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Dietary primary prevention of allergic diseases in children: the Philippine guidelines

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Allergic diseases, such as asthma, allergic rhinitis, eczema, and food allergy, are preventable diseases. Primary prevention strategies of allergic diseases have been in scrutiny. Effective prevention strategies maybe started prenatally, postnatally, during infancy, and even during childhood. These guidelines have been prepared by the Philippine Society of Allergy, Asthma and Immunology and the Philippine Society for Pediatric Gastroenterology, Hepatology and Nutrition. They aim to provide evidence-based recommendations for the dietary primary prevention of allergic diseases in children. The primary audience of these guidelines is all healthcare practitioners who manage patients with potential allergic conditions. These guidelines are based on an exhaustive review of evidences, mostly systematic reviews, randomized controlled trials, and cohort studies. However, there are still many gaps in the evidence of dietary primary prevention of allergic diseases.

Keywords: Allergic disease; Atopy; Child; Dietary intervention; Primary prevention

INTRODUCTION

The incidence of allergic diseases among children has been increasing worldwide. Maternal and child dietary interventions and lifestyle strategies to decrease the risk of sensitization and allergic diseases in children have been an ongoing subject for decades that is met with conflicting views. Primary prevention strategies directed against potential sensitizing factors have

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Table 1. Summary of recommendations

Recommendation	Strength of recommendation	Quality of evidence
1. Increased maternal intake of certain foods during pregnancy to prevent allergy in the child is not recommended.	Strong	Low
2. Maternal avoidance of allergenic foods during pregnancy is not recommended.	Strong	Moderate
3. Supplements (vitamins, minerals antioxidants, and long chain polyunsaturated fatty acids [LCPUFA]) are not recommended in pregnant women.	Strong	Low
4. For ATOPIC pregnant women, Lactobacillus rhamnosus GG from 36-week age of gestation and continued while breastfeeding or given directly to the infant until 6 months old to prevent atopic dermatitis in children is recommended.	Weak	Moderate
5. For NON-ATOPIC pregnant women, maternal probiotic supplementation to prevent allergic diseases in children is not recommended.	Strong	Very Low
6. Any specific type of maternal diet during lactation to prevent allergy in the child is not recommended.	Strong	Low
7. Exclusive breastfeeding for at least 3-6 months is recommended to prevent asthma.	Strong	Moderate
8. In high-risk infants who cannot be breastfed or when breast milk is not available, partially hydrolyzed-whey milk formula or extensively hydrolyzed-casein milk formula for at least 6 months is recommended to prevent allergic diseases until adolescence.	Weak	Moderate
9. In high-risk infants who cannot be breastfed or when breast milk is not available, soy formula to prevent allergic disease is not recommended.	Strong	High
10. In high-risk infants who cannot be breastfed or when breast milk is not available, amino acid based milk formulas, organic cow's milk formula, and non-bovine formulas to prevent allergic disease are not recommended.	Strong	Very Low
11. Delaying complementary feeding beyond the age of 6 months for all infants is not recommended.	Strong	Moderate
12. Timing of introduction of highly allergenic foods in infant diet to prevent allergic diseases is recommended as follows:		
-Cooked egg at 4–6 months	-Weak	-Low
-Wheat at less than 6 months	-Weak	-Moderate
-Fish at 6–9 months	-Weak	-Moderate
-Peanut at 4–11 months	-Strong	-High
13. Organic food to prevent allergic diseases is not recommended.	Strong	Moderate
14. Increased intake of fish rich in LCPUFA in infants and children to prevent asthma is recommended.	Weak	Low
15. Fish oil supplementation in infants and children to prevent allergic diseases is not recommended.	Strong	High
16. Postnatal probiotics to prevent allergic diseases are not recommended.	Strong	Moderate
17. Prebiotics, vitamin D, and virgin coconut oil to prevent allergic diseases are not recommended.	Strong	Low
18. Bovine colostrum, beta-glucan, spirulina, mangosteen, and other dietary supplements to prevent allergic disease are not recommended.	Strong	Very Low
19. Lifestyle modification, including exercise and diet to prevent to prevent allergic diseases in children with obesity is recommended.	Strong	Moderate

been proposed at different stages of early life such as in antenatal period, early postnatal period (infancy), and early childhood (2 years and above). However, many of the studies show conflicting results [1]. These guidelines summarize the evidence on dietary primary prevention of allergic diseases in the general and high-risk population. These present guidelines

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have been prepared by the Philippine Society of Allergy, Asthma and Immunology (PSAAI) and the Philippine Society for Pediatric Gastroenterology, Hepatology and Nutrition (PSPGHAN). The objectives of this document are to give evidence-based guidelines for the primary prevention of allergic conditions in children through nutritional means available in the Philippine setting. These guidelines are the first of its kind in the Philippines and contributory to other foreign guidelines on this topic.

METHODS

Formation of Technical Working Group

The Technical Working Group was composed of members from the PSAAI and the PSPGHAN. The E-mail discussions and face-to-face meetings were held to discuss group composition, formulation of clinical questions and rating of outcomes, preparation of evidence summaries and rating the evidence, panel meetings weighing the desirable and undesirable values and preferences of available dietary interventions pertinent to the Philippine setting, formulation of statements, and consultation (stakeholders meeting) of clinicians and lay person involved in the care of the patient. A nominal group consensus model approach was adopted for making operational definitions for essential terms and framing the questions.

Search strategy for selection of studies

The Cochrane Library, PubMed, Ovid, ClinicalTrials.gov, Google Scholar, and Herdin were searched for publications related to allergic diseases prevention and dietary interventions. Experts in the field were contacted for unpublished studies. Citations and reference lists in reviews and guidelines were searched for additional studies. No language restriction was applied.

Systematic reviews, randomized controlled trials (RCTs), quasi-RCTs, and cohort studies on primary prevention of allergic diseases (asthma, allergic rhinitis, atopic dermatitis, and food allergy) through dietary interventions in the general and high-risk population were included. Qualitative studies, case series/reports, animal studies, letters, and editorials were excluded.

Assessing quality of included studies and formulating recommendations

The Technical Working Group which includes a third-party evaluator reviewed and critically appraised the evidence. The GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach was used to assess the quality of evidence and the strength of recommendation.

The validity, clinical relevance, and applicability of the evidence for the infant and childhood allergy were discussed. After considering the evidence, the Technical Working Group achieved a consensus on a number of recommendations (Table 1).

