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Foods to deliver immune-supporting nutrients

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Purpose of review: This article will briefly describe the role of specific dietary components, mainly micronutrients, in supporting the immune response and summarise the literature regarding foods and dietary patterns in the context of immunity and infectious illness. Literature on SARS-COV-2 infection and COVID-19 is referred to where appropriate.

Recent findings: Micronutrients, other nutrients and plant bioactives have roles in supporting the immune response. Low status of a number of micronutrients is associated with increased risk and severity of COVID-19. Recent studies report associations of plant-based diets with lower risk of, and less severe, COVID-19.

Summary: In order to support the immune response, sufficient amounts of a range of essential and non-essential nutrients and other bioactives, mainly from a plant-based diet should be consumed. Further research should define cause-and-effect relationships of intakes of individual dietary components and foods, and of dietary patterns with susceptibility to, and severity of, viral infections.

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Introduction and scope

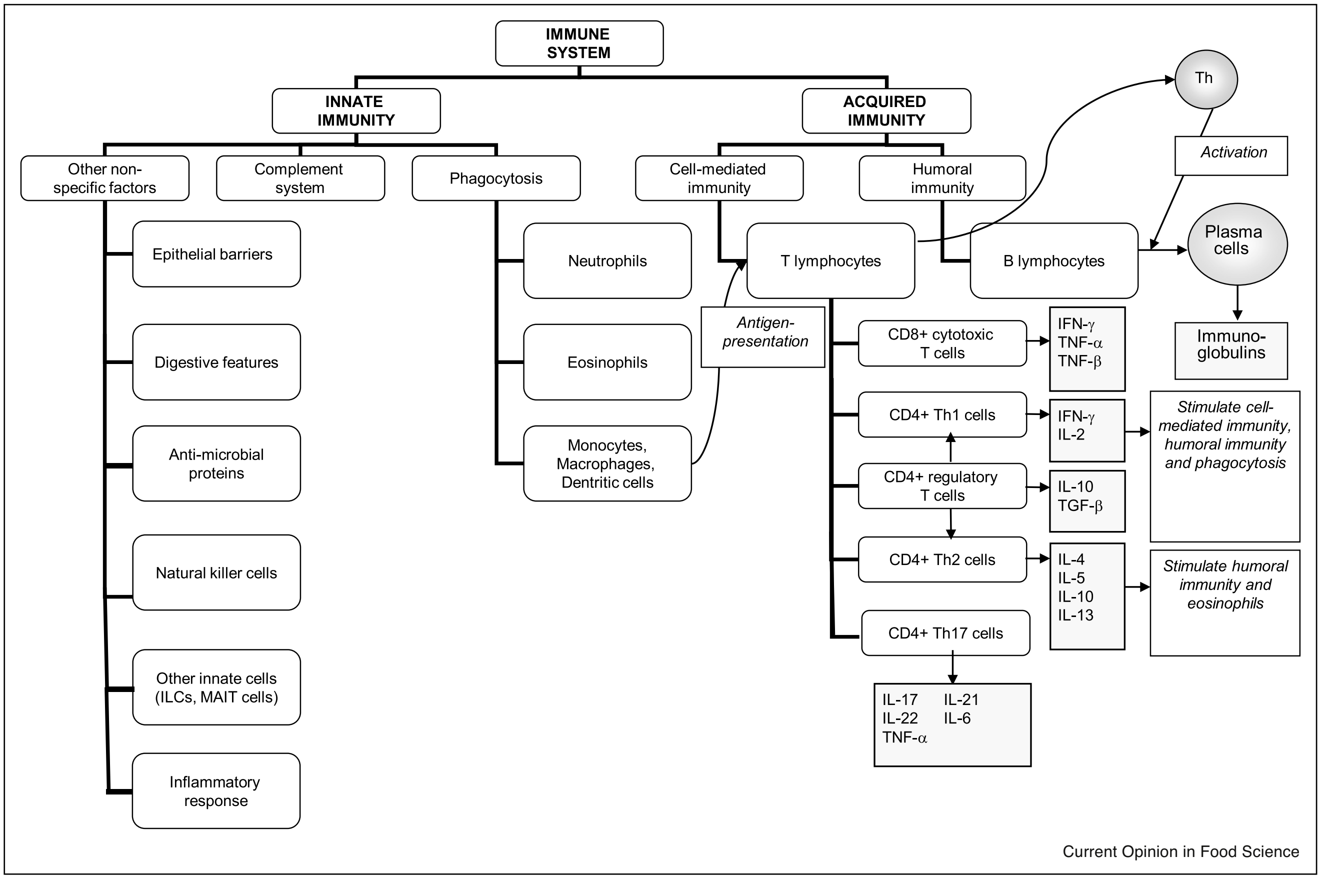
Humans co-exist in an environment with other organisms including bacteria, viruses, fungi and parasites, some of which can be harmful, causing infectious disease. The social, economic and health consequences of infectious disease to humans are well known [1–3], but have been highlighted again over the last two years due to the emergence of severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2) and the disease it causes, COVID-19. The SARS-CoV-2 pandemic has focused the attention of consumers, the health care sector, governments, regulators and industry on the importance of immune health and on the need to develop strategies to provide the population with the protection they require against harmful (i.e. pathogenic) organisms. The primary role of the immune system is to provide defence against harmful bacteria and viruses, which together are termed microorganisms or microbes, as well as fungi and parasites. Importantly, the immune system also provides immunologic tolerance to non-pathogenic organisms, to harmless environmental exposures (e.g. food) and to the individual themselves. In order to be effective against the wide array of possible threatening organisms, the human immune system has evolved to include many different cell types, many communicating molecules and multiple functional responses which are generally classified into innate and acquired immunity (Figure 1) [4•]. These functional responses may be divided into four general features:

- barrier function, preventing (micro)organisms from entering the body;
- recognition of (micro)organisms and identification of whether they are harmful or not;
- elimination of (micro)organisms identified as being harmful;
- generation of memory of immunological encounters.

These complex and sophisticated actions are achieved because the human immune system is comprised of many cell types, each with their own individual functional capabilities. These different cell types interact with one another as part of the immune response to assure effective protection from pathogens and effective tolerance to non-threatening exposures. There is variation in immune parameters among individuals [5] and many factors contribute to this variation (Figure 2) [4•,5]. These factors include genetics, infection history, vaccination history, illness, some medications, sex, and stage of the life course (e.g. pregnancy, infancy, old age). Lifestyle factors including stress, physical fitness and diet also have an influence (Figure 2). Diet is important because it provides the nutrients that have vital roles in supporting the immune response [6,7•], while other 'non-nutrient' components of foods can also play roles in supporting the immune system. The diet provides:

- the fuels that provide energy for the immune system to function;

Figure 1



The components of the immune system and their division into innate and acquired immunity. IFN, interferon; IL, interleukin; ILCs, innate lymphoid cells; MAIT, mucosal associated invariant T; TGF, transforming growth factor; TNF, tumor necrosis factor. Taken from Ref. [4•].

- the building blocks to support the high level of biosynthesis and cell replication required during the immune response;
- substrates for the production of some immune-active metabolites;
- many regulators of immune cell metabolism;
- agents with direct anti-microbial properties;
- anti-oxidants and anti-inflammatories providing the host with protection from the oxidative and inflammatory stress generated during the immune response;
- substrates for the development and maintenance of the intestinal microbiota which in turn modulates the immune system.

The aim of this article is to briefly describe the role of specific dietary components, mainly micronutrients, in supporting the immune response and to survey the literature regarding foods and diets/dietary patterns in the context of immunity and infectious illness. Literature that is relevant to SARS-COV-2 infection and COVID-19 will be referred to where appropriate.

