Nutrition Bulletin

FACTS BEHIND THE HEADLINES

DOI: 10.1111/nbu.12470

Effects of diets, foods and nutrients on immunity: Implications for COVID-19?

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Abstract

The COVID-19 pandemic has sparked an increase in claims that particular food and drink products and nutritional supplements are able to 'boost' immunity. The immune system is highly complex, consisting of many different cell types and processes, and nutritional adequacy is undoubtedly required to support its function. Specific roles have been established for several micronutrients including vitamins A, B6, B12, C and D, copper, folate, iron, selenium and zinc, with documented impacts on particular aspects of immune function as a result of clinical deficiencies. Increased susceptibility to infections and poorer outcomes have been commonly observed in cases of undernutrition. However, high bodyweight, diabetes and ageing are also associated with immune dysfunction. The gut microbiota is intimately linked with the immune system and there is some evidence to suggest that food components that favourably modify its composition, such as pre- and probiotics, may be advantageous in immune modulation. Studies also indicate some benefits of specific supplements; for example, zinc and vitamin C supplements have been shown to reduce the duration of the common cold; probiotics have been suggested to reduce the duration and severity of acute infectious diarrhoea and prevent antibiotic-associated diarrhoea; and anti-inflammatory effects of long-chain omega-3 fatty acids have also been demonstrated. However, at present there are no authorised EU health claims for any of these effects. In the light of the recent media interest in the role of diet and lifestyle on the immune system following the COVID-19 outbreak, this article will summarise why a healthy, balanced diet is key to supporting immune function with consideration given to the latest thinking in relation to COVID-19.

Keywords: BMI, COVID-19, gut microbiota, immunity, long-chain omega-3 fatty acids, micronutrients

Introduction

Nutrition and immunity has been a hot topic in recent months in light of the COVID-19 pandemic, with numerous media reports touting various food components and supplements (including fermented foods, bone broth, elderberry tincture, vitamin C and garlic) as capable of 'boosting' the immune system (*The Conversation* 2020; *The Metro* 2020; *BBC* 2020a). Some articles have also been suggesting that we should be avoiding certain foods (*e.g.* 'ultra-processed' foods, animal foods, too much alcohol, ice cream) in order to protect ourselves from infection (*The Conversation* 2020; *The Guardian* 2020; *BBC* 2020a; *BBC* 2020b), whereas others promote more simple advice such as getting enough good quality sleep, regular exercise,

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reducing stress and consuming a healthy, balanced diet (*Good Housekeeping* 2020; *New York Times* 2020).

Modern, busy lives mean that achieving a healthy diet and lifestyle can be difficult and additional barriers faced by some (*e.g.* those on a low income) (Lockyer & Spiro 2019) have been exacerbated by the effects of the pandemic. Income losses, the loss of free school meals for some children, reduced availability of food due to panic buying and distribution problems, restricted access to supermarket home deliveries for many of those needing to isolate at home and increased pressure on food banks and charities (FSA 2020; *On London* 2020) likely reduced the ability of some individuals to consume a healthy, balanced diet during lockdown. Preliminary analysis of data from a YouGov survey (commissioned by the Food Foundation) indicated that the number of adults in the UK who reported experiencing food insecurity during a 3-week period across March and April 2020 was estimated to be four times higher than pre-pandemic levels (16.2%, compared to an expected figure of 3.8% based on 2018 data) (Loopstra 2020). A later survey commissioned by the Food Standards Agency (FSA) as part of the Food and You series found that self-reported food insecurity in the UK was between 16 and 18% from April to July 2020 (FSA 2020). Consuming an inadequate diet for prolonged periods is likely to impact on health including, potentially, immune function.

As outlined in more detail below, many nutrients are essential for immune function, as evidenced by the impact of deficiencies, though diet is only one modifiable factor that can affect the function of the immune system. This article aims to examine the relationship between nutrition, diet-related disease states and immunity in the context of the COVID-19 pandemic. Micronutrients, pre- and probiotics, long-chain omega-3 fatty acids, and obesity and diabetes are the main aspects that will be discussed. Treatment for COVID-19 patients using anti-inflammatory or antioxidant nutritional interventions is an interesting area, which is outside of the scope of this paper but discussed elsewhere (Carr 2020; Calder 2020).

Function and components of the immune system

The immune system is complex and sophisticated, consisting of many interacting components, which protect the body from pathogens, as well as other harmful intrinsic and extrinsic factors such as cancerous cells (Maggini *et al.* 2018). The immune system comprises both innate and adaptive immune responses (see Fig. 1). The innate immune system, comprising physical barriers such as the skin, defence mechanisms such as the stomach acid and general immune responses such as acute inflammation (mediated by leukocytes, *e.g.* through the production of pro-inflammatory mediators such as cytokines) and the complement system, is the first line of defence and is fast-acting and non-specific, destroying 'non-self' threats. Inflammation is normally resolved quickly at the end of the immune response and any damage caused by this process is repaired, although an excessive inflammatory response can impact upon adaptive immunity (Calder *et al.* 2020). Chronic inflammation (associated with ageing and obesity, *i.e.* long-term inflammation lasting for prolonged periods of several months to years) is thought to contribute to the development of conditions such as cardiovascular disease and type 2 diabetes (Calder *et al.* 2017; Childs *et al.* 2019) and may result in an excessive inflammatory response to infection (Calder 2020). In contrast to the innate immune system, the adaptive or 'acquired' immune system is slow-acting and more specific, involving an antigen-specific response mediated by T lymphocytes ('T cells') and B lymphocytes ('B cells', that can secrete antibodies) (see Fig. 1). The adaptive system generates immunological memory, in that subsequent infections by the same pathogens will result in a faster, specific response. Activating this system is the principle that underpins vaccinations (Calder *et al.* 2020).

