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Micro nutrients as immunomodulators in the ageing population: a focus on inflammation and autoimmunity

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Abstract

Immunosenescence, the slow degradation of immune function over time that is a hallmark and driver of aging, makes older people much more likely to be killed by common infections (such as flu) than young adults, but it also contributes greatly to rates of chronic inflammation in later life. Such micro nutrients are crucial for modulating effective immune responses and their deficiencies have been associated with dysfunctional immunity in the elderly. In this review, we specifically focused on the contribution of major micro nutrients (Vitamins A, D and E, Vitamin C; Zinc and Selenium) as immunomodulators in ageing population especially related to inflame-ageing process including autoimmunity. This review will cover these hologenomic interactions, including how micro nutrients can modulate immune cell function and/or cytokine production to benefit their hosts with healthy mucous-associated immunity along with a sustainable immunologic homeostasis. For example, it points out the modulatory effects of vitamin D on both innate and adaptive immunity, with a specific focus on its ability to suppress pro-inflammatory cytokines synthesis while enhancing regulatory T-cell function. In the same context, also zinc is described as important nutrient for thymic function and T-cell differentiation but exhibits immunomodulatory functions by decreasing inflammation. In addition, the review will go over how micro nutrient deficiencies increase systemic chronic low-grade inflammation and, inflammaging as well as actually enhance autoimmune pathologies in old age. It assesses the potential role of additional targeted nutritional supplementation with micro nutrients to counteract these effects, promoting wider immune resilience in older adults. This review collates the current evidence and highlights the role of adequate micro nutrient intake on inflammation and autoimmunity during ageing, providing plausible origins for nutritional interventions to promote healthy immune aging.

Keywords Immunosenescence, Micronutrients, Immune modulation, Inflammation, Autoimmunity, Ageing population

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Introduction

The immune system undergoes significant changes with aging, known as "immunosenescence," a complex process that impacts both innate and adaptive immunity and plays a crucial role in the development of many chronic diseases in older adults [1]. Aging causes immunosenescence, a complex process that affects innate and adaptive immunity and contributes to chronic diseases in older persons [2–4]. Despite medical advances that have increased life expectancy, aging remains the most significant risk factor for geriatric illnesses. Several major factors causing aging include genomic instability, telomere shortening, epigenetic changes, mitochondrial failure, cellular senescence, and unregulated nutrition sensing [5]. Immunosenescence is also associated with "inflammaging," a type of low-grade, persistent inflammation caused by accumulated stresses. It is an initially adaptive response to infection and tissue injury that promotes pro-inflammatory mediators, resulting in accelerated diseases linked with aging and multimorbidity in the elderly [6–8]. Its contradictory role can occasionally stimulate anti-inflammatory responses, but it also contributes to organ malfunction and mortality in later life [9]. Understanding the relationship between aging, immunological dysregulation, and inflammation could help reduce the burden of chronic diseases in the elderly [10]. Inflammaging is marked by higher plasma levels of pro-inflammatory cytokines, including Interleukin-6 (IL-6), Interleukin-1 (IL-1), and Tumor Necrosis Factor-α (TNF), as well as increased inflammatory markers like C-reactive protein (CRP) and serum amyloid A (A-SAA) [11].

A robust immune defense is crucial for maintaining health and well-being by protecting the body from harmful pathogens and cancerous cells [12]. However, it must be carefully regulated to prevent excessive or self-reactive responses. The immune system encounters a wide range of potential threats, and it relies on a diverse array of immune cells and acellular factors to identify and target these threats while distinguishing them from harmless commensal or beneficial microorganisms [13]. Ideally, the immune system targets the specific vulnerabilities of these invaders. The continuous maintenance and replenishment of the large immune cell population depend significantly on an adequate supply of energy and nutrients [14, 15]. Proper nutrition is crucial, providing the essential fuel for the organism and particularly for the highly active and rapidly dividing immune cells. The adverse effects of malnutrition on infection resistance are well established. In this regard, micronutrients play a critical role in regulating enzyme functions, redox processes, and gene expression [16]. Nevertheless, deficiencies in certain micronutrients are prevalent and not restricted to low-income countries. Micronutrients are crucial for the immune system at all stages of life. Essential micronutrients for maintaining immune competence include vitamins A, C, D, E, B2, B6, and B12, folic acid, beta-carotene, iron, selenium, and zinc [17–19]. Nutrition, infection, and immunity interact in a bidirectional manner: poor nutrition can impair the immune response, increasing susceptibility to infections, while an inadequate nutritional state can be aggravated by the immune response to infections. It is clear that proper immune function depends on good nutritional status. Micro nutrient deficiencies and suboptimal intakes are prevalent worldwide, and some micronutrients may be more likely to be insufficient at various stages of life.

Recent studies have emphasized the potential of certain micronutrients to act as immunomodulators, which are substances capable of enhancing or suppressing the immune response [20]. This has sparked increased interest in their role in managing inflammation and autoimmunity among the ageing population. Micronutrients such as vitamins D, A, C, and E, zinc, selenium, and omega-3 fatty acids have been shown to effect immune function and inflammation through different mechanisms. For instance, vitamin D has been identified as a regulator of both innate and adaptive immunity [21], while zinc is essential for the development and functioning of immune cells [22]. A well-balanced diet supplies the body with an adequate amount of nutrients. Both deficiencies and excesses in an individual's diet can lead to diseases or abnormal conditions. Poor dietary choices can result in deficiencies of iron, calcium, and iodine. Figure 1 depicts the effects of micronutrient deficiencies on immune function. Minerals such as iron, boron, calcium, cobalt, and phosphorus, as well as vitamins K, E, A, D, and riboflavin, have the potential to help prevent and treat serious conditions like Alzheimer's disease, bone development disorders, osteoporosis, anemia, inflammatory bowel disease, and HIV infections [23–25].