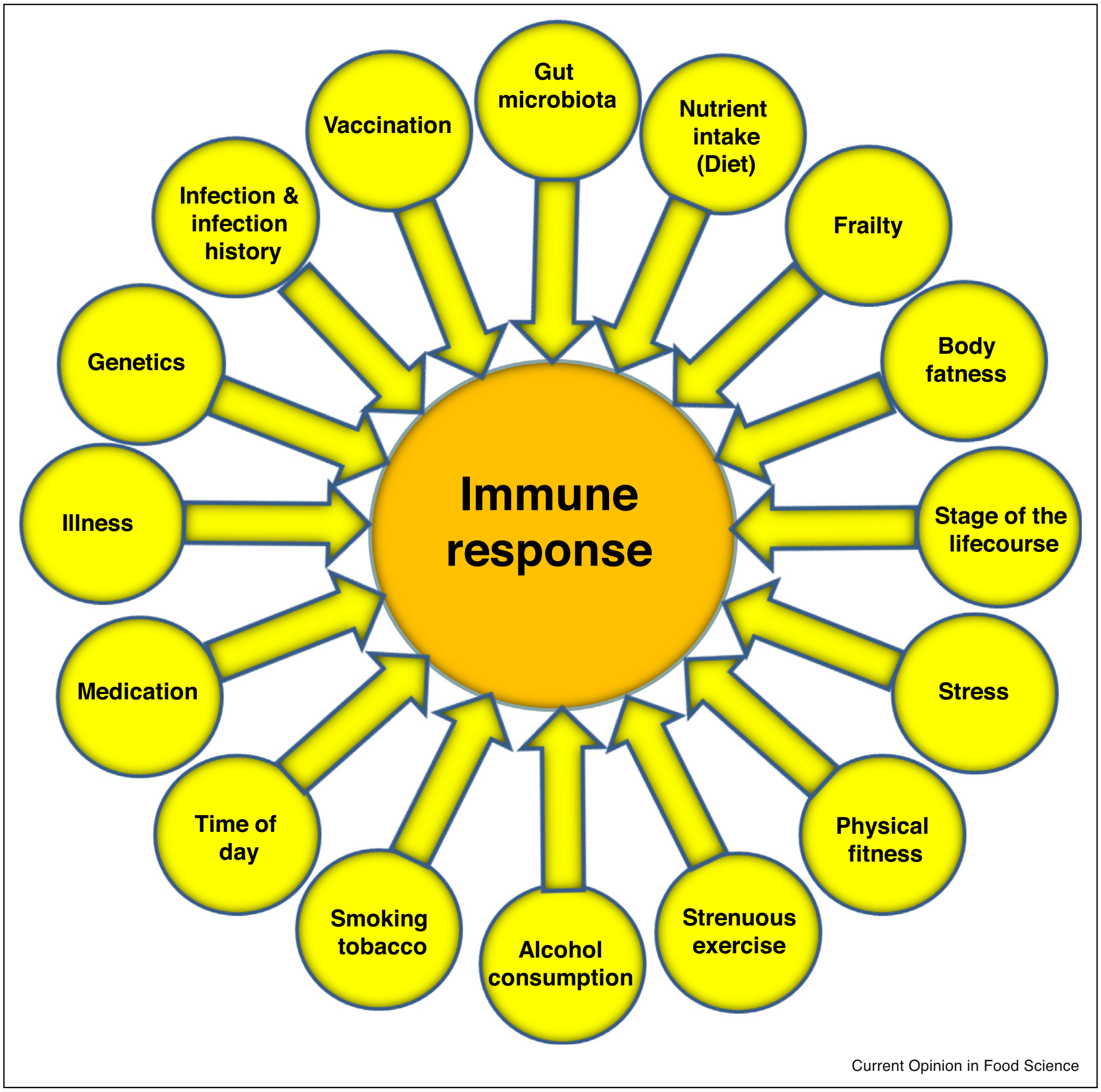
Key immune-supporting nutrients

Multiple micronutrients play vital roles in supporting the immune response [7•,8,9,10••,11] (Table 1). The roles of vitamins A, C and D and zinc, copper and iron are well explored and fairly widely recognized, but B vitamins, vitamin E, vitamin K, selenium, magnesium and others also all have roles. Insufficient intake of several of these micronutrients impairs many aspects of both innate and acquired immunity and increases susceptibility to infections [7•,10••]. In many cases the immune impairments can be reversed by repletion and this reduces susceptibility to infection. Many micronutrients have been discussed in the context of infection with SARS-CoV-2 and COVID-19 but vitamins C [12,13•] and D [14•,15••] and zinc [16••,17•] have received the most attention.

Vitamin C

Vitamin C supports the activity of many cells of the immune system (Table 1) [18] and helps to control oxidative stress and inflammation. People deficient in vitamin C are susceptible to severe respiratory infections such as pneumonia and a meta-analysis reported a

Figure 2



Factors that influence the immune response. Note that the listing is not exclusive. Taken from Ref. [4•].

significant reduction in the risk of pneumonia with vitamin C supplementation, particularly in individuals with low dietary intakes [19]. Vitamin C supplementation has also been shown to decrease the duration and severity of upper respiratory tract infections, such as the common cold, especially in people under enhanced physical stress [20]. Multiple studies report an association between low vitamin C status and increased susceptibility to, and severity of, COVID-19 (e.g. Ref. [21]). Most studies investigating the ability of vitamin C to treat COVID-19 have focused on intravenous infusion rather than the oral route, as reviewed elsewhere [22].

