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Review

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Review

COVID-19: reducing the risk via diet and lifestyle

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Abstract
This review shows that relatively simple changes to diet and lifestyle can significantly, and rapidly, reduce the risks associated with coronavirus disease 2019 (COVID-19) in terms of infection risk, severity of disease, and even disease-related mortality. A wide range of interventions including regular exercise, adequate sleep, plant-based diets, maintenance of healthy weight, dietary supplementation, and time in nature have each been shown to have beneficial effects for supporting more positive health outcomes with COVID-19, in addition to promoting better overall health. This paper brings together literature from these areas and presents the argument that non-pharmaceutical approaches should not be overlooked in our response to COVID-19. It is noted that, in several cases, interventions discussed result in risk reductions equivalent to, or even greater than, those associated with currently available vaccines. Where the balance of evidence suggests benefits, and the risk is minimal to none, it is suggested that communicating the power of individual actions to the public becomes morally imperative. Further, many lives could be saved, and many harms from the vaccine mandates avoided, if we were willing to embrace this lifestyle-centred approach in our efforts to deal with COVID-19.

1. Introduction

Since its initial report in November 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has now been associated with over six million deaths worldwide [1]. With cases continuing to rise in many parts of the world despite public health efforts, the need for reducing the health risks associated with this disease is strong. This review attempts to bring together a diverse field of literature concerning diet and lifestyle interventions that can be used to reduce the risk of coronavirus disease 2019 (COVID-19) infection, severe disease symptoms, and even mortality. Previous authors have also drawn attention to the importance of this health-centred approach [2–5] and have covered some of the topics discussed here, albeit in a more limited manner. This paper builds on their important work and addresses the topic in a more comprehensive way, focussing on changes which can bring about rapid benefits. As such, with the exception of weight management, which will require a more sustained effort, all interventions can confer benefits within just hours to days. Accordingly, it is never too late to improve personal health and reduce the risks of COVID-19.
Given the wide-reaching nature of the topic, this review has been written for the use of both specialists and non-specialists with an interest in health. While many of the sections discussed deserve comprehensive reviews in their own right, this paper seeks to provide an overarching yet

detailed view, currently lacking from the literature, and provide a point of refence for best practice strategies that are beneficial to all, whether vaccinated or unvaccinated.

2. Healthy weight maintenance

It is clear from studies worldwide that maintaining a healthy weight (normal body mass index [BMI] between 18.5 and 24.9 kg/m^2) reduces many aspects of COVID-19 risk, as compared to being underweight (BMI < 18.5 kg/m^2), overweight (BMI between 25 and 30 kg/m^2) or obese (BMI > 30 kg/m^2) [6–14]. Given the high prevalence of obesity and overweight in much of the world, it would be negligent to exclude this from an article reviewing strategies for reducing COVID-19 risk. Indeed, the impact is so significant that the World Obesity Federation states that in 2020, COVID-19 death rates were 10 times higher in countries where more than half of the adult population is classified as overweight or obese, with a linear correlation between a country's COVID-19 mortality and the proportion of adults that are overweight [15]. Working towards or maintaining a normal weight via a healthy diet and exercise should therefore be at the forefront of any plan to reduce COVID-19 risks.

Obesity affects every aspect of COVID-19, from being more likely to test positive [16,17] to having more severe outcomes. In New York, in patients under 60 years old, those with a BMI over 30 kg/m^2 were almost twice as likely to be admitted to critical care, while those with BMI over 35 kg/m^2 were 3.6 times more likely to be admitted [12]. Additional studies have shown that younger patients admitted to hospital are more likely to be obese [7,18]. In a French study, the risk for mechanical ventilation in patients admitted to intensive care with severe COVID-19 was more than 7-fold higher for those with BMI > 35 kg/m^2 [10]. Mortality rate is also higher in obese patients, with Pettit et al. [18] reporting that for every increase from one BMI category to the next, there was a 70% increased risk of mortality. In an analysis of over 900,000 hospitalisations in the United States (US), O'Hearn et al. [13] suggest that 63.5% of all hospitalisations were attributed to just four conditions: obesity, hypertension, diabetes mellitus and heart failure, with obesity being the largest risk factor at 30.2%. This finding is corroborated by data from Mexico showing obesity to be the strongest predictor for severe COVID-19 [19]. Given the wealth of research already indicating obesity as a major risk factor for worsened outcomes with influenza A (H1N1) [20–26], this perhaps should not have been surprising.

While not all studies find obesity to be an independent risk factor for severe disease when other comorbidities are accounted for [27], Hernández-Garduño [19] suggests that the significance of individual comorbidities will often be underestimated by studies including patients with two or more comorbidities. The correlation between comorbidities (such as diabetes and obesity) will impact results, as the assumption of no or little multicollinearity will not be met [19]. At a broader scale, the evidence that obesity is associated with worsened COVID-19 outcomes is nevertheless strong, with several meta-analyses now confirming the link. In data from 219,543 patients across 41 studies, Yang et al. [17] found that the risk of infection, hospitalisation, intensive care unit (ICU) admission, ventilation and mortality were all elevated in obese patients. These findings were supported by meta-analyses of data from Europe, Asia and North America [28–30]. Recent studies have again confirmed these findings, with a 2022 meta-analysis of 57 studies finding a doubling of hospitalisation risk in Western countries and a three-fold increased risk of severe disease in Asian populations among obese individuals [31].

Although this review does not have the scope to fully address the mechanisms by which obesity leads to worsened outcomes from COVID-19 and higher risk of infection, a brief discussion may be informative. A number of authors (e.g., Seidu et al. [28]) have suggested several plausible mechanisms, seven of which are listed here. Firstly, direct impact on lung function due to excess weight and pressure or, secondly, via metabolic anomalies and increased inflammation [32,33] that can ultimately lead to a cytokine storm. In the latter case, it is well established that obesity is characterised by a chronic state of low-grade inflammation with increased circulation of proinflammatory cytokines [34], even prior to viral infection. A third suggestion is that increased

angiotensin-converting enzyme (ACE2) expression in adipose tissue of obese individuals could make it a vulnerable target for COVID-19 infection, especially given the higher expression of ACE2 in adipocytes, compared to lung tissue [34,35]. Evidence that SARS-CoV-2 can directly infect adipocytes [36] supports the hypothesis that adipose tissue represents an important viral reservoir for increased viral shedding [37,38]. This had previously been reported in studies on influenza, with elevated viral loads in exhaled breath, prolonged viral shedding, and obesogenic environments favouring the emergence of novel, more virulent virus strains [39–41]. Fourth, obesity is associated with thrombosis through several mechanisms [42] including increased endothelial dysfunction [34,38], which interacted with and worsened pro-thrombotic processes in severe COVID-19 [28]. Fifth, Chang et al. [30] suggest that B and T cell immunity may be impaired in obese individuals, with Hernández-Garduño [19] suggesting that obese individuals may also exhibit a less responsive immune system after vaccination. Aside from more frequent progression to severe disease, impaired immune responses in obese individuals could plausibly account for observed susceptibility to infection [34]. Again, previous research on influenza supports this finding, and documents the impaired and delayed response to infection and poor recovery in obese individuals [43–45]. Sixth, obese individuals are known to have lower levels of 25-hydroxy vitamin D [35]; the relevance of this, with respect to infection rate, is discussed further in section 6. Several of these mechanisms may be at work simultaneously, but what is clear is that there is no shortage of possible mechanisms by which disease outcomes can be worsened even before considering the links with other comorbidities. It is already well established that obesity (and excess fat mass) is causally linked to hypertension, diabetes mellitus, coronary heart disease, stroke, atrial fibrillation, renal disease and heart failure [8,46]. Many of these maladies are in turn risk factors associated with severe COVID-19 [8,13,17,19], leading to a seventh possible mechanism by which obesity could contribute to severe disease [28].

