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The Influence of Dietary Patterns on Immune Function and Inflammation

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Abstract

Background: Diet significantly impacts immune function and inflammation, with different types of fats, fibers, and micronutrients playing distinct roles. Omega-3 and omega-6 fatty acids, saturated fats, sterols, and dietary fibers all influence immune responses and inflammation, potentially affecting disease risk and management.

Aim: This review examines how dietary components such as omega-3 and omega-6 fatty acids, saturated fats, sterols, and fibers affect immune function and inflammation. It aims to elucidate the mechanisms through which these nutrients influence immune responses and their potential implications for disease prevention and management.

Methods: We conducted a comprehensive review of the literature, focusing on recent studies that investigate the role of dietary fats, fibers, and micronutrients in immune modulation. Key areas of interest included the impact on inflammatory markers, immune cell function, and disease outcomes.

Results: Omega-3 fatty acids exhibit anti-inflammatory properties and may benefit conditions like rheumatoid arthritis, while omega-6 fatty acids are involved in both pro-inflammatory and anti-inflammatory responses. Saturated fats increase inflammation and may exacerbate chronic diseases. Sterols like cholesterol contribute to systemic inflammation and affect immune cell function. Dietary fibers promote gut health and systemic immunity through SCFA production, impacting conditions such as Crohn's disease and metabolic syndrome. Probiotics also modulate immune responses and improve gut health.

Conclusion: Dietary components play a crucial role in modulating immune function and inflammation. Omega-3 fatty acids and fibers show potential benefits for reducing inflammation and disease risk, while saturated fats and sterols may contribute to inflammatory responses. Future research should focus on optimizing dietary recommendations to enhance immune health and manage chronic diseases.

Keywords: Omega-3 fatty acids, Omega-6 fatty acids, Saturated fats, Sterols, Dietary fibers, Immune function, Inflammation..

1. Introduction

The relationship between immunology and nutrition is quite intricate. The immune system is influenced by an individual's general nutritional condition, level of sustenance, and eating habits, which include foods, nutrients, and non-nutritive bioactive chemicals. Physical barriers (such as skin and intestinal mucous membranes), the microbiome, the innate immune system (such as macrophage function and polarization), and the adaptive immune system (such as T- and B-cell function) can all have an impact on this. On the other hand, the immune system influences dietary requirements and metabolism, which impacts the body's reaction to food. The foundation of this analysis is the complex interplay among nutrition, food, and the immune system. Using case studies that explore the connection between immunity and nutrition, the review will go over the developing topic of nutritional immunology.

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There are several ways to evaluate the mutual link between the immune system and food. Researchers have examined the effects of isolated nutrients [2–6], dietary patterns like the Mediterranean Diet [7,8], and bioenergetic status [1] on a variety of immune function indices in both controlled feeding and free-living intervention studies (e.g., circulating cytokines, high-sensitivity C-reactive Protein, antibodies, tissue-specific transcriptomes). In addition to these intervention studies, a growing corpus of research using observational study designs has examined the relationships between dietary intakes and similar immune function outcomes and disease endpoints (e.g., allergy incidence, chronic disease risk) by measuring dietary intakes using self-reported measures and circulating biomarkers. Numerous populations have been involved in these studies: individuals with metabolic syndrome, adults, individuals with chronic diseases, pregnant women and small infants, and people with autoimmune, inflammatory, and/or allergy problems. In order to gain mechanistic insights, research on laboratory animals and cultured cells is typically added to these clinical observations. However, the direct application of findings from animal studies to human contexts is limited due to notable variations in immune system development and function [9,10] and the lack of in vivo interactions.

It is significant to emphasize that there are currently few large-scale randomized controlled trials showing how food affects the risk of immune-mediated disease, including clinical outcomes such as disease remission or event reduction. For example, many clinical investigations have not supported the theories linking early exposure to dairy protein with beta-cell autoimmunity [11]. A further indication of the difficulties in nutritional immunology and the drawbacks of using surrogate endpoints is the extensive history of investigating the inflammation-atherosclerosis hypothesis. It took decades for researchers to use a variety of anti-inflammatory drugs before they could show that interleukin (IL)-1 beta suppression decreased the incidence of cardiovascular events. Although there is a great deal of interest in comprehending the relationship between immune-mediated disease risk and diet, it is crucial to carefully assess the type and caliber of the available data.

Immune System During Aging:

Many physiological systems, including the immune system, see major alterations as we age. There is a reciprocal effect between aging and the immune system as well as other systems like the endocrine, neurological, digestive, cardiovascular, and musculoskeletal systems. These aging-related changes affect both innate and adaptive immunity, changing leukocyte subsets and their main roles, which frequently contribute to an ongoing proinflammatory state [12-13]. Known as "inflammaging," this syndrome is defined by persistently high levels of proinflammatory mediators such TNF-α, interleukin-6 (IL-6), and interleukin-1 beta (IL-1) [14]. Immunosenescence has a significant clinical impact on health outcomes. In the elderly, it increases susceptibility to infections, frequently reactivates latent viruses, and reduces vaccine efficiency; the annual influenza vaccine, for example, only exhibits 40–60% efficacy in those 65 years of age or beyond [15]. Aging is also linked to higher risks of cancer and autoimmune disease. There has been much discussion on how immunosenescence and inflammation can facilitate a variety of illnesses [16].

