Role of micronutrients and omega-3 long-chain polyunsaturated fatty acids for immune outcomes of relevance to infections in older adults – a narrative review and call for action

Manfred Eggersdorfer[1*]; Mette M. Berger[2]; Philip C. Calder[3]; Adrian F. Gombart[4]; Emily Ho[5]; Alessandro Laviano[6]; Simin N. Meydani[7]

[1]Department of Internal Medicine, University Medical Center Groningen, Groningen, The Netherlands;

[2]Lausanne University Hospital; Lausanne, Switzerland;

[3]Faculty of Medicine, University of Southampton and NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton, UK;

[4]Linus Pauling Institute, Department of Biochemistry and Biophysics, Oregon State University, 307 Linus Pauling Science Center, Corvallis, USA;

[5]Linus Pauling Institute, College of Public Health and Human Sciences, Oregon State University, 307 Linus Pauling Science Center, Corvallis, USA;

[6]Department of Translational and Precision Medicine, Sapienza University, Rome, Italy;

[7]Nutritional Immunology Laboratory, Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Boston, MA, USA;

* Correspondence: phone: Münchwilerstrasse 20; 4332 Stein ; Switzerland ; +41 79 244 90 06, m.eggersdorfer@bluewin.ch

Running head: Nutrients and the immune system in older adults

Abbreviations: 25(OH)D: 25-hydroxyvitamin D; CI: confidence interval; COVID-19: coronavirus disease 2019; DHA: docosahexaenoic acid; EAR: estimated average requirement; EPA: eicosapentaenoic acid; PUFA: polyunsaturated fatty acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Abstract

The immune system is weakened by advancing age, often referred to as immunosenescence, increasing the vulnerability to, and frequently the severity of, infectious diseases in older people. This has become very apparent in the current coronavirus disease 2019 (COVID-19) pandemic for which older people are at higher risk of severe outcomes, even those who are fully vaccinated. Aging affects both the innate and adaptive immune systems and is characterized by an imbalanced inflammatory response. Increasing evidence shows that optimal status of nutrients such as vitamins C, D and E, selenium and zinc as well as the omega-3 fatty acids docosahexaenoic (DHA) and eicosapentaenoic acid (EPA) can help compensate for these age-related changes. While inadequate intakes of these nutrients are widespread in the general population, this is often more pronounced in older people. Maintaining adequate intakes is a challenge for them due to a range of factors such as physical, physiological and cognitive changes, altered absorption and the presence of non-communicable diseases. While nutritional requirements are ideally covered by a balanced diet, this can be difficult to achieve, particularly for older people. Fortified foods and nutritional complements are effective in achieving adequate micronutrient intakes and should be considered as a safe and cost-effective means for older people to improve their nutritional status and hence support their defense against infections. Complementing the diet with a combination of micronutrients, particularly those playing a key role in the immune system such as vitamins C, D and E, selenium and zinc as well as DHA and EPA is recommended for older people. Optimal nutrition to support the immune system in older people will remain essential, particularly in the face of the current COVID-19 pandemic and,

thus, developing strategies to ensure adequate nutrition for the growing number of older adults will be an important and cost-effective investment in the future.

Statement of Significance: Prevention and treatment of age-associated decline of immunity contribute to successful ageing. Key nutrients have been proposed and suggested to play a role in supporting immunity in older adults. In contrast with published reviews in which nutrients are discussed separately, this perspective summarizes the available literature on nutrients and immunity and proposes a novel integrative approach, in which recommended nutrients should be provided in combination to maximize their effects.

Introduction

The current severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease 2019 (COVID-19) pandemic has highlighted the vulnerability of older adults to infections, as they have a significantly increased risk for a severe as well as a fatal course of the disease (1, 2). Moreover, their response to vaccines is less pronounced, as shown in a study were one-third of the elderly had no detectable neutralizing antibodies after the second dose of the BNT162b2 COVID-19 vaccine in contrast to only 2.2% of those aged <60 years (3). Similarly, a negative association between antibody titers and age was found despite a high (96%) overall response to the vaccine (4). Before the COVID-19 pandemic, seasonal influenza caused an estimated 3 to 5 million cases of severe illness globally every year, resulting in 290,000 to 650,000 deaths and older adults were at increased risk of severe outcomes also for this viral infection (5).

Nutrition is essential for a well-functioning immune system in the general population (6), but may be particularly important for older people who exhibit a dysregulated immune response as well as nutritional insufficiency (7). Therefore, in this review we aim to explore the role of complementing the diet with specific nutrients which older people have low intakes of and that are particularly relevant for a well-functioning immune system. We will focus on specific nutrients [vitamins C, D and E, selenium, zinc and omega-3 long-chain polyunsaturated fatty acids (PUFA; docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA)] important for maintaining an efficient immune defense against bacterial and viral infections at an advanced age.

The aging immune system

The immune system is comprised of innate and adaptive responses and most of these are affected by advancing age (8). The term Immunosenescence, refers to the most marked changes that occur with ageing in the adaptive immune system, responsible for increased susceptibility to new infections. Inflammageing is the long-term result of the chronic physiological stimulation of the innate immune system, which can become damaging during ageing, the by-product of the degeneracy of a few receptors that can sense a variety of non-self, self and quasi-self-damage signals. (9). Immunosenescence is driven by a range of factors such as reduced immune cell output from the bone marrow and thymus, cell senescence, mitochondrial dysfunction and oxidative stress (1). Physical barriers such as skin, mucus and gut epithelium are components of the innate immune system that help prevent pathogen entry. As regeneration capacity of cells and tissues decreases with age, barrier function weakens and hence is less efficient at preventing pathogen entry into the body (10).

Many important effector functions of neutrophils and monocytes/macrophages including phagocytosis, chemotaxis and cytotoxicity are altered, even in apparently healthy aging (8). A variety of phagocytes and killer cells, cytokines, and proteins quickly recognize and neutralize or destroy invading pathogens, through a coordinated effort between cell-mediated and inflammatory processes, and then resolve the inflammation and repair the damage caused by these processes (11). While the inflammatory response can still be initiated at an older age, its resolution is often impaired. A vicious circle has been described where immunosenescence and inflammaging (i.e the long-term result of the chronic physiological stimulation of the innate immune system (9)) contribute to age-associated chronic disease, which in turn may lead to inflammatory burden and an impaired immune system. Of note,

inflammaging is also influenced by other factors such as type of diet and probiotics, which are beyond the scope of this review. The oxidative burst is another important component of immune defense, where reactive oxygen species are produced, and antioxidant mechanisms are required to prevent damage to host tissues (12).

If the innate defenses cannot resolve an infection, the adaptive response takes over and the timely changes and micronutrient actions are summarized in **Figure 1**: subsets of T lymphocytes coordinate the overall adaptive response or kill infected cells, and B lymphocytes are activated to secrete antibodies specific to the infecting pathogen (11). In addition, the T and B lymphocytes are responsible for generating immunological memory, whereby a repeated infection will generate a fast and vigorous adaptive response.

Activation of the adaptive response by the innate immune system is frequently impaired with older age and the overall immune response is less efficient (8). For example, impaired cytokine regulation combined with decreased viral clearance increases the risk of symptom severity and fatality seen in older people (13). The thymus, a central lymphoid organ and the site of T cell maturation, shrinks with advancing age, resulting in a gradual decline in both cellular and humoral immune responses (1). This is accompanied by a shift in the number of naïve compared to memory T cells as well as changes in their signaling cascades (8). As a result, responses to new infections as well as previously encountered pathogens are less potent than in younger adults. Consequently, the risk of infection increases, they tend to last longer, are more severe and result in more complications (7). Moreover, as mentioned above, efficacy of some vaccines decreases with aging: antibody response to the seasonal influenza vaccine, for example, was significantly lower (17 to 53% protection) in older people compared to younger adults (70 to 90% protection)

(14). One could argue that many of these age-related changes are involved in the increased vulnerability of older people, particularly those with co-morbidities, to viral infections as seen in the current COVID-19 pandemic (15). Vaccines are increasingly available globally to control SARS-CoV-2 infections, but their efficiency, and likely the protective period, appears decreased in older people. There is still no cure for the disease and new virus mutations will likely continue to emerge, thus it is possible current vaccines will not effectively combat these new strains. Therefore, supporting the immune system with optimal nutrition is an important public health measure in addition to other measures such as good hygiene practices and social distancing.

Specific challenges for older adults to achieve adequate intakes

Ideally, optimal intakes of nutrients are achieved through the consumption of a well-balanced diet. However, this is a challenge in the general population, and older adults are even less likely to ingest the required amounts of energy and micronutrients in part due to the so-called anorexia of aging (16). The loss of appetite and/or decreased food intake often observed in advanced age is a complex, multifactorial geriatric syndrome involving physical, physiological, cognitive and social factors associated with the aging process as well as non-communicable diseases (16). While the energy requirements of older adults tend to decrease compared to those for younger people, micronutrient needs remain similar or are even higher (17-20). Moreover, requirements for specific nutrients such as vitamin D and long chain omega-3 PUFA are in a range unlikely to be met by the diet alone (21). Even in affluent countries, inadequate status or deficiencies in a range of micronutrients are observed in a significant proportion of the older population (22).

A recent publication of NHANES data from the US shows the use of micronutrient supplements can decrease significantly the proportion of adults that have intakes of micronutrients below the recommended levels: with supplement use the percentage of the population with usual intakes below the estimated average requirement (EAR) in older adults (≥ 71 years) for vitamin A, vitamin C, vitamin D, vitamin E, and zinc, decreased from 37% to 23%, 44% to 25%, 96% to 44%, 92% to 52% and 26% to 16%, respectively (23).