It is clear that addressing obesity is essential and that public health measures to facilitate healthy weight management have the potential to be extremely beneficial. Such benefits may extend beyond personal health and may also be relevant in discussions of transmission and evolution of the virus, as has been noted by others [2]. Unfortunately, given the weight gain that has been associated with lockdown measures [30,47], this issue has become even more significant. As noted by Sattar et al. [8], communicating the risks while avoiding inducing unnecessary anxiety will be of the utmost importance. Reducing excess fat mass is not a rapid intervention like others discussed here, yet it is one that should not, and cannot be ignored.

3. Exercise

The benefits of exercise and being physically active are numerous, well established, and affect almost every facet of human health [48]. Regular exercise is associated with reduced inflammation, improved cardiovascular health, increased lung capacity and muscular strength, improved glucose and lipid metabolism over time, decreased adipose tissue, better mental health, increased lymphocyte circulation, a more diverse gut microbiota with more beneficial strains of bacteria, a 40%–50% reduced susceptibility to respiratory infections and improved immunosurveillance [48–52]. Of particular note, given the propensity of COVID-19 to be more severe in elderly populations, regular exercise can also decrease immunosenescence, with increased natural killer (NK) cell activity, improved T cell function, reduced rates of illness, and improved vaccination response in elderly individuals[50]. In contrast, lack of regular physical activity is an underlying risk factor for many chronic diseases, including those associated with severe COVID-19 [51] and, even prior to the pandemic, was responsible for around 9% of premature deaths globally [48]. Despite this, as noted by Sallis et al. [51], exercise has received little discussion during the pandemic and has decreased markedly in response to public health measures, such as lockdowns [53,54].

Early data demonstrated the importance of activity, with a multisite study by Huang et al. [55] showing a 19-fold increase in the risk of contracting COVID-19 in sedentary individuals (defined as sitting for 9 hours or more on a workday) compared to their active counterparts. In individuals

exercising irregularly (less than three bouts of 30 min per week) the risk was almost three-fold that of regular exercisers [55]. Large scale studies confirmed these findings, albeit with a reduced effect size. In a study of 48,440 COVID-positive participants in the US, Sallis et al. [51] investigated the impact of meeting the US *Physical Activity Guidelines* for activity (over 150 min of moderate to vigorous exercise each week, including brisk walks) compared to being inactive (less than 10 min of activity each week). Being consistently inactive increased the odds of hospitalisation, admission to ICU and death, with inactive individuals more than twice as likely to be admitted to hospital and die than active individuals (odds ratio [OR], 2.26, 1.73 and 2.49, respectively) [51]. As in the study by Huang et al. [55], there was also a protective effect of being consistently active compared to inconsistently active. These effects were so strong that other than age and a history of organ transplant, being consistently inactive conferred the highest risk for hospitalisation with COVID-19 (excluding COVID-positive women going into hospital to give birth). Further studies across the South Korean, Swedish and British populations have confirmed the importance of being active [48,56,57] and have additionally reported a protective effect in obese individuals [56], discussed further by others [52,58]. As such, physical activity may negate some of the additional risks faced by obese individuals and be even more critical in this sector of the population. Lee et al. [48] showed that a combination of both aerobic exercise and strength training was the most beneficial in reducing infection, severe disease and death and was more beneficial than either aerobic or strength training alone. The same study reported a particularly strong benefit in individuals over 60 years old with a 94% reduction in relative risk of severe disease in those regularly engaging in both aerobic and strength training. This latter finding cannot be overstated given the age-stratified mortality that has been observed in the pandemic; this is especially true since these findings are likely to be conservative given both the association of exercise with BMI and other comorbidities linked with severe COVID-19 (which were controlled for), and the tendency of individuals to inflate the amount of exercise when self-reporting [48,51]. Accordingly, regular (up to 60 min of vigorous exercise per session, repeated several days a week) but not excessive exercise (which can supress the immune system [50]) has been suggested by some to be the most important modifiable risk factor for severe COVID-19 [51].

Despite the clear benefits of physical activity, lockdown measures and reduced access to gyms, parks and sports facilities have limited the ability of individuals, both healthy and those with chronic diseases to exercise [49,51,53]. The WHO recommends staying physically active during quarantine (over 150 min of moderate or over 75 min of vigorous exercise per week) [59] and makes several suggestions, including regularly standing up, playing with children, some simple exercises, and walking on the spot or around the house when taking phone calls. While these suggestions may help to reduce sedentary behaviour and support otherwise inactive portions of the population, they are a poor substitute for usually highly active individuals, particularly those who are used to exercising outdoors, running multiple kilometres out in nature or going for daily ocean swims, or indeed those accustomed to heavy weight training in a gym setting. Unfortunately, the current vaccine pass requirements in New Zealand and many other countries continue to restrict this access and make physical activity more difficult for many. Not surprisingly, therefore, while the average time spent sitting has increased from 5 to 8 h per day [54], physical activity has decreased in response to public health measures [53], while patterns of unhealthy eating have also increased [54]. Reductions in activity have not been uniform across the population, with Ammar et al. [54] reporting that 27% of the study population increased sitting time by more than 5 h per day. Adults who were consistently active prior to the pandemic have been hit the hardest with a 32% reduction in daily exercise [53]. Furthermore, children and adolescents aged 6–17 have reduced weekly physical activity by as much as 80% in some studies [60]. Worryingly, aside from the obvious implications from the discussion above, this reduction in activity was accompanied by increased depressive symptoms, stress and loneliness [53]. Increases in daily screen time had similar outcomes: less positive mental health, more depressive symptoms, and increased stress and loneliness [53]. Forced reduction in physical activity has previously been demonstrated to increase depressive symptoms and anxiety after just 1 week [61], with the largest effects occurring when

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withdrawal lasted for more than 2 weeks [62]. The already significant burden of mental health issues has therefore likely grown considerably after long periods of reduced exercise in many populations around the world. This will be addressed further in section 9.

Ultimately, increasing physical activity is of the utmost importance and has the potential to drastically reduce COVID-19 infection, hospitalisation and mortality, most notably in elderly and obese populations who are at high risk [48,56]. While the greatest benefits are likely to come from long-term physical fitness, with high cardio-respiratory fitness conferring a protective effect [63,64] even decades later [57], many benefits can also be almost immediate. Even one short (under an hour) bout of moderate to vigorous exercise can enhance cytotoxic T cell and NK cell activity and have an anti-inflammatory effect [50]. It is never too late, therefore, for people to become more active; further, addressing the global decrease in cardiovascular and immune system health that results from reduced participation in sports [49] is critical. Thus, public health measures to promote the benefits of exercise and facilitate participation rather than restrict it would be highly advantageous.

4. Plant-based diets

While a plant-based diet (PBD) is strictly defined as consisting of "all minimally processed fruits, vegetables, whole grains, legumes, nuts and seeds, herbs and spices, and excludes all animal products, including red meat, poultry, fish, eggs and dairy products," [65] for the purpose of this review, a broader definition, often used both in research studies and in the public sphere, will be used. Here, PBDs will be defined as those which minimise consumption of animal products while prioritising plant-based foods, particularly fruits, vegetables, whole grains, legumes and nuts [66,67]. While not strictly a PBD, a Mediterranean diet additionally promotes many of the same plant foods, with a focus on fruits, vegetables, legumes, nuts and olive oil [68]. As such, Mediterranean diets will also be discussed within this section.