Rationale behind panel selection

The panel for stakeholders meeting comprised of an allergist, a pediatric gastroenterologist, 2 general pediatricians, an adult patient with allergic disease, a breastfeeding advocate, mother who breastfed, a mother who did not breastfeed, a mother with a child with allergic disease, a lay person, a neonatologist, and an obstetrician. The panel is multisectoral to ensure adequate representation and to make the consensus statement relevant and acceptable to intended end-users.

RECOMMENDATIONS

Diet during pregnancy

Recommendation 1: Increased maternal intake of certain foods during pregnancy to prevent allergy in the child is not recommended (Strong recommendation / Low quality evidence).

The type and quantity of food of a pregnant mother may influence the development of allergic diseases in her child. Famine in pregnancy was associated with obstructive lung disease in the offspring [2]. Intake of protein, carbohydrates, and milk correlated negatively with emergence of allergic disease in the high-risk infant. In contrast, high intake of fats, vegetable oil, celery, citrus, raw sweet pepper, and nuts were associated with increased sensitization [3-5].

Dietary polyphenols from certain plants (cocoa, coffee, tea) and fruits (apples and grapes) have been studied and proposed to possess antiallergic activity through binding allergenic protein in the diet [6]. A systemamic review and meta-analysis showed that a maternal diet high in fruits and vegetables (as well as Mediterranean type of diet) could prevent sensitization and the development of asthma [7]. However, due to the poor quality of the studies evaluated, no concrete recommendations can be

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made. A subsequent study noted increased risk of wheezing in children by 5 years with previous maternal intake of leafy vegetables, certain fruits (apple, pear, peach, apricot, prune, and plum), and chocolate increased the risk of wheezing in children at 5 years of age; fruit juice intake, however, increased the risk of allergic rhinitis [8]. Moreover, increased intake of isoflavones, which are found primarily in soybeans (a highly allergenic food), was associated with decreased asthma risk [6].

Recommendation 2: Maternal avoidance of allergenic foods during pregnancy to prevent allergy in the child is not recommended (Strong recommendation / Moderate quality evidence).

A maternal avoidance diet of foods considered to be highly allergenic, such as milk, eggs, peanuts, nuts, wheat, soy, and seafood during pregnancy has been proposed as a primary prevention strategy against food allergy and other allergic diseases in the high-risk offspring. One study suggested that diet devoid of peanut, nuts, fish, eggs, and sesame during the last trimester of pregnancy in women with high-risk families has a protective effect for the child, but this was contradicted by later studies [9]. Three recent systematic reviews on elimination of highly allergenic foods in maternal diet, particularly milk, egg, and peanut during pregnancy, noted conflicting results in the included studies. Thus, restricting common highly allergenic foods during pregnancy cannot be recommended at present, even for high-risk infants [10-12].

However, this proposed dietary avoidance primary prevention strategy is currently being challenged. Recent literature suggests that oral exposure to food allergens by the mother during pregnancy could promote tolerance to food antigens in her offspring [13]. A Cochrane review on maternal allergen avoidance during pregnancy revealed the absence of a protective effect on atopic dermatitis or asthma in the first 18 months of infancy [12]. Also, its effects on risk of allergic rhinitis, conjunctivitis and urticaria were inconclusive. More importantly, however, this review noted that dietary restrictions during pregnancy had detrimental effects on maternal nutrition and eventually on fetal health.

No special maternal diet is proven to be effective as a form of primary allergy prevention in the child. The pregnant woman's diet should be healthy and well-balanced as it would impact the infant's health. Avoidance of food allergens is only justified if the mother is truly allergic to specific foods.

Supplements during pregnancy

Recommendation 3: Supplements (vitamins, minerals, antioxidants, and long chain polyunsaturated fatty acids [LCPUFA]) to prevent allergic disease in the child are not recommended in pregnant women (Strong recommendation / Low quality evidence).

Supplementation with vitamin A and vitamin C during pregnancy had no preventive effect on the development of wheezing in the child [7]. However, the studies were observational and of low methodologic quality.

Three large birth cohort studies showed consistent positive associations between maternal intake of vitamin E in pregnancy and prevention of childhood asthma or wheeze at 2 years of age [5]. But in a recent systematic review looking into the association of maternal Vitamin E intake in pregnancy on atopic eczema, sensitization, allergic rhinoconjunctivitis, lung function and asthma, a meta-analysis could not be done due to variations in study design. The quality of evidence of included studies was weak [7].

Vitamin D is thought to inhibit the maturation of dendritic cells and may modulate Th1 response. However, studies about its role in allergy prevention are conflicting. Some reported that high maternal vitamin D intake during pregnancy was associated with reduced risk of wheezing in the child, while some showed no effect. In more recent observation studies, high-dose maternal intake of vitamin D was associated with increased atopic diseases such as atopic dermatitis and/or allergic rhinitis [14]. The conflicting results may reflect genetic variability in the general population in the metabolism and allergy preventive effects of vitamin D supplementation in the child [6, 7].

Maternal selenium supplementation, in a systematic review, did not prevent allergy development in the child. Zinc supplementation, however, could be protective against asthma. However, because of the low quality of evidence, strong conclusions could not be made [7].

Intake of antioxidants during pregnancy may be positively associated with prevention of childhood asthma, and to a lesser degree, atopic dermatitis and allergic rhinitis [15, 16].

Increased maternal consumption of LCPUFA may be a promising strategy in allergy prevention. Omega-6 PUFAs were

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noted not to have high levels of anti-inflammatory effects compared to omega-3 PUFA contained in oily fish. The anti-inflammatory effect of omega-3 PUFA has been attributed to the cytokine regulatory effects of TGF-beta [17]. The higher ratio of omega-3 to omega-6 PUFA may be more clinically relevant for allergy prevention. However, omega-6 PUFA also exhibit anti-inflammatory actions and may be needed in synergism with omega-3 PUFA for allergy prevention [18].

The allergy preventive effect of high maternal LCPUFA intake becomes evident if these are taken the last 4 weeks of pregnancy [18]. In a RCT, there was no decrease in atopic dermatitis incidence though, in children born from women supplemented with LCPUFA [19]. Also, a meta-analysis of six RCTs on the use of omega-3 and omega-6 PUFA for allergy prevention in various populations, including pregnant women, concluded that these PUFAs may not have a role in prevention of sensitization or allergic disease in the population [20].

