The immune-supportive diet in allergy management. A narrative review and proposal

Subtitle:

Immune-supportive diet in allergy

Authors:

Berber Vlieg-Boerstra[1,2,3], Marion Groetch[4], Emilia Vassilopoulou[5], Rosan Meyer[6,7] Kirsi Laitinen[8], Anne Swain[9], Raquel Durban[10], Olga Benjamin[1,11], Rachelle Bottse[3], Kate Grimshaw[12],Merryn Netting[13,14,15], Liam O'Manony[16,17,18] Nicolette de Jong[19,20,], Isabel J. Skypala[6,21]

Affiliations

1. OLVG Hospital, department of Paediatrics, Amsterdam, the Netherlands
2. Rijnstate Hospital, Rijnstate Allergy Centre, Arnhem, The Netherlands
3. Vlieg Dieticians, Private Practice for dietary management of food allergy, Arnhem, Amsterdam, the Netherlands
4. Pediatric Allergy & Immunology, Icahn School of Medicine at Mount Sinai, New York, NY, USA
5. Department of Nutritional Sciences and Dietetics, International Hellenic University, 57400 Thessaloniki, Greece
6. Imperial College, Department Paediatrics, London, UK
7. Winchester University, Department Dietetics, UK
8. Institute of Biomedicine & Functional Foods Forum, University of Turku, Turku, Finland.
9. Allergy Unit, Royal Prince Alfred Hospital, Sydney, Australia
10. Carolina Asthma & Allergy Center, Charlotte, NC USA
11. Hospital Group Noord West, location Alkmaar, department of Paediatrics, Alkmaar, the Netherlands
12. Salford Royal NHS Foundation Trust, Salford, UK
13. Women and Kids Theme, South Australian Health and Medical Research Institute (SAHMRI), North Adelaide, South Australia, Australia.
14. Discipline of Paediatrics, Faculty of Health and Medical Sciences, The University of Adelaide, Adelaide, South Australia, Australia.
15. Department of Nutrition, Women's and Children's Hospital, North Adelaide, South Australia, Australia.

16. APC Microbiome Ireland, National University of Ireland, Cork, Ireland.
17. Department of Medicine, National University of Ireland, Cork, Ireland.
18. School of Microbiology, National University of Ireland, Cork, Ireland.
19. Internal Medicine, Allergology & Clinical Immunology, Paediatric Allergology, University Medical Centre Rotterdam, the Netherlands
20. Sophia Children Hospital Erasmus MC, University Medical Centre Rotterdam, the Netherlands.
21. Royal Brompton & Harefield Hospitals, part of Guys & St Thomas' NHS Foundation Trust, London, UK

The authors are all members of the International Network for Diet and Nutrition in Allergy (INDANA; www.indana-allergynetwork.org)

Correspondence
B.J. Vlieg-Boerstra, RD PhD
OLVG Hospital,
Department of Paediatrics,
PO Box 95500
1090HM Amsterdam
E: b.vlieg-boerstra@olvg.nl
M: +31620965612

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Summary

The role of nutrition is increasingly recognized in the management of chronic immune diseases. However, the role of an immune-supportive diet as adjuvant therapy in the management of allergic disease has not been similarly explored. This review assesses the existing evidence for a relationship between nutrition, immune function, and allergic disease from a clinical perspective. In addition, the authors propose an immune-supportive diet to enhance dietary interventions and complementing other therapeutic options for allergic disease from early life to adulthood. A narrative review of the literature was conducted, to determine the evidence of the relationship between nutrition and immune function, overall health, epithelial barrier function, and gut microbiome, particularly in relation to allergy. Studies on food supplements were excluded. The evidence was assessed and utilized to develop a sustainable immune-supportive diet to complement other therapies in allergic disease. The proposed diet consists of a highly diverse range of fresh, whole and minimally processed plant-based and fermented foods supplemented with moderate amounts of nuts, omega-3 rich foods and animal-based products in proportional amounts of the EAT-Lancet diet, such as (fatty) fish, (fermented) milk products which may be full-fat and eggs, lean meat or poultry, which may be free-range or organic.