Immune function changes over the life course. Antibodies can pass through the placenta, meaning the developing fetus can benefit from vaccinations given to the mother during pregnancy (Childs *et al.* 2019). In early life, the gut microbiota, which is inextricably linked to the immune system as outlined below, can be shaped by exposures including breastfeeding, furry pet ownership and antibiotic use and may influence the development of atopy (Kim *et al.* 2019). The gradual deterioration and dysregulation of many aspects of both the innate and adaptive immune systems [described in detail elsewhere (Calder 2020)], which occurs later in life (typically from age 50 years onwards), is called immunosenescence (Yaqoob 2017) and is coupled with chronic, low-grade inflammation (or 'inflamm-ageing') (Yaqoob 2014). This is, in part, caused by a decline in thymic output due to a decrease in the amount of active immune tissue within the thymus, the organ which produces T cells (Berzins *et al.* 2002), thus reducing the diversity in the T-cell repertoire (Yaqoob 2014). Furthermore, senescent T cells

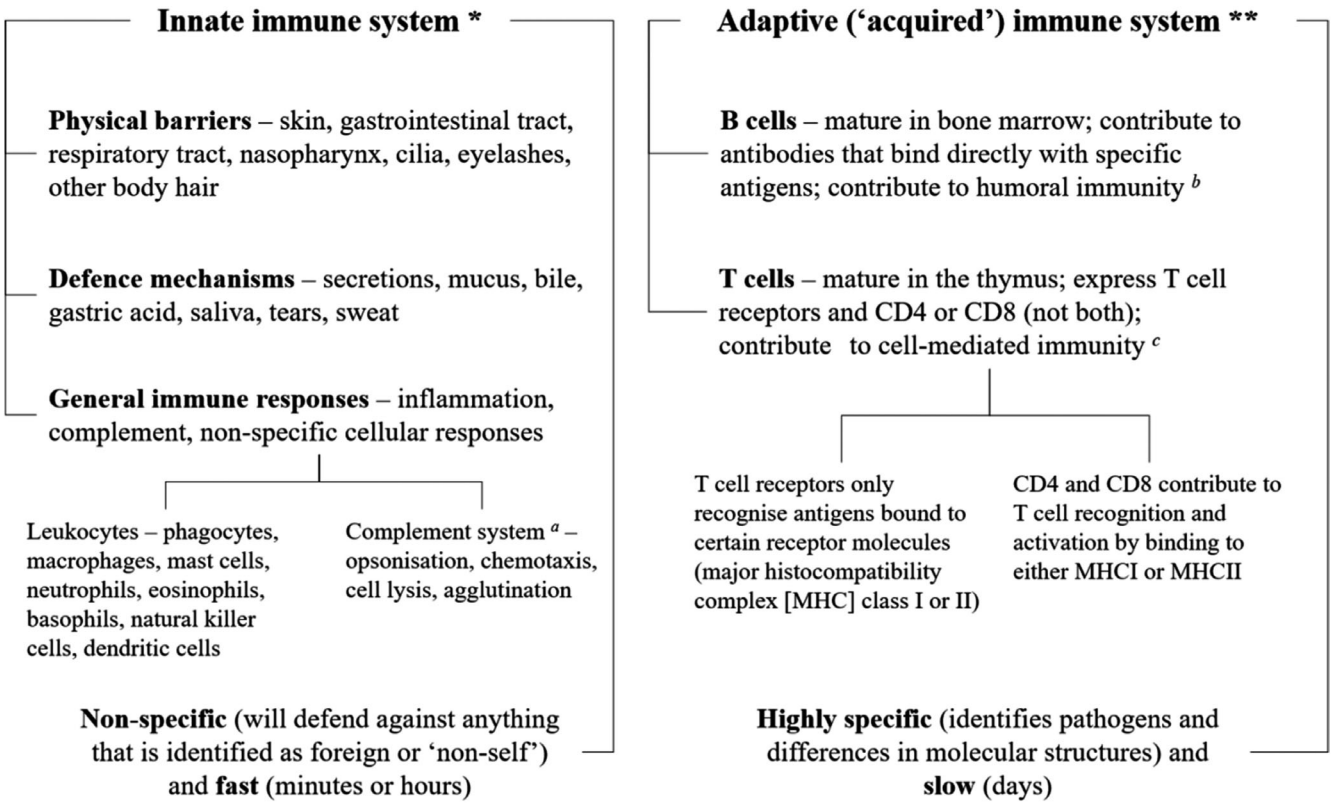

Figure 1 Simple overview of the immune system. Reproduced from Maggini *et al.* (2018). *The innate immune system comprises anatomical and biochemical barriers and an unspecific cellular response mediated mainly by monocytes, neutrophils, natural killer cells and dendritic cells; these work together to fight off pathogens before they can start an active infection. ** The adaptive immune system involves an antigen-specific response mediated by T and B cells that is activated by exposure to pathogens; this works with the innate immune system to reduce the severity of infection. [a] The complement system can work with both the innate and adaptive immune systems. Opsonisation, the coating of a particle with proteins to facilitate phagocytosis; chemotaxis, cell movement towards a gradient of increasing chemical concentration; cell lysis, the dissolution or destruction of cells by disruption of the cell membrane; agglutination, the formation of clumps of cells or inert particles by specific antibodies. [b] immunity from serum antibodies produced by plasma cells. [c] an immune response that does not involve antibodies but responds to any cells that display aberrant major histocompatibility complex (MHC) markers, such as cells invaded by pathogens.

are unable to divide, a process which is required for these cells to function (Brenchley *et al.* 2003; Focosi *et al.* 2010). Reductions in bifidobacteria in the gut with ageing (Arboleya *et al.* 2016) may also be linked to immunosenescence. Other age-related changes that can influence immune function include reduced diversity in the gut microbiota; an increase in bacteria that promote inflammation such as streptococci, staphylococci, enterococci and enterobacteria; and a decrease in bacteria that produce the short-chain fatty acid (SCFA) butyrate (Yaqoob 2014), a metabolite which can directly interact with immune cells (Biagi *et al.* 2013; Li *et al.* 2018). These changes may occur, in part, due to dietary restrictions, for reasons such as health, difficulty chewing or swallowing, reductions in taste and smell or as a result of a repetitive diet in a care setting, all leading to reduced dietary diversity and quality; or reduced intestinal motility (Biagi *et al.* 2013).

Immunosenescence is likely to contribute to the increased susceptibility of older adults to infections such as influenza, and indeed COVID-19 [along with other factors present in older adults such as reduced cardiorespiratory reserve (Sattar *et al.* 2020)]; poorer prognosis when becoming ill; increased prevalence of cancer and autoimmune diseases; and reduced effectiveness of vaccinations compared with younger adults (Tae Yu *et al.* 2015; Yaqoob 2017).

Role of nutrients in supporting the immune system

Function of specific nutrients in the immune system

Adequate nutrition is required for cells in the immune system to function, with demand for energy increasing during infection (Childs *et al.* 2019), and specific nutrients are also needed to fulfil particular roles. For

example, the amino acid arginine is required for the generation of nitric oxide by macrophages (Childs *et al*. 2019) and long-chain omega-3 fatty acids help to resolve inflammation (see later) (Calder *et al*. 2020). In addition, many micronutrients contribute to the normal function of the immune system, often synergistically through a variety of biological processes (see Table 1) (EC 2019). Nutrients with authorised EU health claims relating to immune function are vitamins A, B6, B12, C and D plus copper, folate, iron, selenium and zinc. While there are no authorised EU health claims for vitamin B2, vitamin E and beta-carotene, deficiencies in these micronutrients can also have effects such as reduced numbers of lymphocytes, impaired phagocytosis and microbial killing by innate immune cells, altered cytokine production and reduced antibody responses (Wessels *et al*. 2017; Maggini *et al*. 2018; Gombart *et al*. 2020).