The effects of fish oil supplementation in pregnant mothers on high-risk children were evaluated in 5 RCTs. One study showed a decrease in the risk of egg sensitizations; however, it did not evaluate whether clinical egg or food allergy could be prevented in the infants or if there is any benefit in the general population [21]. Despite the lack of effect of fish oil supplementation in decreasing prevalence of allergic symptoms in children, 2 studies showed a decrease in the cumulative incidence of allergic disease during the first two years of life [22, 23]. However, two other studies did not detect any preventive effect on allergic disease [24, 25]. These studies had heterogenous outcomes indicating the tenuous role of maternal fish oil supplementation for allergy prevention in their offspring.

Recommendation 4: For ATOPIC pregnant women, *Lactobacillus rhamnosus GG* from 36 weeks age of gestation (AOG) and continued while breastfeeding or given directly to the infant until 6 months old to prevent ATOPIC DERMATITIS in children is recommended (Weak recommendation / Moderate quality evidence).

Recommendation 5: For NON-ATOPIC pregnant women, maternal probiotic supplementation to prevent allergic disease in children is not recommended (Strong recommendation / Very low quality evidence).

The hygiene hypothesis postulates that an absence of early life microbial immunomodulation predisposes to development of allergic conditions. The human microbiota, especially in the gut, has been documented to be important in normal immune programming of the host and in the maintenance of a normal gut mucosal barrier. Probiotic supplementation has been proposed as a means of providing optimal microbial stimulation necessary for immune regulation [26, 27]. A meta-analysis of 6 prevention clinical trials showed that probiotics is more efficacious than placebo in preventing pediatric atopic dermatitis [27]; however, its role in preventing other types of allergic disease was not seen in another meta-analysis [28].

Perinatal probiotic supplementation has been proposed as a means of introducing microbial immunostimulation in very early life. Studies have documented that neonatal gut microbiota originate from maternal gut microbiota either transplacentally, through fecal-oral exposure via vaginal delivery or through bacterial translocation from the maternal gastrointestinal tract to the breast milk [29-31]. A landmark RCT on the effect of probiotic *L. rhamnosus GG* given to pregnant women at least 2 weeks prior to delivery and continued after birth for 6 months either through breastfeeding or supplemented to formula-fed infants noted a 40%–50% decrease in pediatric eczema at 2, 4, and 7 years of follow-up [31-33]. Some studies have indicated that earlier probiotic supplementation in late pregnancy rather than postnatal exposure may be more effective in primary prevention of allergic disease [34, 35]. Prenatal probiotic supplementation provides for a microflora predominantly comprised of lactobacilli and bifidobacteria, similar to that of a healthy breastfed baby [36, 37].

One RCT evaluated the efficacy of probiotics in the prevention of eczema when given to women during their pregnancy only. *L. rhamnosus GG* was given from 36 weeks AOG until delivery to pregnant women carrying high-risk infants. Apparently, prenatal probiotic supplementation was not effective in reducing the risk of eczema [38].

There are, however, no studies done to explore the preventive role of prenatal probiotic supplementation in nonatopic pregnant women for prevention of allergic disease in children. Because of the lack of evidence and cost, it is strongly not recommended.

Maternal diet during lactation

Recommendation 6: Any specific type of maternal diet during lactation to prevent allergy in the child is not recommended (Strong recommendation / Low quality evidence).

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There are no RCTs evaluating any specific type of maternal diet during lactation to prevent allergic diseases in the child.

Maternal avoidance diets in the prevention of food allergies are under debate. In a cross-over trial, elimination of cow milk, egg, and soy milk from diet of lactating mothers of infants with established atopic dermatitis was associated with a nonsignificant reduction in the severity of atopic dermatitis [39].

A prospective birth cohort involving 145 dyads showed significant reduction in casein- and beta-lactoglobulin-specific IgA in breast milk of mothers who eliminated cow milk from their diet. The decreased levels of IgA were associated with the development of cow milk allergy in the child [40].

Despite the low quality evidence, the recommendation is strong because of possible consequences on maternal and infant nutrition.

Postnatal diets

Recommendation 7. Exclusive breastfeeding for at least 3 to 6 months is recommended to prevent asthma (Strong recommendation / Moderate quality evidence).

The impact of breastfeeding on the risk of allergy is difficult to establish because no RCTs have been performed for ethical reasons. As the gold standard for infant nutrition, human milk per se is not a "dietary intervention" for primary allergy prevention; although compared to standard cow milk formula, breast milk is less allergenic [41].

Systematic reviews and meta-analyses on breastfeeding to prevent allergic diseases showed conflicting results [42-46]. One systematic review involving 21 prospective cohort studies showed no strong evidence for protective effect of exclusive breastfeeding in the first 3 months of life in atopic dermatitis [42]. Three systematic reviews showed preventive effects of breastfeeding in asthma [43-45]. The most recent of the systematic reviews included 117 studies (57 cohort studies, 47 cross-sectional, 13 case-controls) on breastfeeding among children in the general population [45]. The meta-analysis showed a positive association of breastfeeding with reduced asthma or wheezing. In addition, exclusive breastfeeding for at least 3 months is associated with decrease in asthma incidence at 0 to 2 years old as compared to exclusive breastfeeding for less than 3 months [45]. Another meta-analysis showed that exclusive breastfeeding during the first 3 months of life showed no evidence that it protects against allergic rhinitis in children [46].

Recommendation 8: In high-risk infants who cannot be breastfed or when breast milk is not available, partially hydrolyzed-whey milk formula (pHF-W) or extensively hydrolyzed-casein milk formula (eHF-C) for at least 6 months is recommended to prevent allergic diseases (Weak recommendation / Moderate quality evidence).

Soy protein-based, pHF-W, eHF-C, eHF-W and amino acid formulas are the most commonly used breast milk substitutes to prevent atopic diseases. The appropriate choice should meet certain essential criteria: (1) it should fulfill the nutritional needs of the infant providing adequate growth and development; (2) it should have no or little cross-reactivity with protein from nonhuman sources; and (3) it should have good palatability [47].

There are systematic reviews and a recent 15-year analysis of an RCT evaluating the efficacy of HF in allergic disease prevention [48-55]. Systematic reviews on HF to prevent allergic diseases showed variable preventive effects [50-55]. The meta-analysis of Osborn and Sinn [50] showed that HF compared to cow milk reduced infant allergy but did not show reduction in childhood allergy, eczema, asthma, rhinitis, and food allergy.

