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Review

The immune-nutrition interplay in aging – facts and controversies

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Abstract. Nutrition influences immunity in multiple ways, with different nutrients affecting many immune parameters. Aging also affects immunity, making the outcome of the interplay between nutrition, age and immunity complex. Moreover, a particular nutrient may alter the whole immune constellation as deficiency of one nutrient may affect the proper metabolism of another nutrient and elicit a chain reaction of secondary malnutrition. In this article, we review these interactions and the possible mechanisms mediating such relationships.

Keywords: Nutrition, immunity, immunocompetence, T cells, aging, aging nutrimmunity

List of abbreviations

APC	Antigen Presenting Cells
BMI	Body Mass Index
BMR	Basal Metabolic Rate
CM	Central Memory
CMV	Cytomegalovirus
CR	Caloric Restriction
CRP	C-reactive protein
DTH	Delayed-Type Hypersensitivity
GM-CSF	Granulocyte colony-stimulating factor
IL-1RI	Interleukin 1 receptor, type
I IL-6	Interleukin-6
LBM	Lean Body Mass
IRP	Immune Risk Profile
mTOR	Mammalian target of Rapamycin
MAIT	Mucosal-associated invariant T
MCH	Major Histocompatibility Complex
NK	Natural Killer
PEM	Protein Energy Malnutrition
TCR	T-cell receptor
WEIRD	White, Educated, Industrialized, Rich and Democratic

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1. Introduction

It is well-known that underprivileged people with compromised nutritional status suffer a higher risk of infection [1–3]. However, knowledge of the role that particular nutrients play and the mechanisms involved in immunological defence over the lifespan is relatively sparse and often contentious. Ever since the early 1800's, nutrients have been recognized for their regulatory effects on immune function [4]. Most nutrients are needed for upholding healthy immune functions and deficiency in almost any nutrient will lead to compromised immune functions [5].

For normal immune function, mandatory levels of nutrients range from trace to bulk quantities. Nutrients are generally required to synthesize new molecules during development of immune responses and for cell differentiation that occurs during clonal expansion of adaptive immune cells resulting in large enough numbers of antigen-specific effectors which attack and destroy the invading pathogens.

Impaired immune responses induced by malnutrition can increase susceptibility to infection and illness, which can in turn exacerbate states of malnutrition, for example, by reducing nutrient intake through diminished appetite, impairing nutrient absorption, increasing nutrient losses, or altering the body's metabolism such that nutrient requirements are increased [6]. Thus, states of malnutrition and infection can aggravate each other and lead to the establishment of a vicious circle [1].

Our knowledge of the effects of nutrition on immune function now extends beyond clinical nutrient deficiency. A growing body of literature demonstrates the immune benefits of increasing the intake of specific nutrients. This article will review our current understanding of the role of several nutrients in maintaining host immune defence. An inadequate status of some of these nutrients occurs in many populations in the world, where infectious diseases are a major health concern. We will also review nutrients that may specifically modulate host defence to pathogens.

We begin with a review of the immune system and its components with the main focus on the adaptive immune arm and the role of T-lymphocytes. We also review what particular changes are brought by aging in nutrition and the immune system. Given the limitation of space for the current issue and because we are unable to review all nutrients that are needed to maintain immune function, readers are directed to some seminal and excellent reviews presented in Table 1 and some other work published on this and the relevant topics throughout the text.

2. The immune system

2.1. A brief overview

A detailed description of the immune system and the disorders associated with it is beyond the scope of this review. Therefore, readers are referred to some seminal work on the topic elsewhere [7–9]. Briefly, however, the immune system is a complex organ that includes elements involved in numerous functions in a cohesive mode with other body systems. For protection against foreign agents (bacteria, viruses, parasites, fungi, yeast, pollen, dietary proteins, toxins, cancer cells, etc.), a first line of defence includes physical barriers and certain chemicals such as skin and mucosa (nasal, intestinal, etc.), their secretions (pH of stomach acid, lysozyme, and other antibacterial components sweat and other secretions) and protective native flora.

Once pathogens have traversed this first barrier, the immune system is responsible for defence mechanisms that can be divided into two categories: 1) innate immune responses which are specific for shared microbial factors not found in mammals, respond rapidly via non-polymorphic cell surface receptors and do not mediate immune memory; 2) adaptive immune response (also called acquired immunity), able to recognize myriads of short peptides derived from target cells detected by highly specific polymorphic cell surface receptors and mediating immune memory. Both innate and adaptive immunity act via immune-competent cells (leukocytes) and a number of soluble factors (e.g., complement, antibodies, cytokines etc) [10, 11].

The cells involved in the immune response originate in the bone marrow; they mostly reside in lymphoid organs such as thymus, spleen, lymph nodes and Peyer's patches, and are also disseminated throughout the body in the bloodstream, skin, gut and lung epithelium and lymphatic circulation and directed towards where they are required in each case depending on the type of pathogen and its location [12]. Within the immune system, innate phagocytic cells comprising neutrophils, granulocytes, basophils and eosinophils, monocytes and macrophages act rapidly as first line of defence without prior exposure