Despite there being a number of approved immune function claims, reduced risk of infection is more difficult to demonstrate and all health claims related to immune defence against pathogens submitted to the European Food Safety Authority (EFSA) to date have failed to receive a favourable opinion. Substantiating health claims related to immunity in the context of the EU Nutrition and Health Claims Regulation is challenging for several reasons. It is important to consider that there are several non-modifiable factors that influence the function of the immune system (including age, gender, early life events and genetics), which can also alter an individual's immune response to dietary modification. Furthermore, small changes in parameters of immune function are unlikely to be relevant to host defence against pathogens (Cummings *et al*. 2004). A reduction in the functional capacity of one component of the immune system may be compensated for by another; therefore, attempting to compare immune function between individuals (or within individuals before and after an intervention) by looking at specific immune function markers (*e.g*. cytokine concentrations) lacks clinical relevance, especially if individuals differ greatly in terms of other factors that affect immune function (such as age, gender, smoking status, physical activity level, medication and disease state) (Cummings *et al*. 2004). While there is no single measure of overall immune function, the most meaningful measures are proposed to be rate, severity and duration of infection; response to vaccination and allergen provocation (*e.g*. by measuring delayed-type hypersensitivity response) (Albers *et al*. 2013). Only beneficial changes in the former two (related to infection and vaccination response, measured using appropriate methodology) are considered to be appropriate outcome variables for the scientific substantiation of claims related to immune defence against pathogens according to EFSA guidance (EFSA Panel on Dietetic Products Nutrition & Allergies 2016) and such studies are challenging and resource-intensive to conduct.

The effects of nutrients on immune function will also depend on the underlying nutritional status of an individual, varying according to whether a person is deficient, has low status or is replete in a nutrient. This is discussed in more detail below.

Effects of clinical micronutrient deficiencies on immune function

Clinical deficiencies, commonly seen in cases of malnutrition such as in children living in poverty in low-income countries, compromise the immune system leading to increased rates of infection, which can be life-threatening (WHO 2017). In these settings, micronutrient deficiencies are often caused by a reliance on starchy staple foods (which normally contain forms of nutrients, such as iron and zinc, that are less bioavailable) and a lack of variety in the diet due to an inability to access micronutrient dense foods such as meat, dairy foods and fruits and vegetables in sufficient quantities, if at all (WHO 2006). Supplementation (specifically with vitamin A or zinc in children who are deficient) has been demonstrated to improve antibody titre responses to vaccines, lower the incidence of infections such as pneumonia and reduce mortality from diarrhoea (Khan & Sellen 2011; Lassi *et al*. 2016; WHO 2019). Decreased immune function as a result of malnutrition can also occur in high-income countries, normally among elderly individuals or those experiencing periods of hospitalisation (Yaqoob 2017; Childs *et al*. 2019).

Low micronutrient status and immune function

In considering health claims for the essentiality of micronutrients and maintenance of functions of the immune system (*i.e*. those related to the well-established biochemical role of such nutrients, and/or based on deficiency symptoms involving the immune system) (EFSA Panel on Dietetic Products Nutrition & Allergies 2016), EFSA has stated that the evidence provided to substantiate these claims does not establish that inadequate intakes leading to impaired function of the immune system occurs in the general EU population (EFSA Panel on Dietetic Products Nutrition &

Table 1 Role of nutrients in supporting the immune system and their food sources*

Nutrient	Role in immune system	Food sources
Vitamin A	• Stimulates the proliferation of T cells. • Inhibits the proliferation of B cells and Bcell precursors. • Suppresses T-helper 1 development and enhances T-helper 2 development, thus influencing T-helper cell balance. • Regulates the survival and antigen presentation by immature dendritic cells and the maturation of immature to mature dendritic cells. • Has apoptotic effects on immune-competent cells during back regulation of immune reactions and during thymic selection. • Involved in the alteration of genes relevant to the immune response. • Vitamin A deficiency enhances macrophage-mediated inflammation but impairs the ability of macrophages to ingest and kill bacteria.	Liver, eggs and cheese are dietary sources of retinol ('pre-formed' vitamin A). Dark green leafy vegetables and orange-coloured fruits and vegetables (*e.g.* carrots, sweet potato, butternut squash, cantaloupe melon and spinach) are dietary sources of carotenoids, which can be converted to vitamin A by the body.
Vitamin B6	• Vitamin B6 is required as a coenzyme in the production of antibodies and cytokines. • Lymphocytes isolated from vitamin B6-deficient individuals display reduced proliferation, reduced interleukin-2 production in response to mitogens and reduced antibody production in response to immunisation.	Poultry, some fish, fortified breakfast cereals, egg yolk, soya beans and some fruit and vegetables, such as banana, avocado and green pepper.
Vitamin B12	• Vitamin B12 interacts with immune function through its involvement in nucleic acid and protein biosynthesis (alongside vitamin B6 and folate). • Vitamin B12-deficient patients have been noted to have an abnormally high CD4+/CD8+ ratio and suppressed natural killer cell activity (which could be restored by administration of vitamin B12) and an impaired antibody response to pneumococcal polysaccharide vaccine.	Red meat, fish, shellfish, milk, cheese, eggs, yeast extract and fortified breakfast cereals.
Vitamin C	• Involved in production, differentiation and proliferation of T cells, particularly cytotoxic T cells. • Promotes proliferation of lymphocytes, resulting in increased generation of antibodies. • Involved in proliferation, function and movement of neutrophils, monocytes, phagocytes; maintains or enhances natural killer cell activities and chemotaxis; enhances phagocytosis and reactive oxygen species generation; enhances microbial killing; involved in apoptosis and clearance of spent neutrophils from sites of infection by macrophages; attenuates extracellular trap formation, thus reducing associated tissue damage. • Helps to maintain the skin, our external barrier to infection. • Altered values of immune parameters seen in those with low vitamin C status can be restored by vitamin C intake.	Citrus fruits, blackcurrants, strawberries, papaya, kiwi, green vegetables (*e.g.* broccoli, peppers and tomatoes).
Copper	• The copper-containing enzyme cytochrome c oxidase is needed for energy production of immune cells. • The copper-containing enzyme superoxide dismutase plays a role in the protection of immune cells against reactive oxygen species. • Moderate and even marginal copper deficiency affects some activities of T cells and phagocytic cells adversely. • Severe copper deficiency changes the phenotypic profiles of immune cells in blood, bone marrow and lymphoid tissues and suppresses a number of activities of lymphocytes and phagocytic cells. • Copper deficiency results in abnormally low levels of neutrophils and thymus atrophy.	Brown and wholemeal bread, wheat-based breakfast cereals, quinoa, shellfish, pulses, avocado, dried fruit, nuts and seeds.
Vitamin D	• Plays a regulatory role in the functioning of the immune system and inflammatory responses. • Reduces the inflammatory response of T-helper 1 cells; suppresses antigen presentation by dendritic cells; suppresses proliferation and immunoglobulin production and retards the differentiation of Bcell precursors into plasma cells, exerting an inhibitory action on the adaptive immune system. • Increases expression of cathelicidin (LL-37), an antimicrobial peptide thought to be important for the innate immune system.	Oil-rich fish, eggs, fortified breakfast cereals, fortified spreads and fortified dairy products. In the UK, all individuals are advised to consider taking a supplement of 10 micrograms a day from October to March, and all year round for those with dark skin or for those who receive little sun exposure due to covering up or not being outdoors often.