These preventive effects of HF have been confirmed by the recent follow-up of the German Infant Nutritional Intervention study which looked at the long-term effects of hydrolyzed formulas on allergies [48, 49]. On its fifteenth year, this RCT involving children at high risk for allergy had significantly decreased asthma with eHF-C as compared to cow's milk formula. It also showed that early intervention using eHF-C and pHF-W resulted in lower allergic rhinitis prevalence. There was reduction in the cumulative incidence of atopic dermatitis with pHF-W and eHF-C but not for asthma and allergic rhinitis. eHF-W showed no preventive effects for any allergic disease.

Recommendation 9: In high-risk infants who cannot be breastfed or when breast milk is not available, soy milk formula to prevent allergic disease is not recommended (Strong recommendation / High quality evidence).

One systematic review with a meta-analysis compared soy formula with cow's milk formula among high risk infants [56]. There was no significant difference between the two comparators in the incidence of childhood allergic diseases including asthma,

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atopic dermatitis, rhinitis, infant cow milk allergy, childhood soy protein allergy, and urticaria [56].

Recommendation 10: In high-risk infants who cannot be breastfed or when breast milk is not available, amino acid-based milk formulas, organic cow's milk formulas, and non-bovine formulas to prevent allergic disease are not recommended (Strong recommendation / Very low quality evidence).

There are no RCTs or cohort studies on amino-acid-based, organic cow milk, and non-bovine milk formulas for the primary prevention of allergy. Due to the lack of studies, we do not recommend these formulas. The Australasian Society of Clinical Immunology and Allergy also does not recommend other formulas such as goat milk to reduce the risk of food allergy [57].

Recommendation 11: Delaying complementary feeding beyond the age of 6 months for all infants is not recommended (Strong recommendation / Moderate quality evidence).

Complementary feeding is the process of starting solid food and other liquids on an infant when breastmilk alone is already insufficient. The initiation of complementary feeding entails tolerance to the food antigens consumed. Immune tolerance occurs when there is antigen-specific suppression of host cellular or humoral immune responses. In oral tolerance development, age of exposure has been found to be a factor along with antigen properties, route of exposure, and genetics and age of host [58].

A prospective cohort study of 642 children with late introduction of solids did not show a protective effect in the development of preschool wheezing, transient wheezing, atopy, or eczema [59]. In contrast, late introduction of egg and milk significantly increased the risk of eczema. This association of delayed introduction of solids and the increase in the frequency of atopic diseases have been shown in other cohort studies [60, 61].

A systematic review with nine cohort studies showed conflicting results [62]. Five studies showed positive association of early solid feeding and eczema. Four studies showed no association. Many of the studies included in this review have methodologic problems.

Recommendation 12: Timing of introduction of highly allergenic foods in infant diet to prevent allergic diseases is recommended as follows: cooked egg at 4–6 months (Weak recommendation / Low quality evidence), wheat at less than 6 months (Weak recommendation / Moderate quality evidence), fish at 6–9 months (Weak recommendation / Moderate quality evidence), and peanut at 4–11 months (Strong recommendation / High quality evidence).

There are a few studies on timing of introduction of highly allergenic foods to prevent allergic diseases. Most studies are cohort or cross-sectional. There is only 1 RCT done to evaluate introduction of intake of peanuts among infants.

Inversely, a prospective cohort study enrolling 3,781 children suggested that early introduction of highly allergenic foods such as wheat, egg and fish, seemingly decreases the risk of asthma, allergic rhinitis, and allergic sensitization. Giving wheat at 5 to 5.5 months was inversely associated with asthma and allergic rhinitis. This inverse association is also true with introduction of fish at 9 months or less for allergic rhinitis and atopic sensitization and egg at 11 months for asthma, allergic rhinitis, and atopic sensitization [63].

A population-based cross-sectional study participated by 2,589 infants showed that early introduction of egg at 4–6 months old was associated with lower risks of egg allergy as than if it was introduced at 10–12 months and more than 12 months [64]. Moreover, it is the cooked (hardboiled, fried, scrambled, poached) eggs given at age 4–6 months reduced the risk of egg allergy as compared to egg in baked goods.

A prospective, birth cohort study on 994 including children with HLA-conferred susceptibility to type 1 diabetes mellitus revealed that delayed introduction wheat (>6 months), eggs (>10.5 months), fish (>8.2 months), and other solid foods was significantly directly associated with sensitization to food allergens. Moreover, late introduction of fish (>8.2 months) was significantly associated with sensitization to any inhalant allergen [65].

A prospective cohort study on 516 children did not show significant association between the timing of introduction of solid foods and protection against asthma or other allergic diseases at age 5 years. However, introduction of solid foods after 3 months was associated with an increased risk of atopy at age 5 years [66].

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A RCT involving 530 infants with severe eczema, egg allergy, or both that were given peanuts at 4–11 months had significantly decreased risk for peanut allergy among children at high risk for this allergy [67]. Also, infants with siblings diagnosed with peanut allergy should be assessed prior to giving peanuts because there is a 7% risk of peanut allergy among siblings [68].

If there is no risk or no sibling with nut allergy, peanut butter, as well as tree nut butter, may be introduced between 6 to 12 months. Caution should be exercised in giving nut kernels at an early age due to the risk of aspiration [11].

Recommendation 13: Organic food to prevent allergic diseases is not recommended (Strong recommendation / Moderate quality evidence).

Organic products are known to contain on average more antioxidants such as vitamin and higher amount of n-3 fatty acids. Antioxidants are suggested to prevent wheezing complaints possibly through protect of bronchial epithelium against oxidative stress. Likewise, n-3 fatty acids are hypothesized to be anti-inflammatory and contributory to skin barrier hence reducing atopic reactions. The KOALA Birth Cohort Study found no association between consumption of organic products (meat, fruit, vegetable, and eggs) and development of eczema, wheeze, or atopic sensitization [69]. However, consumption of strictly organic dairy products is associated with reduced risk of eczema. Despite this mere association, organic food is not recommended to prevent allergic diseases. There are no RCTs found to affect this recommendation.

Recommendation 14: Increased intake of fish rich in LCPUFA in infants and children to prevent asthma is recommended (Weak recommendation / Low quality evidence).

High intake of LCPUFA has been hypothesized to prevent asthma, which is an inflammatory process. A meta-analysis of 3 prospective cohort studies showed that infants who consumed fish have lower risk of childhood asthma [70]. There are no RCTs found to confirm this finding. Despite this, fish rich in LCPUFA in is recommended to prevent asthma.

Recommendation 15: Fish oil supplementation in infants and children to prevent allergic diseases is not recommended (Strong recommendation / High quality evidence).

A systematic review including 5 RCTs on the effects of fish oil intake during infancy and childhood on atopic outcomes showed inconclusive evidence [71].