Immune ageing and immunosenescence

Innate immunity plays a crucial role in the immune response, involving various cellular components such as macrophages, NK cells, and neutrophils, which offer a swift, first-line defense against pathogens [26]. The immune system undergoes significant changes as people age and most individuals over 60–65 years old experience some degree of immune dysregulation, making them less capable of responding to immune challenges [27]. This dysregulation is characterized by a gradual loss of lymphoid tissue, particularly in the thymus, which leads to a reduced ability to respond effectively to pathogens, antigens, and mitogens [28, 29]. Furthermore, the aging immune system has a diminished capacity to develop long-term immune memory, resulting in weaker responses to vaccinations and an increased susceptibility to infections. These changes highlight the importance

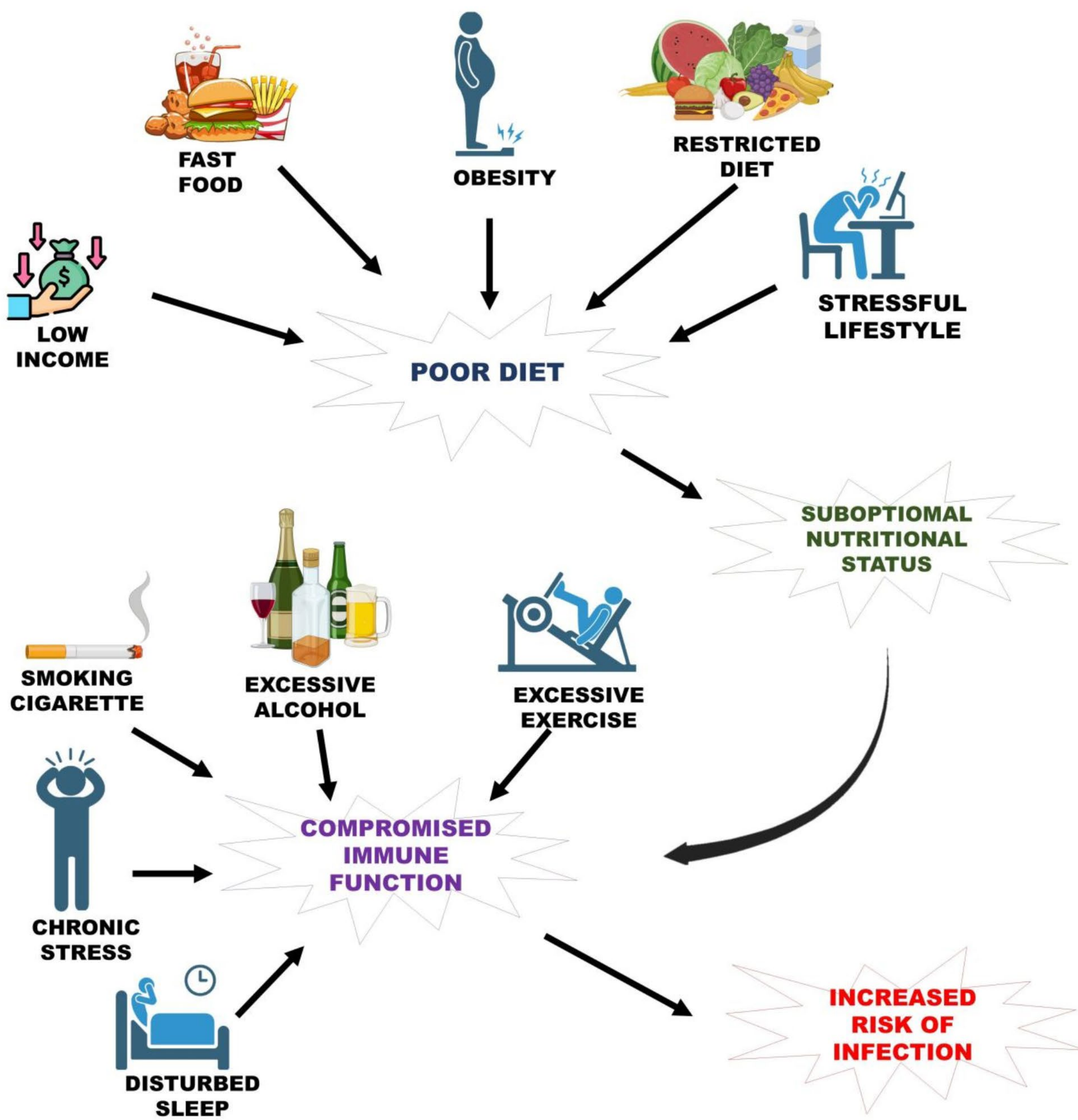

Fig. 1 Effects of micronutrient deficiencies on immune function

of maintaining immune health in older adults through proper nutrition, lifestyle, and medical interventions. After childhood, lymphoid tissues, which play a crucial role in supporting immune responses and producing lymphocytes and antibodies, undergo physical changes [30]. For instance, the thymus, an organ essential for the production and maturation of T cells before birth and throughout childhood, gradually replaces its thymic tissue with adipose tissue after puberty. This results in the thymus appearing larger in children and smaller after adolescence [31].

Cellular and molecular changes

Micronutrients have important roles in influencing changes in cellular and molecular pathways that are required for immunological homeostasis, inflammatory regulation, and autoimmunity [32]. Micronutrients, such as vitamins C and E, selenium, and zinc, are significant drivers of cellular senescence because they act as antioxidants against oxidative stress. Suprathreshold amounts of ROS can damage DNA, lipids, and proteins, activating the NF-κB signaling pathway over time [33]. Chronic activation increases the release of pro-inflammatory cytokines such as IL-6 which contribute to inflammation. Vitamin C reduces ROS and increases the activity of antioxidant enzymes like glutathione peroxidase and Zinc inhibits NADPH oxidase-induced ROS production and preserves redox equilibrium. Immunosenescence is marked by thymic atrophy and decreased naive T-cell production, resulting in an imbalanced T-cell repertoire. It continues to weaken adaptive immunity and has been linked to an increased risk of autoimmunity. Aging significantly impairs immune cell subsets, contributing to immunological dysregulation, inflammation, and autoimmunity [34]. Aging innate immunity has a skewed equilibrium, with neutrophils becoming less proficient at clearing infections and monocytes developing a pro-inflammatory phenotype, resulting in chronic inflammation. The functional part of the thymus gland is significantly diminished through a process known as involution [35, 36]. Thymic involution and poor production from the hematopoietic stem compartment lead to depletion of naïve T and B cells, resulting in a reduction in adaptive immunity [37]. This results in a limited repertoire and poor vaccination immunity. Memory T cells, especially the senescent population, produce pro-inflammatory cytokines, including IL-6 and TNF, which promote autoimmunity. Treg function deficiency may result in lower tolerance to self-antigens. From infancy to adulthood, there is a progressive decline in the percentage and absolute numbers of total lymphocytes, including both T and B cells, in the blood [38]. Despite this overall decline, adults show a notable increase in all T cell subsets (CD3+, CD4+, and CD8+) compared to children. Conversely, the biomarker for B lymphocyte development, CD19, decreases with age [39]. B cell populations may also be changed, resulting in higher autoantibody production and an increased risk of autoimmune disorders. Micronutrient modulators such as zinc, selenium, and vitamin D have previously been shown to modulate aging-associated immunological alterations by restoring cellular homeostasis and reducing inflammation [40]. Such micronutrient therapies hold the possibility of improving immunity as people age. Additionally, there is a significant rise in the number of NK cells during adolescence compared to infancy and childhood, and this increase continues into adulthood compared to infancy, though not necessarily when compared to children. These changes reflect the dynamic nature of immune cell populations throughout different life stages [41]. Micronutrients can influence immune function via epigenetic changes, which change gene expression without altering DNA sequences. Folate provides methyl groups for DNA methylation, which controls the expression of inflammatory genes and Vitamin B12 promotes methylation and genetic stability, which reduces the incidence of autoimmune diseases. Aging alters gut microbiota composition and thus GALT function [42]. Vitamin A improves mucosal immunity by maintaining gut epithelial integrity and producing IgA. Polyphenols from a micronutrient-rich diet increase microbial diversity while decreasing systemic inflammation [43]. Telomeres shrink with each cell division, but inflammation and oxidative stress accelerate this process, causing a large number of immune cells to enter cell senescence. Vitamin E preserves telomere length by lowering oxidative stress. Omega-3 Fatty Acids found in nutrient-dense diets, prevent telomere wear due to general inflammation [44]. Many older people suffer from autoimmune illnesses as a result of a lack of essential micronutrients. Zinc deficiency inhibits Treg function, which promotes autoimmunity in disorders such as rheumatoid arthritis. Vitamin D insufficiency is associated with an increased risk of autoimmune disorders such as multiple sclerosis and systemic lupus erythematosus. Micronutrients are among the most important regulators of immunological function, inflammation, and autoimmunity in the aged. Supplementation may have therapeutic potential by modifying oxidative stress and variables that relate immune cell function to epigenetic regulation and gut microbiota, thereby decreasing immunosenescence, reducing inflammation, and managing autoimmune illnesses [45].