As we age, the innate immune system experiences major modifications. Monocytes are classified into three subtypes: classical (CD14++ CD16−), nonclassical (CD14+ CD16++), and intermediate (CD14++ CD16+). Monocytes make up roughly 5–10% of blood leukocytes. Nonclassical CD14+ CD16+ monocytes become more prevalent as people age, indicating a change towards a proinflammatory, senescent phenotype with shorter telomeres. A shift in the phenotype of macrophages has also been seen; proinflammatory M1 macrophages have been shown to rise, while more immunoregulatory M2 macrophages have decreased [17]. Atherosclerotic plaque growth has been connected to this M1/M2 imbalance, which is assumed to be the cause of age-related illnesses [18-19]. Furthermore, in neutrophils and monocytes/macrophages, aging modifies receptor expression and intracellular signal transduction, which leads to aberrant chemotaxis, diminished phagocytosis, impaired activation, and decreased pathogen detection. Changes also occur in natural killer (NK) cells, which comprise approximately 15% of peripheral blood lymphocytes. Dysregulated cytokine production and decreased cytotoxicity in aged adults are caused by a decrease in CD56bright NK cells, which have regulatory functions, and an accumulation of highly differentiated CD56dim cells [20-21].

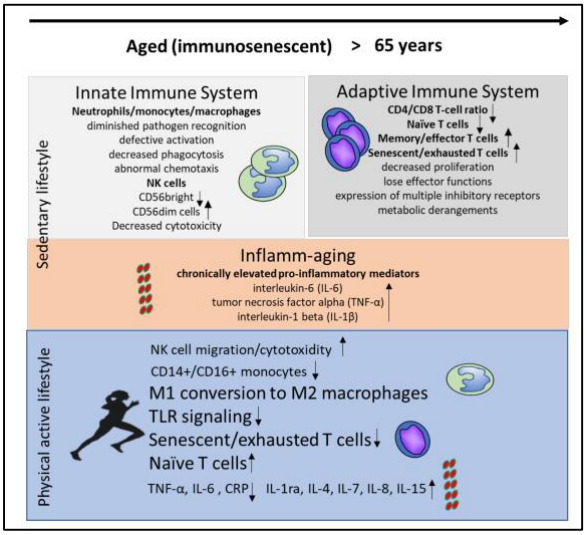

Figure 1: Immune Changes during Age.

While T-cell counts overall stay relatively constant throughout life, aging significantly alters the subpopulations of these cells. In particular, there is a drop in CD4+ T-cells and an increase in CD8+ T-cells, resulting in a lower CD4+/CD8+ ratio, which in some conditions is suggestive of immunosuppression [22]. A decrease in naïve T-cells (expressing CD45RA and CD28) and an increase in more differentiated T-cells are linked to aging. T-cell receptor (TCR) repertoire is reduced as a result of thymic involution and prolonged antigenic stimulation-induced reduction in naïve T-cells. These alterations are accelerated by human cytomegalovirus (HCMV) infection, which affects both naïve CD4+ T-cells and increases CD8+CD28− T-cells specific to HCMV [23]. Senescence and a build-up of highly differentiated CD28− T-cells, especially in CD8+ T-cells, are observed at the age of 65, which results in decreased antigen-induced proliferation [24]. Inflammaging is made worse by senescent T-cells' shorter telomeres, decreased ability to proliferate, and increased synthesis of proinflammatory cytokines [25].

An ongoing, low-grade condition of inflammation that is linked to aging and does not go away is called "inflammatory aging." Cellular immunosenescence is intimately related to this persistent inflammatory illness [26]. Age-related increases in disability and mortality are linked to elevated levels of IL-6 and TNF-α, which are linked to a number of diseases, including cancer, cardiovascular disease, neurological disorders, and type II diabetes [27-28]. One potential predictor of the course of inflammation is the differential regulation of TNF-α and IL-10. The processes underlying age-related inflammation and its links to certain diseases, however, are still complicated and poorly understood [28].

Diet and Immune System Diseases:

It is believed that dietary consumption throughout life—from conception to old age—is essential to the onset, progression, and care of noncommunicable diseases like cancer, diabetes, cardiovascular disease, and allergy disorders. These disorders are distinguished by distinct immunopathological processes, indicating that dietary immunomodulatory variables may have a major impact on the risk and treatment of disease. Immune-mediated disorders are far more common in Westernized nations, where diets tend to be high in total calories, high in fat and added sweets, low in fiber, and with an unbalanced fatty acid composition. An elevated risk of allergy and chronic inflammatory illnesses has been associated with such dietary patterns [29-30]. In an effort to clarify these relationships, a growing corpus of preclinical and clinical studies has examined the effects of certain food components and patterns on immune function markers. We emphasize specific findings on autoimmune and allergic disorders, as well as the possible impacts of diet on disease incidence and management, even if a thorough study of nutritional immunology is outside the purview of this publication.

Dietary Types and Patterns:

The microbiome's synthesis of inflammatory and anti-inflammatory metabolites is influenced by dietary habits [31]. In order to prevent food allergy sensitization, a "tolerant" gut microbiome may downregulate TSLP and IL-33 expression [32]. It has been demonstrated that a Western-style diet heavy in trans and saturated fats and low in fiber affects goblet cell function and thins the mucus layer in mouse models [33]. In both murine models and human research, this dietary pattern can result in decreased microbial diversity by boosting Firmicutes and Proteobacteria and decreasing populations of the phylum Bacteroidetes [34–37]. Although its direct impact in treating food allergies has not been fully explored [38-41], greater dietary diversity has been found to protect allergy disorders [38] and is connected with a more diverse gut flora. Reduced allergy outcomes are linked to diets high in fruits, vegetables, seafood, and fermented foods, such as butyrate and propionate, throughout infancy [42].