A more recent RCT, which is not included in the aforementioned systematic review, included 420 high-risk infants and evaluated n-3 PUFA supplementation from birth up to age 6 months did not prevent childhood allergic disease [72]. With this latest RCT and the inconclusive systematic review, fish oil supplementation in infants and children is strongly not recommended.

Recommendation 16: Postnatal probiotics to prevent allergic diseases are not recommended (Strong recommendation / Moderate quality evidence).

There are 2 meta-analyses on probiotic supplementation during the prenatal and postnatal periods. One meta-analysis involving 14 RCTs on prenatal and postnatal (early-life) probiotic supplementation did not show significant reduction in the risk of atopic sensitization nor risk of asthma. On subgroup analysis, prenatal supplementation showed significant reduction in atopic sensitization as compared to postnatal supplementation [28]. Another meta-analysis involving 13 RCTs on prenatal or postnatal probiotic supplementation showed reduction in atopic dermatitis among children in the probiotic arm [73].

Recommendation 17: Prebiotics, vitamin D, and virgin coconut oil (VCO) to prevent allergic diseases are not recommended (Strong recommendation / Low quality evidence).

Prebiotics are nutritional supplements that stimulate the growth and function of the gastrointestinal microbiome. Giving prebiotics during infancy could lead to modification of the immune development. A meta-analysis of 4 RCTs involving 1,218 infants showed a reduction in eczema among infants given prebiotics [74]. There was no significant difference in asthma. However, included studies were noted to have attrition bias (incomplete outcome data) and were all commercially sponsored (possible publication bias). Moderate heterogeneity was likewise found in the included studies.

There are no RCTs done on vitamin D supplementation in allergy prevention. Also, the 2 cohort studies on vitamin D supplementation have conflicting results. In 1 large birth cohort study, regular vitamin D supplementation was associated with

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the risk of developing atopy (odds ratio [OR], 1.66) and allergic rhinitis (OR, 1.46) than those who received it irregularly or none at all [75]. In another cohort study of infants given peanut oil-based Vitamin D supplement, no significant associations were observed for allergic rhinitis or eczema [76].

VCO, a monounsaturated fatty acid, contains a high amount of lauric acid. When the lauric acid is converted to monolaurin in the small intestine, it has the potential to inactivate the microbes. One RCT involving 13 high-risk neonates evaluated the VCO immunomodulation in the prevention of atopic diseases. There was a decrease in the IgE level among high-risk infants given VCO. However, the study had a small sample size [77].

Recommendation 18: Bovine colostrum, beta-glucan, spirulina, mangosteen, and other dietary supplements to prevent allergic disease are not recommended (Strong recommendation / Very low quality evidence).

No clinical studies are found on bovine colostrum, beta-glucan, spirulina, and mangosteen to prevent allergic diseases. With lacking data, these dietary supplements for allergy prevention are not recommended.

During childhood

Recommendation 19: Lifestyle modification, including exercise and diet modification, to prevent allergic diseases in children with obesity is recommended (Strong recommendation / Moderate quality evidence).

There are no RCTs found on lifestyle modification to prevent allergic disease in children with obesity.

A cohort study showed more patients with asthma among patients with overweight or obesity. Obesity increases the odds of incident asthma in children [78].

A cross-sectional study of 13,153 children aged 6–7 years old showed an association between obesity and atopic dermatitis [79].

A retrospective case-control study involving 414 children with atopic dermatitis showed higher odds of developing atopic dermatitis among those with onset of obesity before less than 2 years of age and 2 through 5 years of age. The development of atopic dermatitis was also seen when obesity was prolonged for 2.5 to 5 years and greater than 5 years [80].

CONFLICTS OF INTERESTS

MTR has received honoraria as a speaker from Nestle Nutrition Institute, Mead Johnson, and Intermed; MLG worked for the Medical Affairs of United Laboratories but she inhibited herself from participating in the evaluation of evidence for supplements and other products similar to the portfolio of United Laboratories i.e. vitamins, probiotics; MRC received research grant from IMS Health; MVS has received honoraria as a speaker from Abbott, Friso, and Mead Johnson; MT has received honoraria as speaker from Nestle Nutrition Institute, Friesland Campina-Alaska, and Pediatrica; KSM has received honoraria as a speaker from Abbott and Westmont. RDC received research grant from IMS Health and another grant from Nestle Nutrition Institute. RCH and DTL have nothing to disclose.

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REFERENCES

1. Pawankar R, Baena-Cagnani CE, Bousquet J, Canonica GW, Cruz AA, Kaliner MA, Lanier BQ. State of world allergy report 2008: allergy and chronic respiratory diseases. World Allergy Organ J 2008;1(6 Suppl):S4-17.
2. Fitzsimon N, Fallon U, O'Mahony D, Loftus BG, Bury G, Murphy AW, Kelleher CC; Lifeways Cross Generation Cohort Study Steering Group. Mothers' dietary patterns during pregnancy and risk of asthma symptoms in children at 3 years. Ir Med J 2007;100:suppl 27-32.
3. Sausenthaler S, Koletzko S, Schaaf B, Lehmann I, Borte M, Herbarth O, von Berg A, Wichmann HE, Heinrich J; LISA Study Group. Maternal diet during pregnancy in relation to eczema and allergic sensitization in the offspring at 2 y of age. Am J Clin Nutr 2007;85:530-7.