Introduction

The prevalence of allergic diseases, such as asthma, eczema, allergic rhinitis, and food allergy has risen dramatically over the last few decades, specifically in industrialized countries (1,2). In parallel, there has been a rise in the incidence of chronic immune disorders (CIDs), such as rheumatoid arthritis, ulcerative colitis and Crohn's disease (inflammatory bowel diseases or IBD) and diet-related chronic diseases i.e., obesity, type 2 diabetes, and several cancers (3). Diet is one of the modifiable lifestyle factors that can impact overall health (4). Nutrition science has progressed from an early focus on individual nutrients and the prevention of nutritional deficiencies, to evaluating whether dietary components and healthy dietary patterns promote, prevent or even treat non-communicable diseases, for example in inflammatory bowel disease (5) and rheumatoid arthritis (6). However, although there is some evidence from observational and, to a lesser extent intervention studies, regarding the effect of diet on the development of some allergic diseases, e.g. asthma (7), the dietary management of food allergy remains largely focused on the elimination of trigger foods, maintaining an age-appropriate intake of energy and nutrients, and ensuring optimal growth (8). Less attention has been paid to the overall dietary composition as adjuvant therapy to support immune function, despite the recognition that nutrients and foods have immunomodulatory and pharmacological effects on immune function and gut permeability (9,10).

Based on data published for other disorders, and epidemiological links already identified, consideration should be given as to whether the effect of nutritional intake on immune function could improve the management of allergic disease. Immuno-nutrition is defined as the direct and indirect effects of macronutrients and micronutrients (vitamins, minerals and trace elements) on immune system development, functionality and responsiveness (11). This article aims to review existing evidence for a relationship between nutrition, immune function and allergic disease from a clinical perspective, and based on this evidence, propose an immune-supportive diet to enhance the dietary management of allergic disease. An overview of the method followed for the evidence of the proposed sustainable and immune-supportive diet the is given in figure 1.

The effect of individual nutrients, dietary patterns, and food processing on immune function

The human diet is required to sustain growth and development and maintain body composition, by providing both macronutrients (protein, carbohydrate, fiber and fat) and micronutrients (vitamins and minerals). Dietary composition can affect immune function from the standpoint of both individual nutrients, such as fiber, vitamins, essential fatty acids, but also from the diversity and variety of foods consumed. It has been proposed that an increase in the consumption of ultra-processed foods, rather than changes in carbohydrate and fat intakes, has been linked to the start of the obesity epidemic in the USA (12), as well as to chronic disease (2). The composition of the diet has changed rapidly in the last few decades, with ultra-processed foods now contributing 30-60% of energy intakes (13-15). Therefore, when considering the effect of the diet on the immune system, it is important to evaluate the contribution of individual nutrients, the synergy between nutrients in different dietary patterns and the role of ultra-processed foods.

Single nutrients

Nutrients and non-nutritive components, including vitamin A, D, C, selenium, zinc, iron, fiber and flavonoids are prerequisite for optimal innate and adaptive immune function, gut microbiome and for adequate resistance to viral or bacterial infections (11,16-22). Nutrients also play a role in mucosal barrier function, induce immunomodulatory effects through interaction with the gut microbiota, and change the intestinal microbiota composition (11) through epigenetic effects and interaction with (pharmacological) receptors (20) (Table 1). The latter leads to both anti-inflammatory and pro-inflammatory processes, depending on the nutrient-receptor complex and interactions (and quantity of nutritional components) (20). However, although supplementation with individual nutrients can be beneficial in states of insufficiency, in healthy individuals they provide no overall benefit and may even provoke adverse effects (16,17). A recent systematic review and meta-analysis reported that nutrient supplementation alone, did not prevent respiratory viral infections (18).

However, some single dietary nutrients could play a role in allergic disease. Essential long-chain polyunsaturated fatty acids (PUFAs) and their metabolites are considered to have anti-inflammatory (omega 3) and pro-inflammatory (omega 6) properties in the pathogenesis of asthma and allergy through their impact on the production of pro- or anti-inflammatory prostaglandins and limiting neutrophil infiltration amongst others (19). As omega-3 and omega-6 PUFA compete for the same elongation and desaturation enzymes needed for conversion (23), a low ratio of omega-6 to omega-3 intake is important to obtain anti-inflammatory effects. Evolutionary dietary models are characterized by a ratio of 1:1, whereas in the Western diet, this ratio may be as high as 16:1 (24), due to the increased use of vegetable oil and changes in animal feed (grass to grains) (24-27). Milk, eggs and meat from grass-fed animals contain higher amounts of omega-3 PUFAs, due to due to high grazing/forage-based diets (25-27). Sources of omega-3 and 6 are given (Table 2) (28,29).

