



Conference on ‘Nutrition at key stages of the lifecycle’ Plenary Lecture One

Nutrition and immunity: lessons from coronavirus disease-2019

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This review will provide an overview of the immune system and then describe the effects of frailty, obesity, specific micronutrients and the gut microbiota on immunity and susceptibility to infection including data from the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic where relevant. A key role for the immune system is providing host defence against pathogens. Impaired immunity predisposes to infections and to more severe infections and weakens the response to vaccination. A range of nutrients, including many micronutrients, play important roles in supporting the immune system to function. The immune system can decline in later life and this is exaggerated by frailty. The immune system is also weakened with obesity, generalised undernutrition and micronutrient deficiencies, which all result in increased susceptibility to infection. Findings obtained during the SARS-CoV-2 pandemic support what was already known about the effects of ageing, frailty and obesity on immunity and susceptibility to infection. Observational studies conducted during the pandemic also support previous findings that multiple micronutrients including vitamins C, D and E, zinc and selenium and long-chain *n*-3 fatty acids are important for immune health, but whether these nutrients can be used to treat those already with coronavirus disease discovered in 2019 (COVID-19), particularly if already hospitalised, is uncertain from current inconsistent or scant evidence. There is gut dysbiosis in patients with COVID-19 and studies with probiotics report clinical improvements in such patients. There is an inverse association between adherence to a healthy diet and risk of SARS-CoV-2 infection and hospitalisation with COVID-19 which is consistent with the effects of individual nutrients and other dietary components. Addressing frailty, obesity and micronutrient insufficiency will be important to reduce the burden of future pandemics and nutritional considerations need to be a central part of the approach to preventing infections, optimising vaccine responses and promoting recovery from infection.

Immunity: Infection: Immune system: Frailty: Obesity: Vitamin: Mineral: Microbiota

The most obvious role of the immune system is to protect the individual from the harmful effects of pathogenic

organisms they encounter, which can include bacteria, viruses, fungi and parasites. The severe acute respiratory

Abbreviations: COVID-19, coronavirus disease-2019; GALT, gut-associated lymphoid tissue; GI, gastrointestinal; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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syndrome coronavirus 2 (SARS-CoV-2) emerged in late 2019. Although human subjects have been previously exposed to many coronaviruses, SARS-CoV-2 was new to the human immune system. As a result, there was no pre-existing immunity against it, perhaps explaining why the virus spread so rapidly and caused such severe illness; this illness is called coronavirus disease discovered in 2019 or COVID-19. The extent of the health, societal and economic consequences that occurred due to the presence of SARS-CoV-2 and the severity of COVID-19 has focused attention on the devastation infectious illness can cause and on the importance of having a well-functioning immune system. The immune system can be weakened through disease, use of certain medications and several aspects of poor lifestyle as well as with ageing. It has been known for decades that inadequate nutrition impairs immunity^(1–5) and during the SARS-CoV-2 pandemic, nutrition emerged as a potentially important factor influencing infection with the virus and severity of the resulting disease^(5–7). This review will provide an overview of the immune system and then describe the effects of frailty, obesity, selected micronutrients, long-chain *n*-3 fatty acids and the gut microbiota on immunity and susceptibility to infection including data from the SARS-CoV-2 pandemic where relevant. Some text is reused in modified form from a previous publication⁽⁶⁾.

Overview of the immune system

The central role of the immune system is to protect against pathogenic bacteria, viruses, fungi and parasites that the individual is exposed to. It is clear that a weakened immune system places the individual at risk of becoming infected and of infections being more severe, even fatal. The immune system also has other important roles. One of these is to assure tolerance to environmental exposures that are non-threatening (e.g. harmless bacteria and components of food) and to the individual itself. A breakdown in such tolerance can lead to disease (e.g. food allergy in the case of loss of tolerance to food and autoimmunity in the case of loss of tolerance to self). In addition, the immune system clears dead and dying host cells and cellular debris, plays a role in surveillance against cancerous cells and tumours and is involved in wound healing. It has now emerged that the immune system also plays a role in whole-body metabolic homeostasis⁽⁸⁾. For example, cytokines such as TNF and IL-6 released during the inflammatory response induce insulin resistance in classic metabolic organs such as skeletal muscle and adipose tissue, perhaps as a strategy to divert energy-yielding substrates to the immune system during infection⁽⁹⁾. When considering the wide range of roles for the immune system, it is clear that strategies to support the immune system and to ensure that it acts at the right time, in the right place and in the right context are vitally important to human health and wellbeing.

The four functional features of the immune system are:

- (1) To act as a barrier to prevent entry of pathogens and other harmful environmental exposures. The

skin and the mucosal lining of the gastrointestinal (GI), respiratory and genitourinary tracts are obvious barriers to entry. There are also antibodies and antimicrobial proteins in secretions such as saliva and tears, while the acid pH of the stomach can kill many bacteria. Commensal organisms on the skin and within the GI tract could also be considered part of this immune barrier since they may act to prevent colonisation by pathogens.

- (2) To recognise structures (e.g. on microbes or of microbial origin) and to identify the source of those structures as harmful or harmless. There are two general recognition/identification systems. The first is recognition of general structural features of microbes (or of damaged tissue), termed molecular patterns (hence microbe-associated molecular patterns and damage-associated molecular patterns), by so-called pattern recognition receptors. The second is recognition of antigens through the interaction of antigen-presenting cells with antigen-specific T lymphocytes.
- (3) To eliminate organisms that have been identified as harmful. There are multiple cellular mechanisms to achieve this. Phagocytosis is the process of engulfing entire microbes, usually bacteria, and then digesting them intracellularly. Neutrophils, monocytes, macrophages and dendritic cells are the main phagocytes. Coating of microbes with antibodies makes phagocytosis more effective. Natural killer cells and cytotoxic T lymphocytes destroy target cells through causing formation of pores in the membrane that permit the transfer of granzymes that induce apoptosis of the target cell; typical targets for these cell types are virally infected host cells and cancer cells.
- (4) To maintain immunological memory of encounters. This is achieved through generation of memory T and B lymphocytes during an immune response. Memory cells can be very long lived and allow for a faster and stronger immune response upon re-exposure to the initial triggering structure. The memory response is the basis of vaccination.