While experimental studies addressing the impact of PBDs are lacking, observational studies conclusively point to the benefits of a PBD for reducing the risk of COVID-19 infection and severe COVID-19. In a case-controlled study of healthcare workers across six countries, Kim et al. [69] found a 73% or 59% reduction in the risk of severe COVID-19 in those consuming either a PBD or PBD/pescatarian diet. Risk reduction was evident after controlling for health and lifestyle factors, indicating that diet has benefits that are independent of other health behaviours. The study employed rigorous participant screening criteria, only including healthcare workers that were at sufficiently high risk of exposure to COVID-19, and was not complicated by vaccine status, because it was conducted early in the pandemic. Similar magnitudes of reductions were reported by Perez-Araluce et al. [70] who found a 64% reduction in infection rate among individuals with high, rather than low, adherence to Mediterranean diets. There is also some suggestion that individuals belonging to regions with higher adherence to Mediterranean diets experienced lower COVID-19 infection and mortality rates [71]. Another early study analysed data from the UK Biobank, addressing diet and lifestyle factors in over 37,000 people [72]. While the study did not specifically address PBDs, it nevertheless found positive associations between higher vegetable consumption and reduced risk of COVID-19 infection. The association remained significant after controlling for other health and social factors [72]. Low-carbohydrate/high-fat diets and high consumption of processed meat were additionally associated with higher risk of severe COVID-19 symptoms and COVID-19 infection, respectively [69,72]. These findings were corroborated by a fifth study that assessed the diets of over half a million people and found that participants eating high-quality diets that were rich in healthy plant-based foods (and low in less healthy animal products) were 40% less likely to have severe COVID-19 symptoms [73]. Most recently, Jagielski et al. [74] reported even greater benefits of healthy diet in a study on young (aged 25–45), non-obese, physically active individuals, when diet was assessed more rigorously. After controlling for other factors, individuals who consumed over 500 g of fruits and vegetables each day, along with at least 10 g of nuts, were 86% less likely to develop COVID-19. Jagielski et al. [74] further reported that individuals who

contracted COVID-19 had lower intakes of water, plant protein, seeds, legumes, garlic, dietary fibre, and various vitamins and minerals, and had diets that were higher on the dietary inflammation index. Since previous research has shown that increased fruit and vegetable consumption in elderly cohorts evokes a greater specific antibody response to (Pneumovax) vaccination [75], this adds support to their role in immune function. High-fibre PBDs are also associated with more favourable gut microbiome composition [76] (discussed in section 8), and asthma is better controlled in individuals who consume greater amounts of fruits and vegetables [77].

Although, to date, no studies have looked at the effect of PBD on long COVID-19, some have suggested that they may be beneficial given the abundance of data showing positive association of PBDs with improved immune function, neurotransmitter balance, pain and inflammation reduction, improved sleep, and mental health (see [78] for a comprehensive review). PBDs that are rich in fruits and vegetables are known to be high in vitamins, folate, fibre, and phytochemicals such as carotenoids, polyphenols and flavonoids [76,79]. Many of these bioactive substances are known to have anti-inflammatory, antibacterial, anti-thrombotic and antiviral properties; as such, their role in modulating the immune system has been widely discussed [68,75,78,80]. In the context of COVID-19, where inflammation and pro-thrombotic predisposition can increase the risk of severe disease, the relevance is clear. Since a Mediterranean diet focuses on many of these same polyphenol-rich foods [68], many of these same benefits may be obtained without following a PBD rigorously, though there may still be benefits strict compliance with PBD. A meta-analysis by Craddock et al. [81] reported lower markers of inflammation in vegetarians than in meat eaters, hypothesising that increased consumption of phytochemicals may be a contributing factor, alongside the decreased intake of saturated fat (both of these factors are also typical of Mediterranean diets). Favourable concentrations of immune and inflammatory markers may further be promoted in PBD however, due to the absence/reduction of pro-inflammatory molecules such as trimethylamine N-oxide (TMAO), a molecule metabolised from choline and carnitine, compounds primarily found in meat [67]. In the latter case, this would point to benefits of a PBD over a Mediterranean diet, which allows small quantities of meat. Overall, however, when compared to a typical Western diet high in processed foods and saturated fats, either Mediterranean diets or those that are more strictly plant-based would both be hugely beneficial. Additionally, there is some evidence that inclusion of particular foods common in Mediterranean diets, such as lupin, garlic, salvia, honey and extra virgin olive oil, has the capacity to confer additional protection against COVID-19 [82,83].

At present, the best available evidence suggests that PBDs are beneficial in directly reducing the risk of severe COVID-19 symptoms and the risk of infection, this reduction being independent of other health-related factors. Furthermore, many studies have now cited PBDs as being able to reduce the risk of coronary heart disease, reverse and prevent atherosclerosis, lower blood pressure, lower blood lipids, assist in weight management, and reduce the risk of developing type 2 diabetes [66,84]. Mediterranean diets have also shown benefits, helping in endothelial function, insulin resistance, weight loss and cardiovascular health [85,86]. Many of these conditions are leading risk factors for severe COVID-19 [8,17,19], suggesting that PBDs may also indirectly reduce COVID risk by mitigating these conditions. The ability of PBDs to further reduce risk, even after these factors are controlled for, strengthens the argument that increasing daily consumption of fruits, vegetables, legumes, nuts, seeds and whole grains, while decreasing consumption of animal products and processed foods, is beneficial. Benefits of PBD can begin to accrue within just 7 days [87]. Thus, potential protection against COVID-19 could be very rapid and time lag should not be a reason for delays in changing dietary habits. Since previous research has indicated that the most significant changes in nutrient profiles [88] and health [89] come from strict vegan diets rather than more broadly defined PBDs, the risk reduction in studies discussed above may even represent a conservative estimate. On this basis, questions have previously been asked about why the medical community is so slow to promote a switch in diet [90], with some now making the argument that it is time to demand such a switch [91].

5. Sleep

While sleep remains somewhat of an enigma [92], sufficient sleep (7–9 h of good-quality sleep for adults) is essential for proper immune function, emotional stability, homeostasis, muscle restoration, metabolism, cognitive function including learning and memory, and neural plasticity [93–95]. Some have suggested that sleep is the single most important pillar of health [95], given that lack of it undermines other healthy choices such as being physically active and eating well [94]. Insufficient sleep affects almost every aspect of human health, increasing inflammation and risk of stroke, obesity, diabetes, cancer, osteoporosis and cardiovascular disease, in addition to many others [93]. Many of these diseases in turn increase the risk of COVID-19. Even small differences in sleep can be profound, with just one night of reduced sleep having significant negative effects, something we get a chance to study annually with daylight saving time in multiple countries around the world [95]. Despite the known benefits of sleep and the harms associated with sleep deprivation, it has however, rarely been addressed with respect to COVID-19.

Prior to the COVID-19 pandemic, a substantial body of research already existed that elucidated the link between lack of good-quality sleep and infectious disease, including, notably, respiratory infections. A combination of challenge and population-based studies have shown that individuals sleeping fewer than 5 h per night had up to a 5-fold increase in the risk of developing the common cold and a 51% increased chance of developing other infections (e.g., influenza, pneumonia and ear infection) [96–98]. Individuals sleeping 5–6 h nightly, those perceiving inadequate sleep, and individuals with sleep disorders have also shown to be at risk, in the latter case with an 88% increased chance of developing an infection [97,99].

