway disease. *Runx3* mRNA and protein levels were found to be suppressed after diet supplementation with methyl donors *in utero*.¹² *Runx3* expression can be attenuated through increased DNA methylation. In another study, *Runx3*-deficient mice had an asthma-like phenotype.¹³ Therefore, excess folate supplementation might modify the epigenetic mechanism by increasing DNA CG methylation,¹² which suppresses the expression of immune genes, such as *Runx3* expression, and promotes the development of asthma.

2.2. Maternal vitamin D

Vitamin D deficiency affects many physiological functions in adults, especially pregnant women. Long hours of indoor work and the lack of exposure to sunshine are the main causes of vitamin D deficiency. Pregnant women in developed countries now have diets supplemented with vitamin D. Maternal vitamin D levels during pregnancy are inversely associated with asthma and allergic rhinitis in offspring at the age of 5 years.¹⁴ Currently, no intervention studies have shown evidence that vitamin D is directly associated with asthma. A few observational studies have shown that vitamin D status is related to asthma and allergic outcomes.

Pregnant women taking vitamin D supplements and infants exposed early to vitamin D have fewer allergic diseases.¹⁵ Recently, Brehm and colleagues in a cohort study of a cross-sectional investigation of 616 Costa Rican children between the ages of 6 and 14 years found that serum vitamin D levels were inversely associated with serum immunoglobulin E levels and peripheral eosinophil counts.¹⁶ Higher vitamin D levels are associated with a lower rate of hospitalization for asthma and have an influence on the functions of helper T cell type 1 (Th1), 2 (Th2), and regulatory T cells (Treg), thereby enhancing the secretion of interleukin-10 (IL-10).¹⁷ The mechanism for the prevention of asthma by vitamin D supplementation may be related to optimal dose, by which the secretion of regulatory IL-10 by Treg cells and super high dose of vitamin D may have the opposite effect.¹⁷ A cohort study from the United Kingdom showed that maternal exposure to higher concentrations of ²⁵(OH)-vitamin D during pregnancy (>75 nmol/l) was associated with an increased risk of asthma in children at 9 years of age compared to those whose maternal concentration fell within the bottom quarter of distribution.¹⁸ This conclusion was drawn from a longitudinal follow-up of a United Kingdom population-based cohort of children at birth, 9 months, and 9 years of age. Taken together, these observational studies could not show evidence that vitamin D was directly associated with asthma. Current research on vitamin D using animal models and human clinical trials are providing information on this topic, particularly on the molecular epigenetic regulatory mechanisms involved. An active metabolite of vitamin D, 1,25-dihydroxyvitamin or D₃, plays an essential role in cellular metabolism and differentiation via its nuclear receptor vitamin D receptor (VDR), thereby mediating complex epigenetic events in vitamin D signaling and metabolism.^{19,20} It remains unclear as to what key epigenetic mechanisms are involved in vitamin D-mediated chromatin modifications, such as regulation of histone deacetylase, and histone acetylation/methylation/demethylation. Further studies are needed before recommendation of maternal vitamin D supplementation for prevention of asthma.

2.3. Maternal vitamin E

Vitamin E is a family of fat-soluble compounds that include both tocopherols (alpha-, beta- and gamma-tocopherol) and tocotrienols. Vitamin E is a fat-soluble antioxidant that stops the production of reactive oxygen species formed when fat undergoes oxidation. The potential antioxidant effect of maternal diet during pregnancy and the risk of childhood

asthma has been highlighted by several birth cohort studies. A longitudinal birth cohort study in the United Kingdom reported that maternal vitamin E levels were associated with fetal crown-rump-length (CRL) during the first trimester of pregnancy. There were positive associations between CRL and forced expiratory volume in forced expiratory volume. CRL was positively associated with maternal plasma alpha-tocopherol. Maternal vitamin E intake may be one factor effecting the growth of the fetus and fetal lungs during early pregnancy²¹ according to one study, whose strength lies in its being a large-scale study with 1,924 children including follow-up until 5 years of age. Another case-control study in Saudi Arabia also showed that childhood asthma was associated with a reduced dietary vitamin E intake.²² The mechanism for the prevention of asthma by vitamin E supplementation may be related to its antioxidant effect, which is known to switch Th2 differentiation towards Th1 differentiation.^{5,23} However, a meta-analysis from 40 studies showed that vitamin E intake did not affect the outcome of asthma.²⁴ Pearson and colleagues conducted a placebo-controlled, double-blind parallel group clinical trial which showed that dietary supplementation with vitamin E was not associated with treatment outcomes in adults with mild-to-moderate asthma.²⁵ The limitation of this study was its small sample size (72 participants).