Table 1
Summary of nutrients affecting the immune system and metabolic health

Nutrients	Functions	Review or key references on immune effects	Review or key references on metabolic health effects
Energy/Protein	• Energy required for producing proteins and generating new immune cells in order to fight infection • Amino acids have been demonstrated to play important roles in immune responses by regulating, a) the activation of T-Lymphocytes; b) lymphocytes, NK cells, and macrophages; c). cellular redox state, gene expression, and lymphocyte proliferation; and d). the production of antibodies, cytokines, and other factors	[118–123]	[124–132]
Fats • Monounsaturated fats • α-linoleic acid (n-6 PUFA) • γ linolenic acid (n-6 PUFA) • n-3 PUFA	• Source of energy • Structures of cell membranes • Signaling molecules • Inflammatory response	[122, 133–136]	[137–139]
Folic Acid	• Immune gene regulation • DNA and protein synthesis	[140–143]	[144–151]
Vitamin A	• NK Cell Activity • Activation of inflammatory response • Differentiation of T cell subsets • Migration of T cells into tissues, proper development of T cell-dependent antibody responses	[152–154]	[156, 157]
Vitamin B12	• As co-enzyme for methionine and L-methylmalonyl-CoA	[158–160]	[161, 162]
Vitamin B6	• Endogenous synthesis • Metabolism of amino acids • Lymphocyte proliferation • Differentiation, and maturation as well as cytokine and antibody production	[73, 163–166]	[167, 168]
Vitamin C	• Antioxidant • Stimulation and production of leucocytes • Cellular motility, chemotaxis and phagocytosis	[6, 77, 169, 170]	[171–173]
Vitamin D	• Monocyte proliferation, production of IL-1	[155]	[124, 174,175]
Vitamin E	• Improved natural killer (NK) cytotoxic activity, neutrophil chemotaxis, phagocytic response • Enhanced mitogen-induced lymphocyte proliferation and interleukin-2 (IL-2) production	[71, 176–178]	[179–180]
Copper	• Thymus growth and integrity • Functional component of a number of essential enzymes known as cuproenzymes, • Antimicrobial	[81, 90, 181]	[182, 183]
Iron	• Structural part of proteins and enzymes that are involved in oxygen transport and storage, electron transport and energy generation, antioxidant and beneficial pro-oxidant functions, and DNA synthesis, • Differentiation and proliferation of T-Lymphocytes and generation of reactive oxygen species (ROS), • Phagocytic function, • Cytokine production, • Complement system activation	[83, 84, 184–188]	[189, 190]
Zinc	• Immune signaling pathways • Immune functions of zinc can be divided into three categories: 1. catalytic, 2. structural, and 3. regulatory	[191–195]	[182, 196]

(*Continued*)

Table 1
(*Continued*)

Nutrients	Functions	Review or key references on immune effects	Review or key references on metabolic health effects
Alcohol/Wine (Note: alcohol/wine only in moderate amounts have beneficial effects)	• Anti-inflammatory effect • Protects against DNA damage • Attenuates monocyte inflammatory response • Absolute values of leucocytes, monocytes, lymphocytes increase • Concentrations of IgG, IgM, IgA increase • IL-2, IL-4 and IL-10 concentrations increase	[196, 197]	[198–201]

to the pathogen by recognising structures not present in mammals ("pathogen-associated molecular patterns", PAMPs). By contrast, the adaptive response requires more specific specialized cells, the lymphocytes, acting through specific recognition of a much wider array of antigens from the microorganisms that have attacked the body. These cells thus are accomplished at generating cell clones specifically against the challenge in question, and retaining specific immunological memory for any future challenge by the same pathogen. Lymphocytes are classified into T and B lymphocytes and immunocompetent natural killer cells (NK), the latter included within innate immunity in general, although their participation in the adaptive mechanisms is becoming increasingly evident [13].

T-Lymphocytes are divided in turn into 'collaborators' (or helper; usually distinguished by the presence of the molecule CD4 + on the surface) and 'cytotoxic/suppressor' (usually characterized by the CD8 + molecule on the surface), both involved in cell-mediated immunity or cellular immunity [14]. The B lymphocytes are responsible for generation of soluble antibodies (immunoglobulins, 'Igs'), the fundamental components of humoral immunity. These molecules circulating in plasma and infiltrate the tissues body-wide. Of course, the above is a very brief picture of the overall protection provided by the interaction between different cells (mature B and various types of T cells) and a large multiplicity of molecules that are part of the immune response (complement factors, enzymes, cytokines and antibodies, etc.) [13].

2.2. Aging and changes in the immune signatures

There are large changes in human immune profiles along the lifespan. A brief overview of these changes is given in the following sections.

2.2.1. Fetal life

In utero, the fetal setting requires that the immune system remains tolerant to maternal alloantigens. After birth, abrupt exposure to environmental antigens, many of them resulting from intestinal commensal bacteria, demands a swift transformation to make discrete immune responses appropriate for early life. The innate immune system offers an early first line of defense against assaulting pathogens. The cells involved are neutrophils, monocytes, macrophages and dendritic cells, which all interact with the adaptive immune system. These cells develop and mature during fetal life, but at diverse times, and the function of all components of innate immunity is frail in newborns compared with later life. Mature neutrophils are already present at the end of the first trimester and precipitously increase in number, stimulated by granulocyte-colony-stimulating factor, just before birth. Their number then returns to a steady level within days, but they display feeble bactericidal functions, meager responses to inflammatory stimuli, weak adhesion to endothelial cells and reduced chemotaxis [15]. These shortfalls are more conspicuous in preterm infants, which also have lower serum IgG and complement. Consequently, the newborn, and particularly premature infants, have compromised neutrophil functions [16], putting the child at increased risk of bacterial infections. In preterm and newborn infants, typical monocytes and macrophages are also undeveloped. They have reduced TLR4 expression with impaired innate signalling pathways [17–19], resulting in reduced cytokine responses compared with adults. Subsequently, there is poor tissue repair, weakened phagocytosis of potential pathogens and poor secretion of bioactive molecules. However, while there is a reduced frequency of pulmonary macrophages in premature and term infants, adult levels of these cells are reached within days after birth [20].

Mature single CD4 and CD8 positive T cells are first identified in the thymus at week 15 and are numerous in the periphery well before birth [21, 22]. However, neonatal T cells differ significantly from adult cells, perhaps because during fetal life, contact to foreign antigens is largely limited to non-inherited maternal alloantigens. The function of early-life T cells is different from adult T cells. For example, although fetal naive CD4 + T cells respond powerfully to alloantigens, they tend to mature towards Foxp3 + CD25 + regulatory T cells (Treg) through the effect of TGF-b [23], and thus vigorously support self-tolerance. Peripheral regulatory T cells (Tregs) make up around 3% of total CD4 + T cells at birth [6] and these cells are maintained for a long time [24], giving the early-life immune response an anti-inflammatory profile [25].