Vitamin D

Vitamin D has pleiotropic actions within the immune system but does support the activity of several immune cell types [23]. Furthermore, some immune cells (e.g. dendritic cells, macrophages) can produce the active form of vitamin D suggesting it is important to immunity. Vitamin D also promotes the production of antimicrobial proteins such as cathelicidin and β-defensins. Vitamin D deficiency impairs the response to the seasonal influenza vaccine [24] and meta-analyses of randomised controlled trials of vitamin D supplementation report reduced incidence of respiratory tract infections [25]. Vitamin D

Table 1

Summary of the effects of various micronutrients on different aspects of immunity

Micronutrient	Role in barrier function	Role in cellular aspects of innate immunity	Role in T-cell mediated immunity	Role in B-cell mediated immunity
Vitamin A	Promotes differentiation of epithelial tissue; Promotes gut homing of B-cells and T-cells; Promotes intestinal immunoglobulin A+ cells; Promotes epithelial integrity	Regulates number and function of NK cells; Supports phagocytic and oxidative burst activity of macrophages	Regulates development and differentiation of Th1 and Th2 cells; Promotes conversion of naïve T-cells to regulatory T-cells; Regulates IL-2, IFN-γ and TNF production	Supports function of B-cells; Required for immunoglobulin A production
Vitamin B6	Promotes gut homing of T-cells	Supports NK cell activity	Promotes T-cell differentiation, proliferation and function, especially Th1-cells; Regulates (promotes) IL-2 production	Supports antibody production
Vitamin B9 (Folate)	Survival factor for regulatory T-cells in the small intestine	Supports NK cell activity	Promotes proliferation of T-cells and the Th1-cell response	Supports antibody production
Vitamin B12	Important co-factor for gut microbiota	Supports NK cell activity	Promotes T-cell differentiation, proliferation and function, especially cytotoxic T-cells; Controls ratio of T-helper to cytotoxic T-cells	Required for antibody production
Vitamin C	Promotes collagen synthesis; Promotes keratinocyte differentiation; Protects against oxidative damage; Promotes wound healing; Promotes complement	Supports function of neutrophils, monocytes and macrophages including phagocytosis; Supports NK cell activity	Promotes production, differentiation and proliferation of T-cells especially cytotoxic T-cells; Regulates IFN-γ production	Promotes antibody production
Vitamin D	Promotes production of antimicrobial proteins (cathelicidin, β-defensin); Promotes gut tight junctions (via E-cadherin, connexion 43); Promotes homing of T cells to the skin	Promotes differentiation of monocytes to macrophages; Promotes macrophage phagocytosis and oxidative burst	Promotes antigen processing but can inhibit antigen presentation; Can inhibit T-cell proliferation, Th1-cell function and cytotoxic T-cell function; Promotes the development of regulatory T-cells; Inhibits differentiation and maturation of dendritic cells; Regulates IFN-γ production	Can decrease antibody production
Vitamin E	Protects against oxidative damage	Supports NK cell activity	Promotes interaction between dendritic cells and T-cells; Promotes T-cell proliferation and function, especially Th1-cells; Regulates (promotes) IL-2 production	Supports antibody production
Zinc	Maintains integrity of the skin and mucosal membranes; Promotes complement activity	Supports monocyte and macrophage phagocytosis; Supports NK cell activity	Promotes Th1-cell response; Promotes proliferation of cytotoxic T-cells; Promotes development of regulatory T-cells; Regulates (promotes) IL-2 and IFN-γ production; Reduces development of Th9 and Th17 cells	Supports antibody production particularly immunoglobulin G
Copper		Promotes neutrophil, monocyte and macrophage phagocytosis; Supports NK cell activity	Regulates differentiation and proliferation of T-cells; Regulates (promotes) IL-2 production	
Iron	Essential for growth and differentiation of epithelial tissue	Promotes bacterial killing by neutrophils; Regulates balance of M1 and M2 macrophages; Supports NK cell activity	Regulates differentiation and proliferation of T-cells; Regulates IFN-γ production	
Selenium		Supports NK cell activity	Regulates differentiation and proliferation of T-cells; Regulates (promotes) IFN-γ production	Supports antibody production