2.4. Polyunsaturated fatty acids

Omega-3 (n-3) long-chain PUFAs and omega 6 (n-6) long-chain PUFAs are mostly evaluated for the prevention of asthma. The n-3 PUFAs are found mainly in fish oil and n-6 PUFAs are mostly found in margarine and vegetable oil. It had been hypothesized that an intake of higher n-3 and lower n-6 PUFA contributed to a decrease in the instance of asthma.⁵

In a randomized placebo-controlled trial in which supplementation with n-3 PUFAs was prescribed to mothers during pregnancy and lactation, high levels of docosahexaenoic acid and eicosapentaenoic acid (EPA) in maternal and infant plasma were associated with a lower prevalence of immunoglobulin E-associated disease.²⁶ In addition, maternal n-3 PUFA supplementation was found to be associated with a lower risk of food allergy and immunoglobulin E-associated eczema during the first year of life in infants with a family history of allergic disease. In a cross-sectional study in Japan, Miyake et al examined the association between intake of specific types of fatty acids and the prevalence of asthma symptoms. The results showed that diets containing total fat, saturated fatty acids, mono-unsaturated fatty acids, and cholesterol but linoleic acid were not associated with wheeze.²⁷

It seems unlikely that all forms of PUFA intake can decrease allergic diseases. An increase in dietary PUFA intake was found to be associated with an increase in inflammatory cell membrane arachidonic acid levels, which consequently enhanced prostaglandin E2 levels, suppressed Th1, and promoted Th2 differentiation.^{5,26} Higher levels of n-6 PUFAs in food intake was found to be associated with elevated levels of inflammatory exhaled nitric oxide concentration and asthma symptoms.²⁸ The therapeutic potential of PUFA for the prevention of asthma requires further studies on subtypes and doses of PUFA.

2.5. Maternal food restriction

Nutrition during pregnancy plays an important role in the development of childhood diseases, including atopic diseases. Vadas et al found that food allergens derived from peanuts, cow milk protein, and eggs were present in breast milk.²⁹ The 2006 Cochrane review showed that restriction of maternal foods (particularly egg and cow milk) did not decrease the incidence of asthma during the first 18 months of life.³⁰

Lovegrove et al demonstrated that maternal food restriction including milk, egg, and fish during breast feeding in 26 lactating women had no protective effect on atopic dermatitis in infants during the first 18 months of life.³¹ Recently, Greer et al found no evidence that maternal avoidance of dietary antigens could prevent childhood atopic disease.³² Two trials performed by Falth-Magnusson et al³³ and Lilja et al,³⁴ involving 334 pregnant women, did not suggest that maternal food restriction had a strong protective effect on the incidence of childhood asthma.

The mechanism for the prevention of asthma by maternal food restriction may be related to the avoidance of prenatal allergen exposure and the prevention of prenatal sensitization. The unresolved problem is to determine which food(s) should be avoided during the first, second and third trimesters in order to minimize perinatal allergy sensitization.

3. Influence of Infant Feeding and Complementary Food on the Development of Asthma

3.1. Breast feeding

The World Health Organization and the American Academy of Pediatrics emphasize the value of breast feeding for mothers as well as for infants. In the 2006 Cochrane Review, Greer et al showed that exclusive breast feeding (for at least 4 months) in high-risk infants is associated with a lower risk of atopic dermatitis than observed for high-risk infants fed with cow's milk.^{30–32} A prospective cohort study in Western Australia also found that exclusive breast feeding during the first 4 months of life was associated with a reduction in the risk of childhood asthma by 6 years of age.³⁵ A meta-analysis, systemic review, prospective study found that exclusive breast feeding during the first 3 months was associated with a lower risk of asthma between the ages of 2 and 5.³⁶

A cohort study in New Zealand, however, found that breast feeding for more than 4 weeks is associated with an increase in the development of asthma at 9 years of life.³⁷ The strengths of this study lies in its 26-year follow-up period and its clear definition of allergy sensitization and asthma outcomes by measurements of airway responsiveness. Wright et al demonstrated that although breast feeding was associated with a lower rate of recurrent wheeze, breast feeding by an asthmatic mother led to a higher risk for wheeze, especially for atopic children, by 13 years of age.³⁸ It remains controversial as to whether breast feeding is beneficial in the prevention of asthma,

particularly breast feeding by an atopic mother. This may be due to different environments, cultures and perinatal food among the different demographic areas where the contents of maternal diets and maternal environments have different effects on the programming of childhood asthma.