2.2.2. Newborns and infants

In the newborn, in addition to conventional T cells that distinguish peptide antigens in the context of classical MHC molecules, there are populations of $\gamma\delta$ T-cell receptor (TCR)-positive and innate-like $\alpha\beta$ TCR-positive T cells. These comprise functionally competent iNKT cells that swiftly produce IFN, mucosal-associated invariant T (MAIT) cells [26] and the newly designated interleukin-8 (CXCL8)-secreting naive T cells that bond innate and adaptive immunity [27]. Children with low gestational weight plus atrophy may exhibit reduced thymus size and display attenuated cellular immunity. On the other hand, it has been found that children who are born underweight have fewer T-Lymphocytes and lower responses to mitogens. The delayed hypersensitivity skin test is also impaired in these cases. Children with low gestational weight show a poor cellular immune response for several months or even years. This result is especially relevant in children whose weight-height is below 80% of normal [28].

The immune system gradually develops during infancy. Precarious early protection against many infectious diseases hitherto experienced by the mother is given by the passive IgG antibody transferred from the mother through the placenta and in the milk. Besides promoting survival, such antigen stimulation results in immunological memory [29, 30].

At the time of birth, nearly all T cells express the CD45RA glycoprotein, typical of naive T cells, which have never encountered foreign antigen. There are also comparatively plentiful Tregs within the CD45RA-negative CD4 + T cell population. During childhood, Treg numbers decline, and memory Th1, Th17 and Th2 cells progressively increase [31].

2.2.3. Adulthood and old age

It is believed that with increasing age the immune system has a decreased ability to mediate adequate defence against micro-organisms, malignant cells and other "foreign" agents. The course of aging is associated with amplified free radical production, contributing to the decreased immune response [32]. The changes in the immune system are associated with decreased responses in the skin hypersensitivity test, lower production of IL-2, reduced response to mitogens and antigens, and lower-titer antibodies after vaccination. Also, the capacity of immunocompetent cells is reduced for clonal proliferation and generation of B and T cells and a marked decrease in the activity of thymus and reduced production of serum IgA, and even decreased primary antibody responses. The number of T-Lymphocytes is marginally decreased, although the number of CD8 + cells has been reported as similar, decreased or even increased (reviwed in 33). Furthermore, those functions that are more associated with stress, such as adhesion, production of free radicals and cytokines, increase with age [32, 34]. As age progresses, the immune system experiences intense remodeling and weakening, with major effects on health and survival [35]. This immune senescence predisposes older adults to a higher risk of acute viral and bacterial infections. Moreover, the mortality rates of these infections are three times higher among elderly patients compared with younger adult patients [36].

Infectious diseases are still the fourth most common cause of death among the elderly in the developed world. The figures are even more worrisome for the developing world. Furthermore, anomalous immune responses in the aged can aggravate inflammation, conceivably contributing to other diseases of old age: cancer, cardiovascular disease, stroke, Alzheimer's disease and dementia, for example [37]. T cells proliferate and increase the 'virtual memory' compartment, but at the same time, the ability to establish immunological memory in response to *de-novo* antigens is reduced, compromising vaccinations. Functions such as cytokine production by CD4 and CD8 T cells are diminished, the expression of key surface markers is altered and the CD4 + to CD8 + T-cell ratio may become inverted [35]. The expanded T-cell responses that keep latent viruses such as EBV and CMV under control, reduces space for CD8 + T cells specific for other potentially lethal

viruses [38], exacerbated by the reduced thymic naive T-cell output. Interestingly, aging presents a unique paradox i.e., it is associated with an increase in the autoimmunity and inflammation that coexist with immunodeficiency [39]. Immunosenescence is a broad concept that reflects the immunological changes associated with age [40–43] and inflammatory potential of the diet [44].

3. Nutrition and the immune system

In the following section, our discussion will mainly focus on the relationship between nutrition and the immune system. We will elaborate on this relationship using data collected mainly in human studies (age 60 and above) throughout this paper. However, results of studies using animal models will also be discussed wherever needed. *In vivo* experiments are widely used to investigate the effects of nutritional interventions on immune-related parameters in animal models which can be challenging in humans. Many studies conducted on human populations in developing countries identify deficiencies in macronutrients (fats, proteins, carbohydrates that lead to protein-energy deficiency), micronutrients (minerals, electrolytes and vitamins that lead to micronutrients deficiency) or both (reviewed in Ref. 45). These studies are very relevant because they permit the identification of the most severely affected regions and consequently can guide intervention by humanitarian organizations and local governments. Nonetheless, laboratory animals have been very useful in studying the effects of different levels of malnutrition, because non-nutritional factors that affect humans can be controlled in this type of evaluation [46]. The use of animal models in malnutrition has yielded a great deal of information on molecular mechanisms involved in the greater susceptibility to infections and also to immunodeficiency secondary to undernutrition.

The most commonly employed models are adult mice and rats (outbred or isogenic) fed with reduced amount of proteins, vitamins or micronutrients [47]. The long history of animal experimentation describes the use of a series of methods that not only include the use of whole animals but isolated organs, isolated tissues, tissue cultures, isolated cells, subcellular components, modeling and structure-activity relationships [48]. As immunodeficiency associated with prepubescent malnutrition underlies a very high burden of infection-related morbidity, acute weanling mice have also been explored to investigate the effects of malnutrition [49]. More recently, transgenic and knockout mice have also been employed to better understand the mechanisms involved in the greater susceptibility to infectious agents in malnourished mice [49] and for studying wound healing [50]. These numerous animal models allowed a growing understanding and characterization of the immunological disturbances triggered by under-nutrition. Some examples of the most relevant findings in this research area are presented in (Table 1).