4. Luengo O, Ying S, Srivastava K, Xiu-Min L. The potential of maternal dietary modification for prevention of food allergy. J Aller Ther 2013;S3:005. https://doi.org/10.4172/2155-6121.
5. Nurmatov U, Devereux G, Sheikh A. Nutrients and foods for the primary prevention of asthma and allergy: systematic review and meta-analysis. J Allergy Clin Immunol 2011;127:724-33.e1-30.
6. Erkkola M, Nwaru BI, Kaila M, Kronberg-Kippilä C, Ilonen J, Simell O, Veijola R, Knip M, Virtanen SM. Risk of asthma and allergic outcomes in the offspring in relation to maternal food consumption during pregnancy: a Finnish birth cohort study. Pediatr Allergy Immunol 2012;23:186-94.
7. Zeiger RS, Heller S, Mellon MH, Forsythe AB, O'Connor RD, Hamburger RN, Schatz M. Effect of combined maternal and infant food-allergen avoidance on development of atopy in early infancy: a randomized study. J Allergy Clin Immunol 1989;84:72-89.
8. Fleischer DM, Spergel JM, Assa'ad AH, Pongracic JA. Primary prevention of allergic disease through nutritional interventions. J Allergy Clin Immunol Pract 2013;1:29-36.
9. de Silva D, Geromi M, Halken S, Host A, Panesar SS, Muraro A, Werfel T, Hoffmann-Sommergruber K, Roberts G, Cardona V, Dubois AE, Poulsen LK, Van Ree R, Vlieg-Boerstra B, Agache I, Grimshaw K, O'Mahony L, Venter C, Arshad SH, Sheikh A; EAACI Food Allergy and Anaphylaxis Guidelines Group. Primary prevention of food allergy in children and adults: systematic review. Allergy 2014;69:581-9.
10. Muraro A, Halken S, Arshad SH, Beyer K, Dubois AE, Du Toit G, Eigenmann PA, Grimshaw KE, Hoest A, Lack G, O'Mahony L, Papadopoulos NG, Panesar S, Prescott S, Roberts G, de Silva D, Venter C, Verhasselt V, Akdis AC, Sheikh A; EAACI Food Allergy and Anaphylaxis Guidelines Group. EAACI food allergy and anaphylaxis guidelines. Primary prevention of food allergy. Allergy 2014;69:590-601.
11. Lack G. Update on risk factors for food allergy. J Allergy Clin Immunol 2012;129:1187-97.
12. Kramer MS, Kakuma R. Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child. Cochrane Database of Systematic Reviews 2012, Issue 9. Art. No.: CD000133. https://doi.org/10.1002/14651858.CD000133.pub3.
13. Weisse K, Winkler S, Hirche F, Herberth G, Hinz D, Bauer M, Röder S, Rolle-Kampczyk U, von Bergen M, Olek S, Sack U, Richter T, Diez U, Borte M, Stangl GI, Lehmann I. Maternal and newborn vitamin D status and its impact on food allergy development in the German LINA cohort study. Allergy 2013;68:220-8.
14. Hanson LA, Korotkova M. The role of breastfeeding in prevention of neonatal infection. Semin Neonatol 2002;7:275-81.
15. Allan K, Kelly FJ, Devereux G. Antioxidants and allergic disease: a case of too little or too much? Clin Exp Allergy 2010;40:370-80.
16. Krauss-Etschmann S, Hartl D, Rzehak P, Heinrich J, Shadid R, Del Carmen Ramírez-Tortosa M, Campoy C, Pardillo S, Schendel DJ, Decsi T, Demmelmair H, Koletzko BV; Nutraceuticals for Healthier Life Study Group. Decreased cord blood IL-4, IL-13, and CCR4 and increased TGF-beta levels after fish oil supplementation of pregnant women. J Allergy Clin Immunol 2008;121:464-470.e6.
17. Anandan C, Nurmatov U, Sheikh A. Omega 3 and 6 oils for primary prevention of allergic disease: systematic review and meta-analysis. Allergy 2009;64:840-8.
18. Lopuhaä CE, Roseboom TJ, Osmond C, Barker DJ, Ravelli AC, Bleker OP, van der Zee JS, van der Meulen JH. Atopy, lung function, and obstructive airways disease after prenatal exposure to famine. Thorax 2000;55:555-61.
19. Høst A, Halken S. Can we apply clinical studies to real life? Evidence-based recommendations from studies on development of allergic diseases and allergy prevention. Allergy 2002;57:389-97.
20. Dunstan JA, Mori TA, Barden A, Beilin LJ, Taylor AL, Holt PG, Prescott SL. Fish oil supplementation in pregnancy modifies neonatal allergen-specific immune responses and clinical outcomes in infants at high risk of atopy: a randomized, controlled trial. J Allergy Clin Immunol 2003;112:1178-84.
21. Furuhjelm C, Warstedt K, Larsson J, Fredriksson M, Böttcher MF, Fälth-Magnusson K, Duchén K. Fish oil supplementation in pregnancy and lactation may decrease the risk of infant allergy. Acta Paediatr 2009;98:1461-7.
22. Furuhjelm C, Warstedt K, Fagerås M, Fälth-Magnusson K, Larsson J, Fredriksson M, Duchén K. Allergic disease in infants up to 2 years of age in relation to plasma omega-3 fatty acids and maternal fish oil supplementation in pregnancy and lactation. Pediatr Allergy Immunol 2011;22:505-14.
23. Lauritzen L, Kjaer TM, Fruekilde MB, Michaelsen KF, Frøkiaer H. Fish oil supplementation of lactating mothers affects cytokine production in 2 1/2-year-old children. Lipids 2005;40:669-76.
24. Palmer DJ, Sullivan T, Gold MS, Prescott SL, Heddle R, Gibson RA, Makrides M. Effect of n-3 long chain polyunsaturated fatty acid supplementation in pregnancy on infants' allergies in first year of life: randomised controlled trial. BMJ 2012;344:e184.
25. Strachan DP. Hay fever, hygiene, and household size. BMJ 1989;299:1259-60.
26. Prescott SL. Early-life environmental determinants of allergic diseases and the wider pandemic of inflammatory noncommunicable diseases. J Allergy Clin Immunol 2013;131:23-30.