3.2. Protein-hydrolyzed formula

Protein-hydrolyzed formula contains hypoallergenic milk protein and is usually referred to as 'predigested' formula. The protein contents of these formulas have been broken down or 'predigested' in order to prevent sensitization and intolerance in infants. There are two protein-hydrolyzed formulas: partial hydrolysate formulas (PHFs) and extensive hydrolysate formula (EHF), depending on the degree of peptide digestion.

The German Infant Nutritional Intervention study published in 2003 showed that PHF decreased the rate of atopic dermatitis but did not reduce the risk of asthma in high-risk infants.³⁹ The German Infant Nutritional Intervention study published in 2008, which included long-term follow-up of the preventive effects of PHF and EHF until the age of 6 years, demonstrated that both formulas were associated with a reduction in allergies and atopic dermatitis.⁴⁰ The strengths of this study are its large sample size (2,252 children) and its long-term follow-up. In our prospective, observational, birth cohort study, infants fed a PHF in the first 6 months were less likely to experience milk protein sensitization but there was no reduction of allergic diseases by the age of 3 years in comparison to those fed regular cow's milk formula within the first 6 months of life.⁴¹ The limitation of this study is that it is an uncontrolled trial. A meta-analysis of 12 independent studies showed that 100% whey PHF was associated with a reduced risk of atopic dermatitis in infants with a family history of allergy.⁴² The authors recommended that infants with a family history of allergy should be fed with PHF instead of cow's milk formula. The mechanism for the prevention of atopic dermatitis by PHF or EHF may be related to the reduction of the allergen complexity for reduced allergy sensitization or improved immune tolerance.

However, in a randomized, double-blind study, Kwint et al evaluated the influence of cow's milk formula and EHF on the incidence of atopic diseases at 5–7 years of age and reported that EHF was not associated with decreases in total serum immunoglobulin E levels, absolute eosinophils, or the prevalence of allergic diseases.⁴³ In another study, de Seta et al found that PHF was not associated with a reduction in allergic disease compared with cow's milk formula.⁴⁴ It was concluded that avoidance of cow's milk protein alone in infancy was not enough to decrease the rates of allergic diseases.

3.3. Complementary food

Complementary foods for infants are foods other than breast milk, infant formula, and water. Questions related to complementary foods are related mainly to their benefits or risks with respect to atopic diseases. The American Academy of Pediatrics recommends that complementary foods should be introduced after the age of 4 months.

A case-control study of the Prospective Cohort on the Influence of Perinatal Factors on the Occurrence of Asthma

and Allergies, in which prospective questionnaires were used to evaluate the data on nutrition, environmental exposure and parent-reported eczema, found that infants with allergic parents who experienced delayed exposure to solid foods did not have a lower rate of eczema up to 4 years of age.⁴⁵ Infants exposed to solid foods after 16 weeks of age had a higher risk of food hypersensitivity and sensitization to foods.⁴⁶ Recently, a study by Du Toit et al reported that peanut allergies in Jewish children in the United Kingdom were 10-fold higher than those in Israel.⁴⁷ They found that the mothers in Israel introduced peanuts to the infants at an earlier age and the children continued to eat peanuts more frequently. By the age of 9 months, 69% of Israeli children ate peanuts compared to only 10% in the United Kingdom.⁴⁷ This suggests that earlier and continual peanut uptake in infancy may reduce peanut allergy sensitization.

In a longitudinal birth cohort study, children exposed to cereals before 6 months of age at a lower risk of wheat allergy.⁴⁸ The strengths of this study were that it had a large sample size (1,612 children) and that the children were enrolled at birth and participated in follow-up to a mean age of 4.7 years of life. In another prospective birth cohort study, in which the infants received late introduction of complementary foods, it was found that late introduction was not associated with a reduction of preschool wheezing, transient wheezing, atopy, or eczema. The late introduction of eggs even induced a significant increase in the risk of eczema.⁴⁹

Few studies show a beneficial effect of the introduction of complementary food before the age of 4 months. It remains inconclusive as to whether it is better to introduce complementary foods earlier or later. Currently, it is suggested that solid complementary foods are introduced after 6 months of age in exclusively breast-feeding infants in Taiwan.⁵⁰