When considering these features, it is evident that the immune system is highly complex and sophisticated in its function and regulation. It includes many different cell types, many communicating molecules and multiple functional responses. These are generally classified into innate (sometimes called natural) and acquired (sometimes called adaptive) immunity as shown in Fig. 1. Innate immunity includes the barrier functions and also the inflammatory response and some cellular responses such as natural killer cell activity and phagocytosis. The innate immune response is induced rapidly upon infection or injury. Acquired immunity takes longer to be activated but is antigen specific. It involves T lymphocytes and B lymphocytes. There are multiple phenotypes of T lymphocytes, including helper T cells, cytotoxic T cells and regulatory T cells, each with a specialised role and a typical profile of production of cytokines. Helper T cells regulate the function of other cell

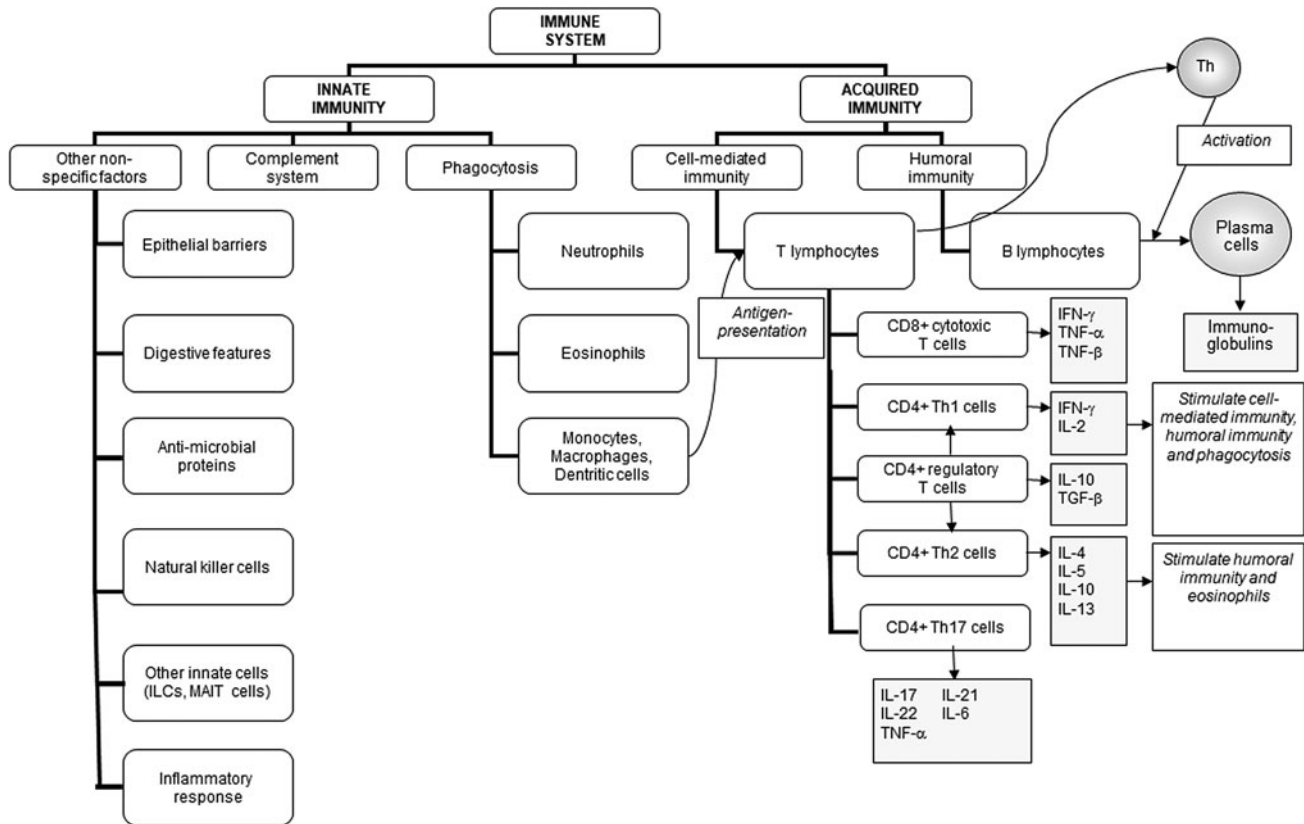


Fig. 1. Components of the immune system and their division into innate and acquired immunity. IFN, interferon; ILC, innate lymphoid cell; MAIT, mucosal associated invariant T; TGF, transforming growth factor; Th, T helper. Reproduced from⁽⁶⁾ (CC BY licence).

types through production of cytokines; there are several subclasses of helper T cells each with different roles including in anti-bacterial and anti-viral defences (type-1 T helper cells) and in anti-parasite defences (type-2 T helper cells). Helper T cells regulate the activity of cytotoxic T cells and phagocytes and control which classes of antibodies are produced by B lymphocytes. Cytotoxic T lymphocytes kill target virally infected cells and tumour cells through induction of apoptosis. Regulatory T cells are important controllers of the activity of other cell types, as their name suggests. B lymphocytes mature into antibody-producing plasma cells. Antibodies are antigen-specific immunoglobulins and these can coat microbes neutralising them and targeting them for phagocytosis.

Immune cells communicate with one another and with cells considered to be outside of the immune system. Some of this communication relates to transferring immunological information about the nature of the initial structure that was recognised (e.g. harmful *v.* harmless; bacterial origin *v.* viral origin) ensuring that the correct response is initiated. Other communication is regulatory in nature resulting in up- or down-regulation of specific cellular responses (e.g. phagocytosis, cytotoxic T lymphocyte activity, antibody production, metabolism). These two types of communication are interlinked and provide bidirectional interaction between innate and acquired immunity. For example,

phagocytes, which are part of innate immunity, process and present antigens to T lymphocytes initiating the acquired immune response. As mentioned earlier, cytokines produced by T lymphocytes regulate the activity of phagocytes and natural killer cells while antibodies (produced by B lymphocytes) coat bacteria enhancing phagocytosis. Hence the immune response is a series of dynamic cellular interactions that are coordinated in such a way as to enable the most appropriate outcome which, in the case of exposure to a pathogen, is clearance of that pathogen with a retained immunological memory of the encounter. Fig. 2 shows a generalised depiction of the immune response to viral infection highlighting some of the key cellular interactions.

All immune cells are generated in the bone marrow and most mature there. The exception to this is T lymphocytes which mature in the thymus. Bone marrow and thymus are referred to as primary lymphoid organs. Immune cells circulate in the blood stream, where they are commonly referred to as leucocytes, and in lymph. However, most immune cell interactions occur in secondary lymphoid organs where the cells can come into close contact with one another. Secondary lymphoid organs include the spleen and lymph nodes. Although most human research is conducted on immune cells isolated from blood, these reflect only the minority of immune cells in the human body. It is