Naturally occurring trans-fatty acids may also offer protective health effects. Consumption of the ruminant milk trans-fatty acids, vaccenic acid (tVA), and conjugated linoleic acid (c9,t11-CLA) from grass-fed ruminants, may reduce sensitization and allergic inflammation (30-32). Conversely, trans-fatty acids derived by partial hydrogenation of vegetable oils are thought to have detrimental health effects (19,33). Saturated fat is also considered to have pro-inflammatory effects, although this may only apply to saturated fatty acids derived from meat, and not from milk or milk products (34,35). Moreover, emerging evidence suggests that dairy foods do not increase concentrations of the biomarkers of chronic systemic inflammation (34,35). Additionally, some short-chain fatty acids (SCFAs) (e.g., in butter), especially butyrate, exert immunoregulatory effects via multiple mechanisms, including epigenetic modifications, beneficial effects on the gut microbiome, microbial barrier function and immune homeostasis (37,38).

Synergistic effects of nutrients in dietary patterns

Although single nutrients have immunomodulatory effects, a combination of nutrients can have synergistic effects, meaning the whole diet has more impact than individual food constituents alone (39,40). Food synergy, based on the proposition that the interrelations between constituents in foods are significant, has become increasingly accepted instead of studying single nutrients (12). For example, nutrients are usually provided by different food sources, nutrients affect each other's absorption, such as copper and zinc, and vitamin C and iron. In contrast, anti-nutrients such as phytate may decrease the absorption of minerals such as iron (16. The food synergy concept supports the idea of dietary variety and of selecting nutrient-rich foods as part of that diet (16,39,41-43).

There is abundant evidence that the Western diet, rich in total fat, saturated fat, meat, refined sugars and processed foods, is related to increased risk of mortality, low-grade inflammation, disturbed gut epithelial barrier function and pro-inflammatory microbiome composition (39,40,42,44,45-48). Specifically, a high intake of animal foods induce a pro-inflammatory composition of the gut microbiome, such as an increase in Firmicutes, Ruminococcus species and a reduction in bifodobacterium, as well as an endotoxin synthesis pathways (42,48). The Western diet is characterized by low nutrient density, meaning that it has a relatively low content of significant nutrients (dietary fiber, essential fatty acids, minerals and vitamins) per calorie, often referred as 'empty calories'. Low nutrient dense foods often contain high levels of refined sugars, saturated fat, and sodium (49). Diets high in empty calories result in a reduced intake of nutrients essential for an optimal innate and adaptive immune system, such as vitamin A, C, D, iron, zinc, selenium, magnesium, copper and omega-3 fatty acids (11,21,50). The high saturated fat content of the Western diet, typical in North American and Northern European dietary patterns (51,52), directly activates the Toll-like receptor 4 (TLR4), which leads to a NF-κB-driven inflammatory cascade, inducing the production of inflammatory cytokines, chemokines and adhesion molecules (53).

Food patterns differ around the world, suggesting that a range of diet types confer beneficial health effects. In contrast to the Western dietary pattern, traditional diets consist of seasonal and local foods, prepared at home, and consumed by the family, with culinary methods, transferred from generation to generation (44). Such diets are sustainable and increase social contact, which also impacts beneficially on health (54-56) (Table 3). Each country has its own guidance on healthy eating reflecting country specific traditional diets, local availability, and recommendations on the intake of macro- and micro-nutrients to support health. The challenge is to establish which overall diet is best for health (45,57). A comparison of the efficacy of seven dietary patterns, found that a diet of minimally processed and predominantly plant-based foods is associated with positive health outcomes and increased life expectancy (57). Fadnes et al. concluded that an optimal diet for prolonged life expectancy, should include more whole grains, legumes, fish, fruits, vegetables, and some nuts, and less red meat, processed meats, sugar-sweetened beverages, and refined grains (58). A dietary pattern rich in complex carbohydrates, plant-based proteins and a limited intake of animal-based protein has also been shown to be beneficial for overall mortality (59,60).

The traditional Mediterranean dietary pattern, which typically has a high ratio of monounsaturated (MUFA) to saturated (SFA) fats and omega-3 to omega-6 polyunsaturated fatty acid (PUFAs) and supplies an abundance of fruits, vegetables, legumes and whole grains, is also protective against chronic disease and associated with a lower prevalence of allergic disease (51-53). Other dietary patterns similar to the Mediterranean diet, which have also been shown to be beneficial include the Nordic diet, (61,62), the Japanese diet, (63,64) and the Atlantic diet (traditional in Spain and Portugal) (65,66) (Table 4).