Table 1 *Continued*

Nutrient	Role in immune system	Food sources
Folate	• Folate deficiency reduces the proportion of circulating T cells and their proliferation in response to mitogen activation.	Green vegetables (e.g. cabbage), pulses, oranges, berries, nuts, some cheeses, brown and wholemeal bread and fortified breakfast cereals.
Iron	• Decreased numbers of naïve T-helper and T-cytotoxic cells have been noted in iron-deficient subjects, suggesting that iron is required for the regeneration of new CD4+ T cells and maintenance of T-cell cytolytic processes. • It has been suggested that iron alters the balance between pro- and anti-inflammatory cytokines (based on reports of serum IL-2 and IL-6 being reduced in iron-deficient children).	Offal, red meat, some pulses (e.g. lentils, haricot beans), nuts, some seafood (such as canned sardines, cockles and mussels), quinoa, brown and wholemeal bread and some dried fruit (e.g. raisins, semi-dried apricots).
Selenium	• Supplementation with selenium has been shown to stimulate the proliferation of activated T cells; an enhanced response to antigen stimulation; an enhanced ability to generate cytotoxic lymphocytes; an enhanced ability to destroy tumour cells; increased natural killer cell activity; up-regulated interleukin-2 receptors on the surface of activated lymphocytes and natural killer cells.	Nuts and seeds (e.g. Brazil nuts, cashews and sunflower seeds), eggs, offal, poultry, fish and shellfish.
Zinc	• Zinc deficiency results in an abnormally low level of lymphocytes in the blood and thymic atrophy and is associated with a decline in most aspects of immune function including cell- and antibody-mediated responses, the production of cytokines by mononuclear cells and the induction of apoptosis, resulting in a loss of Bcell and Tcell precursors within the bone marrow. • Thymulin is a zinc-dependent enzyme that stimulates the development of T cells within the thymus. • Adequate zinc status is necessary for natural killer cell function. • Zinc supplementation in humans has shown benefit in immune responses to bacterial and viral infections.	Meat, poultry, cheese, some shellfish (including crab, cockles and mussels), nuts and seeds (in particular pumpkin seeds and pine nuts), wholegrain breakfast cereals and wholegrain and seeded breads.

*A 'source' of a particular micronutrient nutrient is defined as a food which provides at least 15% of the nutrient reference value per 100 g. It is worth noting that some foods that do not qualify as a 'source' are significant contributors to intakes of particular micronutrients within the UK diet due to the quantities in which they are consumed (e.g. meat and vitamin D, potatoes and vitamin C) (Bates *et al.* 2014; Roberts *et al.* 2018).

Allergies 2009a; EFSA Panel on Dietetic Products Nutrition & Allergies 2009b; EFSA Panel on Dietetic Products Nutrition & Allergies 2009c; EFSA Panel on Dietetic Products Nutrition & Allergies 2009d; EFSA Panel on Dietetic Products Nutrition & Allergies 2009e). This may suggest that supplementation will not enhance immune function in the average healthy and well-nourished individual.

However, low intakes and status for multiple key micronutrients are seen in the UK population, and indeed in other high-income countries across Europe and worldwide (WHO Regional Office for Europe 2014; USDA 2019). For example, data from the UK's *National Diet and Nutrition Survey (NDNS)* indicate that intakes of several micronutrients are below the lower reference nutrient intake (LRNI; the amount of a nutrient that is calculated to be sufficient for only 2.5% of the population subgroup to which it relates) in significant proportions of some population groups, particularly adolescent girls (Roberts *et al.* 2018; Lockyer *et al.* 2020). Furthermore, biochemical status data indicate an increased risk of iron deficiency in 9% of girls aged 11–18 years and 5% of women aged 19–64 years based on the WHO classification for iron deficiency and anaemia. In addition, 9% of adolescent boys, 12% of adolescent girls, 8% of men aged 19–64 years and 11% of women aged 19–64 years have a serum folate concentration indicative of risk of folate deficiency (Roberts *et al.* 2018), and 26% of adolescents aged 11–18 years and 17% of adults aged 19–64 years have low vitamin D status (Roberts *et al.* 2018). This poses the question of whether some individuals could improve (or normalise) their immune function by increasing their intakes of these nutrients, either by improving their diets or by taking supplements.

However, while the impact of clinical nutrient deficiencies on the immune system and the effects of supplementation in preventing rates of infection in these scenarios are well documented, much less is known about the impact of low micronutrient status (seen in a proportion of the UK population, as outlined above)

on immune function (Gombart *et al*. 2020), though effects will likely depend on the extent and duration of the inadequacy and the age of the individual (Wishart 2017; Childs *et al*. 2019). Variation in immune function is seen within the general population (Cummings *et al*. 2004). For example, differences have been shown among healthy volunteers in phagocytosis and oxidative burst (or respiratory burst; the rapid release of reactive oxygen species by cells such as neutrophils and macrophages when infected) in response to *Escherichia coli*; and cytokine production in response to lipopolysaccharide or concanavalin A (Calder & Kew 2002). It is thought that low micronutrient status likely explains some of this variation (along with several other factors including genetics) (Calder 2020).