Micronutrients and immune modulation

Micronutrients are vital vitamins and minerals that are important for a number of body processes. Although they are not required in large quantities, they are essential for promoting growth, preserving health, and preventing illnesses. Even though micronutrients are only needed in trace levels, they are vital for sustaining optimal health since they include critical vitamins and minerals. Vitamin D is necessary for calcium absorption and bone health; Vitamin E shields cells from damage; Vitamin K is necessary for blood clotting; and Vitamin A supports vision and immunological health [46]. Vitamin C functions as an antioxidant and helps in collagen formation. B vitamins, which include folate, B1, B2, B6, and B12, are important for red blood cell formation, energy production, and cognitive function [47]. Anemia results from iron deficiency, which is necessary for the transportation of oxygen and the synthesis of energy; Calcium is necessary for healthy bones and muscles, and deficiency can lead to osteoporosis [48]. Magnesium plays a key role in many biochemical processes, such as those involving muscles and nerves; potassium aids in maintaining fluid balance and controlling muscle contractions; zinc is necessary for wound healing and the immune system; and iodine is necessary for thyroid function and hormone regulation [49]. Figure 2 depicts the role of micronutrients in the human body. A diverse range of nutrient-dense foods included in a balanced diet are essential for

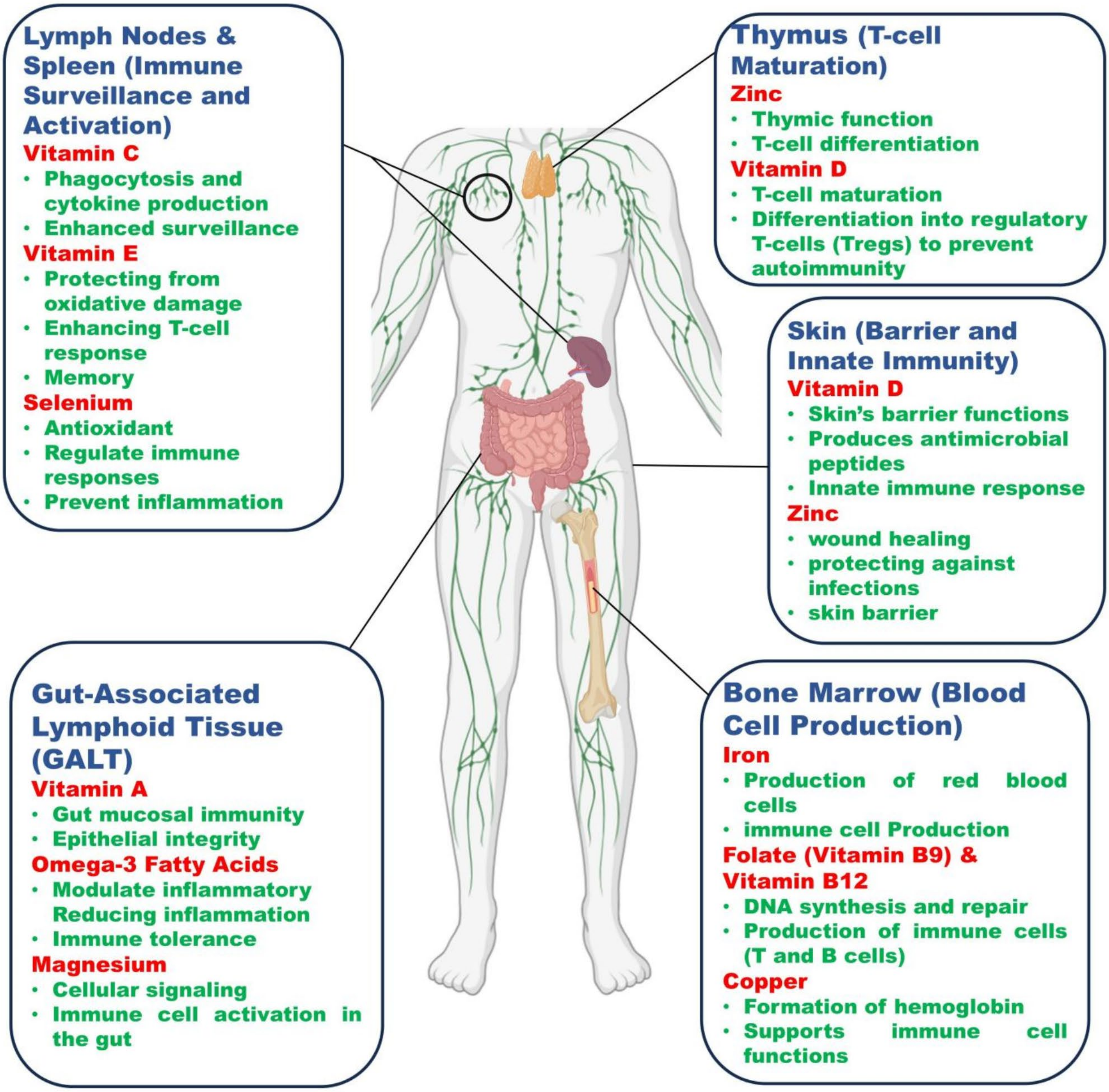

Fig. 2 Micronutrient modulation of immune pathways

avoiding deficiencies and promoting general health. Since every micronutrient has a distinct role in how the body operates, it is critical to have a varied and well-rounded diet in order to meet these nutritional needs [50].