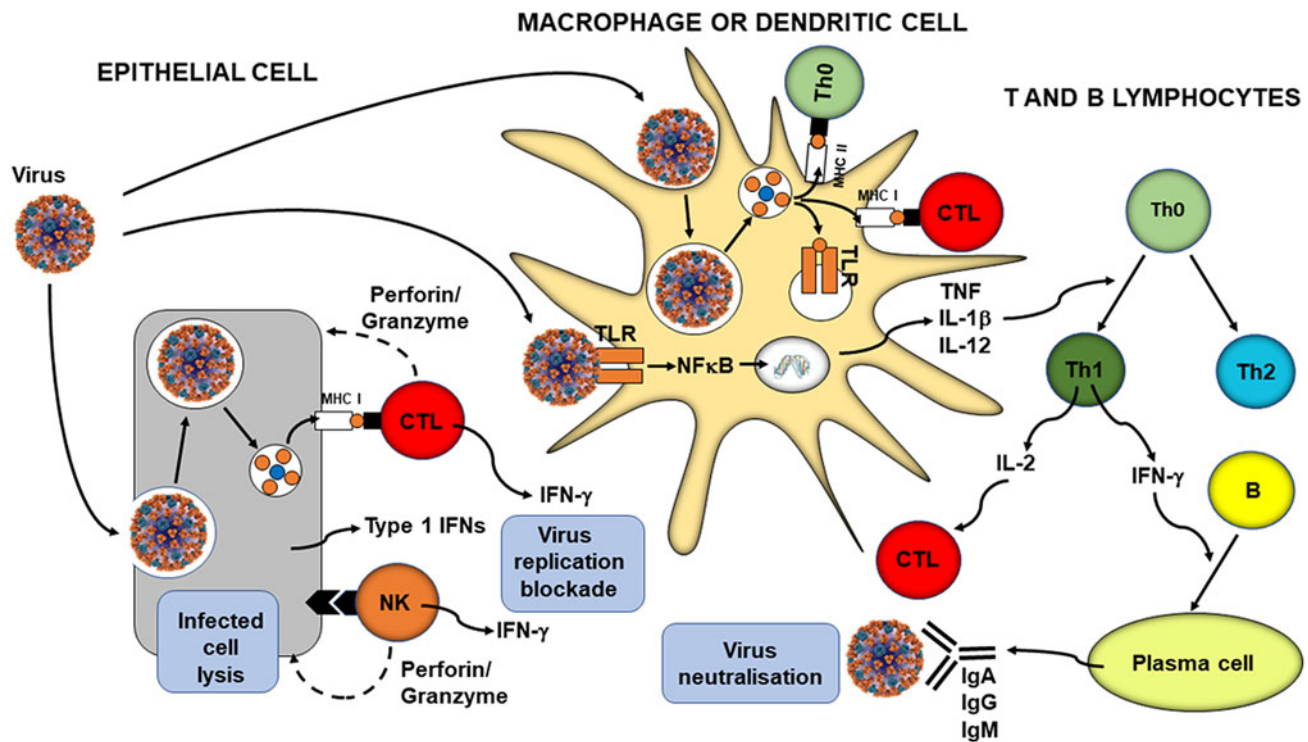


Fig. 2. Overview of anti-viral immunity. B, B cell; CTL, cytotoxic T lymphocyte; IFN, interferon; MHC, major histocompatibility class; NK, natural killer cell; Th, helper T cell; TLR, toll-like receptor. Reproduced from⁽⁵⁾ (CC BY NC licence).

estimated that about 70% of immune cells in human subjects are associated with the wall of the GI tract in structures collectively referred to as the gut-associated lymphoid tissue (GALT)⁽¹⁰⁾. The GALT is designed to interact with the gut luminal contents and to provide a means of communication between these and the host immune system. There are discrete structures in the GALT such as Peyer's patches and immune cells move between these and other immune compartments such as lymph nodes, carrying and sharing immunological signals, including antigens. The importance of the GALT is to assess the luminal contents in order to make immunological decisions and respond accordingly (e.g. active response for defence purposes against pathogens or tolerogenic response to harmless organisms or food components)⁽¹⁰⁾. It is now recognised that there is movement of immune cells between the GALT and other mucosal surfaces such as the lungs (i.e. there is a gut–lung immune axis)⁽¹¹⁾ meaning that immunological information gathered at the gut level can be used elsewhere.

The immune system changes in ageing and this is exaggerated by frailty

Immune competence can decrease with age; this has been termed immunosenescence^(12,13). There are multiple contributors to immunosenescence including decline in components of both innate and acquired immunity. These include:

- (1) decreased output of immune cells from bone marrow;
- (2) thymic involution with decreased production of naïve T lymphocytes, meaning decreased capacity to respond to newly encountered antigens;
- (3) fewer T lymphocytes in the bloodstream;
- (4) an altered balance of naïve to memory T lymphocytes in the bloodstream (fewer naïve and more memory cells) but many of the memory T cells are senescent and do not respond well, meaning decreased capacity to respond to previously encountered antigens;
- (5) decreased antigen presentation activity by dendritic cells;
- (6) decreased phagocytosis, respiratory burst and bacterial killing by neutrophils;
- (7) decreased cytotoxicity of natural killer cells and cytotoxic T lymphocytes towards virally infected and tumour cells;
- (8) decreased ability of T lymphocytes to proliferate and to produce important cytokines such as IL-2 and interferon-γ;
- (9) altered antibody production by B lymphocytes.

Hence, older people can show a broad range of immune impairments, making them more susceptible to infections⁽¹⁴⁾. The increased susceptibility of older people to SARS-CoV-2 infection and to severe outcome from COVID-19 including greater likelihood of hospitalisation, intensive care unit admission, mechanical ventilation and death is well described^(15,16). Immunosenescence also impairs responses to vaccination, which is well known

for the routine seasonal influenza vaccine^(17,18) and there is evidence of poorer responses to COVID-19 vaccines in older compared with younger adults⁽¹⁹⁾ (Fig. 3). Of course, not all older people show immune impairments, so it is important to identify those factors that make these more or less likely to occur. Nutrition may be important in this regard: immune decline is less in older people with better micronutrient intake or status⁽²⁰⁾. Furthermore, amongst older people, undernutrition promotes immune decline and frailty results in significant immune impairments. Yao *et al.*⁽²¹⁾ reported that responses to all three strains within a seasonal influenza vaccine (responses measured as anti-vaccine antibody titres) were much lower in frail compared with non-frail older (72–95 years of age) people; responses of the pre-frail were intermediate. During a post-vaccination follow-up period, 50% of the frail older people developed influenza-like illness and 30% developed confirmed influenza; figures in the non-frail group were 10 and 5%, respectively, and again the pre-frail were intermediate between the frail and non-frail groups⁽²¹⁾. That immune impairments seen with frailty are of clinical significance comes from observations that less well-nourished hospitalised older people had a greater risk of infections than those who were better nourished^(22,23). Frailty is associated with poorer outcome from COVID-19 amongst older people⁽²⁴⁾, as confirmed in the meta-analysis of Zhang *et al.*⁽²⁵⁾ (Fig. 4).