27. Lee J, Seto D, Bielory L. Meta-analysis of clinical trials of probiotics for prevention and treatment of pediatric atopic dermatitis. J Allergy Clin Immunol 2008;121:116-121.e11.
28. Elazab N, Mendy A, Gasana J, Vieira ER, Quizon A, Forno E. Probiotic administration in early life, atopy, and asthma: a meta-analysis of clinical trials. Pediatrics 2013;132:e666-76.
29. Flint HJ, Scott KP, Louis P, Duncan SH. The role of the gut microbiota in nutrition and health. Nat Rev Gastroenterol Hepatol 2012;9:577-89.
30. Buddington RK, Williams CH, Kostek BM, Buddington KK, Kullen MJ. Maternal-to-infant transmission of probiotics: concept validation in mice, rats, and pigs. Neonatology 2010;97:250-6.
31. Kalliomäki M, Salminen S, Arvilommi H, Kero P, Koskinen P, Isolauri E. Probiotics in primary prevention of atopic disease: a randomized placebo-controlled trial. Lancet 2001;357:1076-9.
32. Kalliomäki M, Salminen S, Poussa T, Arvilommi H, Isolauri E. Probiotics and prevention of atopic disease: 4-year follow-up of a randomised placebo-controlled trial. Lancet 2003;361:1869-71.
33. Kalliomäki M, Salminen S, Poussa T, Isolauri E. Probiotics during the first 7 years of life: a cumulative risk reduction of eczema in a randomized, placebo-controlled trial. J Allergy Clin Immunol 2007;119:1019-21.
34. Naaktgeboren CA. Effects of maternal probiotic exposure during pregnancy and lactation on the mother and infant. Int J Probiot Prebiot 2010;5:113-24.
35. Rautava S, Kalliomäki M, Isolauri E. Probiotics during pregnancy and breast-feeding might confer immunomodulatory protection against atopic disease in the infant. J Allergy Clin Immunol 2002;109:119-21.
36. Ismail IH, Oppedisano F, Joseph SJ, Boyle RJ, Robins-Browne RM, Tang ML. Prenatal administration of Lactobacillus rhamnosus has no effect on the diversity of the early infant gut microbiota. Pediatr Allergy Immunol 2012;23:255-8.
37. Grześkowiak Ł, Grönlund MM, Beckmann C, Salminen S, von Berg A, Isolauri E. The impact of perinatal probiotic intervention on gut microbiota: double-blind placebo-controlled trials in Finland and Germany. Anaerobe 2012;18:7-13.
38. Boyle RJ, Ismail IH, Kivivuori S, Licciardi PV, Robins-Browne RM, Mah LJ, Axelrad C, Moore S, Donath S, Carlin JB, Lahtinen SJ, Tang ML. Lactobacillus GG treatment during pregnancy for the prevention of eczema: a randomized controlled trial. Allergy 2011;66:509-16
39. Cant A, Marsden RA, Kilshaw PJ. Egg and cows' milk hypersensitivity in exclusively breast fed infants with eczema, and detection of egg protein in breast milk. Br Med J (Clin Res Ed) 1985;291:932-5.
40. Järvinen KM, Westfall JE, Seppo MS, James AK, Tsuang AJ, Feustel PJ, Sampson HA, Berin C. Role of maternal elimination diets and human milk IgA in the development of cow's milk allergy in the infants. Clin Exp Allergy 2014;44:69-78.
41. von Berg A. Dietary interventions for primary allergy prevention--what is the evidence? World Rev Nutr Diet 2013;108:71-8.
42. Yang YW, Tsai CL, Lu CY. Exclusive breastfeeding and incident atopic dermatitis in childhood: a systematic review and meta-analysis of prospective cohort studies. Br J Dermatol 2009;161:373-83.
43. Gdalevich M, Mimouni D, Mimouni M. Breast-feeding and the risk of bronchial asthma in childhood: a systematic review with meta-analysis of prospective studies. J Pediatr 2001;139:261-6.
44. Simons E, Dell SD, Beyene J, To T, Shah PS. Is breastfeeding protective against the development of asthma or wheezing in children? A systematic review and meta-analysis. Allergy Asthma Clin Immunol 2011;7(Suppl 2):A11.
45. Dogaru CM, Nyffenegger D, Pescatore AM, Spycher BD, Kuehni CE. Breastfeeding and childhood asthma: systematic review and meta-analysis. Am J Epidemiol 2014;179:1153-67.
46. Mimouni Bloch A, Mimouni D, Mimouni M, Gdalevich M. Does breastfeeding protect against allergic rhinitis during childhood? A meta-analysis of prospective studies. Acta Paediatr 2002;91:275-9.
47. Walker-Smith J. Cow's milk allergy: a new understanding from immunology. Ann Allergy Asthma Immunol 2003;90(6 Suppl 3):81-3.
48. von Berg A, Filipiak-Pittroff B, Krämer U, Hoffmann B, Link E, Beckmann C, Hoffmann U, Reinhardt D, Grübl A, Heinrich J, Wichmann HE, Bauer CP, Koletzko S, Berdel D; GINIplus study group. Allergies in high-risk schoolchildren after early intervention with cow's milk protein hydrolysates: 10-year results from the German Infant Nutritional Intervention (GINI) study. J Allergy Clin Immunol 2013;131:1565-73.
49. von Berg A, Filipiak-Pittroff B, Schulz H, Hoffmann U, Link E, Sußmann M, Schnappinger M, Brüske I, Standl M, Krämer U, Hoffmann B, Heinrich J, Bauer CP, Koletzko S, Berdel D; GINIplus study group. Allergic manifestation 15 years after early intervention with hydrolyzed formulas--the GINI Study. Allergy 2016;71:210-9.
50. Osborn DA, Sinn J. Formulas containing hydrolysed protein for prevention of allergy and food intolerance in infants. Cochrane Database Syst Rev 2006;(4):CD003664.
51. van Odijk J, Kull I, Borres MP, Brandtzaeg P, Edberg U, Hanson LA, Høst A, Kuitunen M, Olsen SF, Skerfving S, Sundell J, Wille S. Breastfeeding and allergicdisease: a multidisciplinary review of the literature (1966-2001) on the mode of early feeding in infancy and its impact on later atopic manifestations. Allergy 2003;58:833-43.
52. Hays T, Wood RA. A systematic review of the role of hydrolyzed infant formulas in allergy prevention. Arch Pediatr Adolesc Med 2005;159:810-6.