With respect to COVID-19, the first major evidence to emerge was from a multicentre, retrospective study in China addressing sleep and exercise habitats in hospitalised patients. Huang et al. [55] reported that compared to those getting the recommended amount of sleep, patients reporting sleep that was "potentially appropriate" in the week prior to COVID-19 diagnosis had a 6-fold increase in the risk of severe disease, while in those lacking sleep the risk was increased 8-fold [55]. These observations were corroborated by a case-controlled study on healthcare workers at high risk of exposure to SARS-CoV-2. After controlling for demographics and health data, Kim et al. [100] reported that healthcare workers who were infected were more likely to have reported fewer hours of sleep and more likely to have sleep problems. Just 1 h of additional sleep was associated with a 12% reduction in the risk of infection, while longer sleep duration also led to a 17% reduction in the risk of moderate to severe COVID-19 [100]. Furthermore, in participants reporting three sleep problems (difficulty sleeping at night, poor sleep continuity and frequent sleeping pill use) there was almost a doubling in risk of moderate to severe COVID-19 (OR 1.88) [100].

These findings suggest that, aside from the general health benefits, prioritizing high-quality sleep could significantly reduce the risks of COVID-19 infection and severe disease. Unfortunately, however, this has little been discussed during the pandemic, and evidence suggests that sleep has actually deteriorated during this time. Even prior to the pandemic, recent decades had seen a decrease in the mean amount of sleep reported each night [55], with sleep deficiencies and disorders now widespread [97]. The pandemic and measures put in place to reduce COVID-19 spread, such as social distancing and lockdowns have only heightened sleep issues, with high levels of anxiety, depression and stress contributing to frequent insomnia, frequent waking, early waking, nightmares and other sleep disorders [93,94,101–103]. Issues around increased stress, anxiety and depression are worthy of a review. However, there are many simple changes that can be made to encourage better sleep. Since longer screen time (and especially screen time just before bedtime) is associated with shorter sleep, reduced sleep efficiency and greater sleep onset latency [104], keeping screen time to a minimum, avoiding it before bedtime, and leaving electronic devices outside the bedroom are therefore encouraged to increase quality of sleep [95,105]. In no particular order, other scientifically backed ways to improve sleep include getting sunlight exposure in the morning to re-calibrate circadian rhythms; avoiding or reducing the intake of caffeine, alcohol and nicotine; sticking to a regular bedtime routine; ensuring the bedroom is cool and dark; avoiding hard exercise

before bed (instead shifting hard workouts to earlier in the day); and avoiding heavy meals late at night [95,105]. Many of these interventions represent simple, cost-free and risk-free changes that individuals could make immediately to reduce their COVID-19 risk within just a few days.

6. Individual nutrients and phytochemicals

6.1. Phytochemicals

Phytochemicals are defined as bioactive, non-nutrient chemicals found in fruits, vegetables, grains and other plants, which may provide desirable health benefits beyond basic nutrition [106]. Although most remain unknown, over 5000 individual phytochemicals have so far been isolated and identified [79], many with anti-inflammatory, antibacterial or antiviral properties [78,80]. Of particular relevance are phenols (present in foods such as wild blueberry, blackberry, pomegranate and spinach) and flavonoids, which are associated with a reduced risk for major chronic disease, when consumed regularly [106]. Consumption of a wide range of fruits and vegetables is the best way to gain the general health benefits from many of these compounds, since each particular plant will have its own unique phytochemical content [79]. Additionally, consuming whole foods is the safest way to access these benefits. In agreement with Liu [107], the delicate balance of these compounds in whole fruits and vegetables cannot be replicated in pill form. Aside from the benefits derived from eating a diet rich in all phytochemicals, two specific phytochemicals are of particular interest for reducing COVID-19 risk.

6.1.1. Curcumin

Curcumin, the bioactive ingredient in turmeric [108], has previously been shown to exhibit strong anti-inflammatory property and antiviral activity against several viruses, with capacity to block viral entry into host cells [109]. While larger clinical trials are urgently needed, results from published COVID-19 trials are extremely promising, with oral curcumin administration reducing mortality, recovery time, the need for oxygen, mechanical ventilation, length of hospitalisation, and the presence of several inflammatory markers [110–114]. Most notably, in three placebo-controlled trials, mortality in patients administered daily doses of either 160 mg of nano-curcumin [112,113] or 1050 mg of curcumin with piperine [114], was reduced by 80%, 50% and 82% respectively. A more recent meta-analysis suggests an overall 77% reduction in mortality in patients treated with curcumin [115]. Five of the six clinical trials so far conducted also found a significant reduction in symptom duration in patients with mild, moderate and severe COVID-19 [110–114,116]. In the single trial that failed to show a reduction in symptom duration, more positive lab indices were reported with the authors suggesting an important role for curcumin in immune modulation [116]. Additionally, support comes from a range of molecular modelling, immunological and *in vitro* studies, which elucidate the potential of curcumin, as well as from previous studies that show curcumin's efficacy in other respiratory viruses [117–125]. While larger trials are needed, the data available suggest that curcumin is highly effective for reducing the severity of COVID-19. Given that almost all previous clinical trials have revealed curcumin supplements to be safe and well tolerated, even at doses as high as 8000 mg/d [122], a recommendation of 1000 mg daily at symptom onset, or upon the first positive test, would seem to be highly advisable. While supplements are the best way to reach equivalent doses to those used in trials, turmeric powder used in cooking contains around 3% curcumin [126]. One teaspoon (5 g) of turmeric powder, therefore, contains approximately 150 mg. Though low bioavailability of curcumin has been problematic, piperine (a compound found in black pepper) has been shown to increase bioavailability by 20 times [127] and so any increase in consumption of turmeric with the intention of boosting dietary curcumin intake should be accompanied by black pepper.

6.1.2. Quercetin

Quercetin is a flavonoid (flavanol) present in many fruits and vegetables [128]. Particularly good vegetable sources include onions, asparagus, red leaf lettuce and, to a lesser extent, broccoli, green peppers, peas and tomatoes, while good fruit sources include apples, cherries and berries [129]. Quercetin is thought to be helpful in preventing severe COVID-19 symptoms, due to its known

anti-inflammatory, anti-oxidant and immune-modulating properties [129,130]. Molecular docking and *in vitro* studies have revealed strong antiviral potential via several mechanisms, including preventing attachment to ACE2 receptors and blocking viral replication ([129,131]).

So far, results from clinical trials with quercetin are promising. In a randomised, open label trial Di Pierro et al. [132] tested the effectiveness of quercetin formulated with sunflower phospholipids to increase absorption. Compared to standard care, the quercetin group showed a 68.2% reduction in risk of hospitalisation, a 76.8% reduction in length of hospital stay, and a 93.3% reduction in the need for oxygen therapy [132]. Additionally, while no patients in the quercetin group were admitted to the ICU or died, 10.5% and 3.9% of the control group were admitted to ICU or died, respectively [132]. A further follow-up study by the same group confirmed that quercetin significantly improved viral clearance, reduced symptom length, and improved inflammatory markers [130], with 57% of the quercetin group having fully recovered after 7 days, compared to just 19% of the control group. These results were corroborated by a recent, small study by Shohan et al. [133]. Here, inflammatory markers and length of hospitalisation were significantly decreased in the quercetin group. Additionally, there were lower numbers of patients admitted to ICUs, fewer ICU days, and no deaths in the quercetin group, yet three deaths in the control group; in all cases these results were approaching significance but likely due to small sample size were not statistically significant [133]. While Onal et al. [134] failed to find benefits in patients treated with quercetin, they nevertheless report improved laboratory results and suggested that their study was limited by poor bioavailability of quercetin.