3.4. Mediterranean diet

The International Study of Asthma and Allergies in Childhood reported that the prevalence of asthma was lower in Mediterranean countries. The Mediterranean diet is typically enriched with a high ratio of monounsaturated to saturated fat, and contains more fruits, fish, vegetables, bread and cereals (whole grain). Moderate amounts of milk and dairy products are included and olive oil is the principal source of fat. A cross-sectional study in rural Crete conducted by Chatzi et al found that children in Crete had a higher consumption of Mediterranean diet and a lower risk of childhood asthma.⁵¹ The limitations of this study are the self-administered nature of the questionnaire, and the cross-sectional study that did not establish a causal relationship. In a study using questionnaires in which children were stratified according to whether they had experienced wheezing in the previous year, the Mediterranean diet was found to be a protective factor against clinically-significant asthma.⁵² The mechanism for the prevention of asthma by the Mediterranean diet may be related to its high fruit and vegetable content, which may provide vitamins and/or antioxidants that may switch Th2 differentiation towards Th1 differentiation.

Table 1 Mechanisms of maternal diets that affect the perinatal programming of allergic diseases.

Diets	Potential mechanisms	Effects
Folic acid	Donation of CH ₃ group, which causes DNA methylation and suppresses RunX3 expression ^{11–13}	Increased risk of allergy
Vitamin D	Cellular metabolism and differentiation via its nuclear receptor (VDR) that may enhance epigenetic modification enzymes ^{16–18}	Protects against allergy
Vitamin E	Antioxidant effect, which may switch from Th2 to Th1 immunity ^{21–24}	Less allergic reaction
Prebiotics and probiotics	Increase Treg cells and IL-10 secretion ^{53–55}	Better immune regulatory function
n-3 PUFAs and n-6 PUFAs	Decrease and increase prostaglandin E2 ^{5,26–28}	Switch from Th2 to Th1 immunity

n-3 PUFAs = omega-3 polyunsaturated fatty acids; n-6 PUFAs = omega-6 polyunsaturated fatty acids; VDR = vitamin D receptor.

3.5. Prebiotics and probiotics

Prebiotics are food ingredients that are not hydrolyzed by the human digestive enzymes in the gastrointestinal tract and therefore promote the maintenance of beneficial microflora. Probiotics are gut microorganisms that can provide better intestinal ecology and are beneficial to the host when provided in adequate quantities. Probiotics may promote Th1 polarization and the predominance of Treg cells through changes in the composition of intestinal microflora.⁵³

In a randomized, double-blind allergy prevention trial in Finland, a regimen of probiotics plus prebiotics was prescribed to newborns from birth. The measured exhaled nitric oxide was not significantly different between the probiotic and placebo groups at 5 years of age. Therefore, early intervention with probiotics and prebiotics might be not associated with lower risk of airway inflammation later in childhood.⁵⁴ The strengths of this study lie in its randomized, double-blind design with 1,018 children and a long-term follow-up of 5 years. In contrast, another randomized, double-blind trial conducted by Dotterud et al included children from a nonselected maternal population who received a probiotic supplement or placebo from 36 weeks of gestation to 3 months postnatally via breast feeding. It was reported that probiotics given to nonselected mothers reduced the cumulative incidence of atopic dermatitis, but that probiotics had no effect on allergic sensitization.⁵⁵ In a multicenter randomized trial conducted by van der Aa et al, EHF with a mixture of synbiotics (prebiotics plus probiotics) was administered and found to be associated with a lower risk of asthma-like symptoms in infants with atopic dermatitis.⁵⁶ The main limitation of this study that fact it only included 75 infants. Ou et al⁵⁷ reported that the administration of *Lactobacillus* GG beginning in the second trimester of pregnancy, although improving the allergic symptoms of pregnant mothers, did not prevent childhood allergic sensitization or allergic

disease. Antenatal *Lactobacillus* GG administration alone may not be sufficient to prevent or reduce allergy sensitization or allergy disease in childhood.⁵⁷ It remains controversial whether prebiotics and/or probiotics have significant effects on the development and prevention of asthma. In the future, we may try to use a combination of probiotics with the avoidance of allergen or with dietary supplementation to prevent the development of allergic diseases.