Decreased appetite, lack of energy and depressive symptoms are normal physiological reactions to the release of proinflammatory cytokines, but these symptoms tend to be more pronounced in older adults (8). Moreover, infections frequently lead to decreased intestinal absorption, catabolic losses and increased energy and nutrient requirements to fuel the immune response (24). This results in a vicious cycle where poor nutrition impairs the defense against infection, and infections leads to a further deterioration of nutritional state (24).

Nutritional support for immunity in the older adults

The importance of essential nutrients in maintaining a well-functioning immune system is well established and was reviewed recently elsewhere (6, 7). Adequate intake of micronutrients is consequently recommended for all individuals and in particular those at increased risk of a severe course of COVID-19 infection including older adults (25). A recent publication recommends multivitamin and trace elements supplements in combination with at least 200 mg/d vitamin C, 2000 IU/d vitamin D, 8 to 11 mg/d zinc and 250 mg/d DHA + EPA to support a well-functioning immune system in the general population (6).

While adequate supply of all nutrients is essential for an optimal immune function, this review will focus on the ability of complementation with vitamins C, D and E, selenium and zinc as well as DHA and EPA to counter the negative effects of immunosenescence.

Other nutrients such as the B-vitamins, copper, iron, and magnesium are essential to sustain a strong immune system, but the available data in older adults is lacking to draw firm conclusions on their role in countering immunosenescence.

Vitamin C

Vitamin C is a potent antioxidant and contributes to reduce the inflammatory processes. It plays a key role in immune defense as it is required by cells of the innate and the adaptive immune systems and helps protect the body from damage as a consequence of inflammatory responses (26). Vitamin C promotes barrier function; the function of neutrophils, monocytes and macrophages; the activity of natural killer cells; the differentiation and function of T cells, especially cytotoxic T cells; and production of antibodies (26). Deficiency increases the susceptibility to infections such as pneumonia (26) and blood levels decrease during an acute infection (27). Moreover, a trend towards lower vitamin C levels in the plasma, platelets and immune cells was reported in the most severely ill older patients admitted to the hospital with acute respiratory infection (27). Serum concentrations were inversely associated with overall mortality, resulting in a hazard ratio of 0.54 (95% CI: 0.34 to 0.84) between the highest quintile (>66 μmol/L) and the lowest (<17 μmol/L) in older adults in the UK (28). Randomized controlled trials supplementing vitamin C in older people to improve their ability to deal with infections are relatively scarce (

Table 1). Trials vary significantly in factors such participant characteristics, and the dose, duration and outcomes. In some cases, vitamin C was given in combination with other micronutrients (29-31), complicating the interpretation of the data. In the trial by Thomas et al (31) a wide range of ages was included making conclusions about the effects in older people difficult. Despite insufficient evidence from human studies, the combination of these data with the preclinical and epidemiological evidence on the increased requirements and the critical role of vitamin C in the immune system, suggests that assuring adequate intakes of vitamin C will be prudent for older people.

A recent meta-analysis reported that vitamin C supplementation led to a significant reduction in the risk of pneumonia, particularly in individuals with low dietary intakes in a range of age groups (32). There is also evidence for an effect in the prevention and treatment of respiratory tract infections such as common cold in the general population (33). A recent review concluded that for individuals admitted to hospital with community-acquired pneumonia, vitamin C may improve respiratory function in more severe cases, without any adverse effects (34). On the other hand, it should be noted that a recent study reported that treatment with high-dose zinc gluconate, ascorbic acid, or a combination of the 2 supplements did not significantly decrease the duration of Covid-19 symptoms compared with standard of care (31).

In addition, it has been proposed that persons with non-communicable diseases may have higher requirements of vitamin C given the oxidative potential of such conditions (35). Pooled data on the association between vitamin C intake and resulting serum concentrations showed that older adults (aged 60-96 years) achieve lower blood levels with a given vitamin C intake compared with younger individuals (aged 15-65 years) (36). This led the authors to conclude that older adults have

higher vitamin C requirements. For healthy older people, intakes of at least 200 mg/d proposed as optimal for healthy individuals in general (6) are recommended for immune system support until more evidence is available for this population group.

Vitamin D

Inadequate or deficient serum 25-hydroxyvitamin D (25(OH)D) levels are frequent in older persons, likely due to reduced exposure to sunlight and synthesis in the skin, increased adiposity, low appetite and food intake as well as impaired vitamin D absorption in the gut. Moreover, the decreasing concentration of 7-dehydrocholesterol in the skin with aging results in a 50% reduction of pre-vitamin D synthesis by older people in response to UV light (37). With its hormone-like functions, vitamin D is a key nutrient for a range of functions for the innate as well as adaptive immune system and helps mitigate the negative effects of inflammation as reviewed elsewhere (38). Vitamin D has complex regulatory effects on many cells of the immune system, as reviewed elsewhere (39). It promotes production of antimicrobial proteins such as cathelicidin, the differentiation of monocytes to macrophages and macrophage phagocytosis. Vitamin D promotes antigen processing but it can inhibit antigen presentation. It promotes the development of regulatory T cells and regulates the function of other T cells types and of B cells. Deficiency is associated with a general dysregulation of the immune system and increasing data suggests antiviral properties as well as a role in protecting against infections, including respiratory illnesses. A meta-analysis in the general population reported that daily or weekly vitamin D administration reduced the incidence of acute respiratory tract infections among all participants, but particularly in those with low serum 25(OH)D levels (40). A more recent meta-analysis by the same group including additional data found that this effect was strongest at daily intakes of 400 to

1,000 IU vitamin D and they did not observe significant protective effects in those individuals with the lowest serum 25(OH)D concentrations at baseline (41). However, many of the studies using doses <2,000 IU were done in children, while the studies in adults tended to use higher doses. Mechanistic studies in individuals randomized to different dosing regimens of vitamin D are needed to clarify the findings from these meta-analyses.

The data from the limited number of randomized control trials for vitamin D with and without calcium available in older people are summarized in

Table 1. One of these trials reports that a large majority of participants (97.7%) had baseline serum 25(OH)D levels below 30 ng/mL, which was successfully corrected with 3 months supplementation with 2,000 IU/d (97% >30 ng/mL) and to a lesser degree with 800 IU/d (81% >30 ng/mL) (42). One of the three trials (

Table 1) found no effect, but the authors argue that supplementation might have started too close to the beginning of the cold season, and that baseline levels were not sufficiently low to see an effect (43).

Based on the available evidence in the general population, a previous expert panel recommended 2,000 IU/d for adults to optimize the immune response, particularly against viral infections (6). Given the increased susceptibility of older people to inadequate 25(OH)D status, an intake of 2,000 IU/d vitamin D as a supplement is recommended. In line with this, mounting evidence indicates an increased susceptibility to COVID-19 as well as an increased risk for a complicated course of the disease in individuals with insufficient 25(OH)D levels (44), although the findings are confounded by the observation that those deficient in vitamin D were also older adults. A number of well-designed studies including randomized controlled clinical trials are currently underway to define the best practice for use of vitamin D supplementation in the context of COVID-19 (44). In the meantime, vitamin D supplementation for older people or other at risk groups is recommended as a cost-effective, available tool, particularly when combined with other public health measures. Supporting this recommendation, Louca et al. reported in women a modest but significant association between use of probiotics, omega-3 fatty acids, multivitamin or vitamin D supplements and lower risk of testing positive for SARS-CoV-2 (45).

Vitamin E

Vitamin E impacts various components of the immune system including phagocytosis, T cell proliferation and differentiation, antibody production and modulation of inflammatory responses (46). This is likely via its role in reducing oxidative damage to cell membranes and in correcting age-associated dysregulation of redox status and via its modulatory effect on specific properties of cell membranes (46). Even though the aging process appears to spare the absorption of vitamin E

(18), available evidence suggests increased requirements for this nutrient in older people: while vitamin E supplementation was shown to improve a range of immune markers at varying levels (

Table 1), a dose-response study showed 200 mg/d evoked the greatest increase in delayed-type hypersensitivity response and largest response to hepatitis vaccination compared to the placebo (47). While this intake is significantly above the current recommendations, it is still well below vitamin E upper level (1000 IU/d) (18) and can be regarded as safe (46). No adverse effects were observed (biochemical, disease incidence, mortality) in the study by Meydani et al. (47). However, one intervention with 200 mg/d vitamin E in non-institutionalized older people reported an increase in the severity of infections (48). This was attributed to a pro-oxidative effect of vitamin E in the absence of sufficient antioxidants such as vitamin C and glutathione to recycle the oxidized vitamin E (48). In fact in another study conducted in 647 older adults residing in nursing homes in US, supplementation with 200 mg/day of vitamin E in conjuction with ½ RDA of essential vitamins and minerals (to ensure adequate intake of all other nutrients), significantly reduced all upper respiratory infections, in particular common cold, compared to the control group who received ½ RDA of all vitamins and minerals (49). This highlights the importance of determining the impact of optimal intakes of a particular nutrient on immune response while other nutrients requirements are met.

Selenium

Selenium plays a role in a range of immune functions via selenoproteins primarily involved in antioxidant defense, cell signaling and redox homeostasis (50). Selenium affects both the innate as well as the adaptive immune response via its role in, for example, the activation of B and T cells and hence improved response to vaccines and in mechanisms such as oxidative burst, cytokine production and the regulation of inflammation (51). Administration was shown to promote immune responses in several preclinical studies as indicated by a range of markers such as T cell

proliferation and activity of natural killer cells and is most effective if selenium status is low (51). Selenium status inadequacy or even deficiency is common on the European continent (52), and in other parts of the world, due to low soil content: this may contribute to alterations of immunity.