The disciplines of nutrition and immunology and their interdependency were formally recognized and documented in the 1970s when immunological measures were introduced as a constituent of nutritional status assessment [4, 5]. Understanding of the effect of nutrients on immune function has been refined with the progressive growth of the field of immunology from relatively descriptive science to one in which diverse immune mechanisms can be integrated together coherently and explained in clear-cut structural and biochemical terms. For some time, protein energy malnutrition (PEM) has been considered the major cause of immunodeficiency worldwide [51]. This is not surprising because immune cells have a high requirement for energy and amino acids for cell division and protein synthesis. The influence of PEM on immune function has been reviewed extensively [52–58] and also studied widely, particularly in the context of effects of PEM on viral susceptibility [59, 60], PEM and supressed immunity, PEM and impaired immune organ growth [61] and PEM and thymic atrophy [62].

All nutrients have specific roles in the overall functional capacity of the immune system. For example, certain antioxidants play a key role in protecting immunocompetent cells against oxidative stress [32]. Protein and energy have been studied extensively in relation to immune functions, particularly with an emphasis on their role in overall metabolism (Table 1). Vitamins, minerals and trace elements play an important role as cofactors in many metabolic pathways and are considered essential for the integrity and optimal functioning of the immune system. Some micronutrients such as vitamin A (beta-carotene), folic acid, vitamin B6, vitamin B12, vitamin C, vitamin E, iron, zinc, copper and selenium, exert immunomodulatory effects influencing host vulnerability to infections [63–65].

Malnutrition in humans is generally perceived as a syndrome with numerous nutrient deficiencies. The

impact of micronutrients on immunocompetence has been explored extensively, albeit mostly by experiments on laboratory animals using diets deficient in micronutrients resulting in the development of clinical symptoms of diseases of the immune system. These immunological changes were reversed when animals were fed diets supplemented with those missing elements, noting also that excessive supplementation could result in adverse effects on the immune system [64]. At the same time, obesity, another highly prevent form of malnutrition, has been extensively studied in relation to immunity. The overall impact of obesity on immunity has been recently investigated with looking at obesity as a form of 'low-grade chronic inflammation' (reviewed in 66).

It has been noted that insufficiency of certain vitamins causes a decrease of thymus and spleen size, a drop in the activity of NK cells, lower levels of the pro-inflammatory and anti-viral cytokine interferon-γ (IFN-γ), a decrease in the delayed hypersensitivity skin response, and a low response to mitogen stimulation by lymphocytes [67, 68]. The results of a number of studies concerning supplementation of diets with beta-carotene have shown an escalation in the number of helper T-Lymphocytes and capacity of NK cells. When such supplementation was performed for relatively long periods in elderly subjects, an increase was also observed in the activity of NK cells. In both experimental animals and humans, it has been shown that supplementation with beta-carotene stimulates cellular immunity and humoral immunity and hence may exert a preventive effect against the incidence of certain diseases [69].

An appropriate intake of vitamin E is essential for proper functioning of the immune system. Out of eight naturally occurring forms of vitamin E; namely, the alpha, beta, gamma and delta classes of tocopherol and tocotrienol, alpha-tocopherol and gamma-tocopherol are common forms in supplements and diets and have been usually found to affect immunity (reviwed in Ref. 70, 71). In a small intervention study in older adults (mean age, 70 years), supplementation with 200 mg/day of all-rac-α-tocopherol (equivalent to 100 mg of *RRR*-α-tocopherol) for three months significantly improved natural killer (NK) cytotoxic activity, neutrophil chemotaxis, phagocytic response, and enhanced mitogen-induced lymphocyte proliferation and interleukin-2 (IL-2) production compared to baseline [71]. α-Tocopherol has been shown to enhance specifically the T cell-mediated immune response that declines with advancing age [70–73]. It has been shown that deficiency of this nutrient is associated with an impaired immune response, producing alterations in humoral immunity, cellular immunity and phagocytic functions [72, 73]. Recommended intakes of vitamin E might be sufficient to prevent the onset of neuropathies and myopathies, but only reverse effects of deficiencies rather than amplify normal immune system, a consideration which applies to all such supplementation studies. The immunostimulatory effect of vitamin E increases the resistance of an individual to certain infectious diseases, possibly mediated by increased generation of antibodies as well as augmentation of phagocytic activity [72, 73]. Due to its antioxidant effects, the amount of vitamin E needed depends on the severity of the process which triggers oxidative stress (i.e. consumption of diets high in polyunsaturated fatty acids, the presence of certain diseases and aging). It is established that administering high doses of vitamin E may result in improvement of both humoral immunity and cellular immunity [72]. However, it has also been proposed that the beneficial effect of supplementation with vitamin E may be limited to those individuals who have a severe deficiency of vitamin E as a result of intestinal malabsorption [74].

Vitamin C also affects some parameters of the immune system with deficiency predisposing to infections, especially of the upper respiratory tract. The risk of this type of infection is increased especially in individuals who practice intense physical exercise. In this context, immunological changes of both innate immunity (activity NK cells, phagocytic function and oxidative neutrophils) and specific immunity (function of T cells and B) have been reported. Due to the antioxidant action of vitamin C, supplementation with this micronutrient is often recommended. For example, it was reported that vitamin C supplementation results in an improvement in the immune system and a lower incidence of infections [75]. Vitamin C has been shown to affect the immune system by (A) exciting the production [76] and function [77] of leukocytes; (B) enhancing cellular motility and chemotaxis and phagocytosis [77]; (C) promoting neutrophil activity [78], (D) increase in the serum levels of antibodies and C1q complement proteins [79, 80].