As individuals age, the risk and severity of infections fluctuate depending on the immune system's development, maturation, and decline. Nutrition is one of several factors that influence immune competence. There is a two-way relationship between nutrition, infection, and immunity, where changes in one aspect can have an impact on the others. Resistance to infections can be improved by reintroducing deficient nutrients into the diet and restoring immune function [51]. The specific immune characteristics at each stage of life can influence the type, prevalence, and severity of infections, while inadequate nutrition can weaken the immune system and raise the risk of infections. Several micro nutrients are crucial for maintaining immune competence, including vitamins A, C, D, E, B2, B6, and B12, as well as folic acid, iron, selenium, and zinc. Many micro nutrients contribute, either directly or indirectly, to the biological activity of certain antioxidant enzymes that help maintain immune efficiency and regulate inflammation [52].

Vitamin D: modulation of innate and adaptive immunity

The absorption of calcium, which is necessary for the formation and development of bones, needs vitamin D. It improves bone strength and density. Because bone density normally declines with aged people, there is a greater chance of osteoporosis and fractures. In addition to reducing the chance of fractures and falls, vitamin D contributes to maintaining bone strength [53]. As people age, their immune systems may become less effective. Sufficient amounts of vitamin D helps the immune system, benefiting the body in fighting off infections, and may help strengthen defenses against infections and autoimmune illnesses [54]. Calcitriol acts as a hormone the kidneys secrete it into the bloodstream. As a result, there is insufficient hormonal calcitriol diffusion from the circulation to peripheral target cells to affect their biological function [55]. Thus, the physiological functions of peripheral target cells rely on the intracellular generation of calcitriol [56]. By inhibiting the production of inflammatory cytokines and increasing the production of anti-inflammatory cytokines through the aforementioned pathways, calcitriol reduces inflammation and oxidative stress. The stimulation of immune cells such as T and B cells, macrophages, and dendritic cells, as well as increased synthesis of various antimicrobial peptides and neutralizing antibodies, are among the immunomodulatory effects of vitamin D [57, 58]. The effects of vitamin D on human health and disease are covered in the article. It addresses the skeletal and non-skeletal effects of vitamin D as well as its sources, production, and metabolism. Vitamin D functions as a critical modulator of immunological homeostasis by impacting both arms of the immune system. Getting enough Vitamin D from food, supplements, or sunshine exposure is essential for immune system maintenance and general health as shown in Fig. 3 [59]. The possible therapeutic uses of vitamin D in a number of infectious and autoimmune disorders, including multiple sclerosis, type 1 diabetes, rheumatoid arthritis, TB, and sepsis. The mechanism of vitamin D is shown below.

Vitamin A and E: antioxidant effects and immune regulation

Retinol, another name for vitamin A, is a fat-soluble vitamin that is necessary for many body processes, such as growth, immune system maintenance, vision, and skin health. It comes from plant-based meals as beta-carotene, which the body transforms into vitamin A, or from animal sources (such as meat, fish, poultry, and dairy). For adult males, 900 micrograms should be consumed daily; for adult females, 700 micrograms. Vitamin A deficiency can cause problems such as night blindness, irritable skin, and heightened infection susceptibility. Overconsumption can result in toxicity, which usually manifests as symptoms such as headache and nausea or more serious effects including liver enlargement and bone pain. The normal intake range for toxicity is between 8,000 and 10,000 micrograms per day. potent antioxidant, retinol (vitamin A) reduces the peroxidation of fatty acids and liposomes, outperforming tocopherol as a scavenger in lipid environments. Because of their structural makeup, carotenoids—like lycopene and beta-carotene—are more oxidation resistant than retinoids and are also powerful antioxidants [60]. Their efficiency as antioxidants vary with oxygen content; at high oxygen levels, they may even function as pro-oxidants. This dual activity implies that carotenoids have the ability to act as chemopreventive agents as well as chemotherapeutic drugs that increase oxidative stress to induce cancer cell death in specific situations, such as in cancer cells with high ROS levels. the antioxidant properties of selenium and vitamin E and their role in regulating the health of periparturient dairy cattle. Selenium plays a crucial role in controlling mastitis by reducing oxidative stress and inflammation in the mammary gland [61]. It enhances the antioxidant defense system, decreases somatic cell count, and improves milk quality. Vitamin E, on the other hand, enhances the antioxidant status, energy metabolism, and fat deposition in periparturient dairy cows, thereby improving their overall performance. The article highlights the importance of proper supplementation of these antioxidants in dairy cattle to maintain their health and productivity. the effects of different forms of vitamin E (tocopherols and tocotrienols) on various health conditions, including cancer, cardiovascular disease, and metabolic disorders [62]. Preclinical studies have shown promising results, but human clinical trials have sometimes yielded conflicting findings. In healthy volunteers, vitamin E supplementation has been shown to reduce inflammation, platelet aggregation, and improve vascular function. However, the effects seem to depend on the specific vitamin E form used. For cardiometabolic diseases, vitamin E has been associated with reduced cardiovascular mortality and improved glycemic control, but the evidence is mixed. Potential mechanisms include modulation of oxidative stress, inflammation, and lipid metabolism [63]. The bioavailability and metabolism of vitamin E are influenced by factors like fat content and food matrix, which may contribute to the variable results observed in clinical studies. The effects of vitamin E supplementation on exercise performance and adaptations. It highlights that while antioxidant supplements like vitamin C and E can help reduce muscle damage and oxidative stress during exercise, they may also impair some of the beneficial adaptations to exercise training.