The immune system changes in those living with obesity

Immune competence can be diminished with obesity⁽²⁶⁾, with impairments in the activity of natural killer cells, helper and cytotoxic T lymphocytes, and B lymphocytes and decreased production of antibodies and the cytokine interferon- γ . This means that, compared with healthy weight individuals, those living with obesity have increased susceptibility to a range of infections⁽²⁷⁾. During the 2009 H1N1 influenza A virus pandemic, those living with obesity showed delayed and weakened anti-viral responses to infection and showed poorer recovery from disease compared with healthy weight individuals⁽²⁸⁾. Vaccinated individuals living with obesity had twice the risk of influenza or influenza-like illness than healthy weight individuals, indicating poorer protection from vaccination in those with obesity⁽²⁹⁾. Sheridan *et al.*⁽³⁰⁾ investigated the responses of immune cells taken from the blood of healthy weight individuals and those with overweight or obesity to the influenza vaccine in vitro. Exposure of blood immune cells to the vaccine increased the number of activated cytotoxic T cells, the number of granzyme-expressing cytotoxic T cells and the number of interferon- γ -producing cytotoxic T cells, all key components of anti-viral immunity. However, the responses of cells from individuals living with obesity were reduced by 40%, almost 60 and 65%, respectively. Cells from individuals with overweight showed responses intermediate between those from healthy weight individuals and those living with obesity. Similar findings for the response of blood cells to the pandemic H1N1

influenza A virus were reported by Paich *et al.*⁽³¹⁾. Thus, obesity is linked to multiple immune impairments, including to responses involved in protection against viruses.

There are multiple reports that adults living with obesity were more susceptible to severe COVID-19 and to mortality from COVID-19 than healthy weight adults and there are several meta-analyses of such studies. One systematic review and meta-analysis of twenty-two studies from seven countries in North America, Europe and Asia, reported that obesity is associated with an increased likelihood of more severe COVID-19 symptoms, requiring hospitalisation, being admitted to an intensive care unit, needing invasive mechanical ventilation and developing acute respiratory distress syndrome⁽³²⁾ (Figs 5 and 6). The studies included in this systematic review dichotomised individuals as living with obesity or not, but large datasets from the UK and the USA report that there is a continuous positive relationship between BMI (above about 25 kg/m²) and adverse outcomes from COVID-19^(33,34).

Many nutrients are important in supporting the immune system to function

It has been known for decades that poor nutrition (generalised undernutrition, micronutrient deficiency) is associated with immune impairments, increased susceptibility to infection and poor outcome from infection, with especially severe consequences in infants and children^(1–3). As described elsewhere⁽⁴⁾ nutrition plays multiple roles in supporting the immune system since the diet provides:

- (1) fuels for the immune system to function;
- (2) building blocks for the synthesis of RNA, DNA, proteins (antibodies, cytokines, receptors, acute phase proteins, etc.) and new cells;
- (3) specific substrates for the production of immune-active metabolites (e.g. arginine as a substrate for nitric oxide);
- (4) regulators of immune cell metabolism (e.g. vitamin A, zinc);
- (5) nutrients with specific antibacterial or anti-viral functions (e.g. vitamin D, zinc);
- (6) regulators that protect the host from the oxidative and inflammatory stress imposed by the immune response (e.g. vitamin C, vitamin E, zinc, selenium, long-chain *n*-3 fatty acids and many plant polyphenols);
- (7) substrates for the intestinal microbiota which in turn modulates the immune system (see later section).

Beyond generalised undernutrition, the role of micronutrients in supporting the immune system has been widely studied, as reviewed elsewhere^(35–37). Multiple micronutrients play multiple important roles in supporting multiple components of the immune response (Table 1), so it is no surprise that deficiency in one or more of these has adverse consequence for immunity and infection. The roles of vitamins A, C and D and zinc, copper and

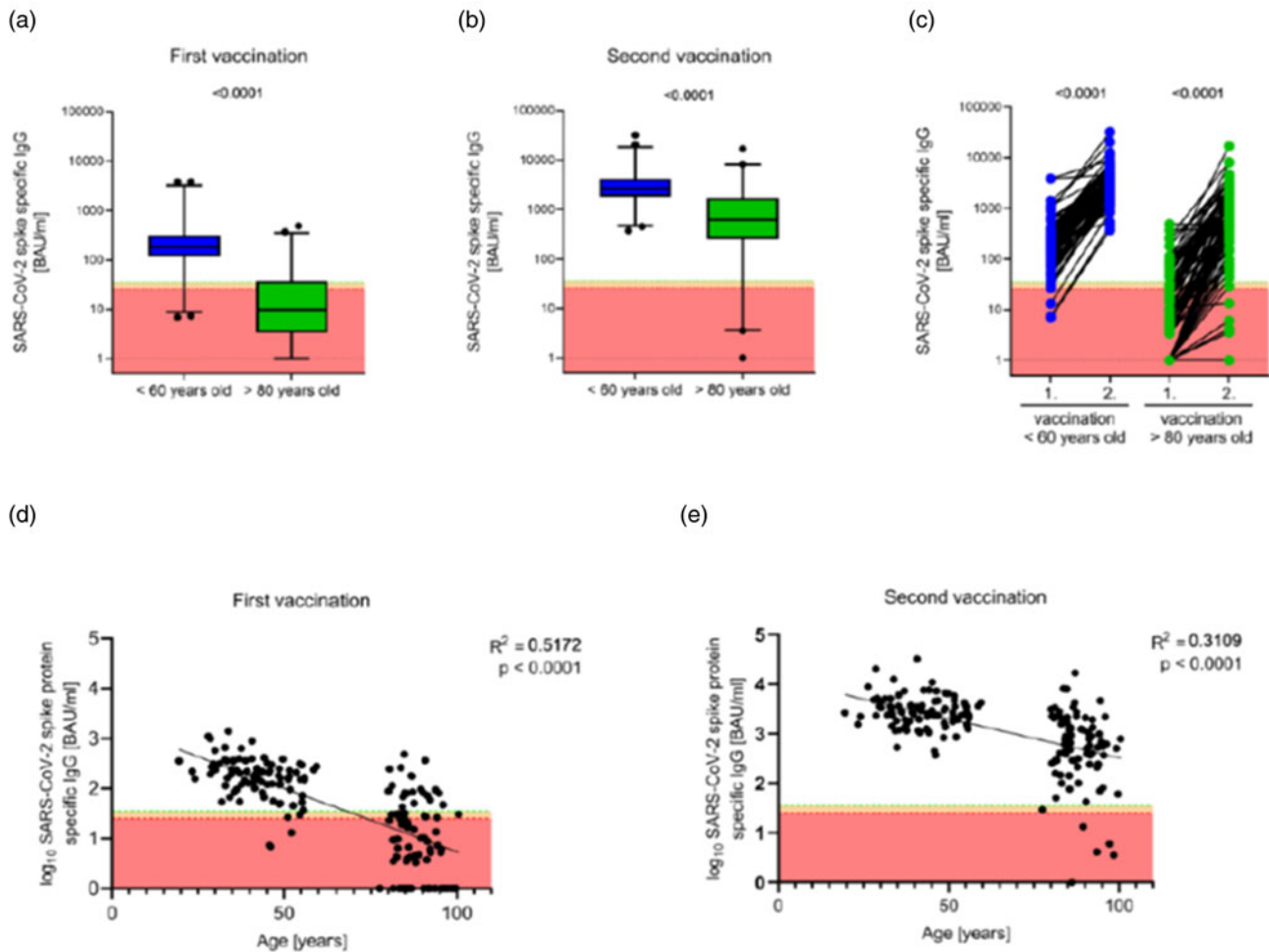


Fig. 3. Anti-SARS-CoV-2 spike protein-specific IgG titres following vaccination of younger and older adults with the Pfizer coronavirus disease 2019 vaccine. (A, B) Antibody titres 17–19 d after the first (A) and second (B) vaccination. Boxes span the interquartile range; the line within each box denotes the median and whiskers indicate the 2.5 and 97.5 percentile values. (C) Pairwise comparisons of antibody titres between the first and second vaccination within the two age groups are shown. (D, E) Linear correlations between participant's age and antibody titre after first (D) and second (E) vaccination. BAU, binding antibody units; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. Reproduced from ⁽¹⁹⁾, with permission from Oxford University Press.

iron are well explored, but B vitamins, vitamins E and K, selenium, magnesium and others all have roles^(4,5,7,35–37). With regards to SARS-CoV-2 infection and COVID-19 there has been much interest in micronutrients, mainly vitamin D and zinc, but also many others⁽⁵⁾.