Pro- and anti-inflammatory properties of food patterns

Pro-inflammatory effects have been demonstrated for high-fat/high-sugar diets, micronutrient deficiencies (folate, manganese, and carotenoids) and obesity through epigenetic mechanisms

(67,68). In contrast, some anti-inflammatory effects resulting from caloric restriction, omega-3 PUFAs, fiber, Mediterranean diet, vitamin D, zinc, polyphenols (i.e., resveratrol, gallic acid, epicatechin, luteolin, curcumin), may also be epigenetically driven (67,68), highlighting the importance of moderate energy intake amongst others. One proposed method of measuring the pro- and anti-inflammatory capacity of the total diet is the Dietary Inflammatory Index (DII), a validated, measure of diet-associated inflammation (40,69). The DII includes 45 pro- or anti-inflammatory foods, nutrients or food components with the total inflammatory score of a diet based on the individual contribution of these components. IL-1β, IL-4, IL-6, IL-10, TNF-α and C-reactive protein were chosen as inflammatory biomarkers (40). This index proposes that the most pro-inflammatory food components are saturated fat, trans fatty acids, and cholesterol from mammalian products. The best anti-inflammatory foods/food components are fruits, vegetables (especially garlic), thyme/oregano, whole grains, fatty fish, green and black tea, omega-3 fatty acids, flavonoids and dietary fiber (69). Studies suggest that following a healthy diet leads to a lower DII score (40,46). A recent study showed that a higher energy adjusted DII score during pregnancy, indicating a more pro-inflammatory diet, was associated with higher risk of asthma in offspring (OR: 1.35; 95% CI: 1.10, 1.65; per 1-SD score increment) (70).

Adverse effects of food processing

The method and intensity of processing is also important. The NOVA food classification system, based on the nature, extent and purpose of industrial food processing, classifies all foods into four groups (Table 5) (71,72. Group 4 consists of ultra-processed foods, which contain additives, including those that imitate or enhance the sensory qualities of foods and processed ingredients (i.e. hydrogenated fat). The processing and ingredients used in the manufacture of ultra-processed foods make them very convenient (ready-to-consume, almost imperishable) and palatable for consumers, and highly profitable (low-cost ingredients, long shelf life) for their manufacturers (71). A report based on studies in 11 countries shows that frequent use of (ultra) processed foods, classified according to the NOVA classification, is associated with a diet high in energy density, fat, sugar and/or salt content and an increased risk of chronic disease (72).

Ultra-processed foods also contain elevated levels of Advanced Glycation End products (AGEs) (73). These are formed due to the Maillard reaction, which occurs during the browning of animal proteins and fats at high temperatures, and also in the presence of a high concentration of sugars. Fast foods, fried meats, sweets, sugars and microwaved foods are particularly high in AGEs. A high intake of d AGEs and AGE-forming sugars could promote the development of food allergy due to the innate immune system misinterpreting a threat from dietary allergens and producing alarmins, which facilitate innate danger signals and immune responses (73). Although a recent study showed that maternal intake of AGEs in pregnancy was not associated with asthma and allergy outcomes in their offspring (74), a high intake of AGEs from fast food is associated with atopic dermatitis, and wheeze (75,76). Also, a high intake of fast foods is linked to the development of allergic diseases in adolescents, possibly due to the AGE content of these foods (77).

Processed foods also contain food additives; bread, margarine, ice cream, mayonnaise and sweets may contain emulsifiers such as polysorbate 80 and carboxymethylcellulose. Studies in mice suggest these products may affect the gut epithelial mucous layer, alter gut microbial composition and promote inflammation (78). Carrageenan (E407), extracted from red and purple seaweeds, is commonly used as a thickening agent or emulsifier in dairy/soy products, infant formula and processed meats. Along with carboxymethylcelluloses, carrageenan has been shown to induce changes in the microbiome, increase intestinal epithelial permeability, inhibit proteins that provide protection against microorganisms and trigger pro-inflammatory cytokines (5,78-81). Glucose, salt, emulsifiers, organic solvents, gluten, microbial transglutaminase, and nanoparticles, used by the food industry, may increase intestinal permeability by breaching the integrity of tight junction paracellular transfer, resulting in entry of foreign immunogenic antigens and activation of the autoimmune cascade (82) Salt can also skew macrophages toward a pro-inflammatory phenotype characterized by the increased differentiation of naive CD4+ T cells into highly inflammatory T helper (TH)-17 cells, and decreased expression and anti-inflammatory activity of T regulatory cells (4,83). In addition, common ingredients in most ultra-processed foods such as isolated sugars and refined grains can cause increased oxidative stress, which in turn can impact the immune system (4,84,85).