3.6. Specific effects of maternal and infant diets on the prevention of asthma

The mechanisms responsible for the effects of pre- and postnatal diets on the risk of or protection from asthma are shown in Tables 1 and 2.^{5,11–13,16–18,21,24,26,28,39–44,48–55} In experimental and clinical studies,^{11–13} it has been shown that excessive folate supplementation might modify the epigenetic mechanism by increasing DNA CG methylation of the *Runx3* gene, causing a decrease in its mRNA expression, and therefore increasing the risk of asthma. In contrast, appropriate administration of vitamin D is shown to protect infants from asthma via the regulation of chromatin modification enzymes, such as histone deacetylase histone deacetylase and histone acetyltransferase.^{15–17} Maternal vitamin E supplementation may also protect against asthma due to its antioxidant effect that may switch immune response from Th2 to Th1 reaction and cause less allergic reaction.^{5,22} A combination of probiotics and breast feeding increased regulatory (Treg) cytokines: IL-10 and transforming growth factor beta (TGFβ).^{58,59} The Treg cytokines may provide immune regulation and maintain intestinal homeostasis. IL-10 regulates Th1 cell activation and several macrophage functions. Supplementation with probiotics and prebiotics may enhance Treg cells and induce IL-10, resulting in improvement in the balance between Th1 and Th2 immune responses and a decreased likelihood of developing asthma. Maternal or infant supplementation

Table 2 Mechanisms by which infant diets can effect the development of asthma.

Infant diets	Potential mechanism	Effects and functions
Protein-hydrolysate formula	Avoidance of foreign allergens	Immune tolerance ^{39–44}
Complementary food	Induction of food tolerance by early allergen exposure	Decrease of sensitization ^{48–50}
Mediterranean diet	Antioxidants	Switch from Th2 to Th1 immunity ^{51,52}

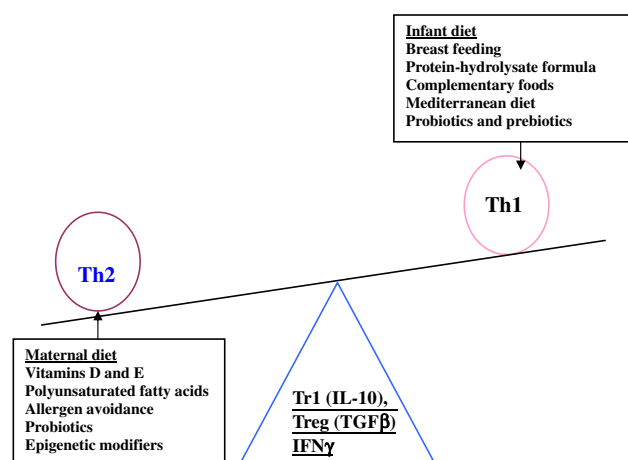


Figure 1 Prevention of asthma through maternal and infant diets. Maternal diets, including supplementation of vitamin D, vitamin E, polyunsaturated fatty acids, allergen avoidance, probiotics, and epigenetic enzyme modifiers may suppress type 2 T helper (Th2) reaction. Infant diets, including breast feeding for at least 4 months, protein hydrolysate formula, early complementary diets between 4 and 6 months, Mediterranean diet and supplementation of probiotics and prebiotics may enhance type 1 T helper (Th1) reaction through type 1 T regulatory (Tr1) response with an increase in IL-10 or the Treg mediator transforming growth factor beta (TGF β) production, and Th1 mediator: interferon-gamma (IFN γ) expression for the prevention of asthma.

with probiotics and/or prebiotics may enhance Treg cells and induce IL-10 production, resulting in better immune regulatory function and less allergic inflammation.

4. Conclusion and Future Implications

Maternal and infant diets have a significant impact on the development of asthma. The protective or augmented effect of these maternal and/or infant diets may have epigenetic or immune regulatory effects on the development and prevention of asthma. During the prenatal stage, certain genes may be epigenetically modified by maternal diets. During the postnatal stage, early introduction of solid food and probiotics or prebiotics may induce Treg cells for better immune regulation and a reduced likelihood of developing asthma. Currently, there is no specific regimen to prevent asthma in the perinatal stage; however, we may consider providing maternal diets with higher vitamin D, vitamin E, and/or probiotics, and encouraging the adoption of infant diets with breast feeding by at least 4 months, as well as early complementary diets between 4 and 6 months (Figure 1). These diets may cause augmentation of Treg mediators: IL-10 and TGF β production, and Th1 mediator: interferon gamma expression for protection from asthma. In the future, with advances in the knowledge of the developmental origins of health and diseases depicting the perinatal influence of nutrition and hygiene on the epigenetic programming of asthma, a prospect for the early prediction and prevention of childhood asthma will be possible.

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