The evidence for the effect of selenium on viral infections and the proposed mechanisms have recently been reviewed (53, 54), highlighting the important role selenium plays concerning host, but also pathogen, related factors. Coxsackie virus B3, an infectious cofactor for Keshan disease first described in Northeastern China, was found to become more virulent if the host is selenium deficient (55). Ensuring adequate selenium status might therefore not only support the host immune system, but also affect the virus itself and consequently the severity of the disease (56). It was suggested as a preventive agent for SARS-CoV-2 (57).

Evidence, albeit limited and somewhat inconsistent, indicates a beneficial effect of selenium complements in older persons (

Table 1). The Institute of Medicine set the Tolerable Upper Intake Level at 400 µg/d selenium (18) and toxicity seems dependent on the form of selenium used and host status (57). Still, as selenium has a relatively narrow safety range, additional intake via supplements in the range of 50 to 100 µg/d of selenium to increase levels to normal for those with low selenium status is recommended.

Zinc

With its presence in a wide range of enzymes and transcription factors and its role in the regulation of intracellular signaling pathways, zinc affects both the innate and adaptive immune systems. Zinc promotes barrier integrity. It supports monocyte and macrophage phagocytosis and natural killer cell activity and promotes the activity of Th1 lymphocytes, the proliferation of cytotoxic T cells, the development of regulatory T cells and the production of antibodies (58). Zinc also has specific anti-viral actions (59). Deficiency is thought to result in immune dysfunction including thymic atrophy, lymphopenia, and impaired adaptive immunity (60). Zinc is crucial in the defense against viruses as it can inhibit the entry of certain viruses into the host cell through stabilization of the cell membrane, and it can interfere with their ability to replicate (61).

A significant percentage of older adults (30 and 22% in nursing home and independently living older adults, respectively) exhibit low serum zinc levels, and those with low serum zinc levels have higher pneumonia incidence compared to older adults with adequate serum zinc levels (62). Several randomized controlled trials assessed the effect of zinc supplementation on a range of markers of the immune system in older people (

Table 1). Even though there are some inconsistencies, these studies support the important role zinc plays in the immune system in general, but also for older people. Importantly, zinc deficiency also manifests as an imbalanced inflammatory response and increased oxidative stress (63), further contributing to the negative effects of inflammaging and associated morbidities.

A review of available studies using a range of biomarkers such as serum zinc concentrations, or zinc levels in specific immune cells showed a decrease in zinc status with age (64-66). This age-related decline is thought to be more dependent on physio-pathological changes occurring with aging rather than nutritional intake (67): the data even suggest that interventions with zinc supplements are required for health and longevity at an advanced age (68). Given the high risk for, and the severe immunological impact of, zinc deficiency in older adults, complements in the range of 8 to 11 mg/d of zinc are recommended. Higher levels are needed for older adults with low serum zinc levels (69).

DHA and EPA

The importance of DHA and EPA to support human health in general is well known and their role in the immune system is increasingly evident (70). In the body, DHA and EPA are incorporated into the phospholipid bilayer of cell membranes, where they affect different aspects of cell function (71). They play an important role in cell signaling and neurotransmission, cell division, gene expression and lipid mediator production (72). Moreover, they are thought to enhance skeletal muscle anabolism, and play an important role in maintenance of muscle mass and function (73), which is key for healthy aging. Incorporation of EPA and DHA into cell membranes is typically at the expense of n-6 fatty acids, including arachidonic acid. This is very important

from the perspective of supporting immune function and controlling inflammation.

Some eicosanoid mediators produced from arachidonic acid such as prostaglandin

(PG) E2 have immunosuppressive effects decreasing the function of T and B cells,

while PGE2, PGD2 and several of the 4-series leukotrienes are involved in the

inflammatory response (74). EPA and DHA act to decrease the production of these

n-6 fatty acids derived mediators and this is one mechanism whereby they can

support adaptive immune responses and control adverse inflammatory responses

(75). EPA and DHA have other actions in inflammatory pathways, for example

inhibiting activation of the NLRP3 inflammasome and of the nuclear factor K B

pathway (75). Such effects are important in regulating anti-viral immune responses.

An important recent discovery is that both DHA and EPA are substrates for the

synthesis of highly active lipid mediators involved in regulating inflammatory

processes and responses (76). Termed specialized pro-resolving mediators, they

support the resolution of inflammatory processes by enhancing phagocytosis and

decreasing production of inflammatory cytokines, chemokines, adhesion molecules,

proteases and enzymes (77). As a result, they encourage healing, which may

consequently be hampered in case of nutritional deficiencies of DHA and EPA (78).

The mitigation of adverse effects of inflammation through adequate intakes of DHA

and EPA might therefore be particularly pronounced in older people (79).

In addition, increasing evidence indicates direct antimicrobial action of bioactive lipids

such as DHA and EPA by inducing leakage in the cell membranes of pathogens (80).

DHA and EPA increase phagocytic capacity of macrophages and other cells to

remove debris from the site of infection and injury and enhance microbial clearance

(81).

Endogenous synthesis of EPA and DHA from α-linolenic acid is limited in most people and is influenced by a range of factors such as age, sex, genetics and disease (82). Conversion is also impaired in conditions such as insulin resistance (83). This further emphasizes the importance of adequate intake of preformed DHA and EPA in older people who frequently suffer from insulin resistance or other features that limit endogenous synthesis.

It is now generally accepted that an intake of 250 to 500 mg/d EPA and DHA is required for optimal nutrition and supplements of up to 3,000 to 5,000 mg/d are regarded as safe (6, 84-87). Global mapping indicates low or even very low blood levels of omega-3 PUFAs (i.e., DHA and EPA) in a large proportion of people for whom data were available (88). This will likely apply to older people to a similar or even higher degree given their difficulties meeting nutritional recommendations in general. Although few randomized controlled trials have assessed the effect of DHA and EPA on the immune system in older people, a complementary intake of up to 500 mg/d of the omega-3 PUFAs EPA + DHA is recommended for older people based on the available evidence for their role in the immune system and emerging evidence (45).

Conclusions and call for action

Older people are at increased risk of infections and of infections being more severe and they exhibit reduced responses to vaccines than younger adults (8). Suboptimal nutritional intakes and malnutrition do contribute to the age-related deterioration of the immune system and may contribute to further deterioration particularly during a hospital stay or prolonged bedrest due to an illness (7). Western diets are high in saturated and n-6 fatty acids and refined carbohydrates and simple sugars, whilst

being low in fiber and also often in micronutrients and other important nutrients like

EPA and DHA (89). The imbalanced consumption of these nutrients can result in

adverse impacts on metabolic processes (90) as well as on immune function and

inflammatory processes (79, 91, 92). Thus, when considering the impact of single or

multiple micronutrients and bioactive omega-3 fatty acids on immunity, inflammation

and anti-viral defences, it is important to recognise that background diet is an

important variable; a strongly "Western" style diet may add a layer of harm to the

healthy aging process that already sees declines in appetite; in intake, absorption

and metabolism of key nutrients; and in immune

defences. Single micronutrients supplementation as treatment of active infection have not produced convincing results. An adequate nutrition (energy and proteins) can exert preventive effects by supporting the immune system and improving its ability to defend against infections. While the results from human studies are somewhat inconsistent and limited, the totality of evidence supports the role of complementary micronutrients and omega-3 PUFAs. Only a few randomized controlled trials have tested the effect of multiple micronutrient supplements on the immune system in older people (

1   Table 1). However, given the interdependence between nutrients for optimal function,

2   it is prudent to ensure adequate intakes for all of them to eliminate intake gaps.

3   Many vitamins and trace minerals have recognized immunomodulatory actions and a

4   variety of observational studies report that adequate micronutrient status or

5   micronutrient supplementation is associated with enhanced vaccine responses,

6   including to COVID-19 vaccination. A systematic review and meta-analysis of nine

7   clinical studies found lower seroprotection rates in people who were vitamin D

8   deficient compared to those who were adequate, when vaccinated with H3N2 and B

9   strains of seasonal influenza (93). A recent meta-analysis by Dissanayake et al. (94)

10   demonstrates that in people with Vitamin D deficiency/insufficiency the odds ratio of

11   developing COVID-19 is 1·46 (p<0.0001), for developing severe disease is 1·90, and

12   for death is 2·07. Holt et al (95) studied the different risk factors for developing

13   COVID-19 in the population based longitudinal study (COVIDENCE UK) and

14   identified that next to other risk factors vitamin A, vitamin D, zinc, selenium, fish oil

15   and probiotic supplement user had a lower risk of COVID-19 infection. Jolliffe et al

16   (96) also report an independent association between vitamin D supplement use and

17   enhanced humoral responses to COVID-19 vaccination. For some of these nutrients,

18   requirements in older people are higher than in the general population due to

19   reduced nutrient absorption and utilization, and to differing physiological status (e.g.,

20   inflammaging, immunosenescence). This is reflected in the recommendations for

21   nutrient supplements to support the immune system in healthy older people (**Error!**

22   **Reference source not found.**). Provision of these nutrients through supplements is

23   safe, as they are well within the recommended upper safety limits set by expert

24   authorities. For the needs of sick older patients who require repletion of

25   micronutrients and omega-3 PUFAs, the specific ESPEN Guidelines should be

26   consulted (97).

27   More focus on nutritional support of the immune system is needed and public health

28   officials are encouraged to advocate for nutritional strategies in supporting immunity

29   in older adults. Healthcare budgets are strained in general and even more so during

30   the current COVID-19 pandemic. Nutritional management, particularly of those at

31   increased risk of nutritional inadequacies due to advanced age or pathologies such

32   as cancer should become or remain an integral part of longer-term public health

33   programs. This applies to communities, hospitals and nursing homes as it provides a

34   promising, cost-efficient way to improve health outcomes.