Vitamin D has pleiotropic actions within the immune system and supports the activity of several cell types^(38,39). Some immune cell types, including dendritic cells and macrophages, can produce the active form of vitamin D suggesting it is important to immunity. Vitamin D promotes the production of antimicrobial proteins such as cathelicidin. Vitamin D deficiency impairs the response to the seasonal influenza vaccine⁽⁴⁰⁾ and meta-analyses of randomised controlled trials of vitamin D supplementation report reduced incidence of respiratory tract infections^(41,42). Multiple studies report an association between low vitamin D status and increased susceptibility to, and severity of, COVID-19^(43–45) while data from the UK BioBank

showed that using vitamin D supplements was associated with decreased risk of a positive test for SARS-CoV-2 after controlling for multiple confounders⁽⁴⁶⁾. Many meta-analyses report that vitamin D deficiency (or low vitamin D status) is associated with an increased risk of severe COVID-19, hospitalisation with COVID-19 and mortality from COVID-19⁽⁴⁷⁾. A report from an Italian residential care home showed that a bolus of vitamin D reduced mortality from COVID-19⁽⁴⁸⁾ and a number of trials with different study designs suggest that vitamin D can be used to treat COVID-19^(49–51). However, while some meta-analyses of such trials report that vitamin D supplementation can reduce COVID-19 severity as determined by hospitalisation, need for intensive care unit admission or mortality^(52,53) other meta-analyses report no significant effect on such outcomes⁽⁵⁴⁾. Reasons for these different findings relate to the exact studies included and the extent of adjustment for confounders. Consequently, it is uncertain whether

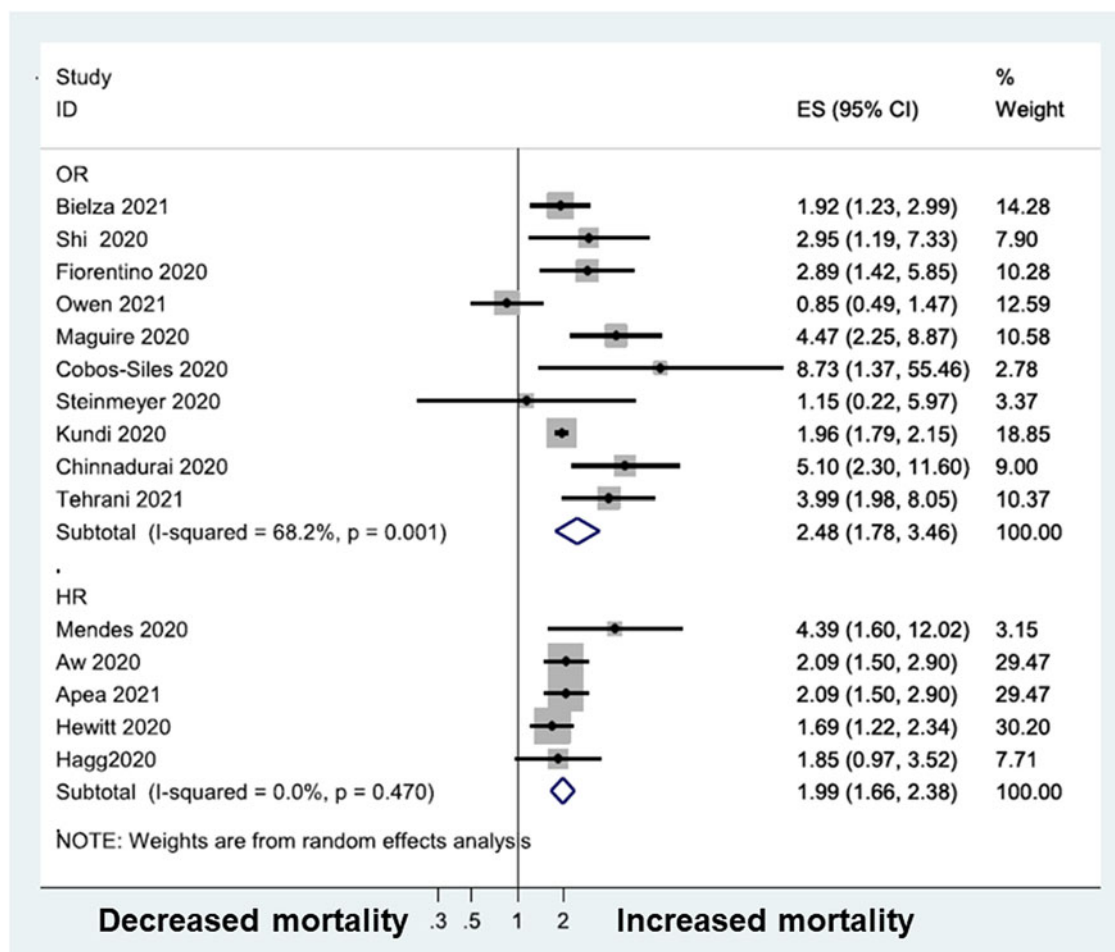


Fig. 4. Meta-analysis of the association of frailty with mortality amongst patients with COVID-19. Non-frail is defined as the reference group. COVID-19, coronavirus disease discovered in 2019; ES, effect size; HR, hazard ratio; OR, odds ratio. Reproduced from⁽²⁵⁾ (CC BY NC SA licence).

vitamin D can be used to treat people with COVID-19, although there are some supportive data for this.

Zinc supports the activity of many cells of the immune system⁽⁵⁵⁾, helps to control oxidative stress and inflammation and has specific anti-viral actions⁽⁵⁶⁾ including inhibiting the replication of coronaviruses⁽⁵⁷⁾. Zinc supplementation improves some markers of immunity especially in older people or those with low zinc intake⁽⁵⁸⁾ and improves vaccination responses⁽⁵⁹⁾. Meta-analyses of randomised controlled trials of zinc supplementation report reduced incidence of diarrhoeal and respiratory tract infections^(60–64). Multiple studies report an association between low zinc status and increased susceptibility to and severity of COVID-19^(65–68). Some studies have reported that zinc supplementation in patients hospitalised with COVID-19 reduces risk of poor outcome including mortality^(69,70) and some meta-analyses support that zinc supplementation reduces mortality^(71,72). However, other meta-analyses report no effect of zinc on mortality and other clinically relevant outcomes⁽⁵⁴⁾. Thus, it is currently uncertain whether zinc can be used to treat people with COVID-19, although there are some supportive data for this.