Beneficial effect of food fermentation

Sourdough fermentation may decrease the glycemic response of baked goods and improves the properties and bioavailability of dietary fiber complex and phytochemicals. In addition, the phytate in sourdough bread, which is known for its mineral binding capacity, is degraded to a higher extent resulting in a related increase in free calcium, zinc, magnesium and iron (86,87). Fermented foods, such as kefir, yoghurt with live bacteria, cheese, sauerkraut, tempeh, kombucha tea, kimchi, and miso have recently gained more attention as related to immune health (88,89). There is evidence that fermented foods have beneficial probiotic-like health effects, including reinforcement of the epithelial barrier by an increase of the mucins, the tight junction proteins and the Goblet and Paneth cells (90). A recent study showed that consumption of fermented foods increases microbiome diversity and decreases large numbers of inflammation markers, while a fiber rich diet did not (43,91). In addition, fermented foods are a natural source of SCFAs (38). Also, fresh and unheated foods, such as raw fruits and vegetables contribute to the total microbial exposure through diet and may therefore contribute to immunomodulatory effects in the gut (92).

The wider role of nutrition in the immune system

Nutrition and the gut microbiome

The intestinal microbiome is in close and continuous contact with the immune system and influences pro-inflammatory and anti-inflammatory responses in the gut (42,43,93-97). A healthy host–microbiome balance and diverse microbiota is required to optimally maintain the intestinal barrier and support immune functions, and consequently prevent disease development (98,99). Many chronic diseases, including allergies, are characterized by a dysbiosis and reduced diversity of the microbiome (100). Studies have convincingly shown that diet can alter microbiota composition rapidly, but also over the course of weeks and months (101-104). In addition to modifying the number and composition of the gut bacteria, metabolites produced by the bacteria subsequently impact the structure and function of the epithelial barrier and eventually human metabolism, immune function and health (103). Dysbiosis and a reduction of gut microbial diversity in terms of phyla and genus has been observed, when the diet becomes Westernized, with an increased consumption of refined foods, high-fat foods, meat, and additives (104). A systematic review by Singh et al. reported that high levels of animal protein, high total and saturated fat reduces the total abundance of bacteria in the gut, especially *Bifidobacterial, Lactobacilli, Eubacteria, and Bacteroides* species, while plant-based proteins and omega-3 PUFAs induce the opposite effect alongside increased abundance of *Prevotella* (48). Dietary fiber increases gut microbiota diversity and generation of metabolites, such as SCFAs, which promote regulatory immune responses. High SCFA levels early in life are associated with protection from atopic sensitization, as well as having an anti-inflammatory effect (42,69,96-98,105-107). Further, evidence is accumulating to indicate the importance of dietary fat quality on gut microbiota (108). In humans, a diet rich in saturated fat seems to associate with bacterial dysbiosis, such as Proteobacteria, while a PUFA intake, particularly that of omega-3 PUFA, has been associated with a decreased Firmicutes to Bacteroidetes ratio and an increased diversity (109).

Nutrients and food components like phytochemicals are utilized by microbes residing in the gut to promote or inhibit their growth and with capability to extract energy to selected members of the gut microbial community, and also to produce metabolites including those with the immunomodulatory capacity (103,110). It is also of note that the human diet is a source of microbes, including those formed during food manufacture (addition of probiotics, fermented foods) (111). Experimental evidence is emerging that non-nutrient components of the diet including artificial sweeteners, additives (emulsifiers including lecithin, mono- and diglycerides of fatty acids) and sodium could alter gut microbiota, increase bacterial translocation across epithelia and induce microbiota-mediated adverse effects in the host (e.g., glucose intolerance) (4,78,83,104,112,113). Based on the current evidence, diets high in fruits, vegetables, legumes, wholegrains, nuts, fatty fish as a source of omega-3 PUFA, and fermented dairy (buttermilk and yoghurt) have the potential to beneficially modify gut microbiota composition and function and prevent intestinal inflammatory processes at the core of many chronic diseases (42,104).

Nutrition and epithelial barrier function

It has been proposed that an increase in epithelial barrier-damaging agents due to industrialization, urbanization and modern life underlies the rise in allergic, autoimmune and other chronic conditions (2). A defective epithelial barrier has been demonstrated in asthma, atopic dermatitis, allergic rhinitis, chronic rhinosinusitis, eosinophilic esophagitis, coeliac disease and inflammatory bowel disease (2,114). Impaired intestinal permeability is also demonstrated in patients with adverse reactions to food (115). Dietary factors may maintain or improve epithelial barrier structure and function, e.g. omega-3 PUFAs, fiber, vitamins and minerals, fermented foods and diets rich in polyphenols (21,95,109,116,117). Food processing may have deleterious effects on intestinal epithelial barrier through AGE formation and additives like emulsifiers (2,82,118). In a small study in adult patients with eosinophilic esophagitis, the intake of sunflower oil and/or stir fry oil, as well as the total amount of added fat, was unfavorably related to in vitro values of permeability, while the consumption of buttermilk/LGG yoghurt drink, milk products and vitamin A were favorably related to mucosal permeability of the esophagus (119).