53. Szajewska H, Horvath A. Meta-analysis of the evidence for a partially hydrolyzed 100% whey formula for the prevention of allergic diseases. Curr Med Res Opin 2010;26:423-37.
54. Alexander DD, Cabana MD. Partially hydrolyzed 100% whey protein infant formula and reduced risk of atopic dermatitis: a meta-analysis. J Pediatr Gastroenterol Nutr 2010;50:422-30.
55. Greer FR, Sicherer SH, Burks AW; American Academy of Pediatrics Committee on Nutrition; American Academy of Pediatrics Section on Allergy and Immunology. Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. Pediatrics 2008;121:183-91.
56. Osborn DA, Sinn J. Soy formula for prevention of allergy and food intolerance in infants. Cochrane Database Syst Rev 2006;(4):CD003741.
57. ASCIA Guidelines - Infant feeding and allergy prevention 2010 [Internet]. Balgowlah (Australia): Australian Society of Clinical Immunology and Allergy; c2016 [cited 2015 Aug 4]. Available from: https://www.allergy.org.au/images/pcc/ASCIA_Guidelines_infant_feeding_and_allergy_prevention.pdf.
58. Sansotta N, Piacentini GL, Mazzei F, Minniti F, Boner AL, Peroni DG. Timing of introduction of solid food and risk of allergic disease development: understanding the evidence. Allergol Immunopathol (Madr) 2013;41:337-45.
59. Zutavern A, von Mutius E, Harris J, Mills P, Moffatt S, White C, Cullinan P. The introduction of solids in relation to asthma and eczema. Arch Dis Child 2004;89:303-8.
60. Zutavern A, Brockow I, Schaaf B, Bolte G, von Berg A, Diez U, Borte M, Herbarth O, Wichmann HE, Heinrich J; LISA Study Group. Timing of solid food introduction in relation to atopic dermatitis and atopic sensitization: results from a prospective birth cohort study. Pediatrics 2006;117:401-11.
61. Poole JA, Barriga K, Leung DY, Hoffman M, Eisenbarth GS, Rewers M, Norris JM. Timing of initial exposure to cereal grains and the risk of wheat allergy. Pediatrics 2006;117:2175-82.
62. Tarini BA, Carroll AE, Sox CM, Christakis DA. Systematic review of the relationship between early introduction of solid foods to infants and the development of allergic disease. Arch Pediatr Adolesc Med 2006;160:502-7.
63. Kiefte-de Jong JC, de Vries JH, Franco OH, Jaddoe VW, Hofman A, Raat H, de Jongste JC, Moll HA. Fish consumption in infancy and asthma-like symptoms at preschool age. Pediatrics 2012;130:1060-8.
64. Koplin JJ, Osborne NJ, Wake M, Martin PE, Gurrin LC, Robinson MN, Tey D, Slaa M, Thiele L, Miles L, Anderson D, Tan T, Dang TD, Hill DJ, Lowe AJ, Matheson MC, Ponsonby AL, Tang ML, Dharmage SC, Allen KJ. Can early introduction of egg prevent egg allergy in infants? A population-based study. J Allergy Clin Immunol 2010;126:807-13.
65. Nwaru BI, Erkkola M, Ahonen S, Kaila M, Haapala AM, Kronberg-Kippilä C, Salmelin R, Veijola R, Ilonen J, Simell O, Knip M, Virtanen SM. Age at the introduction of solid foods during the first year and allergic sensitization at age 5 years. Pediatrics 2010;125:50-9.
66. Mihrshahi S, Ampon R, Webb K, Almqvist C, Kemp AS, Hector D, Marks GB; CAPS Team. The association between infant feeding practices and subsequent atopy among children with a family history of asthma. Clin Exp Allergy 2007;37:671-9.
67. Du Toit G, Roberts G, Sayre PH, Bahnson HT, Radulovic S, Santos AF, Brough HA, Phippard D, Basting M, Feeney M, Turcanu V, Sever ML, Gomez Lorenzo M, Plaut M, Lack G; LEAP Study Team. Randomized trial of peanut consumption in infants at risk for peanut allergy. N Engl J Med 2015;372:803-13.
68. Prescott SL, Macaubas C, Holt BJ, Smallacombe TB, Loh R, Sly PD, Holt PG. Transplacental priming of the human immune system to environmental allergens: universal skewing of initial T cell responses toward the Th2 cytokine profile. J Immunol 1998;160:4730-7.
69. Kummeling I, Thijs C, Huber M, van de Vijver LP, Snijders BE, Penders J, Stelma F, van Ree R, van den Brandt PA, Dagnelie PC. Consumption of organic foods and risk of atopic disease during the first 2 years of life in the Netherlands. Br J Nutr 2008;99:598-605.
70. Yang H, Xun P, He K. Fish and fish oil intake in relation to risk of asthma: a systematic review and meta-analysis. PLoS One 2013;8:e80048.
71. Kremmyda LS, Vlachava M, Noakes PS, Diaper ND, Miles EA, Calder PC. Atopy risk in infants and children in relation to early exposure to fish, oily fish, or long-chain omega-3 fatty acids: a systematic review. Clin Rev Allergy Immunol 2011;41:36-66.
72. D'Vaz N, Meldrum SJ, Dunstan JA, Martino D, McCarthy S, Metcalfe J, Tulic MK, Mori TA, Prescott SL. Postnatal fish oil supplementation in high-risk infants to prevent allergy: randomized controlled trial. Pediatrics 2012;130:674-82.
73. Pelucchi C, Chatenoud L, Turati F, Galeone C, Moja L, Bach JF, La Vecchia C. Probiotics supplementation during pregnancy or infancy for the prevention of atopic dermatitis: a meta-analysis. Epidemiology 2012;23:402-14.
74. Osborn DA, Sinn JK. Prebiotics in infants for prevention of allergy. Cochrane Database Syst Rev 2013;(3):CD006474.
75. Hyppönen E, Sovio U, Wjst M, Patel S, Pekkanen J, Hartikainen AL, Järvelinb MR. Infant vitamin d supplementation and allergic conditions in adulthood: northern Finland birth cohort 1966. Ann N Y Acad Sci 2004;1037:84-95.
76. Kull I, Bergström A, Melén E, Lilja G, van Hage M, Pershagen G,

Wickman M. Early-life supplementation of vitamins A and D, in water-soluble form or in peanut oil, and allergic diseases during childhood. J Allergy Clin Immunol 2006;118:1299-304.

77. Distor CD, Sumpaico MW, Recto MT, Castor MR. A randomized clinical trial on the effects of virgin coconut oil (VCO) on total IgE levels of infants at high risk for the development of atopic diseases: a preliminary study. Philippine J Allergy Asthma Immunol 2008;3:21-32.
78. Moreira A, Bonini M, Garcia-Larsen V, Bonini S, Del Giacco SR, Agache I, Fonseca J, Papadopoulos NG, Carlsen KH, Delgado L, Haahtela T. Weight loss interventions in asthma: EAACI evidence-based clinical practice guideline (part I). Allergy 2013;68:425-39.
79. Suárez-Varela MM, Alvarez LG, Kogan MD, Ferreira JC, Martínez Gimeno A, Aguinaga Ontoso I, González Díaz C, Arnedo Pena A, Domínguez Aurrecoechea B, Busquets Monge RM, Blanco Quiros A, Batlles Garrido J, García de Andoain N, Varela AL, García Merino A, Gimeno Clemente N, Llopis González A. Diet and prevalence of atopic eczema in 6 to 7-year-old schoolchildren in Spain: ISAAC phase III. J Investig Allergol Clin Immunol 2010;20:469-75.
80. Silverberg JI, Kleiman E, Lev-Tov H, Silverberg NB, Durkin HG, Joks R, Smith-Norowitz TA. Association between obesity and atopic dermatitis in childhood: a case-control study. J Allergy Clin Immunol. 2011;127:1180-6.e1.