In contrast to the large literature on vitamin D and zinc that has emerged during the pandemic, there has been less research on selenium. Nevertheless, selenium may have important roles in supporting the immune system in general⁽⁷³⁾ and in promoting anti-viral immunity in particular⁽⁷⁴⁾. Selenium supports the activity of many cells of the immune system and helps to control oxidative stress and inflammation. Extensive research in mice has shown that selenium deficiency impairs immune responses, increases susceptibility to viral infection, permits viruses (including influenza viruses) to mutate and allows normally weak viruses to become more virulent⁽⁷⁵⁾. Some studies show that selenium supplementation improves some markers of immunity especially in older people or those with low selenium intake; for example a supplementation study conducted in UK adults with marginal selenium status showed that selenium improved ex vivo anti-viral immune responses, promoted viral clearance and decreased viral mutation⁽⁷⁶⁾, although other studies have shown only modest effects of selenium supplements on immunity⁽⁷⁷⁾. A recent meta-analysis of selenium and immune function identified that selenium supplementation increased natural

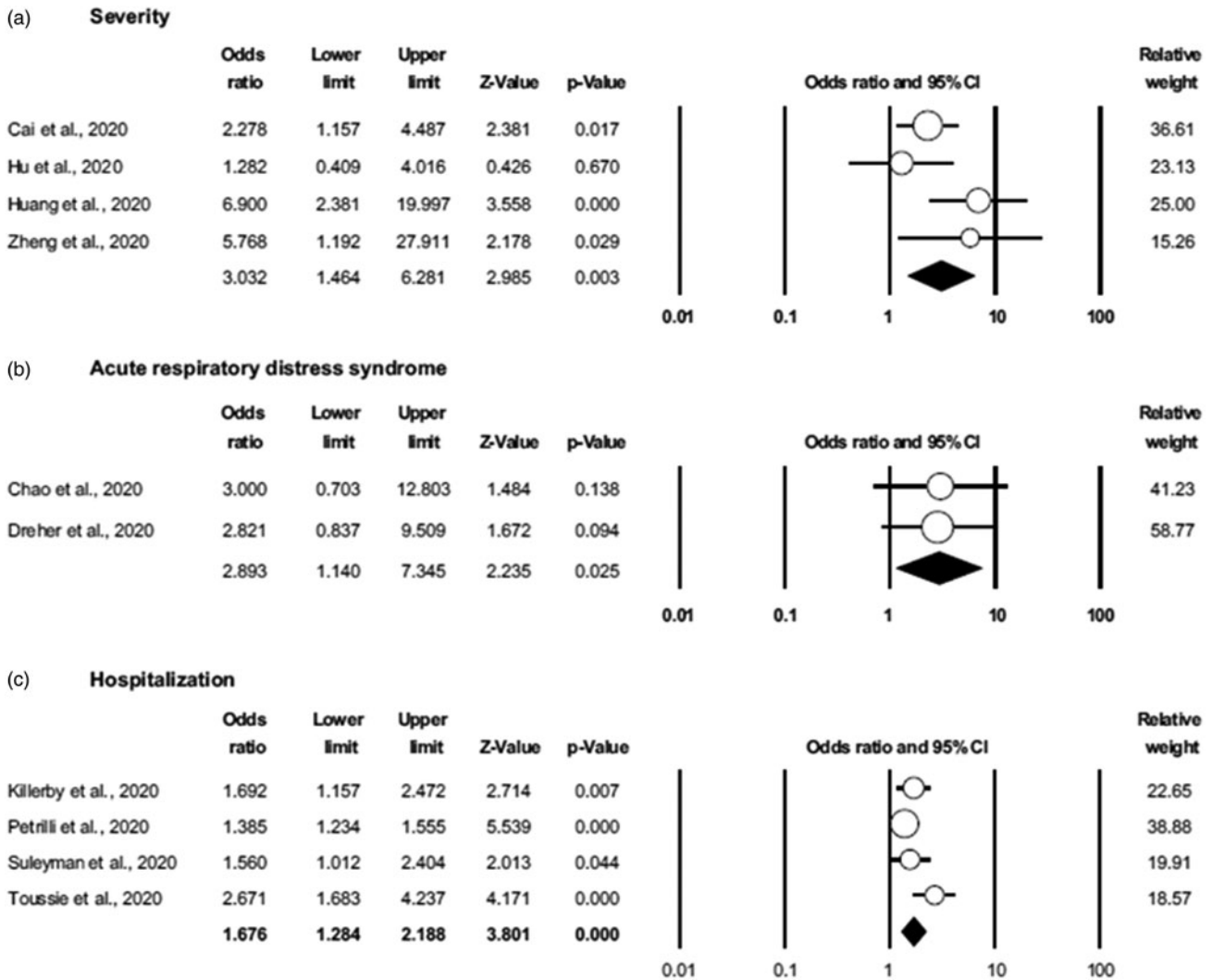


Fig. 5. Association of obesity with severe COVID-19 outcomes: (A) severe COVID-19; (B) developing acute respiratory distress syndrome and (C) being hospitalised. Non-obese is defined as the reference group. COVID-19, coronavirus disease discovered in 2019. Reproduced from⁽³²⁾ (CC BY licence).

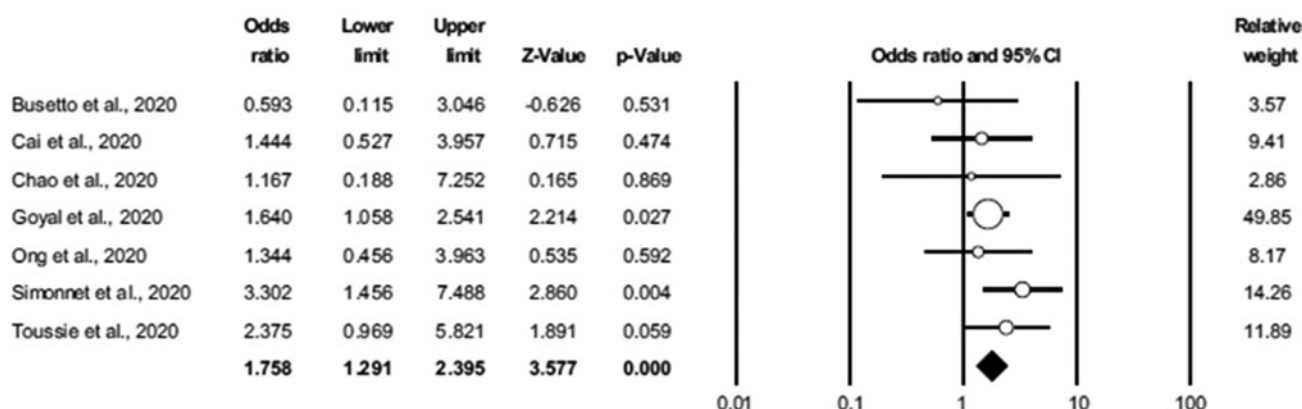
killer cell activity and concluded ‘although some of the data suggested beneficial effects of selenium supplementation on immune function, the overall picture appears to be inconsistent and heterogeneous due to differences in trial duration and interventions, plus evidence of null and even detrimental effects’⁽⁷⁸⁾. Several studies report an association between low selenium status and increased susceptibility to and severity of COVID-19^(65,79,80). There are no randomised controlled trials of selenium as a stand-alone nutrient in patients with COVID-19 reporting on clinical outcomes. Thus, it is currently uncertain whether selenium can be used to treat people with COVID-19.