Ingredients and Nutrients:

As shown in mouse models, some vitamins, including B9 and A, behave as ligands and affect T-regulatory cell function [43-44]. While long-chain polyunsaturated fatty acids, especially omega-3 fatty acids, reduce allergic inflammation by acting on resolvin D1 and peroxisome proliferator-activated receptors (PPAR) [45], omega-6 fatty acids are known to improve tight junctions in these mice [46]. The FADS1 genotype (rs174550) may also be impacted by these fatty acids. Lower levels of TNF-alpha, IL-6, and high-sensitivity C-reactive protein (hsCRP) have been associated with high levels of docosahexaenoic acid (DHA) [47-48]. Dietary sodium raises the ratio of Th-17 to T-regulatory cells [49-52], while soy isoflavones, such as genistein and daidzein, are linked to lower levels of C-reactive protein (CRP) [53]. In mouse models, amino acids are important for the formation of cell walls [54]. They can also have an impact on the generation of bacterial products that have a beneficial effect on immune-mediated illnesses [54].

Additional Nutritious Elements:

As demonstrated in mouse models, advanced glycosylated end products (AGEs) may have an effect on inflammatory processes and epithelial cell function, specifically altering TSLP and IL-33 [55-57]. AGEs can adversely change the composition of the microbiome [58]. High sugar content, grilling or roasting meats, high fat content, highly processed foods, fruit juices, and high fructose corn syrup are among the factors that cause AGEs [59-62]. Acidic foods and cooking techniques including steaming, boiling, and slow cooking can lower AGE levels [57]. Prebiotics may provide defense against the effects of AGEs by promoting the growth of advantageous microorganisms [63]. In mouse models, fiber

improves intestinal barrier integrity and lowers allergic inflammation by encouraging the fermentation of polysaccharides, which produces short-chain fatty acids (SCFAs) [64-65]. While emulsifiers such as carboxymethylcellulose and polysorbate 80 can disturb the epithelial mucous layer, cause inflammation, and alter the microbial composition, polyphenols have been shown to boost gut microbial diversity [66-67].

Food Production and Preparation:

Foods' inherent microbial load can be impacted by the ways in which they are prepared and processed. Fresh foods have their own microbiome, which includes non-pathogenic bacteria on fruits and vegetables like Lactobacillus plantarum [68-70]. Preliminary data on mice suggests that phthalates, a chemical substance present in food packaging and found in fast foods [71], may decrease gut microbial diversity [72].

Nutrients and Allergy:

Allergy is an immunological response brought on by exposure to different allergens, including foods and environmental stimulants [73]. An array of symptoms, such as anaphylaxis, urticaria, angioedema, allergic rhinoconjunctivitis, allergic asthma, allergic vasculitis, and atopic dermatitis (eczema), can be present in almost every organ system affected by this disorder [74]. Asthma, rhinitis, eczema, and food allergies are the most common allergic disorders [75]. Eczema and food allergies typically manifest in early childhood, and those who are impacted frequently go on to acquire asthma and allergic rhinitis—a progression of symptoms referred to as the "allergic march" [76].

The two main stages of allergic disorders are effector and sensitization. When naïve T cells come into contact with an allergen during the sensitization phase, they develop into T helper (Th) 2 cells, which release IL-4, IL-5, and IL-13. These cytokines induce B lymphocytes to secrete immunoglobulin E (IgE) that is specific to allergens [77]. The sensitization phase is completed by the allergen-specific IgE binding to the high-affinity receptor (FcεRI) on mast cells and basophils. The effector phase begins when the allergen is encountered again. Here, the allergen attaches itself to IgE that is surface-bound, cross-linking FcεRI receptors on mast cells or basophils. This causes the release of mediators that have already been generated, like prostaglandins and histamine, which results in the symptoms that are typical of allergies. The importance of a damaged epithelium barrier in allergic reactions has been brought to light by recent studies. Due to this breach in the barrier, allergens, bacterial toxins, and other particles can enter the body, causing inflammation and the release of cytokines such TSLP, IL-25, IL-31, and IL-33 [78]. Through a complex interaction of innate and adaptive immune responses, these mediators facilitate allergy reactions by increasing the synthesis of allergen-specific IgE, attracting eosinophils and other inflammatory cells, increasing mucus production, and decreasing smooth muscle contraction [76].

Research looking at food variety throughout infancy provides the strongest evidence about the effect of total dietary intake on allergy avoidance. According to the European Academy of Allergy and Clinical Immunology (EAACI), there is little chance of negative consequences from a more varied diet in early life, which may be associated with poorer allergy outcomes in children [79]. Diet diversity is the range of various meals or food groups that are consumed over a certain time period, consider both the frequency of intake and the foods' nutritional worth. Diverse diets are thought to impact allergy outcomes by influencing the immune system and microbiota. As seen in previous allergen tolerance models, this impact may be due to a variety of immunological antigen tolerance mechanisms, such as T and B regulatory cells, immune regulatory cytokines, and decreased IgE antibody production [79]. The scope of current food variety studies has been restricted to early life [79]. According to recent research, there may be a correlation between a decreased chance of food allergies during the first ten years of life and a more varied diet and allergen exposure during the first year of life [21]. On the other hand, nothing is known about the effects of dietary diversity on allergy outcomes at other life phases, such as pregnancy and later life. Research on certain dietary patterns, especially the Mediterranean diet, indicates that following such diets while pregnant may lower the risk of wheezing or eczema in the unborn child. Studies on the impact of food patterns on allergy outcomes throughout infancy or other life stages have not, however, been conducted [79].