Analogous results are seen when there are deficits of minerals and trace elements. Iron, zinc, copper and selenium are needed for proper operation of the immune system and are essential for adequate protection against infections [81]. Iron is the most prevalent deficient mineral in most parts of the world and its

deficiency is associated with an increase in morbidity and indisposition from infectious disease as shown by earlier work, both in animals and humans, conducted over the past two decades. Iron is an essential element for the proper development of the immune system [13]. It has been found that iron supplementation in populations showing deficits in this element decreases the frequency of infectious episodes. Iron deficiency causes a failure in the defence mechanisms of individuals reflected in reduced phagocytic capability, a lower response to stimulation of lymphocytes, a decrease in the number NK cell associated with lower production of IFN-g, and low delayed hypersensitivity cutaneous responses [82]. Iron is an essential component of hundreds of proteins and enzymes that are involved in oxygen transport and storage, electron transport and energy generation, antioxidant and beneficial pro-oxidant functions, and DNA synthesis [83]. Iron is required for effective immune responses against pathogens, and iron deficiency impairs immune responses [84]. Sufficient iron is critical to several immune functions, including the differentiation and proliferation of T lymphocytes and generation of reactive oxygen species (ROS) that kill pathogens. However, iron is also required by most infectious agents for replication and survival. During an acute inflammatory response, serum iron levels decrease while levels of ferritin (the iron storage protein) increase, suggesting that impounding iron from pathogens is an important host response to infection [83]. Nonetheless, conditions of iron overload (e.g., hereditary hemochromatosis) can also have deleterious effects on immune function, such as diminishing phagocytic function, cytokine production, complement system activity, and T and B lymphocyte function [84]. Further, data from the first National Health and Nutrition Examination Survey (NHANES), a US national survey, indicate that raised iron levels may be a risk factor for cancer and death, especially in men [85]. For men and women combined, there were significant tendencies for increasing risk of cancer and mortality with increasing transferrin saturation, with risks being higher in those with transferrin saturation >40% compared to $\leq$30% [85].

Zinc is also a good example to illustrate the concept of how the lack of a single nutrient can affect the immune system. In this sense, the literature on the studies showing its deficiency is unequivocal [86, 87]. Zinc is required for the activity of more than 100 metallo-enzymes [88]. Zinc affects multiple aspects of the immune system from the skin barrier to gene regulation in lymphocytes, influences the function of cells mediating non-specific immunity (neutrophils and NK cells), but also has a role in the induction of specific immunity by acting on the activation of T-Lymphocytes, cytokine production and maturation of B lymphocytes [86]. Thus, zinc deficiency is associated with lymphoid attenuation and a decrease in the proliferative response of lymphocytes to mitogens and lower thymic hormone activity [87]. Moreover, experimental evidence shows a decrease in the ratio CD4/CD8. Zinc deficiencies cause an imbalance in Th1 and Th2 function, a decreased production of IL-2, IFN-g and TNF-a, while the production of IL-4, IL-6 and IL-10 is not altered [87].

Copper is also an essential micronutrient for development, growth and maintenance of the immune system; being necessary for differentiation, maturation and activation of various types of immunocompetent cells and for cytokine secretion, thus exercising an impact on host defence. It also plays a role synthesis of haemoglobin and myoglobin, and acts as an antioxidant, since it is an indispensable cofactor for a large variety of enzymes, including cytochrome C oxidase and Cu, Zn-superoxide dismutase [89]. Recently, it has been observed in adult rats and healthy individuals *in vitro* that the activity of T cells is reduced when the diet is deficient in copper, suggesting that ample/increased intake of this micronutrient would reduce the chances of suffering from infectious disease [90]. It has also been shown that insufficient copper intake has adverse consequences for innate and acquired immunity. In this respect, T cells appear to be more affected than B cells, and the microbicidal activity of neutrophils and macrophages as well as the cytolytic activity of NK cells is reduced; hypersensitivity and antibody production *in vitro* in response to mitogens is also affected under these conditions [89].

4. Nutrition, metabolism and immunity

Nutrition and immunity are closely related. In the past few decades, this relationship has been explored and reported extensively. The overall picture emerges from a large body of work that nutrition affects immunity via changes in metabolism and metabolic pathways. Therefore, any discussion on relationships between nutrition and immunity can only be understood by comprehending metabolism and metabolic changes that are associated with nutritional

status. Accumulating data support the notion that understanding how metabolism regulates immune cell function could provide new therapeutic opportunities for the many diseases associated with immune system dysregulation.

One of the important aims in the study of nutrition and immunity is to determine the role of nutrients affecting metabolism of the body (general/organismal metabolism) and hence immunity. Immune cells migrate throughout the body and sometimes take up residence in niche environments with distinct and varied communities of cells, extracellular matrix, and nutrients that may differ from those in which they matured. Imbedded in immune cell physiology are metabolic pathways and metabolites that not only provide energy and substrates for growth and survival, but also instruct effector functions, differentiation, and gene expression [91]. Studies have shown that dietary intakes rich in whole-grain foods have been related to a lower prevalence of a metabolic syndrome (MetSyn) [92, 93], which is a clustering of certain conditions i.e. increased blood pressure, elevated blood sugar, excess body fat around the waist, and abnormal cholesterol or triglyceride levels, insulin resistance, that occur together, increasing risk of diabetes (Type-II) and cardiovascular abnormalities. The association is less reliable for refined-grain intake, with some cross-sectional studies recording a positive association and others no relation [92]. Dairy intake has been shown to be associated with MetSyn both in cross-sectional and prospective studies [94–96]. Higher intakes of fruit and vegetables have also been associated with a lower prevalence of MetSyn [93]. No association has been found between MetSyn and intakes of meat and fish [95]. Intakes of regular and diet soda, however, have been positively associated with MetSyn both cross-sectionaly and prospectively [97]. In cross-sectional dietary pattern analyses, a higher prevalence of MetSyn was found among consumers of "Western" [98] and "empty-calorie" [99] dietary patterns, whereas a lower prevalence was found among those consuming a "healthy" dietary pattern [98, 99].