Vitamin C supports the activity of some components of innate and adaptive immunity^(81,82), as well as the physical barriers that limit entry to pathogens⁽⁸³⁾ and helps to control oxidative stress and inflammation. Vitamin C supplementation improves some markers of immunity especially in older people^(84,85) and a

meta-analysis⁽⁸⁶⁾ suggests that those under physical or physiological stress may show reduced incidence and duration of the common cold with vitamin C supplementation, especially if ‘high’ doses are used. Several studies report an association between low vitamin C status and increased susceptibility to, and severity of, COVID-19^(87,88). Some studies report that high dose vitamin C may reduce the risk of poor outcome in patients hospitalised with COVID-19^(89,90) and some meta-analyses support that vitamin C reduces mortality⁽⁹¹⁾. However other meta-analyses report no effect of vitamin C given orally or intravenously on mortality and other clinically relevant outcomes in patients with COVID-19^(54,92–94). Thus, it is currently uncertain whether vitamin C can be used to treat people with COVID-19.

Vitamin E supports the activity of some components of innate and adaptive immunity^(95,96) and helps to control oxidative stress and inflammation. Vitamin E

(a) Invasive mechanical ventilation



(b) ICU admission

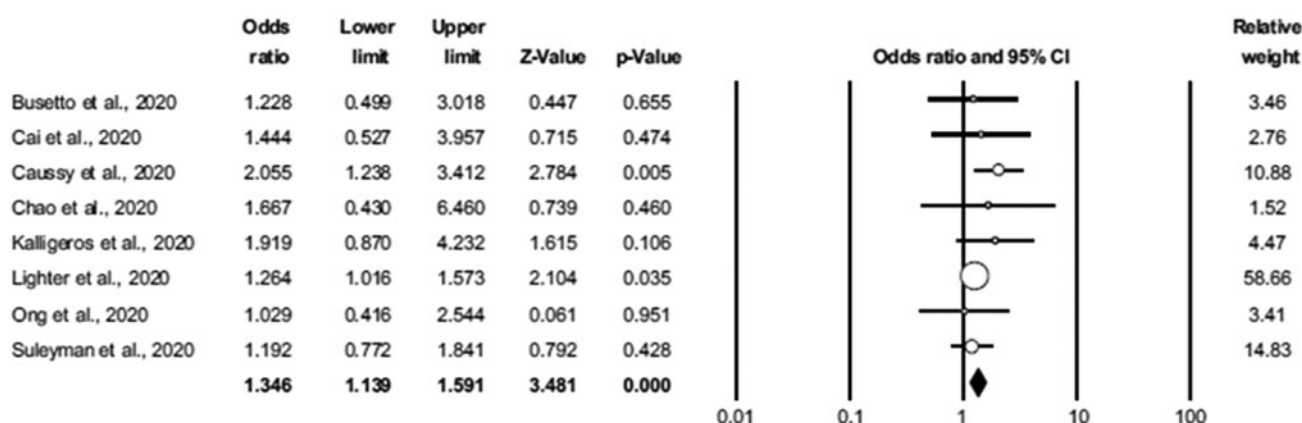


Fig. 6. Association of obesity with severe COVID-19 outcomes (A) requiring invasive mechanical ventilation; (B) admission to the intensive care unit in the setting of COVID-19. Non-obese is defined as the reference group. COVID-19, coronavirus disease discovered in 2019; ICU, intensive care unit. Reproduced from⁽³²⁾ (CC BY licence).

supplementation improves some markers of immunity especially in older people^(97,98) and enhances the response to some vaccines⁽⁹⁹⁾. Vitamin E may reduce the risk of upper respiratory tract infections⁽¹⁰⁰⁾, although not all studies show this⁽¹⁰¹⁾. Studies report lower vitamin E status in those hospitalised with COVID-19 than in healthy controls⁽¹⁰²⁾ and that vitamin E status is lower in those with more severe disease⁽¹⁰³⁾. There are no randomised controlled trials of vitamin E as a stand-alone nutrient in patients with COVID-19 reporting on clinical outcomes. Thus, it is currently uncertain whether vitamin E can be used to treat people with COVID-19.

The long-chain *n*-3 fatty acids EPA and DHA are anti-inflammatory⁽¹⁰⁴⁾ and are precursors to so-called specialised pro-resolving mediators⁽¹⁰⁵⁾. Thus, EPA and DHA could have a role in controlling the adverse inflammation associated with severe COVID-19 that is referred to as a 'cytokine storm'. Furthermore, EPA and DHA modulate immune function, although findings in human trials have been inconsistent⁽¹⁰⁴⁾. A study in school children reported that increased daily intake of EPA and DHA decreased the risk of infection (mainly upper respiratory tract) and shortened the

duration of illness⁽¹⁰⁶⁾. Hence there has been some interest in these *n*-3 fatty acids and COVID-19. Data from the UK BioBank showed that the habitual use of fish oil supplements, a source of EPA and DHA, was associated with a lower risk of hospitalisation with COVID-19 and COVID-19 mortality⁽¹⁰⁷⁾ and that higher DHA status was associated with a lower risk of infection with SARS-CoV-2, hospitalisation with COVID-19 and mortality from COVID-19^(108–110). Small studies reported that lower *n*-3 status was associated with more severe COVID-19^(111,112) and that hospitalised patients with a high *n*-3 status were less likely to die than those with lower *n*-3 status⁽¹¹³⁾. There are few trials of *n*-3 fatty acids in patients with COVID-19. One trial randomised critically ill patients with COVID-19 to a high-protein enteral formula providing EPA and DHA or to a control group that received the formula without added *n*-3 fatty acids; the *n*-3 group had better indicators of some, but not all, physiological functions at day 14 and had better survival at 1 month⁽¹¹⁴⁾. Because of the limited number of studies, it is currently uncertain whether long-chain *n*-3 fatty acids can be used to treat people with

**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 and T cells; promotes intestinal Ig 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 Ig 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 cofactor for gut microbiota	Supports NK cell activity	Promotes T cell differentiation, proliferation and function, especially cytotoxic T cells; controls T helper:cytotoxic T cells ratio	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, connexin 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 Ig 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

IFN, interferon; NK, natural killer; Th, T helper.
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COVID-19, although there are some supportive data for this.