Abbreviations used: IFN, interferon; IL, interleukin; NK, natural killer; Th, T-helper; TNF, tumor necrosis factor. Taken from Ref. [4•].

supplements seem most effective when given regularly, rather than as a bolus, and in individuals with low starting vitamin D status [25]. Multiple studies report an association between low vitamin D status and increased susceptibility to, and severity of, COVID-19 (e.g. Ref. [26]) and meta-analyses report that vitamin D deficiency increases risk of severe COVID-19, hospitalisation with COVID-19 and mortality from COVID-19 [27,28]. A study in an Italian residential care home reported that a bolus of vitamin D reduced mortality from COVID-19 [29]. Vitamin D supplementation in patients hospitalised with COVID-19 is reported to reduce COVID-19 severity (e.g. need for intensive care unit admission, mortality) [30,31].

Zinc

Zinc supports the activity of many cells of the immune system (Table 1) [32], helps to control oxidative stress and inflammation and has specific anti-viral actions [33] including inhibiting the replication of coronaviruses [34]. Zinc supplementation improves some markers of immunity especially in older people or those with low zinc intake [35] and improves vaccination responses [36] and meta-analyses of randomised controlled trials of zinc supplementation report reduced incidence of lower respiratory tract infections [37,38]. Multiple studies report an association between low zinc status and increased susceptibility to, and severity of, COVID-19 (e.g. Ref. [39]). Zinc supplementation in patients hospitalised with COVID-19 is reported to reduce risk of poor outcome including mortality [40,41].

Selenium

Selenium supports the function of many immune cell types (see Table 1) [42,43] and helps to control oxidative stress and inflammation. Extensive research in mice has shown that selenium deficiency impairs multiple immune responses and increases susceptibility to viral infection [44]. Furthermore, selenium deficiency in mice permits viral mutation, including of influenza viruses, so allowing normally weak viruses to become more virulent; research on selenium and viral infections has been comprehensively reviewed recently [44]. The permissive effect of selenium deficiency on viral mutation and virulence seems to relate the higher oxidative stress that exists in the absence of sufficient selenium. Selenium supplementation has been shown to enhance some markers of immunity in humans [45], although not all studies show this. Differences in the findings of different studies might relate to starting selenium status, and the selenium dose and the matrix used. Several studies report an association between low selenium status and increased susceptibility to, and severity of, COVID-19 (e.g. Ref. [39]). The potential for selenium to play a role in defence against SARS-CoV-2 and COVID-19 is nicely discussed elsewhere [46••,47••].

Amino acids and fatty acids

In addition to micronutrients, other essential nutrients, including amino acids and fatty acids, play important roles in supporting the immune system, and even non-essential amino acids and fatty acids seem important in this regard [48,49]. Both amino acids and fatty acids are important biosynthetic precursors (e.g. amino acids for proteins like antibodies and cytokines involved in the immune response and fatty acids for membrane lipid components to support production of new immune cells) and both give rise to specific immunologic mediators (e.g. arginine gives rise to nitric oxide which is toxic to bacteria and omega-6 and omega-3 polyunsaturated fatty acids give rise to lipid mediators that are important regulators of immunity and inflammation). A recent study reported some benefits of omega-3 fatty acids in patients hospitalised with COVID-19 [50].

Important non-nutrient components of the diet

In addition to the 'classic' nutrients described above, the diet also provides non-nutrients that are bioactive and some of these likely have a role in supporting the immune system to function and in helping to control oxidative and inflammatory stress. The effects of plant polyphenolic compounds in promoting resilience to infection have been discussed elsewhere recently [51••,52••,53•], as have the possibilities of these compounds to possess direct anti-viral activities [54,55]. Beta-glucans are another class of compounds of plant origin that have been demonstrated to have unique actions that result in immune training and immune support, as reviewed elsewhere recently [56,57•].