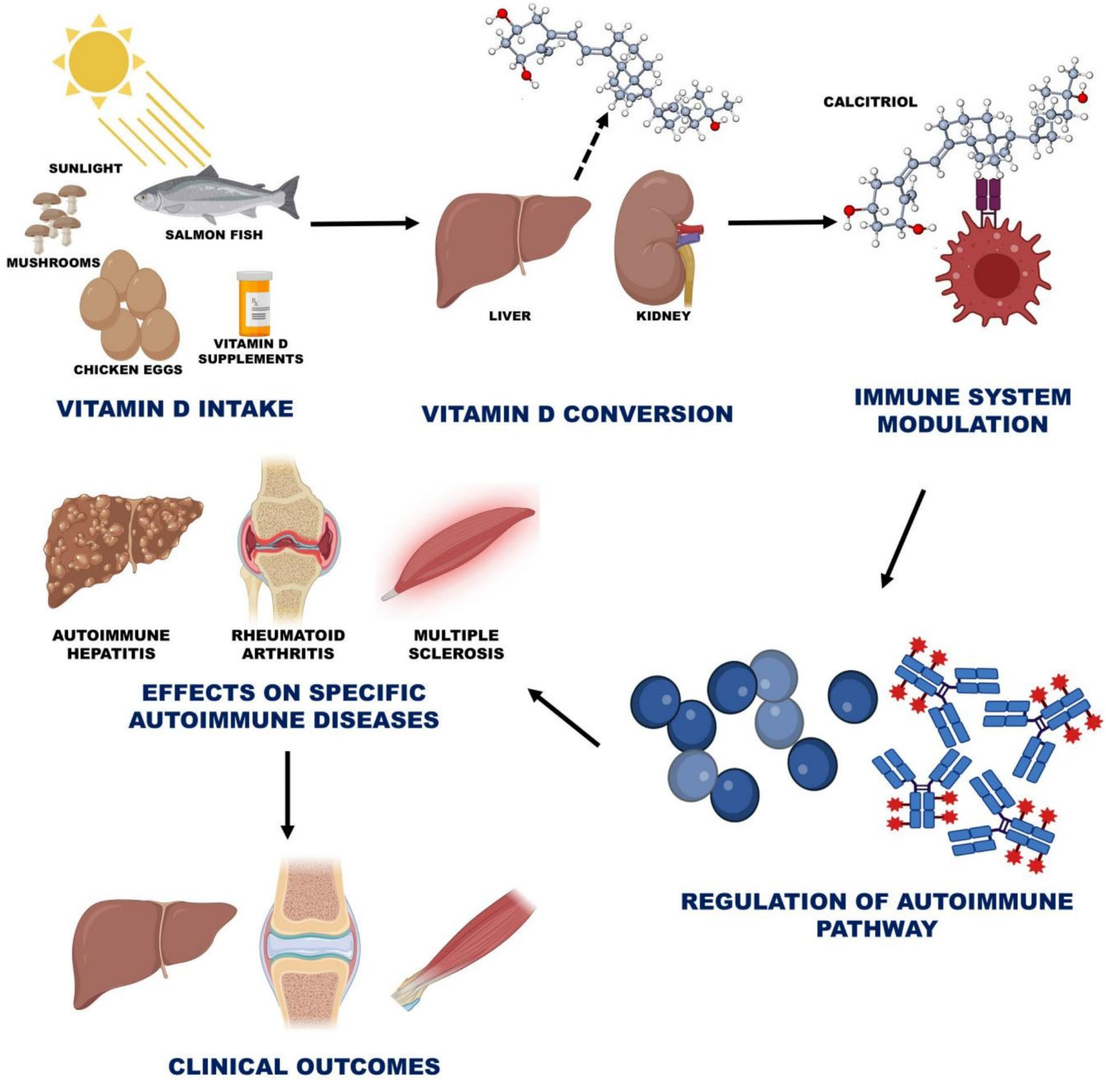

Fig. 3 Mechanism of vitamin D in enhancing human immunity

Vitamin C: immune support and anti-inflammatory actions

Aging is primarily driven by oxidative stress and the overproduction of reactive oxygen species (ROS), which can lead to cellular damage, inflammation, and the development of various age-related diseases. The review highlights several biomarkers and pathways associated with the aging process, including telomere attrition, chromatin disorganization, and impaired cellular signaling [64]. The article emphasizes the antioxidant and free radical scavenging properties of vitamin C, which can help protect cells from oxidative stress and prolong lifespan. The review discusses the mechanisms by which vitamin C can mitigate the negative impacts of aging, including its role in regulating gene expression, modulating cellular signaling pathways, and enhancing the function of the immune system. Vitamin C is an essential nutrient that cannot be synthesized by humans and is required for proper immune function. Vitamin C has several activities that contribute to its immune-modulating effects, including acting as an antioxidant, serving as a cofactor for enzymes involved in collagen and carnitine biosynthesis, and regulating gene expression [65]. Vitamin C is accumulated to high levels in phagocytes and lymphocytes, and it has been shown to enhance various immune functions, such as neutrophil chemotaxis, phagocytosis, and microbial killing, as well as lymphocyte proliferation and differentiation. Vitamin C deficiency is associated with increased susceptibility to infections, and supplementation can help ameliorate respiratory infections. The article also discusses the effects of vitamin C on cytokine production, neutrophil extracellular trap (NET) formation, and epithelial barrier function [66].

Vitamin C is a well-known antioxidant that can act as a cofactor for several enzymes involved in the immune system. It orchestrates the function of both the innate and adaptive immune systems by supporting various aspects such as epithelial barrier function, chemotaxis and antimicrobial activities of phagocyte cells, natural killer (NK) cell functions, and lymphocyte proliferation and differentiation [67]. Severe vitamin C deficiency has been associated with impairments in immunity and increased susceptibility to infections, while vitamin C supplementation can help prevent and treat infections. However, acute infections can also deplete the body's stores of vitamin C.

Zinc: thymic function, T-cell differentiation, and immune resilience

Zinc is a crucial trace element for the immune system, and its deficiency negatively impacts various aspects of both innate and adaptive immunity. Notably, there are significant similarities between the immunological changes observed in aging and those seen in zinc deficiency. These include reduced thymus activity and thymic hormone production, a shift in the balance of T helper cells towards T helper type 2 dominance, weakened vaccine response, and impaired innate immune cell function. Numerous studies have also documented a decline in zinc levels as individuals age [68]. Zinc primarily functions in a structural capacity, playing a key role in zinc finger motifs and DNA-binding domains found in numerous proteins, peptides, enzymes, hormones, transcription factors, and growth factors, including cytokines. These elements are crucial for maintaining the body's homeostatic mechanisms and influence processes such as gene transcription. inc supplementation in vitro can initiate key processes involved in the recruitment of leukocytes to infection sites. For instance, elevated zinc levels stimulate the chemotaxis of polymorphonuclear cells and enhance the adhesion of myelomonocytic cells [69]. Conversely, zinc deficiency in vivo leads to impaired phagocytosis, diminished parasite killing, reduced oxidative bursts in monocytes and neutrophils, and decreased natural killer (NK) cell activity. Additionally, zinc is crucial for the recognition of HLA-C molecules by killer cell inhibitory receptors on NK cells. However, this requirement pertains solely to inhibitory effects, not stimulatory ones. As a result, zinc deficiency might enhance nonspecific killing by NK cells, though this is mitigated by a decline in NK cell lytic activity observed in zinc-deficient patients. Zinc deficiency prominently impairs T cell function through various mechanisms. Thymulin, a hormone produced by thymic epithelial cells, depends on zinc as a cofactor and exists in two forms in the plasma: an active zinc-bound form and an inactive zinc-free form. Thymulin is crucial for the differentiation and function of T cells, which may account for some of the observed impacts of zinc deficiency on T cell function [70]. Studies in mice have shown that zinc deprivation leads to reduced levels of biologically active thymulin in the blood. This effect occurs even without thymic atrophy, and thymulin activity can be restored by adding zinc to the serum in vitro, demonstrating a direct dependence on serum zinc. Similarly, in humans with mild zinc deficiency, thymulin activity is diminished, with zinc supplementation both in vitro and in vivo showing comparable effects. In the United States, the recommended daily allowance (RDA) for zinc is 11 mg/day for men and 8 mg/day for women aged 19 and older, with no specific recommendations for the elderly [71]. Consuming less than the RDA may suggest a potential zinc deficiency, but it is important to note that various factors influence zinc status and the body may adjust its metabolism to lower zinc intake. Table 1 shows key micronutrients and their immune functions.