The gut microbiota is an important determinant of immunity

Commensal bacteria within the GI tract play a role in host immune defence creating a barrier against colonisation by pathogens 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 GALT, through chemicals released from the bacteria or through direct cell-to-cell contact. Conversely the host immune system interacts with the gut microbiota through multiple mechanisms^(115,116). Hence, the interaction between the gut microbiota and the host immune system is bidirectional. Gut dysbiosis may result from inability to sustain commensals (e.g. through use of antibiotics or through poor lifestyle) which in turn would alter signals to the host immune system. Conversely, an ineffective host immune response may not be able to prevent pathogenic organisms from taking hold resulting in dysbiosis. Probiotic organisms, particularly some lactobacilli and bifidobacteria, or prebiotics that promote the growth of such organisms, are proposed as a strategy to support host immunity. Indeed, a large number of studies have examined the influence of various probiotic organisms, either alone or in combination, on immune function and infection in human subjects⁽¹¹⁷⁾. Some probiotic organisms appear to enhance innate immunity (particularly phagocytosis and natural killer cell activity) but they seem to have a less pronounced effect on acquired immunity⁽¹¹⁷⁾. Nevertheless, there are studies reporting improved responses to vaccination, especially with the seasonal influenza vaccine, in individuals taking probiotics as reviewed elsewhere⁽¹¹⁸⁾. Systematic reviews and meta-analyses confirm that probiotics (or prebiotics) enhance the antibody response to seasonal influenza vaccination in adults^(119,120). Systematic reviews and meta-analyses report that some probiotics can reduce the risk or duration of diarrhoea, including antibiotic-associated diarrhoea and *Clostridium difficile*-associated diarrhoea and reduce the incidence of, and improve outcomes in, respiratory infections (see⁽⁵⁾ for references). Gut dysbiosis has been reported in patients with COVID-19⁽¹²¹⁾, although the direction of causality is uncertain in such studies. Nevertheless, the evidence base about probiotics has created some enthusiasm for their role in the treatment of COVID-19. In a study in Italy, d'Ettorre *et al.*⁽¹²²⁾ treated patients hospitalised with COVID-19 with a cocktail of drugs and antibiotics or the same plus oral probiotics (five lactobacilli plus two bifidobacteria plus *Streptococcus thermophilus*): they found better resolution of diarrhoea and of other disease symptoms including respiratory disease in the group receiving probiotics. In a study in Mexicans with COVID-19 but not hospitalised, probiotics (three *Lactiplantibacillus plantarum* strains plus *Pediococcus acidilactici*) increased

SARS-CoV-2-specific Ig M and G and decreased nasopharyngeal viral load, lung infiltrates and duration of both GI and non-GI symptoms, compared to placebo⁽¹²³⁾. In a Russian study treating patients hospitalised with COVID-19 with a mix of multiple lactobacilli and bifidobacteria decreased the risk of hospital-acquired diarrhoea but had no effect on other outcomes⁽¹²⁴⁾. Thus, overall findings with probiotic intervention in patients with COVID-19 are promising though somewhat inconsistent. This could relate to the actual probiotic strains being used and/or to the different characteristics and disease severity of the patients studied.

Is there an immune supporting diet?

The foregoing discussion would suggest that a diet that provides a good intake of quality protein, micronutrients, other essential nutrients, plant polyphenols and fibre (to promote a diverse gut microbiota) without an excess of energy would be one that gives the best opportunity for the immune system to function well, although supplements of some important nutrients such as vitamin D might also be required. In this regard it is important to note the trial of Gibson *et al.*⁽¹²⁵⁾ that reported that older people who normally consumed $\leq$ two portions of fruits and vegetables daily and were randomised to consume $>$ five portions daily for 16 weeks had a higher antibody response to pneumococcus vaccination than seen in the control group who retained their diet of $\leq$ two portions daily. There have been several studies examining the association between diet quality and COVID-19-related outcomes. Five such studies^(126–130) have been recently included in a meta-analysis examining the association of adherence to a high-quality dietary pattern on COVID-19 outcomes⁽¹³¹⁾; these were three cohort and two cross-sectional studies involving a total of over 4 million individuals. Adherence to a high-quality diet was associated with a 28 % (95 % CI 19, 36) decrease in SARS-CoV-2 infection and a 62 % (95 % CI 25, 80) decrease in hospitalisation with COVID-19. Both a plant-based diet and the Mediterranean diet were associated with a lower risk of infection.

Conclusions

A key role for the immune system is providing host defence against pathogenic organisms that the individual encounters and a well-functioning immune system is required for effective defence against such organisms. Impaired immunity predisposes to infections and to more severe infections and weakens the response to vaccination. A range of nutrients, most obviously micronutrients, play important roles in supporting the immune system to function well. The immune system can decline in later life and this is exaggerated by frailty. The immune system is also weakened with obesity, generalised undernutrition and micronutrient deficiencies.

These all result in increased susceptibility to infection. Weakened immunity is an under-recognised result of ageing and of frailty, obesity and poor nutrient intake. Findings obtained during the SARS-CoV-2 pandemic add weight to what was already known about the effects of ageing, frailty and obesity on immunity and susceptibility to infection. Multiple observational studies made during the SARS-CoV-2 pandemic also support previous findings that multiple micronutrients including vitamins C, D and E, zinc and selenium and long-chain *n*-3 fatty acids are important for immune health, but whether these nutrients can be used to treat those already with COVID-19, particularly if already hospitalised, is uncertain from current inconsistent or scant evidence. The gut microbiota has emerged as an important determinant of immunity with much supportive pre-SARS-CoV-2 pandemic data on probiotics and GI and respiratory infections. There is gut dysbiosis in patients with COVID-19 but the direction of causality for this is unclear. Nevertheless, studies with probiotics report clinical improvements in patients with COVID-19. There is a strong inverse association between adherence to a healthy diet and risk of SARS-CoV-2 infection and hospitalisation with COVID-19 which is consistent with the effects of individual nutrients and other dietary components. Looking forward, it seems obvious that addressing frailty and obesity will be important to reduce the burden of future pandemics. This is the major lesson from the study of nutrition and immunity that is relevant for the battle with SARS-CoV-2 and the disease it causes, COVID-19, and for ensuring the population is better prepared for future pandemics. Going beyond that, strategies addressing current nutritional inadequacies that are widespread in the population (e.g. micronutrient insufficiency) are needed to ensure better support of the immune system across the population. This is the second lesson from the SARS-CoV-2 pandemic and nutritional considerations need to be a core part of the approach to preventing infections^(7,132), optimising vaccine responses⁽¹³³⁾ and promoting recovery from infection⁽¹³⁴⁾. Even so, supplements may be necessary to achieve the required intakes of some of the key immune supporting nutrients such as vitamin D. Overall, the focus should be on immune support as a preventative strategy for infection.

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Authorship

The author had sole responsibility for all aspects of preparation of this paper.

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