Nutrition and allergic disease

Food diversity

The effect of diet diversity. i.e. the number of different foods or food groups consumed over a given reference period and dietary patterns in pregnancy, infancy and childhood, was summarized in the review by Venter et al (120). A diverse diet was recommended for at risk infants, but not before the age of 4 months due to an increased risk of atopic dermatitis at two and six years (120). The PASTURE study reported that an increased dietary diversity within the first year of life might have a protective effect on asthma, food allergy, and food sensitization (121). A study of adults aged 20-63 years found that a higher dietary diversity showed a significant inverse dose-response relationship with allergic diseases and allergic rhinitis in women, but not in men (122). Most recently, 135/2251 infants with allergic disease had less food diversity at 6 and 12 months of age than infants without allergic disease, whereas those with the lowest risk of developing allergic disease had the greatest food diversity (123). Increased diet diversity during the first year of life is associated with a decreased risk of asthma in the first year of life, and a reduced risk of atopic dermatitis at 2, 4 and 5 years of age (121,124,125). It is assumed that the beneficial effects of food diversity induce tolerance induction through the effect on a more diverse microbiome, exposure to a larger range of potential allergens as well as beneficial nutrients (120).

Food Allergy

A nested, case-control, within-cohort prospective study, found that an infant diet consisting of high levels of fruits, vegetables, and home-prepared foods was associated with less food allergy by the age of 2 years (126). Another study reported that a higher dietary intake of vitamin A and carbohydrates was associated with increased threshold levels for peanut reactivity in peanut allergic children whereas a higher intake of PUFAs (mainly omega-6 fatty acids or linoleic acid) intake was associated with lower threshold level for peanut. (127). A case-control study in Greece showed that components of a maternal Mediterranean diet may protect against the development of Food Protein Induced Enterocolitis Syndrome in the offspring, when traditional cooking methods are adopted and fish, fruit, and whole wheat products are consumed frequently during pregnancy and breastfeeding (128). The allergenicity of raw (unprocessed) milk may be lower than pasteurized and processed milk. In an oral provocation pilot, up to 50 ml of raw milk was tolerated in cow’s milk allergic children as compared to 8.6 ± 5.3 mL pasteurized milk suggesting that processing increases the allergenicity of milk (36).

Atopic dermatitis

Relatively few studies have evaluated the relationship between dietary patterns and atopic dermatitis (129). A large study in Colombia of 6–7 years old children showed that fresh fruit and pulses (peas, beans, lentils) consumed at least 3 times per week as part of a more traditional diet were inversely related to atopic dermatitis (130). Unpasteurized mare's milk was associated with a decrease in atopic dermatitis symptoms, and yoghurt consumption in infancy in Japan was shown to be inversely associated with atopic dermatitis and food sensitization at 5 years of age (131,132).

Asthma

A systematic review on dietary interventions in asthma reported that 15/28 studies showed improvements in either asthma-related outcomes, immunological parameters, or both; promising interventions included herbs, herbal mixtures/extracts, and omega-3 PUFAs (133). Four systematic reviews found an inverse relationship between adherence to the Mediterranean diet and wheeze and asthma (19,134-137). Additionally, a single center-controlled study evaluation of the efficacy of a Mediterranean diet supplemented with fatty fish twice weekly reported a significant positive effect for pulmonary function (138). An overview of systematic reviews on asthma and dietary intake reported a negative association between asthma or wheeze and dietary intake of vitamins C, E and D, as well as intake of fruits and adherence to a Mediterranean diet (7). However, a large survey of European adults, found no association between fruit and vegetable intake and asthma (139). Data from 9–10 years old Greek children showed an inverse association between lifetime asthma and the pro-antioxidant score of the diet (vegetables, fruits, fresh juice, fish), independent of other cofounders (140). A larger study of younger children from 11 Latin American countries found a negative association between current wheeze and a higher fruit intake, and a positive association between fast food/ burgers and wheeze in the older children (130). A six-month trial of a high-quality diet in adults with poorly controlled asthma resulted in decreased proinflammatory markers (IL-1β, TGF-α, and IL-6), and proteins associated with asthmatic conditions, i.e. T-helper (Th) 2 and Th17 associated cytokines and growth factors (141).