Micro-nutrients, inflammation, and autoimmunity

Autoimmune disorders affect 5–8% of the world population, and there is a need to understand the underlying mechanisms that trigger these conditions. The immune system's energy varies for people of every age. As people get old their immune system is also low and cells like T cells, B cells, and phagocytes are less. The immune system is weak and less effective. This condition makes old people more infected like autoimmune disorder and cancer. Aging is linked with chronic inflammation and can impair the immune system. The body was also very weak [88]. The play main role that diet plays in maintaining a balanced immune system, particularly in terms of zinc and vitamin D. Vitamin regulates the immune system and is important as an inappropriate immune response can lead to tissue damage [89].

A frequent indication of aging is inflammation the elderly typically have two to four times higher levels of circulating pro-inflammatory cytokines (like interleukin (IL)-6 and TNF and acute phase proteins (like C-reactive protein (CRP) and serum amyloid A (SAA)) than the young. There are multiple possible processes responsible for the inflammation linked to aging [90]. Many processes probably contribute to inflammation linked with

Table 1 Key micronutrients and their immune functions

Sl. No.	Micronutrient	Source	Mechanism of Action in Immune Function	Target Immune Cells or Molecules	Impact on Inflammation and Autoimmunity	References
1	Vitamin D	Sunlight, fortified foods, fish oils	Promotes antimicrobial peptides; reduces Th1 and Th17 responses	Dendritic cells, T-cells (Th1, Th17)	Reduces chronic inflammation;	[72]
2	Vitamin A	Liver, carrots, sweet potatoes	Supports epithelial integrity; promotes T reg cells	T-cells, B-cells, epithelial cells	Modulates immune responses; reduces susceptibility to infections	[73]
3	Vitamin E	Nuts, seeds, green leafy vegetables	Antioxidant protection of immune cells; modulates T-cell signaling	T-cells, NK cells	Reduces oxidative stress; improves function in autoimmune conditions	[74]
4	Vitamin C	Citrus fruits, tomatoes, potatoes	Enhances phagocytosis; supports collagen synthesis	Phagocytes, T-cells	Reduces pro-inflammatory cytokines; supports immune resilience	[75]
5	Zinc	Meat, shellfish, legumes	Essential for thymic function;	Thymus gland, T-cells (CD4+), cytokines (IL-2)	Enhances immune resilience; reduces autoimmunity risk	[76]
6	Selenium	Brazil nuts, seafood, eggs	Cofactor for antioxidant enzymes; prevents excessive inflammation	Antioxidant enzymes, T-cells, NK cells	Reduces oxidative stress; modulates immune responses	[77]
7	Omega-3 Fatty Acids	Fatty fish, flaxseeds, walnuts	Modulates eicosanoid production; reduces pro-inflammatory cytokines	Membrane phospholipids, T-cells, B-cells, cytokines (IL-1, IL-6, TNF)	Anti-inflammatory; supports immune regulation in autoimmunity	[78]
8	Iron	Red meat, beans, fortified cereals	Essential for hemoglobin production; supports immune cell function	T-cells, macrophages, NK cells	Iron deficiency impairs immune function; excess iron can exacerbate inflammation	[79]
9	Copper	Shellfish, nuts, seeds	Involved in the formation of hemoglobin; modulates immune responses	Macrophages, neutrophils, T-cells	Copper deficiency impairs immune responses; excess can be toxic	[80]
10	Magnesium	Leafy greens, nuts, whole grains	Modulates cellular signaling in immune cells; necessary for DNA synthesis	T-cells, B-cells, macrophages	Deficiency linked to chronic inflammation; supports immune homeostasis	[81]
11	Folate (Vitamin B9)	Leafy greens, legumes, fortified cereals	Essential for DNA synthesis and repair; supports T-cell function	T-cells, B-cells, DNA repair enzymes	Deficiency linked to impaired immune responses and increased autoimmunity	[82]
12	Vitamin B6	Poultry, fish, potatoes	Supports amino acid metabolism and neurotransmitter synthesis; modulates immune responses	T-cells, B-cells, cytokines (IL-2, IL-4)	Deficiency impairs immune function; excess may lead to neurological issues	[83]
13	Vitamin B12	Meat, dairy products, fortified cereals	Supports red blood cell production;	Red blood cells, nerve cells, DNA synthesis enzymes	Deficiency leads to anemia and impaired immunity; excess rare but can cause harm	[84]
14	Calcium	Dairy products, fortified plant milks	Necessary for signaling in immune cells; supports bone health	T-cells, B-cells, macrophages	Deficiency affects bone health and may impair immune function	[85]
15	Iodine	Iodized salt, seafood, dairy products	Crucial for thyroid hormone production; supports metabolism and immune function	Thyroid gland, T-cells, B-cells	Deficiency linked to thyroid dysfunction, impacting overall immune function	[86]
16	Manganese	Whole grains, nuts, leafy vegetables	Cofactor for enzymes involved in immune responses and antioxidant defense	Superoxide dismutase, macrophages, neutrophils	Supports antioxidant defenses; deficiency impairs immune cell function	[87]

aging. As with all other physiological systems, there are notable declines in immune function with aging that promote inflammation; hence, it has been hypothesised that the excessive inflammation in ageing may also be caused by an exaggerated acute-phase response either a cause or a result of a delayed recovery from an insult that promotes inflammation [91].

Older people have more autoimmunity but less frequency of autoimmune illnesses. One possible reason for this could be the development of many extremely unique protective regulatory mechanisms seen in the elderly. Especially noteworthy is the increased synthesis of peripheral T-regulating cells. the choice of T cells with higher affinity to self-antigens would help to explain the common development of autoimmunity in the elderly. These cells were proven to have more capacity to be pro-inflammatory, hence aggravating autoimmunity. Thymic T-regulatory cell output reduces with aging in line with thymic ability loss to produce fresh T cells. But age-related increase in peripheral CD4+CD25 T-regulatory cells helps to balance the above described autoimmunity and stop the development of autoimmune disorders [92]. Table 2 illustrates micronutrient deficiencies and their effects on immune function.