The intake of diets that are lower in carbohydrate, lower in saturated fat, but higher in protein than the average American diet - which consists of almost 47% carbohydrate, 38% fat (20% SFA), and 15% protein - have a tendency to be beneficial for improving features of the metabolic syndrome, including effects on insulin sensitivity and blood lipids [99]. In particular, insulin resistance has been recognized as a chronic inflammatory and metabolic disease, playing a pivotal role in the development of diabetes [100]. Obesity and abnormal lipid metabolism increases infiltration of inflammatory cells, affects immune homeostasis, and reduces insulin sensitivity, consequently leading to the occurrence of insulin resistance. [100]. In their study, Musselman et al. found that obesity-associated insulin resistance led to increased susceptibility of flies to infection, as in humans [100].

There have been many proposed dietary patterns claiming health benefits ranging from those related to metabolic and immune health. For example, the Mediterranean dietary pattern [45–48, 73, 99, 101, 102], Ornish Diet [50, 103, 104], Atkins Diet [105, 106], Zone Diet [107], the South Beach Diet [108] etc. Adherence to these diets in relation to metabolic health and expansion in the immune parameters have been studied extensively. The Mediterranean dietary pattern, in particular has fascinated nutritionists focused in immunity. This diet, high in fruits, vegetables and olive oil, and fish consumption [109] has been shown to be related to anti-inflammatory processes [110–112] and thus has been recommended for the maintenance of health [113].

In the discussion of nutrition and immune interplay, obesity in particular has attracted a great deal of attention. Obesity is considered as a state of chronic inflammation, which affects both the metabolic health and the immune system in a number of ways. For example, adipose tissue is considered to be responsible for a possible link between obesity and the immune system (reviewed by de Heredia et al., [114]. Histological studies in mice showed that macrophage infiltration in adipose tissue was greater in obese than in lean animals [115]. Macrophages appeared as crown-shaped aggregates, similar to those observed in other known inflammatory conditions, such as rheumatoid arthritis, and grew larger with increasing degrees of obesity. This finding led to the idea that macrophage aggregates could partially explain the obesity-related inflammatory state. There are of higher rates of infections and impaired wound healing in obese subjects [116]. Excess body fat is accompanied by changes in leucocyte counts, with elevated leucocyte, neutrophil, monocyte and lymphocyte counts, but lower T- and B-cell mitogen-induced proliferation [116]. In addition, other studies have shown that the production of antibodies after vaccination is diminished in obese patients [116, 117].

5. What is the mechanism whereby nutrition affects the immune system?

The mechanisms behind immunological alterations with respect to nutrition are still not adequately understood. Nevertheless, there have been many theories put forward to explain this phenomenon. For example, the lack of energy and the amino acid building blocks to synthesize the required proteins in marasmic children may be one possible cause [202]. However, lack of building blocks does not explain why some immune parameters seem unaffected or paradoxically even raised in malnutrition, such as plasma IgA, acute-phase proteins, leucocytes in blood, and production of Th2 cytokines. If it was solely a matter of lack of building blocks, all parameters of the immune system should be affected in the same way. Other explanations include a confounding role of infections in influencing immune parameters in malnourished individuals [203], low levels of certain hormones in malnourished children, e.g. leptin [204], prolactin [205] and growth hormone [206], all of which impact growth and function of thymus – an important specialized primary lymphoid organ where T cells mature till puberty. In support of this, a recent study found that a low leptin level was associated with a higher risk of death in malnourished children [207]. Growth hormone therapy has been found to augment thymic size and output in adult HIV + patients [208]. In contrast, cortisol and adrenalin prompt thymic atrophy in mice [209, 210], and cortisol is high in children with malnutrition and other forms of stress. Zinc deficiency causes thymic atrophy [211, 212], and acute phase responses lower plasma zinc, so zinc status may contribute to the immune deficiency of both malnutrition and acute phase responses.

The intracellular receptor, mammalian target of Rapamycin (mTOR), is present in most cells. It responds to the concentrations of nutrients in the cell's surroundings, enabling the cell to adapt its metabolism to locally available nutrients. Immune cells also use mTOR to regulate their state of activation. Nutrient availability may thereby determine whether an immune cell is activated [213], and whether T-cells differentiate towards a pro-inflammatory or a tolerance-inducing phenotype [214]. Some immune cells may even deplete the microenvironment of certain nutrients, to manipulate the activation of mTOR. Accordingly, the significance of nutrients in the microenvironment expands from simple building blocks to signal molecules. Obviously, this mechanism could be involved in the immunological profile in malnutrition. However, no publications have yet described the activity of mTOR in malnourished children. A research group working with animal models of malnutrition has proposed a theory called the "tolerance hypothesis" [215]. This suggests that the depression of cellular immunity in malnutrition is an adaptive response to prevent autoimmune reactions, which would otherwise occur as a result of catabolism and release of self-antigens. Such phenomena have apparently not been studied further.

6. Effects of aging on nutrition

The relation between aging and nutrition is complex one as what affects what is difficult to decide. Natural aging cannot be stopped but can be delayed by nutritional interventions. This is the main theme of discussions on relationships between aging and nutrition in this section of the paper. The aging process involves changes in pathological, physiological, social, and psychological conditions of individuals. Nutrition is an important element of health in the elderly, and it affects the whole process of aging [216]. The prevalence of malnutrition is cumulative in this population and is related to weakening functional status, diminished muscle function, reduced bone mass, immune dysfunction, anemia, diminished cognitive function, poor wound healing, delayed recovery from surgery, higher hospital readmission rates, and mortality. Due to altering socioeconomic environments, elderly people are often left alone to fend for themselves to maintain their health, which may hinder the maintenance of a good nutritional status.