Dietary Effect on Immune System:

There is increasing interest in how dietary strategies might enhance immune function in older adults. Nutritional approaches are particularly advantageous for this demographic as they often require less intensive care compared to medical treatments and can promote a more active lifestyle, thereby contributing to overall well-being and active aging. Given that the elderly are more prone to poor nutritional status, which further exacerbates their already compromised immune function, recent advances in this field are critical. This review will concentrate on essential amino acid tryptophan, n-3 polyunsaturated fatty acids (PUFAs), and probiotics, with a specific focus on the kynurenine pathway due to its significant role in linking kynurenine metabolism to inflammatory responses.

The Essential Amino Acid Tryptophan:

Tryptophan, an essential amino acid found in protein-rich foods such as eggs, fish, dairy products, legumes, and meat, plays a crucial role in various physiological processes [80]. Its levels in plasma are regulated by dietary intake and its role in protein biosynthesis. Tryptophan is a precursor for serotonin,

making its availability critical for cognitive function and mood [81]. The ratio of tryptophan to other large neutral amino acids (LNAAs) in the blood can indicate tryptophan availability for serotonin synthesis. More importantly, tryptophan metabolism is essential for immune system regulation [82]. The kynurenine pathway is the primary route of tryptophan degradation, with over 95% of free tryptophan undergoing metabolism via this pathway [83]. This degradation is facilitated by the enzymes indoleamine-2,3-dioxygenase (IDO) and tryptophan-2,3-dioxygenase (TDO). TDO is predominantly hepatic and activated by corticosteroids, whereas IDO is widely distributed and inducible by inflammatory stimuli. Notably, the Th1-type cytokine interferon-gamma (IFN-γ) can trigger various biochemical pathways, including tryptophan degradation [84]. Research indicates that the elderly and individuals with heightened proinflammatory immune activation exhibit increased tryptophan breakdown rates [85-86].

Elevated kynurenine/tryptophan ratios, reflecting IDO activity, are observed in these populations. Although kynurenine metabolites are often studied in relation to the brain, they can influence multiple body systems, inducing both local and systemic adaptations [83]. Chronic low-grade inflammation can increase circulating kynurenine levels, leading to the accumulation of neurotoxic compounds and disruption of neurotransmitter receptors, which can affect cognition and mood [84-87]. Regular physical activity enhances anti-inflammatory capacity by inducing anti-inflammatory cytokines and reducing proinflammatory cytokines. Exercise has been shown to lower IDO activity by promoting anti-inflammation. Furthermore, a preclinical study by Agudelo and colleagues revealed that exercise stimulates the expression of peroxisome proliferator-activated receptor gamma coactivator 1-alpha-1 (PGC-1α1), which in turn enhances the expression of kynurenine aminotransferases (KATs) in skeletal muscle [88]. KATs degrade kynurenine into kynurenic acid, a compound that does not cross the blood–brain barrier, thus limiting central nervous system exposure to excess kynurenine and potentially benefiting mood and cognition. Kynurenine metabolites also significantly impact the immune system. The activation of IDO, a key defense mechanism in cell-mediated immunity, is primarily driven by IFN-γ. Beyond its role in innate immunity, the kynurenine pathway also contributes to immunosuppressive and anti-inflammatory activities, mainly through T-cells of the adaptive immune system [85]. Kynurenine promotes the development of regulatory T-cells (Tregs), and some tryptophan metabolites, such as 3-hydroxyanthranilic acid and quinolinic acid, selectively induce apoptosis in Th1 cells while sparing Th2 cells [89]. This creates a negative feedback loop that helps prevent excessive immune responses and fosters an immunotolerant state. Emerging evidence suggests that gut microbiota influence kynurenine pathway metabolism, potentially affecting brain function and behavior as well as local gastrointestinal function. Thus, alterations in the microbiome could impact the gut–brain axis through changes in microbial composition, tryptophan metabolism, immune activation, vagus nerve signaling, and the production of microbial neuroactive metabolites [90-91].

It is increasingly recognized that dietary composition and lifestyle changes, such as physical exercise and weight loss, can influence tryptophan availability and kynurenine pathway metabolism [92–96]. Despite this, the impact of dietary tryptophan intake on the immune system of older individuals remains poorly understood. Recent research explored the effects of a combined exercise and protein intervention on the kynurenine/tryptophan ratio and neopterin concentrations in older patients recovering from hip fractures [97]. This perioperative nutritional intervention aimed to improve immune system response during the early rehabilitation period, particularly since many patients in this group were malnourished, which negatively impacts outcomes [98].

The study revealed that older hip fracture patients exhibited greater immune activation compared to healthy elderly individuals. However, protein enrichment (targeting a consumption of 1.2 g protein/kg body weight per day) did not mitigate the Th1-type immune response during hospitalization. This suggests that the lower tryptophan levels observed in these patients were not due to insufficient dietary intake, which was well above the recommended 250–425 mg/day, but rather due to immune activation and inflammation. Tryptophan levels were found to correlate with IDO activity, neopterin concentrations, and serum C-reactive protein levels, aligning with earlier findings that inflammation upregulates IDO activity, increasing tryptophan catabolism via the kynurenine pathway [99]. Conversely, in inflammatory arthritis and similar disorders, kynurenine has been shown to protect against disease development, while IDO inhibition or deletion exacerbates severity [100].

In hemodialysis patients, low tryptophan levels could not be attributed to high IDO activity or an inflammatory state. Moreover, there was no correlation between dietary tryptophan intake and plasma tryptophan, nor with all-cause mortality, suggesting that plasma albumin may be a more significant determinant of survival during dialysis [101]. Given that most individuals, including older adults and patients, consume adequate amounts of tryptophan, the presumed benefits of a diet rich in tryptophan and antioxidants are likely not due to increased tryptophan availability, as previously suggested based on in vitro studies [81]. Further research is needed to clarify the biological roles of tryptophan and related kynurenine metabolites in the diet. There are limited studies examining tryptophan

in both diet and plasma. As tryptophan availability is influenced by free albumin-binding sites, exploring fatty acid profiles for potential correlations could be beneficial. Additionally, understanding how dietary tryptophan is absorbed in the gut and the role of intestinal microbiota in regulating tryptophan availability and kynurenine metabolism will enhance our knowledge of environmental factors and host-microbiome interactions.