Intakes higher than reference nutrient intakes and immune function

It has also been suggested, based on the results of human studies reporting increases in immune function after supplementation, that intakes that are higher than dietary reference values might be advantageous for some micronutrients from an immune function perspective (Wishart 2017; Wu *et al*. 2019; Calder *et al*. 2020), especially as requirements can be increased under some circumstances (*e.g*. periods of psychological stress or strenuous exercise). Ultimately, however, definitive 'optimal' intakes of micronutrients for immune function remain largely unknown (Calder 2020; Gombart *et al*. 2020) and any advice to take supplements needs careful consideration. Excessive intakes (normally only easily achieved through supplementation) of some micronutrients may be largely excreted (and therefore a waste of money) depending on the micronutrient but could cause health issues if safe upper limits are exceeded. In fact, intakes of certain micronutrients that are too high can negatively affect immune function (*e.g*. copper and zinc) (Wessels *et al*. 2017; Gombart *et al*. 2020). The NHS website states that there is little evidence that supplements (it gives vitamin C, Echinacea and garlic as examples) prevent colds or speed up recovery (NHS 2017). Furthermore, commentaries on a 2011 Cochrane review published on the NHS website point out that, while the evidence indicates that zinc may help to shorten a cold, colds are a minor illness for most people and zinc supplements/preparations can have side effects such as nausea and an unpleasant taste, and it is therefore up to the individual to weigh this up (NHS 2011; NHS 2012). The articles also highlight that it should be possible to obtain amounts of zinc needed through a normal, balanced diet and warns consumers to be mindful of safe upper limits when using supplements.

Further evidence for the effect of a few specific nutrients on immune function across the nutrient status spectrum is discussed in more detail below.

Vitamin D

Vitamin D can be synthesised in response to the action of direct sunlight on the skin when outdoors but, between October and early March in the UK, synthesis is insufficient to meet daily requirements and, due to the small number of dietary sources of vitamin D, standard government advice has been to consider taking a 10 μg daily supplement in the winter months (SACN 2016). However, with many individuals experiencing reduced access to sunlight while following government advice to stay at home during the COVID-19 pandemic, PHE reissued its recommendation for supplementation in April 2020, advising that the public should additionally consider taking a vitamin D supplement throughout Spring and Summer, should restrictions continue (NHS 2020b). PHE stated that the supplementation advice was in place due to the importance of vitamin D for bone and muscle health and that there was no evidence that vitamin D supplementation would help to prevent COVID-19 infection as some news reports had suggested (Heart.co.uk 2020; *The Sun* 2020).

Interest in vitamin D in the context of COVID-19 was stimulated by the fact that the vitamin D receptor is expressed by many types of immune cells and data suggest several roles for vitamin D in supporting the immune system including anti-inflammatory effects and increasing the ability of the innate immune system to fight against pathogens (Sassi *et al*. 2018) (see Table 1). Data from cohort studies suggest an inverse association between vitamin D status and risk of upper respiratory tract infections (Scientific Advisory Committee on Nutrition 2016) and there is some evidence that vitamin D supplementation at levels above the reference nutrient intake (RNI) can reduce the incidence of acute upper respiratory tract infections, especially in those with low baseline levels of 25-hydroxyvitamin D (25 studies, daily dose equivalent <20 μg to ≥ 50 μg) (Martineau *et al*. 2017), though the results of randomised controlled trials (RCTs) are inconsistent and the overall quality of studies and relevance to the UK population has been questioned (Lanham-New *et al*. 2020). A recent rapid evidence review from SACN concluded that 'The evidence at this time

does not support recommending vitamin D supplementation to prevent acute respiratory tract infections in the general UK population' (SACN 2020).

A report from PHE confirmed that among those diagnosed with COVID-19, risk of death (not taking into account comorbidities) is higher in individuals aged 80 years or over, males, those living in deprived areas and those in Black, Asian and Minority Ethnic (BAME) groups (PHE 2020a). Twenty-seven per cent of deaths from COVID-19 in England up to 8 May 2020 occurred among people in care homes and obesity has also been linked to COVID-19 infection and poorer outcomes among those infected (*i.e.* critical illness and death) (PHE 2020a). The fact that groups at higher risk of hospitalisation and death due to COVID-19 infection (*i.e.* those in BAME groups, older and obese individuals) also have a higher prevalence of low vitamin D status has been highlighted in the literature (Brown 2020; Lanham-New *et al.* 2020). Other factors affecting immune function in groups that appear to be at higher risk are discussed later. Data linking low vitamin D status with COVID-19 test results and clinical outcomes among patients are emerging (Baktash *et al.* 2020; Munshi *et al.* 2020), with more studies underway (Chinese Clinical Trials Registry 2020a; Chinese Clinical Trials Registry 2020b). An analysis of UK Biobank data did not support a potential link between vitamin D status and risk of COVID-19 infection, nor that vitamin D status may explain ethnic differences in COVID-19 infection, although vitamin D status was assessed a decade before the pandemic, in 2006–2010 (Hastie *et al.* 2020). A rapid evidence review from the National Institute for Health and Care Excellence (NICE), published at the end of June 2020, concluded that 'there is no evidence to support taking vitamin D supplements to specifically prevent or treat COVID-19' (NICE 2020) although the topic remains controversial and the focus of ongoing research (Cereda *et al.* 2020).

Vitamins A and C and zinc

As mentioned previously, supplementation with vitamin A and zinc has been successfully used to lower rates of infection (including respiratory tract infections) among malnourished children. The effects of supplementation on the common cold in apparently well-nourished populations are described below. A 2013 Cochrane review reported that regular vitamin C supplementation (5 studies, dose <1 g/day; RNI 40 mg/day for adults) decreased the incidence of the common cold in people under heavy short-term physical stress (*i.e.* marathon runners, skiers, soldiers) but did not affect the incidence of the common cold in studies carried out in the general population (24 studies, dose ≥0.2 g/day; including 17 studies, dose ≥1 g/day) (Hemila & Chalker 2013). Vitamin C supplementation did significantly reduce the duration and severity of common colds, which occurred while taking supplements (most trials used 1 g/day); however, these effects were not seen in trials in which supplementation began after the development of cold symptoms. Conversely, meta-analyses have demonstrated that oral zinc (most studies have used zinc lozenges) significantly reduces the duration of a cold when used after the onset of symptoms (7 studies, dose ≥75 mg; RNI 7.0 mg women, 9.5 mg men) (Hemila & Chalker 2013) (3 studies, dose ≥75 mg; 5 studies, dose ≤75 mg) (Science *et al.* 2012) but has no significant impact on the severity of symptoms (Science *et al.* 2012).