At present, the available evidence suggests that quercetin may be beneficial against COVID-19. Whilst multiple reviews, *in vitro* experiments, and molecular docking studies espouse the benefits of quercetin and its ability to inhibit SARS-CoV-2 [135–137], large clinical trials are frustratingly lacking. Nevertheless, despite limitations, the studies discussed above have shown benefits in symptom reduction, progression to severe disease, and mortality. Given the excellent safety profile of quercetin when taken for short periods [132,134,135,138,139] in addition to its wide availability and multitude of other health benefits [140], it is suggested that the limitations of the existing trials should not stand in the way of a potentially life-saving supplement being discussed with patients.

6.2. Vitamins and minerals

6.2.1. Vitamin D

Vitamin D is a fat-soluble vitamin and steroid hormone with important roles in enhancing cellular immunity and modulating physiological processes including bone metabolism, absorption of calcium and phosphorus, and zinc metabolism [128,141]. It is increasingly clear that vitamin D deficiency is associated with COVID-19 infection and severe cases of COVID-19. In a study of over 190,000 patients with information available on vitamin D status in the preceding 12 months, Kaufman et al. [142] found that patients who were deficient in vitamin D were more likely to be infected with COVID-19 (12.5% infection rate) compared to those with adequate (8.1% infection rate) or the highest (5.9% infection rate) levels. Similarly, Meltzer et al. [143] found patients who were vitamin D-deficient in the previous year had 77% increased risk of testing positive for COVID-19. The latter study had a higher overall infection pressure and was corroborated by Hernández et al. [136], who also found that the majority of patients with COVID-19 (but not controls) were vitamin D-deficient, and by Seal et al. [137], who further found a 29% increased risk of hospitalisation and an 82% increased risk of death in vitamin D-deficient patients [144]. Overall, a meta-analysis by Kazemi et al. [145] reported that vitamin D deficiency resulted in a 157% increased chance of severe disease, a tentative (due to limitations of the papers reviewed) 77% increased risk of infection and, using the Cox survival method, a seven-fold increase in risk of mortality. Accordingly, vitamin D supplementation has been proposed to be an effective means for reducing the risk of COVID-19 infection and severity [146] via its potential to decrease production of pro-inflammatory cytokines [128].

Previous research has shown the ability of vitamin D to reduce the risk of upper respiratory infection [147]. Since vitamin D deficiency, mainly due to lack of sunlight, is a widespread public health problem affecting more than a billion people (especially individuals with darker skin and to a

lesser extent, obese individuals), the significance is clear [55,141,143,148]. In previous studies, even those not deficient have still benefited from vitamin D supplementation [147]. This finding is corroborated by the observations of Kaufman et al. [142] and Seal et al. [137] who found that risks of infection and severe disease (respectively) were reduced in individuals with the highest levels of vitamin D as compared to those with intermediate (but adequate) levels. In the case of Seal et al. [137], a dose-dependent, inverse relationship was observed between hospitalisation and mortality risk and levels of vitamin D, after adjusting for socio-demographics and comorbidities.

There is growing evidence that vitamin D supplementation may reduce COVID-associated risks [149]. In a study of 445,850 participants, Louca et al. [150] found women were between 9% and 24% (depending on country of residence) less likely to be infected if taking vitamin D supplements (of any strength). More broadly, in a meta-analysis of 13 studies, Pal et al. [146] calculated the risk of severe disease to be reduced by 73% in those supplementing with vitamin D. The most notable reduction in risk was seen in studies addressing supplementing after the onset of COVID-19 (88% reduction, OR 0.12). Overall, Pal et al. [146] indicated that supplementation is safe and has the potential to significantly improve various clinical outcomes, including length of time in hospital and recovery time. Accordingly, given the low cost and safety profile of vitamin D, some have suggested the benefits of population-wide supplementation, particularly aimed at groups likely to be deficient [143]. Shah Alam et al [141] suggests that adults take a dose of 8000 IU daily, higher than many other recommendations, in order to ensure sufficient circulating levels. Previous research on supplementation revealed that daily doses rather than bolus have greater benefits against upper respiratory infections [147], but more work is required to confidently address appropriate doses, delivery method, and timing of supplementation.

6.2.2. Vitamin C

Among many physiological roles, vitamin C is important in immune function and wound healing, and has antioxidant, antiviral and anti-inflammatory properties [128,151–153]. In their analysis of circulating levels of vitamin C within 24 h of ICU admission, Tomasa-Irriguible and Bielsa-Berrocal [151] found up to 82% of COVID-19 patients were deficient, with many showing levels of only 0.1 mg/dL (normal values are 0.4–2 mg/dL), and 18% having undetectable levels of vitamin C (below 0.1 mg/dL). Although the study was small, these findings have nevertheless been replicated by other groups [154,155], including Chiscano-Camón et al. [153] who found vitamin C levels to be undetectable in over 90% of patients admitted to ICUs with COVID-19. It is well established that several severe respiratory infections can lead to a high requirement (increased by a factor of ten) for vitamin C, which then must be replenished [156]. It is therefore uncertain whether patients are vulnerable to infection due to existing vitamin C deficiencies or whether deficiencies are the result of severe disease. In either case, vitamin C has been proposed as a potential treatment for severe disease and also as a prophylactic to reduce risk of infection, due to its ability to modulate immune cell activity and reduce inflammation [157].

Results from studies conducted so far have been very mixed and confounded by small sample sizes, premature termination of trials, inadequate doses, inconsistencies in the timing of treatment, and statistical errors [156,158]. Despite this, evidence suggests there is still reason to be optimistic about the use of vitamin C at appropriate doses. In their pilot study on the use of high-dose intravenous (IV) vitamin C, Zhang et al. [159] did not detect any significant reduction in mechanical ventilation-free days, yet they did observe improved oxygen saturation and a 78% reduction in ICU mortality among patients with severe cases, with baseline sequential organ failure assessment > 3. This finding agreed with earlier research that showed IV vitamin C to be effective for reducing inflammation and incidence of multiple organ failure in patients with sepsis, in a dose-dependent manner [160]. Similarly, Gao et al. [161] reported reduced mortality risk, oxygen support status, and inflammatory markers in patients receiving high-dose IV vitamin C, while Kumari et al. [162] failed to find any effect on mortality but did report shorter hospital stays and more rapid cessation of symptoms in the vitamin C group. This agreed with observations that vitamin C was beneficial in preventing moderate cases of COVID-19 from progressing to severe cases [163].

while Louca et al. [150] did not find oral vitamin C to be effective in preventing COVID-19 infection, there was no standardisation of dose; as such, a participant taking a supplement with 125 mg would contribute to statistics equally with someone taking a dose of 1000 mg or more daily. Previous studies on the common cold have however indicated that, while vitamin C is not able to prevent infection (aside from in physically active individuals), regular supplementation is beneficial in reducing symptom duration [164]. There is some evidence that effects are similar in COVID-19 cases, with high-dose (8000 mg/d) oral vitamin supplements increasing COVID-19 recovery rate by as much as 70% [158]. Lower oral doses (1000 mg) in hospitalised patients have had more mixed results [165] but, although not reducing mortality, were nevertheless found to be effective in reducing risk of thrombosis [166].

Overall, when used appropriately, many benefits of vitamin C have emerged, whether in the form of IV administration or high-dose oral supplements. While larger, rigorously conducted trials are needed, vitamin C may have a role in reducing COVID-19 risks. Positive outcomes are most likely to occur with early administration [163], where vitamin C may be helpful in preventing mild COVID from progressing to more severe disease [156]. Since vitamin C is cheap, widely available and safe in doses up to several gram per day [164], it currently would seem to be another supplement in the toolbox of things that may be taken regularly to improve COVID-19 outcomes.