Unsaturated Fatty Acids:

Chronic immunological activation increases with age and is a factor in diseases such as sarcopenia, where proinflammatory cytokines impair muscle metabolism [102-103]. According to recent research, older people's handgrip strength is correlated with greater levels of inflammatory markers, which suggests inflammation may play a role in muscle weakness [104]. Nevertheless, neopterin levels, a measure of immunological activity, have been connected to decreases in muscle strength gains brought about by exercise and protein supplements [97]. Omega-3 polyunsaturated fatty acids (PUFAs) have been shown to have anti-inflammatory and immune-stimulating actions, making them attractive candidates as therapeutic agents for sarcopenia. Because of their effects on T-cell proliferation, eicosanoid synthesis, and leukocyte function, dietary intake of n-3 PUFAs has been linked to lower inflammation [105]. Combining n-3 PUFAs with exercise has produced encouraging results, even though n-3 PUFA supplementation alone usually has negligible impact on muscle development and function when compared to resistance training [106-108]. For instance, a study that combined an n-3 PUFA-rich diet with increasing resistance training showed decreased inflammatory markers and enhanced muscle growth. In particular, the proinflammatory cytokine IL-1β was downregulated and the regulator of cellular development, mechanistic Target of Rapamycin (mTOR), was increased in the skeletal muscle of older women following six months of training in conjunction with an n-3 PUFA diet [109].

There is little information on how n-3 PUFAs affect the metabolites of the kynurenine pathway. The Western Norway B-Vitamin Intervention Trial investigated the connection between plasma concentrations of kynurenines, neopterin, and the kynurenine/tryptophan ratio in patients with coronary artery disease and dietary intake of fish or n-3 PUFAs. Higher intakes of n-3 PUFAs were inversely correlated with neopterin levels and the kynurenine/tryptophan ratio, however the correlations were weak, indicating a possible reduction in immunological activation [110-111]. Significant improvements in hydroxyproline and muscle protein synthesis were observed in older persons in a recent study examining the effects of n-3 PUFA supplementation (3.9 g/day over four months) in young and older adults. Moreover, circulating kynurenine levels were decreased by n-3 PUFA supplementation in healthy older adults, who had higher levels than younger people [112-113]. These results support the potential function of n-3 PUFA supplementation in the management of age-related inflammatory diseases by suggesting that it may positively regulate both muscle protein metabolism and immunological activation.

Omega-3 and Omega-6:

Polyunsaturated fatty acids (PUFAs) from the omega-6 and omega-3 series are crucial for the initiation and resolution of immune responses. These fatty acids serve as substrates for the synthesis of signaling molecules such as eicosanoids and docosanoids, which play a key role in modulating immune function [114-115]. Key PUFAs include linoleic acid (18:2n-6) and alpha-linolenic acid (18:3n-3), along with their longer-chain derivatives such as arachidonic acid (20:4n-6), eicosapentaenoic acid (20:5n-3), and docosahexaenoic acid (22:6n-3). These longer-chain omega-3 PUFAs (LCn3PUFAs) have generated significant interest due to their potential to enrich immune cells, reduce membrane arachidonic acid levels, and antagonize arachidonic acid metabolism.

Several eicosanoid derivatives of arachidonic acid, such as prostaglandin E2 and 4-series leukotrienes, are involved in promoting allergen sensitization and increasing disease severity. Therefore, adequate LCn3PUFA levels might influence disease risk by affecting early immunological development and established immune-antigen interactions [115]. According to the EAACI position paper, supplementation with LCn3PUFAs might be beneficial for allergy prevention, particularly in individuals with low preexisting levels of these fatty acids [116]. This is especially relevant for pregnant and lactating women, where increased LCn3PUFA levels are associated with reduced risks of atopic dermatitis (AD) and food allergies. However, evidence is heterogeneous and depends on factors such as dosage, baseline LCn3PUFA status, supplementation timing, genetic variants, and microbiome composition [116]. LCn3PUFAs are also explored for their role in managing immune-mediated diseases. They act as substrates for the production of less potent eicosanoids and specialized pro-resolving mediators (SPMs) such as resolvins, protectins, and maresins, which help resolve inflammation and exert analgesic effects [117-118].

In inflammatory bowel diseases (IBD) like Ulcerative Colitis and Crohn's Disease, systematic reviews and meta-analyses show that LCn3PUFA supplementation does not significantly prolong remission and may even have adverse effects such as increased diarrhea and gastrointestinal issues. The complexity of IBD, involving impaired mucosal barriers, diverse immune cells, gut microbiota, and

luminal factors, complicates the influence of LCn3PUFAs [119-125]. Some animal studies suggest that high-dose LCn3PUFAs might worsen disease phenotypes, highlighting the need for further research to optimize dosing and timing [126-127]. In rheumatoid arthritis, LCn3PUFA supplementation shows more promising results. It has been associated with reduced levels of leukotriene B4, a key inflammatory mediator, leading to decreased use of non-steroidal anti-inflammatory drugs (NSAIDs), improved pain, joint tenderness, and better physical function [128-131]. Effective doses are typically in the pharmacological range (>2.5 g/d EPA + DHA), though self-reported intake from food sources also correlates with improved disease outcomes. Nevertheless, further large-scale trials are needed to refine recommendations for LCn3PUFA use, addressing optimal dosing, duration, and the role of these supplements in combination with modern medications [129,132].