The importance of the gut microbiota to the immune system

Commensal bacteria within the gastrointestinal tract play a role in host immune defence by creating a barrier against entry of pathogens into the body and through the production of lactic acid and antimicrobial proteins which can directly inhibit the growth of pathogens. Commensal organisms also interact with the host's gut epithelium and gut-associated immune tissues [58]. These communications with the host occur through chemicals released from the bacteria (e.g. short chain fatty acids) or through direct cell-to-cell contact [58]. As a result of such actions, it likely that nutritional strategies that promote the growth of such commensal organisms will contribute to supporting the immune system. Some of the dietary components already mentioned, including vitamin D, omega-3 fatty acids, plant polyphenolics and beta-glucans, can influence the gut microbiota, but dietary fiber and prebiotic oligosaccharides have a much greater effect and typically promote the growth of lactobacilli and bifidobacteria that are considered to support immunity. In this regard, probiotic organisms are more widely studied and some lactobacilli and bifidobacteria have been shown to enhance some aspects of immunity including the response to vaccination [59–62]. These immune effects suggest that modifying the gut microbiota, particularly with probiotic organisms, could protect against infections. Systematic reviews and meta-analyses report that some probiotics can reduce the risk or duration of gastrointestinal infections (see Ref. [7•] for references), but there is also evidence that they reduce the incidence of respiratory infections and promote a better outcome, particularly in children [63–69]. This effect is likely due to the so-called gut-lung axis [70•], whereby altered gut microbiota affects cells that are part of the gut-associated immune system and these cells move to the lung-associated immune system to elicit beneficial actions.

Foods as sources of immune-supporting nutrients and non-nutrients

It is evident that a wide range of micronutrients (vitamins and minerals), amino acids, fatty acids and plant bioactives have roles in supporting the immune response, so contributing to host defence against pathogens, and in controlling oxidative and inflammatory stress, which are damaging to the individual. Therefore, in the interests of assuring the best possible immune response if an individual becomes infected, it would seem prudent to consume sufficient amounts of a broad range of essential and non-essential nutrients and other bioactives, although in most cases the amounts needed are not explicitly defined for the immune response [7•,11]. Many, although not all, of the important dietary components come from plant foods. Therefore, as stated elsewhere [7•] probably 'the best diet to support the immune system is one with a diverse and varied intake of vegetables, fruits, berries, nuts, seeds, grains and pulses along with some meats, eggs, dairy products and oily fish to provide the nutrients that are hard to get enough of from plant-based foods'. This diet is consistent with those regarded as generally healthy [71], is consistent with current dietary guidelines [72] and would also promote a healthy gut microbiota [73], particularly if some fermented foods were included. Although a number of studies have examined the effects of individual foods and entire diets on inflammation, there are few such studies focussing on immune outcomes. However, in one randomised controlled trial researchers compared the effect of low ($\leq$2 servings per day) and high ($\geq$5 servings per day) intakes of fruits and vegetables on immune outcomes in older people [74]. After 12 weeks of the dietary intervention, the antibody response to the pneumococcal vaccine was higher in the group consuming the higher amount of fruits and vegetables [74]. This is good evidence that a diet richer in fruits and vegetables supports a stronger immune response, most likely because of the nutrients and bioactives that fruits and vegetables can deliver to the body. In this regard, studies of fruit juice and of an encapsulated concentrate of fruits and vegetables reported improvements in immune biomarkers [75–77] and a decrease in respiratory illness [77,78]. Recent studies have reported relationships between dietary patterns and susceptibility to, or severity of, COVID-19 [79•,80•].

Merino *et al.* [79•] used data from 592 571 users of a smartphone-based COVID-19 symptom app which also collected dietary information via a short food frequency questionnaire. The authors assessed diet quality using a 'plant-based diet score', which emphasises healthy plant foods such as fruits and vegetables. 31 815 COVID-19 cases were reported. Compared with individuals in the lowest quartile of the diet score, high diet quality was associated with lower risk of COVID-19 (defied as a self-reported positive SARS-CoV-2 test) and severe COVID-19 (defined as self-reported hospitalisation with need for oxygen support): the hazards ratios for highest versus lowest quartile of diet quality were 0.91 (95% confidence interval (CI) 0.88–0.94) and 0.59 (95% CI 0.47–0.74) for infection and severity, respectively. The authors concluded that 'a diet characterised by healthy plant-based foods was associated with lower risk and severity of COVID-19'.