6.2.3. Zinc

In addition to having important roles in cell growth and differentiation, bone formation, wound healing, brain development and structural integrity, zinc is also integral for heathy immune function [128,152]. Since the body has no storage system for zinc, a steady supply is essential [152]. As with vitamins C and D, zinc levels have been found to be lower in COVID-19 patients than in healthy controls [155]; similarly, among hospitalized COVID-19 patients, zinc levels were lower among patients who died, compared to those who survived [144]. Further, Jothimani et al. [167] reported that low levels of zinc were associated both with COVID-19 infection and worse outcomes, with zinc-deficient patients being more than five times more likely to develop complications (OR 5.54). Accordingly, zinc may be beneficial against COVID-19 (see [168] for a review of potential mechanisms).

Despite many suggestions that zinc may be beneficial, direct evidence for its role in COVID-19 is lacking. Louca et al. [150] found no evidence for zinc supplementation being able to prevent infection, as with vitamin C; however, this study did not control dose and, further, does not supply information on which form of zinc was taken by participants. Eby [169] has previously discussed the effect of differing forms of zinc in treatment of the common cold, claiming that while ionic zinc is highly effective in shortening cold duration, many zinc products on the market provide inadequate levels of ionic zinc and are unlikely to be beneficial. Further, Hemilä [170] pointed out that while zinc tablets and syrups have systemic effects, zinc lozenges show local effects which may work to reduce symptoms in the mouth, throat and nose. Accordingly, the form and dose of zinc are critical. In previous research, zinc acetate and zinc gluconate lozenges have been shown to reduce duration of the common cold by 40% and 28%, respectively, when administered at doses of around 80–92 mg/d; however, higher doses provided no additional benefit [171]. Further, in a meta-analysis of respiratory tract infections by Hunter et al. [172], prophylactic administration of zinc reduced the risk of moderately severe symptoms (fever/influenza-like symptoms) by 87%.

With respect to COVID-19, at the time of writing, the majority of clinical trials and observational studies have addressed the benefit of zinc in combination with other medications or supplements but have not investigated the effect of zinc in isolation. Thomas et al. [173] assessed the effect of vitamin C in combination with zinc in clinical trials and found no benefit, but this study has been severely criticised for inadequate dosing ([158] supplementary material). Yao et al. [174] also found no effect of zinc in reducing negative outcomes, yet the majority of patients in this observational study had severe to critical disease and were being administered a wide variety of other medications. In advanced stages of disease, it is unclear to what extend blocking viral replication would be beneficial, yet subgroup analysis on the milder cases is not presented. In contrast, Carlucci et al. [175] reported that among non-ICU patients, zinc was effective for increasing the frequency of

patients being released (OR 1.33) and reducing mortality and transfer to hospice (OR 0.449). In the latter study, hydroxychloroquine was used as an ionophore for zinc and was given in combination with azithromycin (controls had hydroxychloroquine and azithromycin). This result was not supported by a clinical trial looking at zinc and hydroxychloroquine with no difference in mortality or recovery compared with hydroxychloroquine [176].

At present more research on the role of zinc is urgently needed as, despite the clear benefits of prophylactic zinc [172], and particularly zinc lozenges [171] in upper respiratory infections, this has not been sufficiently studied with respect to COVID-19. It is nevertheless clear that zinc deficiencies are associated with more severe outcomes, so promoting the consumption of adequate amounts of dietary zinc may have a strong role in risk reduction, particularly in those more at risk of deficiencies, such as elderly individuals and women taking the contraceptive pill [168,177–179]. Good plant-based sources of zinc include wholegrains, legumes, soy products, nuts and seeds, as well as fortified cereals [180].

6.3. Other beneficial dietary interventions

Many other micro-nutrients may be beneficial; for a full discussion, readers are directed towards more specialised reviews such as Calder [157] and Iddir et al. [76]. Discussion here is limited to multivitamins, omega-3 fatty acids, vitamin B12 and vitamin E.

Louca et al. [150] reported that, after controlling for all other health factors and comorbidities, participants in the UK, US and Sweden were, respectively, 13%, 12% and 22% less likely to be infected with COVID-19 if they were taking multivitamins. In the same study, a similar reduction in infection risk (12%–21%) was associated with omega-3 fatty acid supplements [150]. A trend towards lower COVID-19 mortality with increased omega-3 index was additionally indicated [181]. While the recommended ratio of omega-6 to omega-3 fatty acids is between 1:1 and 4:1, many people eating standard Western diets have ratios in the region of 10:1 [76]. Supplementing with omega-3 or eating high-quality plant sources such as brussels sprouts, flax, chia and hemp seeds, and walnuts may therefore aid in rebalancing this ratio and accessing the numerous anti-inflammatory and immune modulating benefits that omega 3 confer [76].

While more research is needed, several authors have hypothesized mechanisms by which vitamin B12 may be beneficial given the similarity in symptoms of vitamin B12 deficiency and COVID-19, including elevated oxidative stress and lactate dehydrogenase, renal and pulmonary vasculopathy, elevated blood homocysteine levels, and coagulation cascade activation [182,183]. Until more research becomes available, ensuring adequate intake of vitamin B12 via nori, shiitake mushrooms [184], fortified whole grain cereals, plant milks and nutritional yeast, or via supplements may be prudent.

Vitamin E is known to have important roles in immune function and to exhibit strong antioxidant properties [128]. In animal studies, deficiency leads to increased susceptibility to pathogens [157], a finding potentially supported by the observation that vitamin E levels were lower in COVID-19 patients compared to healthy controls [155]. Vitamin E supplementation has previously been shown to increase immune activity, in particular T cell proliferation, improve response to vaccination in elderly patients, and to reduce the risk of rehospitalisation in elderly pneumonia patients by 63% [76,157]. Incidence of pneumonia in smokers receiving 50 mg/d for 5–8 years was additionally 69% lower than in controls [76]. While evidence that vitamin E can reduce susceptibility to COVID-19 is lacking, its benefits, particularly in elderly patients, may warrant increasing intake via either supplements or consumption of rich sources such as wheat germ, sunflower seeds, almonds, hazelnuts, pine nuts, avocado and sweet red peppers.

7. Time in nature

The practice of "shinrin-yoku," or forest bathing, is common in Japan and involves spending time among the trees for relaxation and recreation [185]. Although in some countries (e.g., Japan, Norway and China) forest bathing is prescribed as preventative and curative medicine for a variety of ailments, outside of these areas it has received relatively little attention [49] and has rarely been

discussed with respect to COVID-19. In a pioneering series of experiments, Li and colleagues [186] demonstrated that an overnight trip with several forest walks, was able to reduce the concentration of stress hormones in urine, while increasing both the number and activity of NK cells in both male [186] and female [187] participants. Elevated NK cell activity was maintained for 7 days, with detectable increases still evident after 30 days. Further experiments showed that spending the same amount of time away on a city break was not able to induce equivalent changes [188]. In the context of COVID-19, these findings are particularly significant, given that the primary role of NK cells is to kill cells infected by viruses [189].

While the previous experiments focussed on overnight trips to the forest, a suite of other studies have now shown benefits from short (as little as 2 h long) walks among trees. Benefits include reduced stress and cortisol levels, lower blood pressure and pulse rate, reduced inflammatory markers, improved mood, lower anxiety scores, and increased antioxidant activity [190–195]. Indeed, during the pandemic many people reported that spending time in nature "helped them to cope" with the situation [196]. While few of these studies directly addressed COVID-19, stress and inflammation are known to be detrimental to immune function, inhibiting innate and adaptive immune responses [189]. It has therefore been hypothesised that reductions in adrenaline and noradrenalin may explain the observed boost in NK cell activity [185]. The implications for COVID-19 are clear: a well-functioning immune system is vital in fighting infectious disease.