Saturated Fats:

Diets high in saturated fats are known to increase inflammation and elevate the risk of chronic inflammatory diseases. Saturated fatty acids, major components of high-fat diets (HFDs), have been extensively studied for their effects on the immune system [133-134]. Mice fed a diet rich in saturated fatty acids for two weeks exhibited heightened inflammatory responses to systemic lipopolysaccharide (LPS) injections, leading to increased endotoxemia and associated mortality [135]. Common saturated fatty acids include palmitic acid, stearic acid, myristic acid, and lauric acid. Studies have shown that:

- **Palmitic Acid:** This fatty acid increases the expression of pro-inflammatory markers such as monocyte chemoattractant protein 1 (Mcp1), IL-6, IL-8, and Cxcl10 in macrophages, and promotes the secretion of neutrophil-attracting nucleotides [136-139]. It also activates TLR4 on dendritic cells, stimulating IL-1b production [140-141]. Additionally, palmitic acid reduces macrophage phagocytic capacity and promotes T cell activation, increasing cytokine secretion including TNFα, IL-1b, IL-2, IL-6, IL-8, and IL-10 [142-146].
- **Myristic Acid:** While it increases Mcp1 expression in macrophages, its effects are less pronounced compared to palmitic acid [137].

Saturated fatty acids, particularly palmitic acid, can activate inflammatory pathways through TLR4, NF-κB, and NLRP3, though recent evidence suggests that these fatty acids may not directly activate TLR4 but rather induce inflammation by altering macrophage lipidome and phenotype [141, 147-150]. Palmitic acid, for instance, can change macrophage lipid composition, decreasing phosphatidylcholines and increasing phosphatidylethanolamines and ceramides, which affects macrophage function and promotes M1 polarization [150]. Other saturated fatty acids like lauric acid and stearic acid also contribute to inflammation, both dependently and independently of TLR signaling [151-152]. Saturated fatty acids influence various immune cells across the innate, adaptive, and tissue-specific immune systems. They increase M1 macrophage activation, cytokine production, and nucleotide release, while reducing macrophage phagocytic capacity and natural killer cell activity [136–139,140,153]. In adaptive immunity, saturated fatty acids elevate T-cell cytokine production, although their effects on B-cells remain less understood. For individuals with chronic inflammatory diseases, limiting saturated fat intake may help mitigate pro-inflammatory immune responses.

Sterols:

Excess cholesterol, similar to saturated fat, can activate pro-inflammatory immune cells and impact both innate and adaptive immune systems. Cholesterol influences inflammatory signaling by integrating into lipid rafts, which support TLR4 complex formation [154,155].

Effects on Immune Function

Excess dietary cholesterol has been shown to:

- **Macrophages:** Increase infiltration and accumulation in adipose tissue, contributing to systemic inflammation [156-157].
- **Mast Cells:** Promote systemic activation and foam cell formation [159,160]. A high-cholesterol Western diet has been associated with increased mast cell activation and subsequent uptake of LDL-C by macrophages.
- **T Cells:** Elevated membrane cholesterol content in T cells is linked to an enhanced inflammatory response [161].

While cholesterol metabolism's role in lymphocyte function has been reviewed [162-164], the specific impact of dietary cholesterol on lymphocyte functions and proliferation remains an area needing further research. Cholesterol, like saturated fats, affects immune cell function and systemic inflammation. It contributes to macrophage infiltration, mast cell activation, and T-cell inflammatory responses. The impact of dietary cholesterol on lymphocyte proliferation and function is less well-documented, suggesting a need for more research in this area.

Fibers and Immune System:

Dietary fibers are non-digestible carbohydrates that are present in fruits, vegetables, and grains and provide energy to gut flora. Short-chain fatty acids (SCFAs), which are essential for preserving gut health and general wellbeing, are produced when these bacteria digest fibers. Because they improve the function of the epithelial barrier, decrease pathogen-induced cytotoxicity, and stop pathogenic bacteria from colonizing the colon, fibers are important for preserving intestinal homeostasis. Studies reveal that a

diet rich in fiber encourages the formation of SCFA and microbial diversity, both of which can reduce the incidence of Crohn's disease and colon cancer [165-166]. Because diminished microbial diversity causes altered metabolic pathways in disorders such cystic fibrosis and asthma, SCFAs taken into the bloodstream may potentially prevent these conditions [167-168]. Consuming fiber over an extended period of time has been linked to better lung function and a decreased chance of developing chronic obstructive pulmonary disease (COPD) [169-170]. Dietary fibers can potentially have a favorable effect on the gut-brain axis. Research has demonstrated that supplements such as human milk oligosaccharides or glucose-oligosaccharides can influence hunger through regulatory neuropeptides and lessen anxiety in individuals with irritable bowel syndrome [171-172]. Furthermore, the benefits of fiber on metabolic syndrome are highlighted by the association between a high fiber intake (30 g/day) and a lower risk of type 2 diabetes and cardiovascular disease [173-175]. Fiber influences immunological-mediated illnesses by interacting with G-protein coupled receptors (GPRs), which are expressed on immune cells and include GPR41, GPR43, and GPR109A [176-178]. Histone deacetylase (HDAC) activity can be inhibited by SCFAs such as acetate and butyrate, which can affect chromatin structure and the epigenetic state of cells [176-179]. The information now available indicates that HDAC inhibition in epithelial cells is essential for preserving barrier function and regulating immunological responses, even if further study is required to completely comprehend these pathways [180]. A possible method of preventing disease is including enough amounts of fiber in diets. According to current recommendations, one should consume 25–31 g of fiber per day. Personalized strategies are required, though, as high-fiber diets have the potential to have negative consequences, including diarrhea, constipation, stomachaches, and flatulence, particularly in people with certain medical disorders such inflammatory bowel disease [181]. Optimizing health outcomes will require educating adults and children on the value of fiber and tailoring dietary recommendations to each person's requirements.