Body mass index, diabetes and immunity

In the context of the COVID-19 pandemic, the UK government lists those with the most common diet-related non-communicable diseases [specifically anyone with a BMI of 40 or above, as well as people with diabetes and chronic heart disease (among other, non-diet-related, conditions)], as clinically vulnerable (Cabinet Office 2020). In 2018/2019, 67% of men and 60% of women in England were overweight or obese and 20% of children in Year 6 were classified as obese (NHS Digital 2020). Obesity is associated with immune dysfunction (Andersen *et al.* 2016), leaving obese individuals more susceptible to infections and displaying poorer responses to vaccinations compared with healthy-weight individuals (Calder 2020; Luzi & Radaelli 2020). Impairments are seen in both the adaptive and innate immune systems (see Fig. 1) (Luzi & Radaelli 2020) and effects may also be exacerbated by micronutrient deficiencies (Kaidar-Person *et al.* 2008; Lefebvre *et al.* 2014; Sánchez *et al.* 2016; Cano-Ibáñez *et al.* 2019). The obese state is also associated with chronic low-grade inflammation, mainly derived from adipose tissue (Rogero & Calder 2018), which can increase the risk of an excessive inflammatory response during infection (Calder 2020). Lipid-engorged hypertrophic obese adipose tissue tends to contain more macrophages than healthy adipose tissue, often with a pro-inflammatory phenotype, and obesity also leads to the accumulation of lipid in immune tissues including the bone marrow and thymus, disrupting tissue integrity and altering leukocyte

development, migration and diversity and therefore immune function (Andersen *et al*. 2016; Rogero & Calder 2018). It has been proposed that immune dysfunction is one factor that likely contributes to the observed increased disease severity and risk of death from COVID-19 seen in obese patients, with other suggested contributing factors described in detail elsewhere (Dietz & Santos-Burgoa 2020; Kassir 2020; Kruglikov & Scherer 2020; Sattar *et al*. 2020). Interestingly, a study in 122 overweight and obese subjects found that long-term mild weight loss (>2 kg) reduced inflammatory cytokine levels, leukocyte counts and oxidative stress levels over 3 years (Chae *et al*. 2013).

Changes in hormones and cytokines (resulting in decreased inflammation) and decreased responses to vaccination are also seen with undernutrition and linked to dysfunction in both innate and adaptive immunity and to susceptibility to infections in those who are underweight (Alwarawrah *et al*. 2018). Atrophy of lymphatic tissues, such as the thymus and gut mucosa (see later), and a lack of energy and the nutrients (including protein and micronutrients) required to produce immune cells are key issues in malnutrition (Iddir *et al*. 2020), though not all aspects of the immune system are compromised (Rytter *et al*. 2014). Indeed, both morbidly obese and underweight patients are more likely to be hospitalised as a result of influenza-like illnesses than normal-weight patients (Moser *et al*. 2019) and this U-shaped relationship between bodyweight and infection rates (with the exception of anorexia nervosa patients) has been seen in many studies (Dobner & Kaser 2018).

Obesity is responsible for 80 to 85% of the risk of developing type 2 diabetes (Diabetes UK 2019). Diabetes (particularly uncontrolled) is also a risk factor for poor outcomes with COVID-19 infections (PHE 2020a) and it has also been proposed that heightened inflammation and immune dysfunction play a role (Cole *et al*. 2020; Filardi & Morano 2020). Individuals with diabetes are more likely to experience complications during infections (American Diabetes Association 2020; Sardu *et al*. 2020) as more glucose is released into the bloodstream as a stress response and, in the case of diabetes, sufficient insulin cannot be produced in order compensate (Diabetes UK 2020; Elnaem & Cheema 2020; Guo *et al*. 2020; Sattar *et al*. 2020; Schofield *et al*. 2020).

Immunity, the gut and pre- and probiotics

The majority of the immune system is associated with the gut (Childs *et al*. 2019). Immune cells reside both within the lamina propria and within Peyer's patches, surveying the contents of the gut lumen to check what has been ingested for potential pathogens and providing protection (Rescigno *et al*. 2001; Stagg *et al*. 2003). Gut bacteria that are thought to be beneficial for health play a role in defence by preventing the colonisation of pathogenic bacteria, increasing the production of metabolites such as SCFAs and lactic acid, which further inhibit the growth of pathogenic bacteria, and enhance host immunity both locally and systemically through a variety of mechanisms (Rooks & Garrett 2016; Pickard *et al*. 2017; Calder 2020). Due to the relationship between the gut microbiota and the immune system, it seems logical that dietary components that have been demonstrated to favourably change the composition of the gut microbiota, such as prebiotics (So *et al*. 2018) and probiotics which temporarily colonise the gut, providing opportunity for interactions with commensal bacteria, pathogens and host tissues through direct contact or released substances (Calder 2020), may influence immunity. Probiotics are 'live microorganisms that, when administered in adequate amounts, confer a health benefit on the host' (Hill *et al*. 2014a). Probiotics are commercially available in the form of dairy products or supplements and typically comprise bifidobacteria and lactobacilli. Substrates currently defined as prebiotics are selectively utilised by host microorganisms thus conferring a health benefit (Gibson *et al*. 2017) and are all types of dietary fibre, either present naturally in plant-derived foods or commercially available in purified form as supplements (Lockyer & Stanner 2019). Prebiotics are more readily degraded by bifidobacteria and lactobacilli than by other gut bacteria (Gibson *et al*. 2017; Wilson & Whelan 2017). At present, however, there are no approved EU health claims for pre- or probiotics in relation to immune function. According to guidance from EFSA, increases in abundance of types of bacteria that are thought to be beneficial for health and changes in many of the immunological markers employed in human studies do not in themselves indicate beneficial physiological effects, though may be used as supportive evidence (EFSA Panel on Dietetic Products Nutrition & Allergies 2016).

Despite the absence of approved claims, there is a substantial amount of research investigating the impact of probiotics on infections. A 2011 Cochrane review, which included 57 studies, concluded that probiotics consumed alongside rehydration therapy reduce the duration and severity (indicated by stool frequency) of acute infectious diarrhoea (Allen *et al*.

2010). Probiotics can have both strain- and species-specific effects, as well as general effects (Hill *et al.* 2014b). The authors of the Cochrane review noted that studies have tested several different probiotics in different settings with nearly all reporting beneficial outcomes, suggesting a mechanism against gut pathogens common to most probiotics (*e.g.* colonisation resistance), rather than strain-specific effects. A 2020 systematic review and meta-analysis including 22 studies reported that probiotics can prevent antibiotic-associated diarrhoea and that mixtures of probiotics were no more effective than single probiotic strains (McFarland 2020). Information on the NHS website acknowledges that there is some evidence that probiotics can prevent diarrhoea when taking antibiotics (NHS 2018). A 2015 Cochrane review, which included data from 12 studies, reported that probiotics can significantly reduce the prevalence and duration, respectively, of acute upper respiratory tract infections in children, adults and older people, by 47% and 1.89 days (Hao *et al.* 2015), though the quality of the evidence was graded as low or very low. Included studies used several different strains including single- and multistrain preparations.