Allergic rhinitis

Several observational studies have shown an association between dietary composition and the prevalence of allergic rhinitis (AR). Cepeda et al (130) found a negative association between fruit intake and allergic rhinitis in all children, and vegetable intake and allergic rhinitis in younger children. Fast food/burger intake was positively associated with allergic rhinitis in the older children (130). The link with fruit and vegetable intake in childhood has been shown in other studies. A dietary pattern rich in vegetables and higher serum vitamin D level was related to a lower risk of mild and persistent AR in Korean children (142). Also, flavonoids in fruits and vegetables have been associated with a lack of allergic rhinitis in Italian adults (143). In a prospective study in 7-year-old Japanese schoolchildren, the prevalence of asthma, rhinitis, or any allergic symptoms at age 10 was significantly decreased in those with a high intake of fruit, as was the onset of any allergic symptoms during the study period (144).

Studies also indicate that children regularly consuming high carbohydrate foods such as cereals, rice and pasta, have a reduced risk of rhino-conjunctivitis' whereas the opposite was true for those consuming a diet high in fat and low in carbohydrates (145,146). A regular consumption of sweets and animal fats was associated with reported rhino-conjunctivitis in children, and the same is true for high meat intakes in adults (147). The consumption of processed and fast foods has also been linked to AR in children (130,148). One dietary pattern linked to an increased risk of AR in Hong Kong school aged children was higher intakes of legumes, butter, nuts and potatoes (149).

The immune-supportive diet in the management of allergic disease

The evidence cited in this paper strongly supports the premise that the dietary management of allergic conditions should include consideration of total dietary composition and its effects on immune function, although far most evidence is based on observational studies. Nutrients, foods and dietary patterns have a beneficial effect on immune function, either directly or through the enhancement of the gut microbiota, epithelial barrier and overall health through metabolic, epigenetic and antioxidant effects. Given the effects of processing and the immunomodulatory properties of specific foods, dietary advice and support should enable individuals with a food allergy change to more healthy dietary patterns in addition to excluding the trigger food(s). Such advice may be especially important in adults as aging is associated with progressive alteration of intestinal permeability, chronic low-grade inflammation, gastritis and a decreased ability to digest food, which often results in nutritional deficiencies including low levels vitamin D, zinc and iron (150). More emphasis should also be on achieving an immune-supportive diet, especially since it may support immune function to maintain or even achieve tolerance (151). This active management is also warranted to counteract the unnecessary avoidance of foods, especially wheat and milk, which is an increasingly worldwide phenomenon (152), and highly prevalent in individuals with allergic diseases, especially atopic dermatitis and/or food allergy (153). Elimination of wheat and milk may lead to deficiencies in dietary fiber, B vitamins, minerals such as iodine, iron and calcium and vitamin B2. In addition, as nutrition works through interaction with (pharmacological) receptors (20), an immune-supportive diet could be integrated in a more holistic management of allergic diseases to enhance the efficacy of allergen immunotherapy, biologicals or other drugs.

An immune-supportive and sustainable diet also ensures that the amount of animal proteins are proportionate to the amounts included in the sustainable, healthy and planetary-proof EAT-Lancet diet (154).

Based on the available evidence as outlined in this paper, in addition to tailoring the diet to meet individual nutritional needs, an immune-supportive diet and selected foods should meet the following criteria (figure 1 and Table 6):

- Complies with national and international balance and ratio of macronutrients and energy;
- Contain an abundancy of fresh, whole or minimally processed foods (NOVA-classification 1-3, home cooked, locally produced, and seasonal food, a high diversity of foods taken from all food groups, plant-based foods, foods rich in dietary fiber, foods rich in flavonoids, fermented foods and foods naturally rich in beneficial food microbes and omega 3 fatty acids;
- Contains moderate amounts of animal-based foods proportionate to the EAT- Lancet diet and omega 6 fatty acids;
- Contains minimal amounts of ultra-processed foods, foods high in trans/ saturated fatty acids, foods high in added sugars, and low in dietary fiber.