35   To support immune responses in older adults, they should receive a yearly

36   assessment of their individual nutrient status to tailor personalized interventions. For

37   screening, validated public health nutrition tools such as the mini-nutritional

38   assessment short form should be used. These should be complemented with the

39   assessment of micronutrient status in biological samples (e.g. blood or urine as

40   appropriate) to identify specific, likely marginal, deficiency. Optimal nutrition to

41   support the immune system, particularly at an advanced age, will remain essential

42   even after the current COVID-19 pandemic (98). Areas for future research should

43   address the further elucidation of the role of micronutrient deficiencies and

44   supplementation to vaccination efficacy. Hence, developing strategies to ensure

45   optimal nutrition for the growing number of older adults to increase their health-span,

46   and reduce health care costs associated with their care will be an important and cost-

47   effective investment in the future of our societies.

48

78 **Author Contributions:** The design of the manuscript was developed by all authors

79 (M.E., M.M.B., P.C.C., A.F.G., E.H., A.L., S.N.M.). Writing and final content was done

80 by M.E., M.M.B., P.C.C., A.F.G., E.H., A.L. and S.N.M.. All authors read and

81 approved the final version.

References

1. Bauer ME, Fuente Mde L. The role of oxidative and inflammatory stress and persistent viral infections in immunosenescence. Mech Ageing Dev. 2016;158:27-37.

2. Wang T, Du Z, Zhu F, Cao Z, An Y, Gao Y, Jiang B. Comorbidities and multi-organ injuries in the treatment of COVID-19. The Lancet. 2020;395(10228):e52-e52.

3. Müller L, Andrée M, Moskorz W, Drexler I, Walotka L, Grothmann R, Ptok J, Hillebrandt J, Ritchie A, Rabl D, et al. Age-dependent Immune Response to the Biontech/Pfizer BNT162b2 Coronavirus Disease 2019 Vaccination. Clin Infect Dis. 2021;73(11):2065-2072.

4. Causa R, Almagro-Nievas D, Rivera-Izquierdo M, Benitez-Munoz N, Lopez-Hernandez B, Garcia-Garcia F, Alvarez-Estevez M, Soto-Perez MO, Bermudez-Tamayo C. Antibody Response 3 Months after 2 Doses of BNT162b2 mRNA COVID-19 Vaccine in Residents of Long-Term Care Facilities. Gerontology. 2021:1-7.

5. World Health Organization. Influenza (Seasonal) 2018 [Available from: https://www.who.int/news-room/fact-sheets/detail/influenza-(seasonal).

6. Calder PC, Carr AC, Gombart AF, Eggersdorfer M. Optimal nutritional status for a well-functioning immune system is an important factor to protect against viral infections. Nutrients. 2020;12(4):1-3.

7. Maggini S, Pierre A, Calder PC. Immune Function and Micronutrient Requirements Change over the Life Course. Nutrients. 2018;10(10):1531.

8. Fulop T, Witkowski JM, Pawelec G, Alan C, Larbi A. On the immunological theory of aging. Interdisc Top Gerontol. 2014;39:163-76.

9. Franceschi C, Garagnani P, Parini P, Giuliani C, Santoro A. Inflammaging: a new immune-metabolic viewpoint for age-related diseases. Nat Rev Endocrinol. 2018;14(10):576-590.

10. Castelo-Branco C, Soveral I. The immune system and aging: a review. Gynecol Endocrinol. 2014;30(1):16-22.

11. Murphy KM, Weaver C. Janeway's Immunobiology. 9th ed: Garland Science/Taylor & Francis Group, LLC; 2017.

12. Calder PC. Feeding the immune system. Proc Nutr Soc. 2013;72(3):299-309.

13. Goldstein DR. Aging, imbalanced inflammation and viral infection. Virulence. 2010;1(4):295-298.

14. Goodwin K, Viboud C, Simonsen L. Antibody response to influenza vaccination in the elderly: a quantitative review. Vaccine. 2006;24(8):1159-69.

15. Richardson DP, Lovegrove JA. Nutritional status of micronutrients as a possible and modifiable risk factor for COVID-19: a UK perspective. Br J Nutr. 2021;125(6):678-684.

16. Landi F, Calvani R, Tosato M, Martone AM, Ortolani E, Savera G, Sisto A, Marzetti E. Anorexia of Aging: Risk Factors, Consequences, and Potential Treatments. Nutrients. 2016;8(2):69.

17.   Institute of Medicine. Dietary reference intakes of vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. Washington, DC: National Academic Press; 2001.

18.   Institute of Medicine. Dietary reference intakes of vitamin C, vitamin E, selenium, and carotenoids. Washington, DC: National Academic Press; 2000.

19.   Institute of Medicine. Dietary reference intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin and Choline. Washington, D.C.: The National Academic Press; 1998.

20.   Institute of Medicine. Dietary reference intakes for calcium and vitamin D. Ross AC, Taylor CL, Yaktine AL, Del Valle HB, editors. Washington: The National Academies Press; 2011.

21.   Saternus R, Vogt T, Reichrath J. A Critical Appraisal of Strategies to Optimize Vitamin D Status in Germany, a Population with a Western Diet. Nutrients. 2019;11(11):2682.

22.   Troesch B, Eggersdorfer M, Weber P. The Role of Vitamins in Aging Societies. Int J Vitam Nutr Res. 2012;82(5):355-359.

23.   Blumberg JB, Frei B, Fulgoni VL, Weaver CM, Zeisel SH. Contribution of Dietary Supplements to Nutritional Adequacy in Various Adult Age Groups. Nutrients. 2017;9(12):1-11.

24.   Scrimshaw NS, SanGiovanni JP. Synergism of nutrition, infection, and immunity: an overview. Am J Clin Nutr. 1997;66(2):464s-477s.

25.   Barazzoni R, Bischoff SC, Breda J, Wickramasinghe K, Krznaric Z, Nitzan D, Pirlich M, Singer P. ESPEN expert statements and practical guidance for nutritional management of individuals with SARS-CoV-2 infection. Clinical Nutrition. 2020;39(6):1631-1638.

26.   Carr AC, Maggini S. Vitamin C and immune function. Nutrients. 2017;9(11):1211-1211.

27.   Hunt C, Chakravorty NK, Annan G, Habibzadeh N, Schorah CJ. The clinical effects of vitamin C supplementation in elderly hospitalised patients with acute respiratory infections. International journal for vitamin and nutrition research Internationale Zeitschrift für Vitamin- und Ernährungsforschung Journal international de vitaminologie et de nutrition. 1994;64(3):212-219.

28.   Fletcher AE, Breeze E, Shetty PS. Antioxidant vitamins and mortality in older persons: findings from the nutrition add-on study to the Medical Research Council Trial of Assessment and Management of Older People in the Community. Am J Clin Nutr. 2003;78(5):999-1010.

29.   Girodon F, Lombard M, Galan P, Brunet-Lecomte P, Monget AL, Arnaud J, Preziosi P, Hercberg S. Effect of Micronutrient Supplementation on Infection in Institutionalized Elderly Subjects: A Controlled Trial. Ann Nutr Metab. 1997;41(2):98-107.

30.   Girodon F, Galan P, Monget AL, Boutron-Ruault MC, Brunet-Lecomte P, Preziosi P, Arnaud J, Manuguerra JC, Herchberg S. Impact of trace elements and vitamin supplementation on immunity and infections in institutionalized elderly

patients: a randomized controlled trial. MIN. VIT. AOX. geriatric network. Arch Intern Med. 1999;159(7):748-54.

31.   Thomas S, Patel D, Bittel B, Wolski K, Wang Q, Kumar A, Il'Giovine ZJ, Mehra R, McWilliams C, Nissen SE, et al. Effect of High-Dose Zinc and Ascorbic Acid Supplementation vs Usual Care on Symptom Length and Reduction Among Ambulatory Patients With SARS-CoV-2 Infection: The COVID A to Z Randomized Clinical Trial. JAMA Network Open. 2021;4(2):e210369-e210369.

32.   Hemilä H, Louhiala P. Vitamin C for preventing and treating pneumonia. Cochrane Database Syst Rev. 2013;8(8):CD005532.

33.   Cerullo G, Negro M, Parimbelli M, Pecoraro M, Perna S, Liguori G, Rondanelli M, Cena H, D'Antona G. The Long History of Vitamin C: From Prevention of the Common Cold to Potential Aid in the Treatment of COVID-19. Front Immunol. 2020;11:574029.

34.   Schloss J, Lauche R, Harnett J, Hannan N, Brown D, Greenfield T, Steel A. Efficacy and safety of vitamin C in the management of acute respiratory infection and disease: A rapid review. Adv Integr Med. 2020;4:187-191.

35.   Linus Pauling Institute. Linus Pauling Institute Recommendation Vitamin C 2020 [Available from: https://lpi.oregonstate.edu/mic/vitamins/vitamin-C.

36.   Brubacher D, Moser U, Jordan P. Vitamin C concentrations in plasma as a function of intake: a meta-analysis. Int J Vitam Nutr Res. 2000;70(5):226-37.

37.   Kinyamu HK, Gallagher JC, Petranick KM, Ryschon KL. Effect of parathyroid hormone (hPTH[1-34]) infusion on serum 1,25-dihydroxyvitamin D and parathyroid hormone in normal women. J Bone Miner Res. 1996;11(10):1400-1405.

38.   Charoenngam N, Holick MF. Immunologic Effects of Vitamin D on Human Health and Disease. Nutrients. 2020;12(7):2097.