On the basis of the evidence above, it has been suggested that forests may offer protection against the worst effects of COVID-19, with Roviello et al. [49] describing a double benefit of forests in potentially reducing mortality. Firstly, trees are able to intercept the fine particulate matter which is common in areas with high levels of pollution [49] and is linked to worsened respiratory outcomes [197,198]. Secondly, many trees release immune-strengthening volatile organic compounds, including phytoncides (wood essential oils) [49,185,199]. These secondary plant metabolites are used by plants to protect against herbivores and pathogenic micro-organisms, but they have also been shown to exhibit strong anti-inflammatory and antioxidant properties, and can stimulate autophagy [199]. Indeed, an early experiment by Li et al. [200] demonstrated that phytoncides are independently able to influence immune cell function *in vitro*, therefore suggesting that one benefit of forest bathing may be exposure to beneficial volatile organic compounds often found in relatively higher concentrations in forests [186].

Tentative evidence for the role of forests in fighting COVID-19 comes from Italy where lower mortality rates were observed in areas with greater forest cover per capita (normalised for total population) [201]. These findings were corroborated by similar work in Poland and the US, indicating the importance of green and blue spaces [202,203]. Of course, it is not possible for everyone to live in areas with greater forest cover; however, green spaces in the form of urban parks and gardens are generally available to even those living in the densest of cities. As such, advising people to get out into nature may be highly beneficial. This is especially true given that individuals spending increased amounts of time indoors due to lockdown measures are exposed to more indoor aerosols and ultrafine particles, which have been linked to respiratory disorders and increasing susceptibility to COVID-19 [204]. Since previous work has shown the benefits of forest walks to persist for several days, even a weekly walk in a wooded area has the potential to immediately boost the immune system and reduce risks from COVID-19.

While most research has centred around forests, there is evidence that other natural settings may also confer benefits. Frequent exposure to blue spaces (rivers, lakes and the sea), for example, is known to be beneficial in reducing stress, improving mental health and wellbeing, promoting physical activity, and potentially improving general health [205–211]. While these studies have not directly addressed COVID-19, the benefits of exercise for COVID-19 have already been discussed at length, and reductions in stress are likely to directly improve immune function. Roviello et al. [212] further suggest that swimming in or walking along (clean) rivers may be directly beneficial in a similar way to forest bathing, given the occurrence of many secondary plant metabolites in rivers. In addition to the already known benefits of rivers, such as sights and sounds, and gentle exercise, the compounds from riparian vegetation may act in a similar way to the forest phytoncides [212].

More broadly, interaction with nature of all types, from walking in the mountains to watching wildlife in grass meadows, has been suggested to improve health outcomes through a myriad of mechanisms: these are discussed at length by Kuo [213]. To conclude this section, spending time in nature is a free and relatively easy way for most people to immediately improve their immune function and reduce risks associated with COVID-19.

8. Gut health

Understanding of the role of the gut microbiome has dramatically increased over the last decade, with many recent studies now showing it to exert a large influence on multiple aspects of health, including chronic inflammation, disease, and both the innate and adaptive immune systems [214,215]. Thus, the potential to impact COVID-19 outcomes through immune modulation warrants discussion. Some bacterial species may be especially relevant here, particularly those that are able to produce butyrate (one of three short-chain-fatty acids produced from undigested food) [215]. Butyrate is the preferred energy source of colonic cells and has many important roles: maintenance of the gut barrier, regulation of mucus production, reducing anxiety and depression, protecting against metabolic diseases, and, significantly, promoting differentiation of naïve T cells into regulatory T cells (Tregs) [216,217]. Since Tregs dampen excessive immune and inflammatory responses and given that under and over-active immune responses are both problematic [214], the significance in relation to COVID-19 is clear.

Although not all studies conducted have found associations between microbiota and COVID-19 [74], there are clear mechanisms through which disease outcomes could be influenced. It was already known that gut microbes could affect pulmonary health via cross talk between microbiota, with the balance of microbes directly affecting lung immunity [214]. Many patients with COVID-19 additionally experience gastrointestinal upset, with SARS-CoV-2 present in the stool samples of some patients [214,218]. The SARS-CoV-2 virus uses ACE2 receptors for entry into host cells; ACE2 receptors are found in the lungs, kidneys and heart, but also in the gastrointestinal tract [214,219,220]. This suggests a role of the gut-lung axis [214] which may be of particular significance for individuals with poor gut health, as unbalanced or reduced microbiota (dysbiosis) and "leaky gut" may contribute to more severe disease [219]. In individuals with dysbiosis (such as the elderly and those with chronic disease), impaired gut barrier integrity and reduced mucus may allow SARS-CoV-2 to not only bind to ACE2 on the intestinal cells, but also to exit the gastrointestinal tract and enter the bloodstream, allowing access to various organs expressing ACE2 throughout the body [220]. It is clear how this could lead to more severe disease. Accordingly, Gu et al. [221] reported significantly lower bacterial diversity in samples collected from hospitalised patients compared to those obtained from healthy controls. This was accompanied by enrichment of opportunistic pathogens and reduced abundance of beneficial bacteria, a finding corroborated by Zuo et al. [218]. In particular, 23 taxa, mostly Firmicutes, were associated with disease severity, 8 had positive correlations and 7 had negative correlations [218]. Firmicutes have previously been shown to either up- or down-regulate ACE2 expression; here, one of the species found to most strongly correlate with severe disease is known to greatly up-regulate colonic ACE2 expression in mice [218]. Further work by Al Kassaa et al. [219] addressed the gut health in COVID-19-positive individuals with severity ranging from asymptomatic to severe disease. Recording gut health as a score between one and five (based on healthy food, unhealthy food, overweight/obesity, chronic medication, and gut symptoms), they found a strong association between gut health and the severity of COVID-19 symptoms, with the likelihood of worse symptoms being reduced by 33% for each level increase in gut health. The authors report that intake of unhealthy food and excessive consumption of both sugar and fast food were additionally associated with more severe disease. Since diet is highly influential in microbiota composition, this is not surprising.

While probiotics (live microorganisms), which, when administered in adequate amounts, confer a health benefit to the host [214], have received much attention in recent years, a full discussion is beyond the scope of this review. There is, however, some evidence for their benefit against COVID-

19, with Louca et al. [150] reporting a 14%–37% reduction in infection rate in those taking probiotic supplements (depending on country). Previous research has also suggested that probiotics can improve or alleviate lung disease and improve immune response to the common cold, while outcomes are less clear with respect to influenza [214,222]. Other probiotic foods, such as kefir, have additionally been suggested to have potential preventative and curative benefits for COVID-19 [223]. At present there is, however, little consensus around the duration, dose and type of probiotics supplementation that are most beneficial, and any changes in gut microbiota unfortunately appear to be transient [222,224], possibly because poor diet may inhibit the survival of any probiotics consumed. Accordingly, here the focus will be on ways in which the diversity of gut microbiota can be increased in general, without particular focus on individual strains.