Based on these criteria the following foods are selected:

- Recommended foods in age-appropriate amounts are raw and cooked vegetables, (sweet) potatoes and starchy roots, fresh fruits, whole grains, legumes, fermented foods and foods naturally rich in beneficial food microbes (e.g. kimchi, sauerkraut, kefir, yoghurt, raw fruits and vegetables), herbs and spices and black and green tea;
- Recommended for moderate use, according to the sustainable, planetary proof and healthy EAT-Lancet diet are oily fish, walnuts, flax seed, omega-3 PUFA rich oils and raw or roasted unsalted nuts and seeds will help to achieve a decreased omega-6: omega-3 ratio. Omega-3 containing tub margarines which, although highly processed, may be included depending on individual preferences. Apart from oily fish, other

sources of animal protein, e.g. eggs, white fish, shellfish, unprocessed poultry and lean meat, can still be included in the diet but in lesser amounts. The same applies to milk and milk products such as yoghurt, butter and cheese, with intake proportionate to the nutritional needs, especially during infancy and childhood, and preferably from grass-fed animals.

- Finally, an immune-supportive diet should reduce or exclude stick margarines, refined grains, fatty meat and meat products and ultra-processed foods e.g. sweets, biscuits/cakes, savory snacks, fast food, sugary drinks, and ready meals due to the presence of trans fatty acids, AGEs, emulsifiers etcetera.

A detailed outline and rationale of an immune-supportive diet is given in Table 7. Such a diet can achieve individual dietary requirements, whilst also ensuring the components of an immune-supportive diet are met. A caveat to any dietary advice is that the impact of nutritional manipulation on the immune system may vary on an individual basis. Based on the individual clinical history and age of the patient this sample menu should be personalized and individually adapted.

Conclusions

Nutrients, foods and dietary patterns may have a beneficial effect on immune function, either directly or through the enhancement of the gut microbiota, epithelial barrier and overall health through metabolic, epigenetic and antioxidant effects. In addition, the origin of products and how they are processed contribute to their immunomodulatory effects. However, although there is emerging evidence that healthy food choices play a meaningful role in the treatment of allergic disease beyond elimination of the causative allergen(s), the role of an immune-supportive diet as adjuvant therapy has not been adequately explored. Observational studies in humans suggest that higher food diversity and higher intakes of healthy foods such as fruits, vegetables and complex carbohydrates, and lower intakes of animal products, sugars and fast food are associated with improved outcomes of asthma, atopic dermatitis and allergic rhinitis. Future intervention studies testing the efficacy of an immune-supportive diet on clinical symptoms, inflammatory markers and in the treatment of allergic disease are needed. Many open questions are still unanswered and many research needs are to be addressed, including inter-individual effects (Box 1). There is currently insufficient evidence to actively promote the use of an immune-supportive diet to complement other therapies in the management of allergic disease. However, such a diet meets dietary guidelines, is sustainable and high in nutritional quality, so we should take this opportunity to support patients by active dietary management which may also have immune-modulatory effects.

Statement of conflict of interest:

The authors declare no conflict of interest in relation to this work

Statement of contribution:

BVB developed the concept, BVB and IS wrote the manuscript, all authors approved the concept and actively reviewed and commented on the paper. NdJ drafted the graphical abstract.

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Table 1: Nutrients with acknowledged immunomodulatory function (11,16-20)

Table 2 **Sources of omega-3 and omega-6 fatty acids (28,29)**

Table 3. Social and cultural context of diet and nutrition – comparison between traditional Mediterranean diet and Western diet (54-56)

Table 4. Regional dietary patterns that have been shown to be beneficial

Table 5: classification of processed NOVA foods (71,72)

Table 6: Rationale for the selection of foods that fit in an immune-supportive diet

Table 7. Immune-supportive sample menu for an adult*

Figure 1. Structure of the evidence base for the immune-supportive diet

Box 1. Unanswered questions and research needs

- What is the effect of an immune-supportive diet on clinical symptoms of the individual allergic diseases i.e. food allergy (e.g. threshold levels, severity of symptoms), atopic dermatitis, allergic asthma, allergic rhinitis, eosinophilic esophagitis?
- Which dietary components contribute (most) to immunomodulatory effects and symptom reduction?
- How do nutritional components interact to obtain immunomodulatory effects and symptom reduction?
- Which immunological (anti-inflammatory) pathways are induced by the immune-supportive diet and its components?
- Which changes in microbiome and permeability of the gut, lung and skin are obtained by the immune-supportive diet?
- How is the feasibility of the diet and the adherence to the diet by the different patient groups, including children?
- What are the extra costs of the immune-supportive diet?
- What is the overlap with immune-supportive diets in other chronic immune disorders such as IBD?
- Is the proposed immune-supportive diet applicable to the general population to prevent the development of allergic disease and other chronic immune diseases?