39.   Prietl B, Treiber G, Pieber TR, Amrein K. Vitamin D and immune function. Nutrients. 2013;5(7):2502-2521.

40.   Martineau AR, Jolliffe DA, Hooper RL, Greenberg L, Aloia JF, Bergman P, Dubnov-Raz G, Esposito S, Ganmaa D, Ginde AA, et al. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. The BMJ. 2017;356:i6583.

41.   Jolliffe DA, Camargo CA, Jr., Sluyter JD, Aglipay M, Aloia JF, Ganmaa D, Bergman P, Bischoff-Ferrari HA, Borzutzky A, Damsgaard CT, et al. Vitamin D supplementation to prevent acute respiratory infections: a systematic review and meta-analysis of aggregate data from randomised controlled trials. Lancet Diabetes Endocrinol. 2021;9(5):276-292.

42.   Bischoff-Ferrari HA, Dawson-Hughes B, Platz A, Orav EJ, Stähelin HB, Willett WC, Can U, Egli A, Mueller NJ, Looser S, et al. Effect of High-Dosage Cholecalciferol and Extended Physiotherapy on Complications After Hip Fracture: A Randomized Controlled Trial. Arch Intern Med. 2010;170(9):813-820.

43.   Li-Ng M, Aloia JF, Pollack S, Cunha BA, Mikhail M, Yeh J, Berbari N. A randomized controlled trial of vitamin D3 supplementation for the prevention of symptomatic upper respiratory tract infections. Epidemiol Infect. 2009;137(10):1396-1404.

44.   Brenner H. Vitamin D Supplementation to Prevent COVID-19 Infections and Deaths-Accumulating Evidence from Epidemiological and Intervention Studies Calls for Immediate Action. Nutrients. 2021;13(2):411.

45.   Louca P, Murray B, Klaser K, Graham MS, Mazidi M, Leeming ER, Thompson E, Bowyer R, Drew DA, Nguyen LH, et al. Modest effects of dietary supplements during the COVID-19 pandemic: insights from 445 850 users of the COVID-19 Symptom Study app. BMJ Nutr Prev Health. 2021;4(1):149-157.

46.   Meydani SN, Lewis ED, Wu D. Perspective: Should Vitamin E Recommendations for Older Adults Be Increased? Adv Nutr. 2018;9(5):533-543.

47.   Meydani SN, Meydani M, Blumberg JB, Leka LS, Siber G, Loszewski R, Thompson C, Pedrosa MC, Diamond RD, Stollar BD. Vitamin E supplementation and in vivo immune response in healthy elderly subjects. A randomized controlled trial. JAMA. 1997;277(17):1380-1386.

48.   Graat JM, Schouten EG, Kok FJ. Effect of daily vitamin E and multivitamin-mineral supplementation on acute respiratory tract infections in elderly persons: a randomized controlled trial. JAMA. 2002;288(6):715-721.

49.   Meydani SN, Leka LS, Fine BC, Dallal GE, Keusch GT, Singh MF, Hamer DH. Vitamin E and respiratory tract infections in elderly nursing home residents: a randomized controlled trial. JAMA. 2004;292(7):828-836.

50.   Labunskyy VM, Hatfield DL, Gladyshev VN. Selenoproteins: Molecular Pathways and Physiological Roles. Physiol Rev. 2014;94(3):739-777.

51.   Avery JC, Hoffmann PR. Selenium, Selenoproteins, and Immunity. Nutrients. 2018;10(9):1203.

52.   Rayman MP. Selenium and human health. Lancet. 2012;379(9822):1256-1268.

53.   Guillin OM, Vindry C, Ohlmann T, Chavatte L. Selenium, Selenoproteins and Viral Infection. Nutrients. 2019;11(9):2101.

54.   Martinez SS, Huang Y, Acuna L, Laverde E, Trujillo D, Barbieri MA, Tamargo J, Campa A, Baum MK. Role of Selenium in Viral Infections with a Major Focus on SARS-CoV-2. Int J Mol Sci. 2021;23(1):280.

55.   Beck MA, Handy J, Levander OA. Host nutritional status: The neglected virulence factor. Trends in Microbiology. 2004;12(9):417-423.

56.   Huang Z, Rose AH, Hoffmann PR. The role of selenium in inflammation and immunity: from molecular mechanisms to therapeutic opportunities. Antioxid Redox Signal. 2012;16(7):705-743.

57.   Kieliszek M, Lipinski B. Selenium supplementation in the prevention of coronavirus infections (COVID-19). Med Hypotheses. 2020;143:109878.

58.   Wessels I, Maywald M, Rink L. Zinc as a Gatekeeper of Immune Function. Nutrients. 2017;9(12):1286.

59.   Read SA, Obeid S, Ahlenstiel C, Ahlenstiel G. The Role of Zinc in Antiviral Immunity. Adv Nutr. 2019;10(4):696-710.

60. Fukada T, Yamasaki S, Nishida K, Murakami M, Hirano T. Zinc homeostasis and signaling in health and diseases: Zinc signaling. J Biol Inorg Chem. 2011;16(7):1123-34.

61. Kumar A, Kubota Y, Chernov M, Kasuya H. Potential role of zinc supplementation in prophylaxis and treatment of COVID-19. Med Hypotheses. 2020;144:109848.

62. Meydani SN, Barnett JB, Dallal GE, Fine BC, Jacques PF, Leka LS, Hamer DH. Serum zinc and pneumonia in nursing home elderly. Am J Clin Nutr. 2007;86(4):1167-1173.

63. Gammoh NZ, Rink L. Zinc in infection and inflammation. MDPI AG; 2017.

64. Haase H, Rink L. The immune system and the impact of zinc during aging. Immun Ageing. 2009;6:9.

65. Baarz BR, Rink L. Rebalancing the unbalanced aged immune system - A special focus on zinc. Ageing Res Rev. 2022;74:101541.

66. Ho E, Wong CP, King JC. Impact of zinc on DNA integrity and age-related inflammation. Free Radic Biol Med. 2022;178:391-397.

67. Giacconi R, Costarelli L, Piacenza F, Basso A, Rink L, Mariani E, Fulop T, Dedoussis G, Herbein G, Provinciali M, et al. Main biomarkers associated with age-related plasma zinc decrease and copper/zinc ratio in healthy elderly from ZincAge study. Eur J Nutr. 2017;56(8):2457-2466.

68. Yasuda H, Tsutsui T. Infants and elderlies are susceptible to zinc deficiency. Sci Rep. 2016;6:21850.

69. Barnett JB, Dao MC, Hamer DH, Kandel R, Brandeis G, Wu D, Dallal GE, Jacques PF, Schreiber R, Kong E, et al. Effect of zinc supplementation on serum zinc concentration and T cell proliferation in nursing home elderly: a randomized, double-blind, placebo-controlled trial. Am J Clin Nutr. 2016;103(3):942-951.

70. Calder PC. Chapter 8 - Metabolism of Polyunsaturated Fatty Acids by Cells of the Immune System. In: Burdge GC, editor. Polyunsaturated Fatty Acid Metabolism: AOCS Press; 2018. p. 135-155.

71. Hishikawa D, Valentine WJ, Iizuka-Hishikawa Y, Shindou H, Shimizu T. Metabolism and functions of docosahexaenoic acid-containing membrane glycerophospholipids. FEBS Lett. 2017;591(18):2730-2744.

72. de Carvalho C, Caramujo MJ. The Various Roles of Fatty Acids. Molecules. 2018;23(10):2583.

73. McGlory C, Calder PC, Nunes EA. The Influence of Omega-3 Fatty Acids on Skeletal Muscle Protein Turnover in Health, Disuse, and Disease. Front Nutr. 2019;6:144.

74. Calder Philip C. Eicosanoids. Essays Biochem. 2020;64(3):423-441.

75. Calder PC. n-3 PUFA and inflammation: from membrane to nucleus and from bench to bedside. Proc Nutr Soc. 2020:1-13.

76. Serhan CN, Levy BD. Resolvins in inflammation: emergence of the pro-resolving superfamily of mediators Protection versus uncontrolled inflammation: first responders and resolution. J Clin Invest. 2018;128(7):2657-2669.

77.   Carracedo M, Artiach G, Arnardottir H, Back M. The resolution of inflammation through omega-3 fatty acids in atherosclerosis, intimal hyperplasia, and vascular calcification. Semin Immunopathol. 2019;41(6):757-766.

78.   Basil MC, Levy BD. Specialized pro-resolving mediators: endogenous regulators of infection and inflammation. Nat Rev Immunol. 2016;16(1):51-67.

79.   Calder PC, Bosco N, Bourdet-Sicard R, Capuron L, Delzenne N, Doré J, Franceschi C, Lehtinen MJ, Recker T, Salvioli S, et al. Health relevance of the modification of low grade inflammation in ageing (inflammageing) and the role of nutrition. Ageing Res Rev. 2017;40:95-119.

80.   Chanda W, Joseph TP, Guo X-F, Wang W-D, Liu M, Vuai MS, Padhiar AA, Zhong M-T. Effectiveness of omega-3 polyunsaturated fatty acids against microbial pathogens. Journal of Zhejiang University Science B. 2018;19(4):253-262.

81.   Das UN. Can Bioactive Lipids Inactivate Coronavirus (COVID-19)? Arch Med Res. 2020;51(3):282-286.

82.   Baker EJ, Miles EA, Burdge GC, Yaqoob P, Calder PC. Metabolism and functional effects of plant-derived omega-3 fatty acids in humans. Prog Lipid Res. 2016;64:30-56.

83.   Brenner RR. Hormonal modulation of delta6 and delta5 desaturases: case of diabetes. Prostaglandins Leukot Essent Fatty Acids. 2003;68(2):151-162.