Nutritional choices remain crucial throughout life, having great influence on overall health and wellness of the individual and potentially also generations to come due to developmental programing. All healthy people need the same basic nutrients, including carbohydrates, essential amino acids, essential fatty acids, and as many as 28 vitamins and minerals, in order to maintain life and health and reproduce successfully. However, the amounts of needed nutrients change as an individual passes from one stage of life to the next. Clearly, young children require a higher caloric intake relative to body size to facilitate physical and mental development as compared to the elderly [216–218]. It is also important to note that nutrition at one particular stage of life span may

be profoundly reflected in another stage, particularly during the latter years. This can be seen in the findings of a number of studies based [219, 220] on the famous historical famine known as "the Dutch Hunger Winter". The famine was a humanitarian disaster, but it left an opportunity to study the effects of maternal malnutrition on the offspring's health and ageing in later life. Using birth records of babies born around the time of the Dutch famine in the Amsterdam area, the long-term consequences of pre-natal undernutrition have been investigated [219]. It has been shown that those who were conceived during the famine — and had thus been undernourished during the earliest stages of their development—have an increased risk for coronary heart disease, diabetes, an atherosclerotic lipid profile, altered clotting and breast cancer.

The relationship between nutrition and aging, complex as it is, has a bidirectional association, i.e., aging affects nutrition and vice versa (Table 2). However, in the forthcoming section, we will restrict ourselves mainly to the discussion on how aging may affect nutrition. In general, there is a decline in the overall nutritional status with aging – a fact confirmed by both cross-sectional as well as longitudinal studies [219–221]. This age-associated decline in nutritional status may be more obvious in societies with low economy, literacy rate and lack of nutrition-related awareness. Nevertheless, the so called Westernized, Educated, Intelligent, Rich, and Democratic (WEIRD) societies also suffer from age-associated malnutrition in one way or the other. Extraordinary changes in the regulation of energy intake in the elderly as compared to the young have been extensively reported [222–227]. The day-to-day variability in energy intake (20%–25%) and energy expenditure (10%) [228, 229] suggests substantial fluctuation in day-to-day energy balance. Energy balance in old age is significantly impaired as compared to that in young age suggesting markedly impaired regulation of energy intake in late life [224, 225]. There are also several animal studies conducted in the past that reported impaired regulation of food intake in old age [225, 230–238].

Old age is often associated with reduced hunger and early satiety due to a number of physical, physiological and social reasons (reviewed in 225, 239–242). Several studies have recorded abnormally low hunger following fasting or experimental induction of negative energy balance in elderly subjects [222–224, 227, 238, 243–245]. Alterations in glucose homeostasis in old age may contribute to altered hunger and satiety. Blood glucose has long been a postulated trigger for hunger signals in both rodents and humans [240, 246–249]. In addition, delayed gastric emptying in general has been linked to reduced hunger and increased satiety [222, 246, 250–252]. Also, taste and smell of food play important roles in regulating intake, and impairment in old age has been reported to be partly responsible for reduced hunger signals and thus lower intake [225, 253–258]. Hunger and satiety are also related to food variety; a characteristic of food that has been reported to play a pivotal role in overall food intake [227, 259, 260]. A study [260] recently reported on the long-term association between dietary variety and body fatness in healthy adult men and women.

Many studies examining gastric emptying in relation to age have reported a decreased rate of gastric emptying in the elderly [222, 261–264]; a phenomenon responsible for a number of other related complications including disturbance in those hormone systems related to energy regulation [243, 252, 264, 267]. Some well-known examples are glucagon (responsible for the signals of satiation) [243, 252, 264–267], which has been reported [249] to be significantly elevated by up to 25% in response to consumption of meals of 2,092 kJ (500 kcal) or greater, identifying a potential role for glucagon in the apparently enhanced satiation associated with old age. Similarly, another satiety hormone CCK, has been shown to be as much as 5-fold higher in the elderly than in young adults, particularly following consumption of diets with high fat content [268–271].

Basal Metabolic Rate (BMR) is a strong surrogate indicator of the physiological functioning of various organs. Age associated physiological changes in the organ system brings about adverse changes in energy expenditure, resulting in a fall in BMR with aging. In addition, there is a decrease in thermic energy, total energy expenditure and physical activity level. Also there is a decline in energy expenditure responsiveness to energy imbalance [249, 316–318]. A seminal work by Keys et al. [318] documented a decline in BMR with age, which was as much as 1–2% per decade. In this way, during the life span stage of 20–70 years of age, a reduction in BMR of about 400 kJ/day can be predicted based on the findings [318] Age-associated reduction in BMR may be mainly due to changes in the body composition in old age [317]. Changes in body composition with aging (more adipose tissue, lesser lean body mass), also cause drastic decline in thermic effect of feeding, which is equivalent to nearly 8–15% of ingested

Table 2
Summary of nutrients affecting aging

Nutrients	Effects related to old age	Key References
Carbohydrates	• Increased glucose intake accelerates aging • High concentrations of glucose in media accelerate the senescence of cultured human cells • Other carbohydrates or carbohydrate metabolites, including trehalose, pyruvate, malate, fumarate, and N-acetylglucosamine (GlcNAc), have been shown to promote longevity in C. elegans • Low-carbohydrate diet is beneficial for human health • Age-related diseases including diabetes and heart diseases	[190, 272–282]
Protein	• Low-protein/high-carbohydrate diet is associated with long lifespan. • High animal-protein intake positively correlates with the risk of developing urothelial cell carcinoma, whereas high plant-protein intake negatively correlates with the risk	[283–285]
Fats	• A high-fat diet (HFD) is generally associated with increased mortality and increased incidence of many metabolic diseases, including type II diabetes and cardiovascular problems • Diets enriched in unsaturatedfattyacidsleadtoreducedbloodlevelsofharmfullow-density lipoproteins and increased levels of protective high-density lipoproteins • Diets enriched in natural unsaturated fattyacidslowerbloodpressure,improveinsulinsensitivity,andreducethe risks of cardiovascular and metabolic diseases • Dietary trans-fats (unsaturated fatty acids with trans-isomers) trigger inflammatory responses, which increase the risks of developing cardiovascular and metabolic diseases • Arachidonic acids, which are omega (x)-6 PUFAs, induce apoptosis of cancer cells • Dietary lipids may affect mammalian health and longevity by altering the compositions of body fat and cellular membranes.	[276, 286–296]
Vitamins and Minerals	• Vitamin E/tocopherol intake significantly increases the lifespan of rotifers, nematodes, and fruit flies • Supplementation of vitamin C/ascorbic acid, a well-known antioxidant, increases the lifespan of the bean beetle Callosobruchus maculatus Many members of the vitamin B family also lengthen the lifespan of flies, Zucker fatty rats, and C. elegans, a mega-dose of vitamins and minerals mildly increases human mortality selenium (Se), an antioxidant mineral, significantly reduces DNA breakage and extends the replicative lifespan of cultured adrenocortical cells	[297–315]