Kim *et al.* [80•] analysed data from a web-based survey of healthcare workers from six countries (France, Germany, Italy, Spain, UK, USA) who had substantial exposure to COVID-19 patients. There were 568 COVID-19 cases (138 moderate-to-severe and 430 mild-to-moderate) and 2316 controls. Participants self-reported habitual consumption of one of eleven dietary types. These were then combined to create three different dietary patterns: plant-based, pescatarian, and low carbohydrate high protein. After adjusting for various confounders, participants who reported following 'plant-based diets' and 'plant-based diets or pescatarian diets' had lower odds ratios (0.27 (95% CI 0.10–0.81) and 0.41 (95% CI 0.17–0.99)) of moderate-to-severe COVID-19 compared with those who did not follow these diets. The authors concluded that 'plant-based diets or pescatarian diets were associated with lower odds of moderate-to-severe COVID-19. These dietary patterns may be considered for protection against severe COVID-19'.

Summary and perspectives

The existing evidence indicates that multiple micronutrients, other essential and non-essential nutrients, certain bioactives and also those dietary components that promote a diverse, healthy gut microbiota play vital roles in supporting all aspects of the immune response. Thus, the intake of these nutrients and non-nutrients needs to be considered in the context of susceptibility to viral (and other) infections and the subsequent severity of illness. The roles of specific nutrients including vitamin D and zinc in anti-viral immunity seem to be important. Amongst other micronutrients, selenium may be more important than is generally considered: the ability of selenium to prevent viral mutation is intriguing in the context of the emergence of SARS-CoV-2 variants. Furthermore, low intakes of several micronutrients impair vaccination responses [81] and so intakes of these must be considered in the context of the current and future COVID-19 and other vaccination programmes. Although infection with SARS-CoV-2 and the resulting disease, COVID-19, have focussed attention on the need for individuals to have a sufficiently strong immune response to remain healthy, concern about 'immune health' will remain relevant in the contexts of recovery from infection, emergence of new variants of viruses, vaccination and possible future pandemics.

Research published over the last two years has reported many times that low status of a number of vitamins and minerals is associated with increased risk and severity of COVID-19. It is important to keep in mind that such observations do not demonstrate cause-and-effect relationships. Furthermore, although some trials providing (often high doses of) specific micronutrients to patients with COVID-19 report benefits, many of these trials do not have an optimal design and not all trials do report benefit. It is also important to differentiate protective strategies from treatment strategies. Actions like wearing face masks, frequent hand washing and using hand sanitiser, social distancing and isolation limit exposure to pathogens and so they work to reduce infection risk. Having a strong immune response also reduces infection risk because it enables the individual to deal with the pathogens that they are exposed to, keeping them in check and even eliminating them. The result is that the individual will be infection free or have a low level of infection and remain asymptomatic or with low grade symptoms. Thus, strategies to support the immune system, including dietary strategies, can be an important contributor to prevention (and control) of infection. Once an individual has signs of significant infection and requires hospitalisation their immune system still requires support: it is well described that in individuals hospitalised with COVID-19, those with a weaker immune response and with exaggerated inflammation show a poorer outcome [82–84]. However, these individuals also show progressive impairments of other physiological systems [82]. Hence, where specific nutrients such as vitamin C [22], vitamin D [30,31], zinc [43,44] and omega-3 fatty acids [50] have been used therapeutically in patients hospitalised with COVID-19 it is unclear whether the benefits reported are due to effects on the immune system, on inflammation or on other systems in the body, or indeed on all of these.

Research in this field is important to help society deal with the continuing pandemic and to prepare for future pandemics. Further research is needed to define cause-and-effect relationships of intakes of individual nutrients, other dietary components and foods, and dietary patterns with susceptibility to, and severity of, viral infections. Even so, although many nutrients and bioactives are provided as part of a diverse, plant-based diet there is a question about whether sufficient amounts of some of the key immune active micronutrients (vitamin D, vitamin C, vitamin E, zinc, selenium), and perhaps some of the other bioactives, can be obtained from the diet [7•,11]. Thus, whether supplements are necessary to provide the relevant intakes of these components and whether immune-targeting functional foods with enriched levels of some of the key components can be developed are important questions.

Conclusions

Multiple micronutrients, other essential and non-essential nutrients, certain bioactives and also those dietary components that promote a diverse, healthy gut microbiota play important roles in supporting all aspects of the immune response. In order to support the immune response to help individuals deal effectively with pathogens should they become infected it would seem prudent to consume sufficient amounts of these nutrients and other bioactives, mainly from a plant-based diet. In support of this, recent studies report associations of plant-based diets with lower risk of, and less severe, COVID-19.

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Conflict of interest statement

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