84.   Food and Agricultural Organization. Fats and fatty acids in human nutrition-Report of an expert consultation. Rome: Food and Agricultural Organization; 2010. Report No.: ISSN 0254-4725.

85.   Chinese Nutrition Society. Chinese Dietary Reference Intakes Summary (2013). Beijing, China: People's Medical Publishing House; 2013.

86.   Institute of Medicine. Dietary Reference Intakes: The Essential Guide to Nutrient Requirements. Otten JJ, Hellwig JP, Meyers LD, editors. Washington, DC: The National Academies Press; 2006.

87.   EFSA NDA Panel. Scientific opinion on the Tolerable Upper Intake Level of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and docosapentaenoic acid (DPA). EFSA Journal. 2012;10(7):1-48.

88.   Stark KD, Van Elswyk ME, Higgins MR, Weatherford CA, Salem Jr N. Global survey of the omega-3 fatty acids, docosahexaenoic acid and eicosapentaenoic acid in the blood stream of healthy adults. Prog Lipid Res. 2016;63:132-152.

89.   Cena H, Calder PC. Defining a Healthy Diet: Evidence for The Role of Contemporary Dietary Patterns in Health and Disease. Nutrients. 2020;12(2):334.

90.   Cordain L, Eaton SB, Sebastian A, Mann N, Lindeberg S, Watkins BA, O'Keefe JH, Brand-Miller J. Origins and evolution of the Western diet: health implications for the 21st century. Am J Clin Nutr. 2005;81(2):341-354.

91.   Calder PC, Albers R, Antoine JM, Blum S, Bourdet-Sicard R, Ferns GA, Folkerts G, Friedmann PS, Frost GS, Guarner F, et al. Inflammatory disease processes and interactions with nutrition. Br J Nutr. 2009;101 Suppl 1:S1-S45.

92.   Calder PC, Ahluwalia N, Brouns F, Buetler T, Clement K, Cunningham K, Esposito K, Jönsson LS, Kolb H, Lansink M, et al. Dietary factors and low-grade

inflammation in relation to overweight and obesity. Br J Nutr. 2011;106 Suppl 3:S5-S78.

93.   Lee MD, Lin CH, Lei WT, Chang HY, Lee HC, Yeung CY, Chiu NC, Chi H, Liu JM, Hsu RJ, et al. Does Vitamin D Deficiency Affect the Immunogenic Responses to Influenza Vaccination? A Systematic Review and Meta-Analysis. Nutrients. 2018;10(4):409.

94.   Dissanayake HA, de Silva NL, Sumanatilleke M, de Silva SDN, Gamage KKK, Dematapitiya C, Kuruppu DC, Ranasinghe P, Pathmanathan S, Katulanda P. Prognostic and therapeutic role of vitamin D in COVID-19: systematic review and meta-analysis. J Clin Endocrinol Metab. epub Dec11, 2021 doi: 10.1210/clinem/dgab892.

95.   Holt H, Talaei M, Greenig M, Zenner D, Symons J, Relton C, Young KS, Davies MR, Thompson KN, Ashman J, et al. Risk factors for developing COVID-19: a population-based longitudinal study (COVIDENCE UK). Thorax. 2021;0:1-13.

96.   Jolliffe DA, Faustini SE, Holt H, Perdek N, Maltby S, Talaei M, Greenig M, Vivaldi G, Tydeman F, Symons J, et al. Determinants of antibody responses to two doses of ChAdOx1 nCoV-19 or BNT162b2 and a subsequent booster dose of BNT162b2 or mRNA-1273: population-based cohort study (COVIDENCE UK). medRxiv. epub Feb 15, 2022, doi: 10.1101/2022.02.14.22270930.

97.   Berger MM, Shenkin A, Amrein K, Augsburger M, Biesalski H-K, Bischoff SC, Casaer MP, Gundogan K, Lepp H-L, de Man AME, et al. ESPEN Micronutrient guideline. Clin Nutr. 2022;S026:5614.

98.   Kim H, Rebholz CM, Hegde S, LaFiura C, Raghavan M, Lloyd JF, Cheng S, Seidelmann SB. Plant-based diets, pescatarian diets and COVID-19 severity: a population-based case-control study in six countries. BMJ Nutr Prev Health. 2021;4(1):257-266.

99.   Hodge C, Taylor CL. Vitamin A Deficiency StatPearls 2022.

100.   Sasazuki S, Sasaki S, Tsubono Y, Okubo S, Hayashi M, Tsugane S. Effect of vitamin C on common cold: randomized controlled trial. Eur J Clin Nutr. 2006;60(1):9-17.

101.   Aloia JF, Li-Ng M. Re: epidemic influenza and vitamin D. Epidemiol Infect. 2007;135(7):1095-1096.

102.   De la Fuente M, Hernanz A, Guayerbas N, Victor VM, Arnalich F. Vitamin E ingestion improves several immune functions in elderly men and women. Free Rad Res. 2008;42(3):272-280.

103.   Pallast EG, Schouten EG, de Waart FG, Fonk HC, Doekes G, von Blomberg BM, Kok FJ. Effect of 50- and 100-mg vitamin E supplements on cellular immune function in noninstitutionalized elderly persons. Am J Clin Nutr. 1999;69(6):1273-1281.

104.   Meydani SN, Barklund MP, Liu S, Meydani M, Miller RA, Cannon JG, Morrow FD, Rocklin R, Blumberg JB. Vitamin E supplementation enhances cell-mediated immunity in healthy elderly subjects. Am J Clin Nutr. 1990;52(3):557-563.

105.   Hemilä H. Vitamin E administration may decrease the incidence of pneumonia in elderly males. Clin Interv Aging. 2016;11:1379-1385.

106.   Hemilä H, Virtamo J, Albanes D, Kaprio J. The effect of vitamin E on common cold incidence is modified by age, smoking and residential neighborhood. J Am Coll Nutr. 2006;25(4):332-339.

107.   Bentley-Hewitt KL, Chen RK, Lill RE, Hedderley DI, Herath TD, Matich AJ, McKenzie MJ. Consumption of selenium-enriched broccoli increases cytokine production in human peripheral blood mononuclear cells stimulated ex vivo, a preliminary human intervention study. Mol Nutr Food Res. 2014;58(12):2350-2357.

108.   Ivory K, Prieto E, Spinks C, Armah CN, Goldson AJ, Dainty JR, Nicoletti C. Selenium supplementation has beneficial and detrimental effects on immunity to influenza vaccine in older adults. Clin Nutr. 2017;36(2):407-415.

109.   Duchateau J, Delepesse G, Vrijens R, Collet H. Beneficial effects of oral zinc supplementation on the immune response of old people. Am J Med. 1981;70(5):1001-1004.

110.   Bogden JD, Oleske JM, Lavenhar MA, Munves EM, Kemp FW, Bruening KS, Holding KJ, Denny TN, Guarino MA, Krieger LM, et al. Zinc and immunocompetence in elderly people: effects of zinc supplementation for 3 months. Am J Clin Nutr. 1988;48(3):655-663.

111.   Bogden JD, Oleske JM, Lavenhar MA, Munves EM, Kemp FW, Bruening KS, Holding KJ, Denny TN, Guarino MA, Holland BK. Effects of one year of supplementation with zinc and other micronutrients on cellular immunity in the elderly. J Am Coll Nutr. 1990;9(3):214-225.

112.   Cossack ZT. T-lymphocyte dysfunction in the elderly associated with zinc deficiency and subnormal nucleoside phosphorylase activity: Effect of zinc supplementation. Eur J Cancer Clin Oncol. 1989;25(6):973-976.

113.   Boukaïba N, Flament C, Acher S, Chappuis P, Piau A, Fusselier M, Dardenne M, Lemonnier D. A physiological amount of zinc supplementation: effects on nutritional, lipid, and thymic status in an elderly population. Am J Clin Nutr. 1993;57(4):566-572.

114.   Prasad AS, Fitzgerald JT, Hess JW, Kaplan J, Pelen F, Dardenne M. Zinc deficiency in elderly patients. Nutrition. 1993;9(3):218-224.

115.   Fortes C, Forastiere F, Agabiti N, Fano V, Pacifici R, Virgili F, Piras G, Guidi L, Bartoloni C, Tricerri A, et al. The effect of zinc and vitamin A supplementation on immune response in an older population. J Am Geriatr Soc. 1998;46(1):19-26.

116.   Provinciali M, Montenovo A, Di Stefano G, Colombo M, Daghetta L, Cairati M, Veroni C, Cassino R, Torre FD, Fabris N. Effect of zinc or zinc plus arginine supplementation on antibody titre and lymphocyte subsets after influenza vaccination in elderly subjects: a randomized controlled trial. Age Ageing. 1998;27(6):715-722.

117.   Mocchegiani E, Muzzioli M, Gaetti R, Veccia S, Viticchi C, Scalise G. Contribution of zinc to reduce CD4+ risk factor for 'severe' infection relapse in aging: parallelism with HIV. Int J Immunopharmacol. 1999;21(4):271-281.

118.   Mocchegiani E, Muzzioli M, Giacconi R, Cipriano C, Gasparini N, Franceschi C, Gaetti R, Cavalieri E, Suzuki H. Metallothioneins/PARP-1/IL-6 interplay on natural killer cell activity in elderly: parallelism with nonagenarians and old infected humans. Effect of zinc supply. Mech Ageing Dev. 2003;124(4):459-468.

119.   Kahmann L, Uciechowski P, Warmuth S, Malavolta M, Mocchegiani E, Rink L. Effect of improved zinc status on T helper cell activation and TH1/TH2 ratio in healthy elderly individuals. Biogerontology. 2006;7(5):429-435.