metabolizable energy. Some studies report a decrease in the thermic effect of feeding in old age, while other studies report no change [249, 318].

Old age is also responsible for a decrease in energy expenditure responsiveness to energy imbalance. In this way energy balance is drastically disturbed in old age [319]. A decrease or increase in energy intake is normally triggered by the energy expenditure of the body. Any disruption in this mechanism, as usually observed in old age, will result in malnutrition (i.e. underweight as a result of underfeeding or overweight/obesity as a result of overfeeding. The consequences in case of overfeeding are particularly crucial in case when fat is ingested above the requirements – a condition necessarily demanding for the extra fat to be stored by the body as the ability of fat oxidation decreases with aging [321].

Daily energy expenditure consists of basal or resting energy expenditure, diet-induced thermogenesis and that associated with activity [322]. Changes in all components may occur with age. Firstly, as lean mass drops, BMR in relation to body weight falls off, although per kg fat-free mass remains unchanged or only somewhat diminished. Second, with diminished food intake there is less diet-induced thermogenesis; third, activity lessens, particularly with disability. These changes, despite the age-related decline in energy intake, result in a positive energy balance in middle life and the changes in body composition described above. Finally with the onset of anorexia in the very old, energy balance becomes negative and BMI and fat mass decline. Similarly, anorexia and weight loss associated with chronic disease may also be associated with a fall in BMR. These changes have an effect on the immune system.

7. Conclusion and future outlook

In short, in the previous sections, we have provided a brief overview for understanding how diet and nutritional factors influence immune functions, thereby regulating health and disease outcomes. Beyond providing essential nutrients, diet can actively influence the immune system. Naturally occurring compounds

like vitamins and minerals modulate immune responses. We also see changes in the immune system with normal aging which may be partially a function of changes in overall nutrition at various life stages. The challenge remains to capture these interactions and complexities to better understand nutritional immunology in the context of aging. In this review, several aspects of this complexity have been explored. We first gave an overview of the immune system, and its mode of action. To characterize interactions between nutrition and immunity, we discussed the effects of multiple food components on immune functions. In the next sections, we discussed effects of aging and finally we discussed effects of aging on the immune system.

We further emphasize the fact that both nutrition and immunity are complex and multi-dimensional traits. The same is true for normal aging. Aging, nutrition and immunity ("aging nutrimmunity") hence form a complex network and nutritional interactions via multiple direct and indirect pathways. Future research will need to focus on how these pathways interact with each other and explore nutrient allocation strategies of the body, and the effects of aging thereon. Excellent initial work in this connection includes the "selfish brain" theory [323] and "the "selfish immune system" theory [324], which we will analyse in separate reviews. We believe that there is need for both further research as well as for the development of theoretical frameworks in the particular discipline of nutritional immunology of old age which we propose to term "aging nutrimmunity". In short, as argued by Stanga [322], five main conclusions concerning nutrition and immunity in the elderly can be drawn: firstly, immunological decline is not an inevitable part of ageing; thus, many elderly subjects maintain vigorous immune responses at a level that is comparable to that seen in younger subjects. Second, nutritional deficiencies are quite common in this old age; a large proportion of the elderly show evidence of PEM or selected nutrient deficiencies. Third, correction of nutritional deficiencies does improve immune responses even in old age. Fourth, appropriate nutritional counselling and dietary therapy, sometimes with medicinal supplements, results in reduced respiratory illness. And fifth, multivitamin, multi-mineral supplements in the elderly can lead to improved lymphocyte function and fewer infections.

As we have previously reported that the aged are already having a malfunctioning in their energy metabolism, energy allocation mechanisms and inflammation [325], more exposed to pro-inflammatory diets [44], have negative changes in their body composition and have compromised immunity [326–328]. There is a need of studies that look into the combined effects of diet with various life style factors, for example, sleeping, exercise, sun exposure and social issues. The area of discussion on nutrition, immune and aging relationship is much extensive, wide and varied that this is beyond the scope of a single review. However, a snapshot of such a relation was presented here in the present review. It is suggested that in future the following areas of research may be addressed:

1. Randomized controlled trials that include older adults with disease and n use to make nutrient recommendations within these altered metabolic states.
2. Randomized controlled trials in various life stages for prevention of mild cognitive decline and in different stages of Alzheimer disease with patient-tailored lifestyle nutrition treatments for evidence to support individual or broad recommendations on diet, lifestyle, or nutrient supplementation.
3. Studies examining other biomarkers beyond nitrogen balance to fully understand the impact of advancing age on protein requirements and skeletal muscle protein turnover.
4. Clinical trials to establish optimal nutrient requirements and to identify food components for older adults to improve immune function and reduce inflammatory diseases Design of an effective, interoperable electronic medical record, integrated across health care settings, to promote improved documentation and communication across health care providers, enhance care coordination, and facilitate continuity in nutrition care as an older individual transitions between health care settings.
5. Re-evaluation of how the current BMI guidelines are used in older adults and incorporation of nutrition screening and assessment into general practice and community settings.

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