Modulation of cytokine production

Depending on the quantities and circumstances in which they are generated, the pro-inflammatory cytokines and oxidant molecules generated during the inflammatory response—which comes after infection and injury—may be advantageous or harmful to the patient [93]. Sepsis and inflammatory diseases have been linked to abnormal or excessive production. The possibility of cytokine-induced mortality and morbidity rises with the elevation of cytokine production by activation by oxidants. The generation of cytokines and the activities of oxidants are regulated by intricate systems [94]. The former comprise endogenous inhibitors of interleukin (IL)-1 and TNF, acute phase proteins, and hormones of the hypothalamus-pituitary-adrenal axis. The latter group consists of antioxidants that are produced by the body itself, like glutathione, and antioxidants that are found in food, including tocopherols, ascorbates, and cachectins [95]. Cytokine production is altered by nutrients and potency by altering the tissue concentrations of numerous molecules related to the biology of cytokines. This effect is more likely to be caused by changes in eicosanoid production than by changes in membrane fluidity [96]. Increased synthesis and effects of cytokines are the consequence of low antioxidant consumption. The anorexia that follows an injury or infection may be intentional, allowing the substrate to be released from internal sources to support and regulate the inflammatory process. Because they can start and facilitate cell-to-cell contact, soluble substances called cytokines are essential to systemic function. Extracellular vesicles (EVs) are a crucial intercellular communication mechanism that has drawn a lot of interest in the last ten years. All cells release extracellular vesicles (EVs) in normal physiological conditions, during activation and resting phases, and

Table 2 Micronutrient deficiencies and their effects on immune function

Sl. No.	Micronutrient	Deficiency Prevalence in Elderly (%)	Impact on Immune Function	Immune Cells Affected	Associated Autoimmune/Inflammatory Conditions	References
1	Vitamin D	40–80%	Impaired T-cell activation, reduced pathogen defense	T-cells, macrophages	Rheumatoid arthritis, multiple sclerosis	[57]
2	Vitamin A	15–30%	Impaired mucosal immunity,	B-cells, epithelial cells	Increased susceptibility to infections	[73]
3	Vitamin E	10–20%	Decreased antioxidant defenses, increased oxidative stress	T-cells, NK cells	Chronic inflammation, atherosclerosis	[74]
4	Vitamin C	20–50%	Reduced neutrophil and macrophage activity	Neutrophils, macrophages	Increased infection risk, weakened wound healing	[75]
5	Zinc	30–50%	Impaired thymic function, delayed wound healing	T-cells, thymus	Chronic inflammation, autoimmune disorders	[70]
6	Selenium	15–25%	Decreased antioxidant defense, reduced selenoprotein levels	B-cells, T-cells	Increased oxidative stress, Hashimoto's thyroiditis	[98]
7	Omega-3 Fatty Acids	60–70%	Increased inflammation due to lack of anti-inflammatory lipids	Macrophages, dendritic cells	Cardiovascular diseases, inflammatory bowel disease	[99]
8	Iron	20–40%	Impaired hemoglobin production, reduced oxygen transport	Red blood cells, macrophages	Anemia, fatigue, weakened immunity	[100]
9	Magnesium	30–50%	Increased inflammatory cytokine production	T-cells, macrophages	Cardiovascular diseases, metabolic disorders	[100]
10	Folate	10–20%	Impaired DNA synthesis, reduced cell division	B-cells, T-cells	Cognitive decline, megaloblastic anemia	[82]
11	Calcium	40–60%	altered immune signaling	Bone marrow cells, T-cells	Osteoporosis, inflammatory conditions	[16]
12	Vitamin B12	20–30%	Impaired DNA synthesis, nerve damage	Nerve cells, bone marrow cells	Cognitive decline, pernicious anemia	[84]
13	Copper	5–15%	Impaired oxidative stress defense, poor iron absorption	Red blood cells, macrophages	Anemia, immune suppression	[80]
14	Manganese	5–10%	Reduced antioxidant enzyme function	Macrophages, neutrophils	Osteoporosis, poor wound healing	[87]
15	Iodine	10–20%	Impaired thyroid function, reduced metabolic rate	Thyroid cells	Hypothyroidism, autoimmune thyroid diseases	[86]

illness [97]. A growing body suggests that cytokines can be packaged into extracellular vesicles (EVs) and that these EVs can be controlled by cytokines, both during the packing process and during the condition, and the effectiveness of the treatment was found to have a significant impact on the relationship between particular cytokines. These findings collectively confirm that EV-associated cytokine overload and Secretion can be controlled in a way that depends on the kind of cell and the stimulus in autoimmunity. imbalanced cytokine production may well account for the pattern of immune response which may be observed in the elderly. i.e. a normal or increased humoral response (including autoimmune responses) in the face of a low T cell immune responsiveness.

Interaction with gut microbiota

The human gut microbiota exhibits significant interindividual diversity, which can be attributed to varying exposures to environmental stimuli and the impact of the host phenotype. Habitual eating has a strong influence on the human gut microbiota. Furthermore, the microbiota's makeup is greatly influenced by age and the existence or absence of illnesses. For instance, as we age, our bodies produce more streptococci, staphylococci, enterococci, and enterobacteria, but fewer bifidobacteria overall. The microbiota of older persons living independently and those receiving residential care differs significantly. In light of the gut microbiota's function that age-related alterations in the microbiota are associated with immunosenescence and inflammation via supporting the host immune system. The microbiota and the host-human have a symbiotic relationship in which the latter supplies the microbes with nourishment and defense while the former ensures the synthesis of specific vitamins, defense against pathogen invasion, and the capacity to ferment some indigestible carbohydrates [101]. According to the relationship between nutrition, immunity, and infection, some nutrients and other dietary elements may be able to positively influence immune cell activity, inflammatory responses, and the prognosis and susceptibility to infectious diseases. The immune system and gut microbiome interact in both directions. The gut microbiota may be affected differently by different dietary components. For example, fiber and carbs serve as the main sources of carbon and energy for colonic microbes and are processed by them to produce beneficial metabolites like short-chain fatty acids. These changes have beneficial effects on the intestinal barrier's integrity, motility, satiety, and insulin sensitivity as well as better lipid metabolism and reduced inflammation [102]. Consequently, considering that diet is one of the modifiable factors that has the biggest influence on the composition of the microbiota and that the intestinal microbiota plays a fundamental role in the modulation of the immune response and the onset and progression of pathologies on an autoimmune basis. The gastrointestinal tract's commensal bacteria contribute to the host's immune defense by forming a barrier that prevents infections from entering the body and by producing lactic acid and antimicrobial proteins that can directly stop pathogen growth [103]. Additionally, commensal organisms interact with immunological tissues linked with the gut as well as the host's gut epithelium. These interactions with the host take place either directly between cells or through substances that the bacteria emit (such as short chain fatty acids. Probiotic organisms have been the subject of increased research in this area, and it has been demonstrated that certain lactobacilli and bifidobacteria can improve certain aspects of immunity, such as the body's reaction to vaccinations. These immunological effects imply that altering the gut microbiota—especially with probiotic organisms—may offer some infection protection [104]. Probiotics may help lower the risk or lengthen the course of gastrointestinal infections, according to systematic reviews and meta-analyses. However, there is also evidence that probiotics can lower the incidence of respiratory infections and improve outcomes, especially in children. This impact is probably caused by the so-called gut-lung axis, which describes how changed gut microbiota influences gut-associated immune system cells, which then migrate to the lung-associated immune system to produce advantageous effects. Table 3 represents clinical trials on micronutrient supplementation and immunity in the ageing population.