120.   Hodkinson CF, Kelly M, Alexander HD, Bradbury I, Robson PJ, Bonham MP, O'Connor JM, Coudray C, Strain JJ, Wallace JMW. Effect of Zinc Supplementation on the Immune Status of Healthy Older Individuals Aged 55–70 Years: The ZENITH Study. J Gerontol A Biol Sci Med Sci. 2007;62(6):598-608.

121.   Meydani SN, Barnett JB, Dallal GE, Fine BC, Jacques PF, Leka LS, Hamer DH. Serum zinc and pneumonia in nursing home elderly. American Journal of Clinical Nutrition. 2007;86(4):1167-1173.

122.   Prasad AS, Beck FW, Bao B, Fitzgerald JT, Snell DC, Steinberg JD, Cardozo LJ. Zinc supplementation decreases incidence of infections in the elderly: effect of zinc on generation of cytokines and oxidative stress. Am J Clin Nutr. 2007;85(3):837-844.

123.   Wong CP, Magnusson KR, Sharpton TJ, Ho E. Effects of zinc status on age-related T cell dysfunction and chronic inflammation. Biometals. 2021;34(2):291-301.

124.   Lenhart JG, Vu PT, Quackenbush K, LaPorte A, Smith J. The efficacy of a compounded micronutrient supplement on the incidence, duration, and severity of the common cold: A pilot randomized, double-blinded, placebo-controlled trial. PLoS One. 2020;15(8):e0237491.

125.   Schmoranzer F, Fuchs N, Markolin G, Carlin E, Sakr L, Sommeregger U. Influence of a complex micronutrient supplement on the immune status of elderly individuals. Int J Vitam Nutr Res. 2009;79(5-6):308-318.

Legend to the figure

Figure 1. Temporal interaction between cells of the innate and adaptive immune systems and how their functions are affected by the vitamins A, C, D and E, the trace elements selenium and zinc, and omega-3 PUFA DHA and EPA; for further vitamin A data, please see reference (99). (Created with BioRender.com).

Table 1: Randomized controlled trials (RCTs) of supplementation with micronutrients in older adults on immune response

Author, year (reference)	Micronutrient	Participants	Intervention and control group	Baseline serum level [mg/dL]	Endpoint serum level [mg/dL]	Immune-related results
Hunt et al., 1994 (27)	Vitamin C	Older patients (66-93 y); acute respiratory infections	0 (n= 29) or 200 mg/d (n= 28); 4 wk	0.41 ± 0.40[1]	PG 0.43 ± 0.35[1] IG 1.67 ± 0.57[1, a]	Increased plasma and white cell vitamin C concentration even during infection; Better recovery, particularly in those most severely ill on admission
Sasazuki et al., 2006 (100)	Vitamin C	Patients ; chronic atrophic gastritis (40-69 y; mean 57 y)	50 (n= 120) or 500 mg/d (n= 124); 5 y	LD 1.38 ± 0.03[1] HD 1.35 ± 0.03[1]	NA	Reduced risk (RR 0.34; 95% CI: 012-0.97) of suffering from a common cold ≥3 times during the survey period; No effect on severity and duration of common cold
Thomas et al., 2021 (31)	Vitamin C	Patients; SARS-CoV-2 infection (≥18 y)	0 (n= 108) or 8,000 mg/d with or without 50 mg zinc (n= 106); 10 d	NA	NA	No effect on time to reach 50% reduction in symptoms, composite 4-symptome score, hospitalization or death
Aloia and Li-Ng 2007 (101)	Vitamin D	Post-menopausal African American women (50-75 y)	0 (n= 104) or 800 IU/d (2 y) + 2,000 IU/d (1 y) (+ Ca for 3 y) (n= 104)	NA	NA	Reduced reported cold and influenza symptoms (P<0.002)
Bischoff-Ferrari et al., 2010 (42)	Vitamin D	Older people; recent hip fracture (≥65 y)	800 (n= 89) or 2,000 IU/d + Ca; 3 mo (n= 100)	HD 13.2 ±8.1[1] LD 12.3 ±7.7[1]	HD 44.7 ±10.4[1] LD 35.4 ±10.1[1, a]	Decreased number of participants with hospital readmission due to infection (-39%; 95% CI -62%, -1%)

Li-Ng et al., 2009 (43)	Vitamin D	Adults (18-80 y)	0 (n= 70) or 2,000 IU/ d; 3 mo (n= 78)	IG 25.7 ± 11.48[1] PG 25.2 ± 10.32[1]	IG 35.5 ± 9.3[1] PG: NA Δ IG: 9.6 (95% CI 8.7 12.3)[2] Δ PG -0.84 (95% CI -2.8 1.1)[2, a]	No effect on duration or severity of upper respiratory infection symptoms
De la Fuente et al., 2008 (102)	Vitamin E	Healthy older adults (70.4 ±5.1 y)	200 mg/d (n= 33) or CG (29.7 ± 4.9 y) (n= 30) ; 3 mo	NA	NA	Normalization of a range of immune parameters (lymphocytes, neutrophils etc.)
Pallast et al., 1999 (103)	Vitamin E	Healthy older adults (65-80 y)	0 (n= 50), 50 (n= 54), or 100 mg/d (n= 53) ; 6 mo	PG 1.27 ± 0.30[1] LD 1.24 ± 0.30[1] HD 1.34 ± 0.26[1]	ΔPG 0.02 ± 0.16[1] ΔLD 0.44 ± 0.22[1, a] ΔHD 0.68 ± 0.32[1, a]	Trend to increased delayed-type hypersensitivity and IL-6 production with increasing dose of vitamin E
Meydani et al., 1990 (104)	Vitamin E	Healthy older adults (≥60 y)	0 (n= 14) or 800 mg/d (n= 18); 30 d	PG 1.13 ± 0.07[1] IG 1.10 ± 0.06 [1]	PG 1.03 ± 0.06[1] IG 3.05 ± 0.27[1, a]	Increased peripheral blood mononuclear cells, delayed-type hypersensitivity skin test, mitogen-stimulated lymphocyte proliferation and other immune markers
Meydani et al., 1997 (47)	Vitamin E	Free-living healthy older adults (≥65 y)	0 (n= 19), 60 (n= 20), 200 (n=	PG 1.06 ± 0.20[1] LD 1.17 ± 0.26[1] ID 1.10 ± 0.25[1]	PG 1.00 ± 0.09[1] LD 1.65 ± 0.23[1, a] ID 2.20 ± 0.59[1, a]	Increased a range of markers of adaptive immunity, including delayed type

			20), 800 mg/d (n= 19); 235 d	HD 1.11 ± 0.27[1]	HD 3.08 ± 1.14[1, a]	hypersensitivity skin test and response to vaccination, plateauing at 200 mg/d
Graat et al., 2002 (48)	Vitamin E	Non-institutionalized older adults (≥60 y)	0 (n= 153) or 200 mg/d (n= 164); 15 mo	PG 1.25 ± 0.27[1] IG 1.23 ± 0.27[1]	NA	No effect on incidence of acute respiratory tract infections; Severity of infection was greater in the vitamin E group
Meydani et al., 2004 (49)	Vitamin E	Nursing home residents (≥65 y)	½ RDA (n= 220) or 200 IU/d (n= 231); 1 y	PG 1.15 ± 0.43[1] IG 1.14 ± 0.39[1]	PG 1.21 ± 0.41[1] IG 2.12 ± 0.69[1, a]	No effect on incidence or number of days with infection for all, upper, or lower respiratory infections; Fewer vitamin E-supplemented subjects acquired one or more respiratory infections or upper respiratory infections, common colds and shorter duration of colds
Hemilä et al., 2016 (105)	Vitamin E	Male smokers (50-69 y)	0 (n= 1265) or 50 mg/d (n= 1286) ; 5-8 y	NA	NA	Decreased incidence of pneumonia (-69%; 95% CI -83 -43%)
Hemilä et al., 2006 (106)	Vitamin E	Male smokers (50-69 y)	50 mg/d (n= NA) or control group (n= NA); 5-8 y	NA	NA	Reduced risk of common cold (RR 0.54; 95% CI 0.37 0.80) in those who smoked 5 - 14/d cigarettes; Increased risk (RR 1.58; 95% CI 1.23 to 2.01) in those smoking more

Bentley-Hewitt et al., 2014 (107)	Selenium	Adults (24-65 y)	200 µg/d selenium from enriched broccoli; cross-over with normal broccoli (n= 18); 3 d	F 1.3 (0.97-1.72)[3] M 1.2 (0.95-1.54)[3]	N.S. change from baseline; actual values NA	Increased several markers of immune response
Ivory et al., 2017 (108)	Selenium	82 adults (50-64 y)	0, 50, 100 or 200 µg/d; 12 wk	NA	NA	Mixed results on cellular immune response to influenza vaccine
Duchateau et al., 1981 (109)	Zinc	Institutionalized healthy older adults (>70 y)	100 mg/d (n= 15) or control group (n= 15); 1 mo	NA	NA	Increased some (e.g. number of circulating T lymphocytes), but not all markers of immune function measured
Bogden et al., 1988 (110)	Zinc	Community-dwelling older adults (60-89 y)	0 (n= 36), 15 (n= 36) or 100 mg/d + vitamin-mineral capsule (n= 31); 3 mo	PG 85.0 ± 9.8[1] LD 83.7 ± 19.0[1] HD 85.6 ± 13.1[1]	PG 81.7 ± 13.1[1] LD 85.6 ± 13.7[1] HD 109.8 ± 22.9[1, a]	No effect on delayed type hypersensitivity skin test
Bogden et al., 1990 (111)	Zinc	Community-dwelling older adults (60-89 y)	0 (n= 22), 15 (n= 20) or 100 mg/d + vitamin-mineral capsule (n= 19); 1 yr	PG 87.0 ± 2.6[1] LD 84.3 ± 3.3[1] HD 85.6 ± 3.3[1]	PG 88.9 ± 2.6[1] LD 87.0 ± 17.0[1] HD 109.8 ± 3.9[1, a]	No effect on immune cell numbers; Natural killer cell activity was transiently increased at the higher zinc dose; Progressive improvement in delayed type hypersensitivity skin test