Modulation of the risk of infection by probiotics may be due to improvements in intestinal barrier function, competitive inhibition of potential pathogen-binding sites, enhanced natural killer cell activity and higher rates of phagocytosis or oxidative burst activity (Calder 2020), with the latter effect particularly relevant to probiotic strains whose cell walls are resistant to digestion. It has been suggested that monocytes phagocytose the probiotic bacteria and that the insoluble cell wall components induce the production of IL-12, which augments natural killer cell activity (Yaqoob 2014). Furthermore, it has been proposed that probiotics can be either 'immunoregulatory' (most bifidobacteria) or 'immunostimulatory' (most lactobacilli), based on their effects on cytokine production, and studies suggest that probiotics may be of benefit to older adults as 'anti-immunosenescence' therapy (Childs & Calder 2017). For example, two recent systematic reviews and meta-analyses reported that probiotics can improve antibody responses to influenza vaccination (Lei *et al.* 2017; Yeh *et al.* 2018).

A recent systematic review and meta-analysis reported that synbiotics (combinations of pre- and probiotics) were more effective than probiotics alone in reducing the duration of diarrhoea and hospitalisation among children with acute diarrhoea, though the number of studies using synbiotics was much smaller (Yang *et al.* 2019). There is some evidence that β-galacto-oligosaccharides (prebiotics) may be beneficial in preventing travellers' diarrhoea (Drakoularakou *et al.* 2010; Hasle *et al.* 2017). As well as influencing the composition of the gut microbiota, prebiotics may also exert microbiome-independent changes to immune function by inhibiting the adherence of pathogens to epithelial cells, exerting direct effects upon sugar receptors on immune cells, interfering with leukocyte recruitment to sites of inflammation or inhibiting cell-to-cell interactions (Jeurink *et al.* 2013), suggesting that a role for prebiotics is worthy of further investigation. However, while several mechanisms have been proposed, the effect of prebiotics on immunity remains to be fully elucidated.

Data suggesting links between gut microbial composition and the presence of gastrointestinal symptoms with severity of COVID-19 among hospitalised patients; differences observed in gut microbial composition between COVID-19 patients ('dysbiosis') and healthy controls (Jin *et al.* 2020; Xu *et al.* 2020; Zuo *et al.* 2020); and evidence that probiotics can prevent upper respiratory tract infections (Calder 2020) have led to calls for the role of gut health and interventions that can modify the gut microbiota to be considered in relation to both prevention and treatment of COVID-19 (Baud *et al.* 2020; Dhar & Mohanty 2020; Liang 2020). This has stimulated vigorous discussion (Gao *et al.* 2020) and raised some concerns regarding safety among vulnerable patients (*Nutraingredients* 2020). At the time of writing, there is no direct evidence in support of the use of probiotics in preventing or treating COVID-19.

Long-chain omega-3 polyunsaturated fatty acids

Despite a lack of approved EU health claims, the role of dietary fatty acids, particularly long-chain omega-3 polyunsaturated fatty acids predominantly present in oil-rich fish (EPA, DPA and DHA), in shaping inflammatory responses is well documented. When consumed, these fatty acids replace arachidonic acid within cell membranes, increasing their fluidity thus aiding some immunological processes including phagocytosis (Schumann 2016), and decreasing the production of inflammatory mediators such as cytokines, eicosanoids, adhesion molecules and particular enzymes (Calder 2019). Long-chain omega-3 polyunsaturated fatty acids are also precursors for cell signalling molecules that are typically less inflammatory or are inflammation resolving (*e.g.* resolvins, neuroprotectins) (Kohli & Levy 2009). An application for a

health claim for EPA/DPA/DHA supporting normal immune function in the context of decreasing the level or production of eicosanoids, arachidonic acid-derived mediators and pro-inflammatory cytokines was rejected by EFSA (EFSA Panel on Dietetic Products Nutrition & Allergies 2010). The Opinion states that adequate inflammatory responses are of primary importance for defence against injury and additionally points out that though chronic inflammation is associated with a number of diseases and so reducing levels of markers of inflammation under certain circumstances might be a beneficial physiological effect, this would depend on the context and the evidence provided had not demonstrated that a benefit would apply to the general population.

Due to their recognised anti-inflammatory properties, there is considerable research interest in the use of fish oils in the treatment of rheumatoid arthritis (a chronic inflammatory autoimmune disease characterised by infiltration of inflammatory cells and elevated inflammatory mediators within the tissue lining the joints) (James *et al.* 2010) and fish/fish oils during pregnancy for the prevention of asthma in children (Lee-Sarwar *et al.* 2019). However, their use for both of these potential applications remains controversial and, despite what is considered to be robust data by some researchers in this field (Calder 2015), along with plausible biological mechanisms, fish oils are not recommended for rheumatoid arthritis by NICE (NICE 2018). Anti-inflammatory bioactivity is thought to partly explain the heart health benefits of consuming oil-rich fish (Del Gobbo *et al.* 2016; Calder 2017), for example their role in increasing the stability of atherosclerotic plaques (Thies *et al.* 2003; Cawood *et al.* 2010), with other mechanisms including the maintenance of normal blood pressure, triglyceride levels and cardiac function (EFSA Panel on Dietetic Products & Allergies 2009; EFSA Panel on Dietetic Products Nutrition & Allergies 2010). There has been some speculation in the literature around whether or not fish oils could be useful in the treatment of severe cases of COVID-19 in which excessive, uncontrolled inflammation occurs (Bistrian 2020; Calder 2020; Calder *et al.* 2020; Messina *et al.* 2020; Rogero *et al.* 2020; Vorland *et al.* 2020).

Healthy dietary patterns

As well as featuring oil-rich fish, healthy dietary patterns such as Mediterranean-style diets and a dietary pattern that corresponds to the Eatwell Guide in the UK tend to be plant-based, consisting of high amounts of fibre-rich foods providing a variety of fibre types (such as wholegrains and pulses), which are important for gut health (Lockyer & Stanner 2019; Lockyer & Spiro 2020). Healthy dietary patterns additionally contain plenty of fruit and vegetables, which also provide fibre alongside a range of micronutrients and plant-specific compounds such as polyphenols, which have been suggested to have immune regulatory and anti-inflammatory effects (Sangiovanni & Dell'Agli 2020). Though several mechanisms have been suggested for polyphenols, a key mechanism proposed is that these compounds interfere with the nuclear factor κB (NF-κB) pathway, which ordinarily promotes the expression of adhesion molecules, cytokines and other pro-inflammatory mediators (Yahfoufi *et al.* 2018).