Challenges and future directions

A major challenge in understanding the regulation of immune function from a basic to a clinical level is complex interplay between nutrition, immunity, and chronic diseases. With advancing age, impairment in the absorption and metabolic processing of essential nutrients such as zinc and selenium leads to deficiencies that further promote immunosenescence and inflammation. Additionally, genetic and lifestyle differences make general dietary recommendations for optimal immune function difficult. There is also a lack of large-scale, longitudinal studies that can clearly establish a link between supplementation with a particular micronutrient and long-term immune benefits, especially among older adults. Besides, ethical concerns and methodological limitations in human trials, such as adherence to supplementation and placebo effects, are significant impediments to the establishment of evidence-based guidelines. Other challenges are the general lack of clarity of the interacting synergistic effects of various micronutrients in immune health support.

Table 3 Clinical trials on micronutrient supplementation and immunity in the ageing population

Sl. No.	Population Characteristics	Micronutrient Supplemented	Immune Markers Measured	Main Outcomes	References
1	Elderly (65+), Healthy	Vitamin D	IL-6, TNF, T-cell count	Reduced IL-6, improved T-cell function	[105]
2	Elderly (70+), Autoimmune	Vitamin A	CRP, T-helper cells	Lower CRP, better T-helper cell activity	[27]
3	Elderly (65+), Frail	Vitamin E	Oxidative stress markers, NK cells	Decreased oxidative stress, increased NK cell activity	[106]
4	Elderly (60+), Rheumatoid Arthritis	Omega-3	Inflammatory cytokines (IL-1, IL-6)	Reduced inflammatory cytokines, improved symptoms	[107]
5	Elderly (65+), Healthy	Zinc	T-cell differentiation, cytokine levels	Enhanced T-cell differentiation, reduced inflammation	[108]
6	Elderly (70+), Diabetes	Selenium	Antioxidant enzyme levels, TNF	Increased antioxidant activity, lower TNF	[109]
7	Elderly (60+), Cardiovascular Disease	Omega-3	IL-6, IL-10, NF-κB	Decreased NF-κB activity	[110]
8	Elderly (65+), Alzheimer's	Vitamin C	Inflammatory cytokines, ROS	Reduced ROS, improved cognitive markers	[110]
9	Elderly (65+), Hypertension	Magnesium	BP, immune cell function	Improved blood pressure, enhanced immune resilience	[106]
10	Elderly (70+), Healthy	Multivitamin (D, C, E, Zinc)	T-cell count, IL-2, TNF	Improved T-cell counts, reduced TNF	[111]
11	Elderly (65+), Osteoporosis	Vitamin D, Calcium	Bone density markers, IL-6	Increased bone density, reduced IL-6	[112]
12	Elderly (60+), Autoimmune	Selenium	CRP, TNF	Lower CRP, reduced TNF levels	[113]
13	Elderly (65+), Frailty	Vitamin E, C	Oxidative stress markers, T-cell function	Reduced oxidative stress, improved immune response	[110]
14	Elderly (65+), Healthy	Zinc	IL-1, IL-6, NK cell function	Lower IL-6, increased NK cell activity	[114]
15	Elderly (60+), Cognitive Decline	Vitamin B12	Cognitive function, IL-1	Improved cognitive function, reduced IL-1 levels	[18]

Conclusion

The immune system undergoes various transformations throughout life, beginning with its development and maturation in childhood, potentially reaching peak efficiency in early adulthood, and progressively declining in most individuals as they age. Each stage of life is characterized by unique immune traits, with distinct factors influencing immune function, leading to variations in the type, frequency, and severity of infections across age groups. A constant factor throughout these stages is the necessity for an adequate intake of micronutrients, which are essential for supporting immune function. Micronutrient deficiencies are prevalent globally, and the likelihood of such deficiencies increases with age. Customized supplementation, tailored to the specific requirements of each age group, may help maintain optimal immune function. Clinical data indicate that micronutrient supplementation can lower the risk and severity of infections and promote faster recovery. However, further research is needed to better understand the effects of micronutrient supplementation on immune function and clinical outcomes. Despite this, current knowledge on the role of micronutrients in immunity, the impact of deficiencies on infection risk and severity, and the global prevalence of inadequate micronutrient levels provides a solid foundation for using targeted micronutrient supplementation to support immune health throughout life.

Abbreviations

A-SAA	Serum amyloid A
ACPA	Anti-citrullinated protein antibodies
ANA	Anti Nuclear Antibodies
B Cells	Bursa Derived Cells
CD^{3+}	Cluster of Differentiation
CMV	Cytomegalovirus
CRP	C-reactive protein
CVD	Cardiovascular disease
DAMP	Damage-associated molecular patterns
DHA	Docosahexaenoic Acid
DNA	Deoyribo Nucleic Acid
EPA	Eicosapentaenoic Acid
EV	Extracellular vesicles
HIV	Human Immunodeficiency Virus
HLA-C	Human Leukocyte Antigen-C
HLA-DR4	Human Leukocyte Antigen- Death Receptor 4
IL	Interleukin
IU	International unit
mcg	Microgram
mg	Milligram
NET	Neutrophil Extracellular Trap
NK	Natural Killer cells
NSAID	Non-steroidal anti-inflammatory drugs
RA	Rheumatoid Arthritis
RCT	Randomized controlled trials
RDA	Recommended daily allowance
ROS	Reactive Oxygen Species
SLE	Systemic Lupus Erythematosus
T Cells	Thymic Cells
Th1	Type 1 T helper cells
Th2	Type 2 T helper cells
TNF	Tumor Necrosis Factor

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