Cossack 1989 (112)	Zinc	Zinc-deficient older adults (60-89 y)	60 mg/ d (n= 8); 4.5 mo compared to baseline	75 ±15[1]	115 ± 19[1, a]	Increase in erythrocytes, lymphocytes, neutrophils and erythrocyte nucleoside phosphorylase
Boukaïba et al., 1993 (113)	Zinc	Institutionalized older adults (73-106 y)	0 or 20 mg/ d cross-over (n= 44); 8 wk	HBW 79.8 ± 2.9[1] LBW 70.0 ± 1.8[1]	PG HBW 81.7 ± 4.4[1] PG LBW 69.3 ± 2.1[1] IG HBW 94.8 ± 5.9[1] IG LBW 88.0 ± 2.0[1]	Increased serum thymulin activity
Prasad et al., 1993 (114)	Zinc	Zinc-deficient older adults (50-80 y)	30 mg/d (n= 13); 6 mo compared to baseline	105.85 ± 14.8[1]	140.75 ± 31.48[1, a]	Increased delayed type hypersensitivity skin test and normalization of various immune markers
Fortes et al., 1998 (115)	Zinc	Retirement home residents (≥65 y)	0 (n= 61) or 25 mg/d +/- vitamin A (n= 57); 3 mo	NA	NA	Increased cell-mediated immune response
Provinciali et al., 1998 (116)	Zinc	Institutionalized older adults (64-100 y)	90 mg/d (n= 33) or CG (n= 31); 60 d	CG 69.7 ± 18.8[1] IG 66.1 ± 13.6[1]	CG 5.8 ± 14.8[1, 4] IG 89.0 ± 26.5[1, a]	No effect on immune parameters measured

Mocchegiani et al., 1999 (117)	Zinc	Older adults; chronic obstructive bronchitis (63-75 y)	0 (n= 14) or 12 mg/d (n= 15); 1 mo	76.8 ± 4.3[1]	NA	Increased CD4+ count
Mocchegiani et al., 2003 (118)	Zinc	Healthy older adults (63-75 y)	0 (n= 23) or 12 mg/d (n= 24); 1 mo	NA	NA	Restored natural killer cell activity and decreased incidence of severe infections
Kahmann et al., 2006 (119)	Zinc	Healthy older adults (65-82 y)	10 mg/d (n= 19); 7 wk compared to baseline	72.6 ± 2.7[1]	79.9 ± 2.3[1, a]	Decreased number of activated T helper cells, but no change in ratio of Th1/ Th2 cells
Hodkinson et al., 2007 (120)	Zinc	Healthy older adults (55-70 y)	0 (n= 31), 15 (n= 28) or 30 mg/d (n= 34); 6 mo	PG 86.3 ± 1.8[1] LD 85.0 ± 2.0[1] HD 84.3 ± 1.2[1]	PG 81.1 ± 1.8[1] LD 85.0 ± 3.1[1] HD 93.5 ± 5.0[1, a]	Increased ratio of CD4 to CD8 T lymphocytes, but no effect on long-term immune status
Meydani et al., 2007 (121)	Zinc	Nursing home residents ((≥65 y)	7 mg/d (n= 420); 12 mo;	NA	NA	Lower incidence of pneumonia; Fewer new antibiotic prescriptions; Shorter duration of pneumonia; Fewer days of antibiotic use
Prasad et al., 2007 (122)	Zinc	Healthy older adults (55-87 y)	0 (n= 25) or 45 mg/d (n= 24); 12 mo	NA	NA	Lower incidence of infections, ex vivo generation of TNFα and lower plasma markers for oxidative stress

Barnett et al., 2016 (69)	Zinc	Nursing home residents (≥65 y)	0 (n= 16) or 30 mg/d (n= 14); 3 mo	PG 66.3 ± 10.0[1] IG 63.9 ± 9.7[1]	PG 65.4 ± 8.8[1] IG 73.2 ± 14.6[1, a]	Increased T cell function
Thomas et al., 2021 (123)	Zinc	Patients; SARS-CoV-2 infection (≥18 y)	0 (50) or 50 mg/d with or without 8,000 mg vitamin C (n= 116); 10 d	NA	NA	No effect on time to reach 50% reduction in symptoms, composite 4-symptome score, hospitalization or death
Girodon et al., 1997 (29)	Multiple vitamins and trace elements	Nursing home residents (≥65 y)	0 (n= 20) or 120 mg/d vitamin C, 6 mg/d β-carotene, 15 mg/d vitamin E, 20 mg/d Zn, 100 μg/d Se (n= 21); 2 y	Improvement in the status for the supplemented nutrients		Decreased incidence of respiratory and urogenital infections (p <0.01); No effect on mortality
Girodon et al., 1999 (30)	Multiple vitamins and trace elements	Nursing home residents (≥65 y)	0 (n= 182) or 120 mg/d vitamin C, 6 mg/d β-carotene, 15 mg/d vitamin E, 20 mg/d Zn, 100	Significant improvement in α-tocopherol, β-carotene, vitamin C, Zn and Se status		Increased antibody response to influenza vaccine; Higher number of serologically protected patients; No effect in the incidence of respiratory tract events

			µg/d Se (n= 181); 2 y			
Lenhart et al., 2020 (124)	Multiple vitamins and trace elements	Healthy (asymptomatic) adults (18-65 y)	Placebo (n= 130) or multi-micronutrient supplement (129); 12 wk	NA	NA	Trend for reduced odds of upper respiratory infection (p =0.14); Lower odds of reporting symptoms for runny nose (OR 0.53, p = 0.01) and cough (OR 0.51, p = 0.04); No effect on severity
Schmoranzer et al., 2009 (125)	Multiple vitamins and trace elements	Residents of nursing homes (62-98 y)	Placebo (n= 42) or micronutrient supplement (n= 40); 3 mo	NA	NA	Increased number of various types of immune cells; No effect on specific antibody response to influenza vaccination

Abbreviations: CG: control group; CI: Confidence Interval; F: female; HBW: high body weight (BMI ≥24 kg/m²); HD: high-dose group; IG: intervention group; LBW: low body weight (BMI ≤21 kg/m²); LD: low-dose group; ID: intermediate-dose group; M: male; NA: not available; PG: placebo group; RCT: randomized controlled trial;

[1] Mean ±Standard deviation

[2] Mean (95% CI)

[3] Mean (Range)

[4] Reported in error as 5.8 ±14.8 µg dL;

[a] p<0.05

Table 2: Principal nutrients supporting the immune system in the general population (6)

Nutrient	Rationale	Suggested intake	Dietary reference intake (DRI)[1]	
			Recommended Dietary Allowances	Tolerable upper levels of intakes
Vitamins and trace elements	These micronutrients play important roles in supporting the cells and tissues of the immune system. Deficiencies or suboptimal status negatively affect immune function and can decrease resistance to infections.	Daily multivitamin and trace element complements that supply the micronutrient requirements (e.g., DRI) are recommended in addition to the consumption of a balanced diet	Varies according to nutrient	
Vitamin C	Doses of ≥200 mg/d provide saturating levels in the blood, and support reduction in the risk,	Daily intake of at least 200 mg/d for healthy older adults.	Men: 90 mg/d Women: 75 mg/d	Men: 2,000 mg/d Women: 2,000 mg/d

			DRI[1]	
	severity and duration of upper and lower respiratory tract infections.			
Vitamin D	Daily supplementation of vitamin D reduces the risk of acute respiratory tract infections. Dietary intake and endogenous synthesis is low in most older people.	Intake of 2000 IU/d (50 µg/d).	Men: 20 µg/d Women: 20 µg/d	Men: 100 µg/d Women: 100 µg/d
Vitamin E	Emerging evidence indicates that current recommendations are too low to compensate for age-related losses and to counter imbalances in the immune system resulting in hyperinflammation in older people.	A complementary intake of 200 IU/d[2]	Men: 15 mg/d Women: 15 mg/d	Men: 1,000 mg/d Women: 1,000 mg/d
Selenium	Selenium is important in the regulation of inflammation by preventing excessive and chronic inflammation and is essential for a well-functioning immune system.	An intake from supplements in the range of 50 to 100 µg/d of selenium for those with low selenium status.	Men: 55 µg/d Women: 55 µg/d	Men: 400 µg/d Women: 400 µg/d
Zinc	Marginal zinc deficiency can impact immunity. Those deficient in zinc, are prone to increased diarrheal and respiratory morbidity.	Daily intake in the range of 30 mg/d in those with low zinc status; a higher level maybe needed for older adults with very low serum zinc level	Men: 11 mg/d Women: 8 mg/d	Men: 40 mg/d Women: 40 mg/d
DHA + EPA	DHA and EPA support an effective immune system, including by helping to resolve inflammation.	Daily intake of up to 500 mg/d of EPA + DHA.	NA	NA

Abbreviations: DHA: docosahexaenoic acid; DRI: dietary reference intake; EPA: eicosapentaenoic acid; NA: not available;

[1] For those aged >70 years based on values from the Institute of Medicine (17, 18, 20); [2] 1 IU = 0.67 mg for *d-alpha-tocopherol* (natural), 1 IU = 0.9 mg for *dl-alpha tocopherol* (synthetic)