Intakes of both oil-rich fish and fruits and vegetables in the UK are low, with average intakes of oil-rich fish among adults aged 19–64 years being 11 g per day (equivalent to 77 g per week) (Bates *et al.* 2019), compared with the dietary recommendation to consume two 140 g portions of fish per week, one of which should be oil-rich (PHE 2018). Only 31% of adults are meeting the 5 A DAY recommendation and average intakes are particularly low in adolescents (Roberts *et al.* 2018). This suggests that there might be some capacity for improving the immune status of the general population if more people followed dietary recommendations. Interestingly, in a randomised controlled trial of healthy older adults with low fruit and vegetable consumption (≤2 portions/day) at baseline, antibody responses to pneumococcal vaccination (but not the tetanus vaccination) were significantly improved among subjects in the group assigned to consume ≥5 portions of fruit and vegetables per day for 16 weeks who had never previously received the vaccine, compared with those following their normal diet (Gibson *et al.* 2012).

Non-nutritional lifestyle factors

Regular exercise of moderate intensity is thought to be of benefit for immune function, including enhancing responses to vaccinations, with differences observed in a range of immune biomarkers between active compared with sedentary individuals (Walsh *et al.* 2011; Simpson *et al.* 2015; Zheng *et al.* 2015; Wong *et al.* 2019). Proposed mechanisms include the selective apoptosis of senescent T cells, which can then be replaced by naïve cells that are more capable of responding to antigens; prolonging thymic activity; reducing inflammation by reducing visceral fat and the inducing the release of hormones that have anti-

inflammatory properties such as cortisol and adrenaline; increasing the frequency and efficiency of immune cell trafficking between the circulation, lymphoid and peripheral tissues; and reducing stress (Simpson *et al.* 2015). However, excessive exercising is thought to suppress the immune system, as evidenced by the high infection rates seen among elite athletes and soldiers (Simpson *et al.* 2020), though whether this effect is due to exercise *per se* causing a transient depression in immune function or other conditions experienced by such individuals (such as increased stress, reduced sleep, increased exposure to pathogens due to frequent travel and exposure to different climates) is debated (Gleeson 2016). Similarly, getting enough good quality sleep is thought to play an important immunomodulatory role, due to the fact that disturbed or short sleep has been associated with increased inflammation, reduced functional capacity of leukocytes and increased susceptibility to infection (Ibarra-Coronado *et al.* 2015; Besedovsky *et al.* 2019). While the protective effect of sleep is not fully understood, it has been proposed that slow wave sleep (the deepest form of sleep) induces an immune-supportive hormonal environment (Besedovsky *et al.* 2019).

Conclusion

Interest in the topic of nutrition and immunity has hugely increased due to the search for means to increase resistance to COVID-19. The trend for products to be touted as 'immune boosting' is concerning, especially given the link between excessive inflammation and severe COVID-19, and has resulted in widespread calls for the scientific community to actively speak out against pseudoscience linked with COVID-19, in order to protect the public (Nature 2020; United Nations 2020). Nutritional adequacy is vital for supporting normal immune function, with several nutrients playing specific roles in essential processes and clinical deficiencies of these nutrients leaving individuals more vulnerable to infections. Individuals with low intakes of a range of these specific nutrients may benefit from increased intakes through diet or, where this is not possible, supplements. Emerging evidence also points to potentially supportive roles for specific food components, such as sources of fish oils and products that improve gut health, although more evidence is needed to demonstrate immunomodulatory effects and the mechanisms of action. While there is some evidence that specific supplements and food components may be useful with respect to particular infections, for example zinc (perhaps as lozenges) and vitamin C reducing the duration of the common cold; probiotics reducing the duration and severity of acute infectious diarrhoea and preventing antibiotic-associated diarrhoea, at present there are no authorised EU health claims for these effects and more information is needed on specific type (*e.g.* strain for probiotics), preparation and dose. Regarding the use of supplements in general, the NHS advises that taking too much or taking them for too long could be harmful (NHS 2020a). Importantly, no individual food or supplement can prevent infection with COVID-19.

The COVID-19 pandemic has highlighted the state of the nation with regards to nutrition, health and inequalities both generally and more specifically due to interplay between illness severity among COVID-19 patients and diet-related disease, the prevalence of which is linked with socio-economic status. Considering the sources of nutrients required to support the normal functioning of the immune system, dietary patterns that are varied and plant-based but also include some animal foods (meat, dairy foods, eggs and oil-rich fish), in line with the Eatwell Guide, coupled with vitamin D supplements during times when sun exposure is low, is a good basis and promotes health overall, along with the other elements of a healthy lifestyle such as adequate sleep, regular exercise and not smoking. It is important that this message is clearly communicated to the public in the midst of confusing headlines around 'immune-boosting' foods or foods to be avoided in order to protect against COVID-19 infection.

Yet, pre-existing barriers for some to achieving a healthy diet and lifestyle have been exacerbated by the impact of the pandemic and unfortunately, increased food insecurity is likely to persist as the effect on the economy continues to be felt. Furthermore, the closures of schools, exercise and leisure venues, restrictions on time spent outside for those isolating at home and general reductions in physical activity, including increased time spent sitting, due to many people working at home or being unable to work, coupled with increased eating and drinking in response to stress, upset and boredom during lockdown may have led to weight gain by some (BNF 2020; Rundle *et al.* 2020; Sattar *et al.* 2020; Wang *et al.* 2020). Obesity is associated with chronic, low-grade inflammation (Rogero & Calder 2018), which can increase the risk of an excessive inflammatory response during infection. Overweight and obesity are already prevalent in many countries, including the UK, and are responsible for a considerable amount of ill health including, now, severity of illness among those contracting COVID-19

(PHE 2020b), bringing the human cost of obesity and the importance of consuming a healthy, balanced diet that does not exceed energy requirements into sharp focus. New measures announced by the UK government aiming to tackle obesity are therefore very welcome (Department of Health & Social Care 2020).

Conflict of interest

The authors received no direct financial contribution towards the production of this article.

Funding information

Funding to support BNF's charitable aims and objectives comes from a range of sources including membership, donations and project grants from food producers and manufacturers, retailers and food service companies. Further information about BNF's activities and funding can be found at www.nutrition.org.uk/aboutbnf/.

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