Diet, Probiotics, Gut Microbiota, and Immune System:

Accumulating evidence suggests a significant link between gut microbiota and health during the aging process. As individuals age, disturbances in the gut microbiome often result in chronic inflammation, primarily due to impairments in the mucosal barrier. This inflammation can impact various metabolic organs, such as the liver and adipose tissue, contributing to metabolic inflammation. Additionally, aging affects barrier function and nutrient requirements, which can influence skeletal muscle composition and function [182].

Diet, Exercise, and Gut Microbiota:

Diet and exercise have been shown to modify the composition and diversity of gut microbiota [183–185], potentially enhancing both gut and systemic immune functions. Strategies to address metabolic inflammation linked to gut microbiome alterations may include:

- **Time-Restricted Feeding:** Can influence metabolic processes and inflammation [186].
- **High-Fiber Diets:** Fiber intake promotes a healthy gut microbiome and reduces inflammation [187].
- **Low-Carbohydrate Diets:** Restricting carbohydrates can also mitigate inflammation [188,189].
- **n-3 PUFA Supplementation:** Omega-3 fatty acids have anti-inflammatory properties [190].
- **Kynurenic Acid:** A metabolite of the kynurenine pathway activated by exercise, promotes lipid metabolism and anti-inflammatory responses in adipose tissue [191].

Probiotics and Immunomodulation:

Probiotics are notable for their immunomodulatory effects, impacting both local and systemic immunity. They modify gut microbiota populations and enhance various aspects of immune function, including:

- **Cytokine Production:** Probiotics can alter cytokine levels, contributing to immune modulation.
- **Natural Killer Cell Activity:** Probiotics increase the cytotoxic activity of natural killer cells.
- **Secretory IgA Levels:** Enhanced levels of secretory immunoglobulin A (IgA) are observed with probiotic use.
- **Resistance to Infections:** Probiotics may enhance resistance to infections [192].

Probiotics also have important anti-inflammatory "tolerogenic" effects, potentially reducing infection severity to non-damaging levels [193]. Evidence suggests:

- **Gastrointestinal Disorders:** Probiotics can improve recovery rates from gastrointestinal disorders and enhance resistance to upper respiratory tract infections (URTIs) in the general population [194,195].
- **Athletes:** Probiotic intake may reduce infection incidence in athletes by modulating gut microbiota and immune functions [196,197].

Recent studies indicate that probiotics might influence tryptophan metabolism. Probiotic supplementation has been associated with reduced exercise-induced tryptophan degradation rates,

possibly due to changes in gut microbiome composition affecting downstream immunoregulatory pathways [198]. While the effect was not statistically significant, daily probiotic intake did reduce URTI incidence. The kynurenine/tryptophan ratio was significantly higher in individuals who developed infections compared to those who did not.

Mechanisms and Optimal Use

Probiotics likely exert their effects through:

- **Direct Interaction with Gut Microbiota:** Modulating gut microbiome composition.
- **Mucosal Immune System Stimulation:** Affecting both gut and systemic immune responses.
- **Immune Signaling:** Enhancing communication between immune cells [199].

A daily dose of approximately 10^10 colony-forming units (CFUs) is generally recommended, though optimal dosage and duration of supplementation remain debated. Research in mice has shown that long-term consumption of fermented milk containing probiotic bacteria maintains intestinal homeostasis without adverse effects [200]. In elderly populations, fermented milk with *Lactobacillus johnsonii* La1 has shown promise in reducing infection rates and improving nutritional and immunological status [201–203].

Interestingly, varying probiotic doses may have different immune effects. For example:

- **High Dose (5 × 10^9 CFUs/day):** Increases activated T-suppressor (CD8+CD25+) and natural killer (CD56+ CD16+) cells.
- **Low Dose (5 × 10^8 CFUs/day):** Increases activated T-helper lymphocytes (CD4+CD25+), B-lymphocytes (CD19+), and antigen-presenting cells (HLA-DR+) [204]. These differing effects suggest that probiotics can have varying immune-enhancing outcomes depending on the dose, potentially leading to better clinical results in elderly individuals.

Novel Association between Diets and Immune system:

Deciphering the complex interaction between diet and immune system aging is crucial to finding dietary components that support longevity and boost immunity, since nutrition plays a critical role in supporting healthy aging. Because systemic senescent T cells are less common in healthy older persons who follow the Mediterranean Diet (MedDiet), this study offers new evidence that a stronger adherence to the diet is associated with a lower immunological age. Following the MedDiet involves consuming higher amounts of dietary fiber, which are mostly found in fruits, vegetables, and grains. Our results are consistent with other studies that show higher fiber intake is associated with improved immune function, decreased production of pro-inflammatory cytokines, and increased dendritic cell release of IL-10 [205]. Gut microbes convert dietary fibers to produce immune-modulatory short-chain fatty acids (SCFAs) with anti-inflammatory properties, like propionate, butyrate, and acetate [206-207].

On the other hand, consuming too much saturated fat—found in most Western diets and primarily sourced from red and processed meats—can cause pro-inflammatory reactions. According to this study, dietary cholesterol intake and pro-inflammatory Th17 cells are positively correlated. This relationship makes sense because cholesterol production controls the transcription factor retinoic acid receptor-related orphan receptor γ (RORγ), which promotes CD4 T cell development into Th17 cells [208]. On the other hand, omega-3 polyunsaturated fatty acids (PUFAs), which are present in fish, almonds, avocados, and olive oil, have anti-inflammatory qualities [209]. In line with studies demonstrating that PUFAs attenuate senescence in endothelial cells, our research revealed a correlation between a diet high in PUFA-containing fish and a decrease in systemic senescent T cells in older persons [210]. Furthermore, it was discovered that giving older persons an omega-3 PUFA supplement for four months decreased their levels of circulating IL6 [211].

Micronutrients are essential for preserving the health of the host. Although our study did not find an age-related drop in nutritional consumption, moderate deficits in vitamins B6, B12, C, D, and E, as well as calcium, magnesium, folate, iron, and zinc, are common in older persons [212]. Inadequate intake of these nutrients has been associated with an increased risk of bacterial and viral infections, autoimmunity, and impaired immunological function in the elderly [213]. Important nutrients for thymus homeostasis and thymic hormone production, such as thymulin, which promotes T cell growth, include magnesium, selenium, and vitamin B6 [214]. Therefore, it should come as no surprise that vitamin B6 consumption was linked to slower immunological aging, fewer senescent CD8 T cells, and a higher frequency of circulating naïve CD8 T cells. It has been demonstrated that vitamin E, a fat-soluble antioxidant that is plentiful in the MedDiet, improves immunological functions, especially in elderly people. Our research revealed novel correlations between increased vitamin E intake and a rise in B cells that regulate immunity.

Despite the fact that this study provides insightful mechanistic understanding of immunosenescence and diet-immune interactions, it is crucial to recognize its limitations, which include the use of self-reported dietary data from a limited group of participants who were Caucasian. To better investigate these nutritional and immunological connections, larger and more diverse groups should be included in future study. The statistical analyses and conclusions might have been impacted by the small sample size. Our study of the impact of dietary components on the immune system in older persons highlights the importance of nutrition as a modifiable

element in immunological aging, in addition to genetic and environmental factors influencing immune aging [215]. For the first time, lower immune scores in senior people have been associated with dietary fibers and polyunsaturated fats (PUFAs), which are abundant in the MedDiet. A workable, economical strategy for reducing immunosenescence and encouraging healthy aging is provided by the MedDiet. Even though the MedDiet appears to have the potential to reverse immunological aging, a single dietary strategy might not be enough on its own. It might work better to combine the MedDiet with dietary supplements like vitamin B6. Future intervention studies are advised to assess the influence and effectiveness of multinutrient supplementation on immunological homeostasis in the elderly population. As the recently formed Food4Years Ageing Network [216] demonstrates, such studies should drive policy guidelines and educational campaigns encouraging lifelong healthy eating [217].

Conclusion:

In summary, dietary components such as omega-3 and omega-6 fatty acids, saturated fats, sterols, and dietary fibers significantly influence immune function and inflammation. Omega-3 fatty acids are renowned for their anti-inflammatory effects, offering potential therapeutic benefits for managing inflammatory diseases like rheumatoid arthritis. Their ability to reduce pro-inflammatory eicosanoids and promote the production of specialized pro-resolving mediators underscores their importance in immune regulation. Conversely, omega-6 fatty acids, while essential, can also contribute to inflammatory processes depending on their balance and metabolism. Saturated fats, particularly palmitic acid, are associated with increased inflammation and heightened disease risk. They activate inflammatory pathways through Toll-like receptor 4 (TLR4) and impact macrophage function, leading to enhanced cytokine production and reduced phagocytic capacity. Limiting saturated fat intake may therefore be a crucial strategy in managing chronic inflammatory conditions. Sterols, such as cholesterol, further complicate this balance by influencing inflammatory signaling pathways and immune cell function. Excess dietary cholesterol has been linked to systemic inflammation and altered immune responses, affecting macrophages, mast cells, and T cells. Dietary fibers, on the other hand, play a protective role by promoting gut health and systemic immunity. Their fermentation by gut microbiota produces short-chain fatty acids (SCFAs), which support the intestinal barrier, reduce pathogen-induced inflammation, and contribute to overall immune function. High fiber intake is associated with a lower incidence of inflammatory and metabolic disorders, highlighting the importance of dietary fibers in maintaining immune homeostasis. Probiotics also offer significant immunomodulatory benefits, enhancing gut microbiota diversity and improving immune responses. They can influence cytokine production, natural killer cell activity, and overall resistance to infections. Overall, optimizing dietary intake of these components can be a powerful approach to modulating immune function and managing inflammation. Future research should continue to explore the complex interactions between diet and immune health, with a focus on personalized nutrition strategies to enhance overall health and prevent disease.

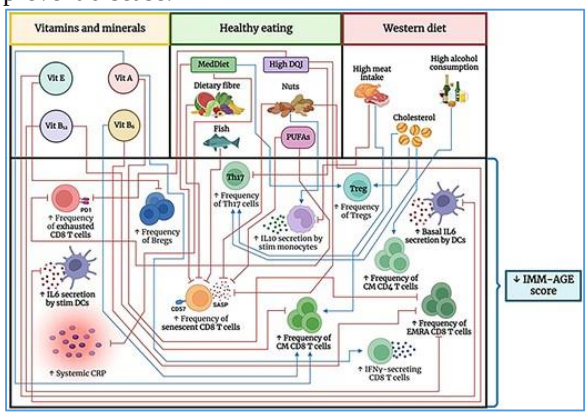

Figure 2: Diet, Nutrition, and Immune Responses.

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