The benefits of a PBD have already been discussed at length, but additionally, a plant-centred, high-fibre diet may lead to better gut health. Previous research shows that diets rich in plants, and low in fat and animal products tend to promote symbiosis, a balanced gut, and high abundance of beneficial microorganism, while those that are low in fibre and high in fat and meat, tend to promote opportunistic pathobionts and a reduction in beneficial bacteria [89,217,225–227]. There appears to be a continuum of human gut microbiota, on which vegans and meat eaters have the most divergent gut biology, with vegans showing the highest ratios of anti-inflammatory bacteria and lowest pathobionts, and vegetarians being intermediate [89]. These differences can have stark effects on harmful metabolites and therefore inflammation; while TMAO levels dramatically increase hours after an omnivore eats meat, the same does not occur when a vegan is experimentally given meat, since vegans lack the microbiota responsible for converting carnitine to TMAO [217,228]. These differences are likely to be, in part, due to the higher amounts of fibre consumed by vegans, which is essential for many microorganisms and is used directly to produce butyrate [89,220]. A change to a high-fibre diet can, in fact, not only alter the intestinal microbiota, but also affect the lung microbiota [229], leading some to suggest that increasing fibre may be the easiest and most effective method that can be implemented immediately to prevent severe COVID-19 [220]. Aside from increasing fibre consumption in general, increasing the diversity of plants in the diet has been linked with both a more stable and diverse gut microbiome, along with increases in several butyrate producers [230,231]. Since different types of fibre are present in different foods [226], a variety of foods, and ideally over 30 different plant foods each week [231], are important to nourish a wide range of microorganisms.

As noted with many of the other interventions reviewed here, the benefits of a change in diet can be extremely rapid. Stella et al. [232] demonstrated that metabolic phenotypes were distinct within less than two weeks of initiating a new diet, when individuals were rotated between vegetarian, high-meat and low-meat diets for 14 days. More recently, David et al. [225] reported that changes in microbiota were detectable after just one day, when diets were switched from animal-based to plant-based. Although a complete shift in microbiota is unlikely to occur rapidly, significant changes can be brought about in very short periods of time, and these changes may be highly beneficial with respect to protection against COVID-19. A diet high in fibre with a large variety of plant foods, including fruits, vegetables, whole grains, legumes, nuts and seeds, is therefore likely to be beneficial.

Aside from diet, probiotics, and avoiding antibiotic use, gut health can additionally be influenced by interactions with microbes in the environment. Linking back to section 7, spending time in biodiverse environments and particularly around vegetation and soil with diverse microbial populations, can have significant effects on both skin and gut microbiota [213,233,234]. In a study on young children in day care centres, Roslund et al. [235] demonstrated significant changes in the microbiota after 28 days of a nature intervention. Children in the experimental group were encouraged to interact with diverse vegetation and soil placed in the yard, compared to bare control yards with little green vegetation. Changes in the microbial composition included relative increases in butyrate-producing species and decreases in pathobionts; these changes were accompanied by a higher ratio of anti- to pro-inflammatory cytokines [235]. These findings were later corroborated in a similar experiment by Sobko et al. [236]. Selway et al. [234] further expands the idea that

exposure to vegetated ecosystems could restore microbial diversity and balance in humans and therefore help with reducing disease burden, an idea supported by several other authors who research green spaces and microbiota [237–239]. Benefits may be extremely rapid with increases in skin microbiota and alterations in gut microbiota observed after just 15–30 min spent in urban green spaces [234]. Aside from the already discussed benefits of time spent in forests, exposure to green spaces could therefore be beneficial for gut health. More broadly, having indoor plants, interacting with a dog who plays outside, and eating from home or community gardens are all expected to also be beneficial for gut health [234].

9. Other lifestyle factors

9.1. Smoking and alcohol

While this review has attempted to cover major ways in which risks associated with COVID-19 can be reduced via diet and lifestyle measures, there are undoubtedly many more strategies which could have been discussed here. The negative effects of smoking on heath, and specifically respiratory health, are well understood and not controversial. Thus, a detailed review of this literature was not deemed necessary. Notwithstanding, smoking, or history of smoking has been found in multiple meta-analyses to increase the risk of severe COVID-19 and death from the disease [240–242]. A large body of literature on the harms of alcohol already existed prior to the pandemic, with alcohol misuse accounting for around 3 million, largely preventable deaths each year [243]. Despite this, many governments around the world took steps to ensure continued, easy access to alcohol during lockdown [244], keeping "essential" alcohol stores open, while many health care providers remained closed. Unfortunately, but perhaps not surprisingly, lockdown measures and social isolation only served to worsen existing problems; many people increased their alcohol consumption, particularly those suffering with anxiety and depression, and problematic drinking became a concern [245,246]. Given the effects of alcohol misuse on every aspect of lung health [247], the ramifications for severe outcomes with COVID-19 are clear. While beyond the scope of this review, it is notable that in many areas, hospitalisations due to alcohol are likely comparable to those from COVID-19 [244], reductions in alcohol consumption are therefore beneficial for both individuals and for the health service.

9.2. Stress

As noted previously, increased levels of stress hormones supress the immune system and may therefore increase the risks associated with COVID-19; indeed, anxiety and fear disorders have been identified as major risk factors [14]. Unfortunately, the incidence of stress, anxiety, depression and life dissatisfaction has been common throughout the pandemic [102,248–252] and has increased in response to social distancing and isolation measures, beyond levels explained by increased screen time and reduced exercise [54]. Perhaps not surprisingly, alongside these mental health issues, antidepressant prescriptions have also risen [253]. Such increases were, unfortunately, highly predictable, given what was already known about the psychological effects of quarantine, even short (less than two weeks) periods of quarantine having previously been associated with anxiety, post-traumatic stress disorder, depressive symptoms, and alcohol abuse and dependency [254–258]. In the latter two cases, symptoms of depression and alcohol dependency have been shown to be long lasting, still being prevalent three years after quarantine [254,255]. Aside from directly impairing the immune response, high levels of chronic stress have previously been linked with overeating and increased consumption of high-energy and high-sugar foods; this then potentially leads to obesity (see [259] for a full review). Indeed, during the pandemic, unhealthy eating patterns increased the intake of "comfort food" and, additionally, poor sleep quality (known to impact food choices) has been widely reported [54,252,253]. As such, impacts may be wide-reaching and extend beyond the immediate effects, potentially encompassing elevated COVID-19 risks, due to several independent mechanisms, and also lead to a long-term erosion of health, as noted by Mattioli et al. [253]. Some of these effects may have asymmetrically affected different genders, with women being more likely to have suffered distress during lockdown as well as to

have experienced food cravings that influence unhealthy dietary choices [252,253]. In contrast, the effects of unemployment, either due to business closures (following lockdown measures) or due to later vaccine mandates, may have disproportionately affected men. In a meta-analysis of over 20 million people, unemployment resulted in a 73% increase in mortality among individuals under 40 years of age and a 77% increase in 40–50-year-olds with men being hit the hardest [260]. Risks are known to be multifaceted with, for example, increases in alcohol consumption and binge drinking as coping mechanisms after job loss, and decreases in personal expenditure (i.e., spending on food/self-care), this often leading to reduced diet quality which can result in either obesity or, in some cases, unhealthy weight loss [260,261]. Unfortunately, increased risk of mortality remains high for several years after a period of unemployment [260]. As such, taking steps to mitigate some of the stress associated with the pandemic may be essential to health, in addition to focussing on positive health behaviours reviewed in sections 1–8. While not attempting to fully address these issues here, it is noted that efforts to avoid excessive viewing of fear-based television media, reducing screen time, participating in mindfulness, meditation and yoga, or spending time with companion animals or in nature [262–265] are reported to be beneficial. Given the previous discussion on exercise, ensuring adequate physical activity may also improve mental health and reduce depressive symptoms.

10. Conclusions

This review has provided evidence that PBDs, adequate sleep, regular exercise, maintaining healthy weight, attention to micronutrients and phytochemicals, gut health, and time in nature all help to reduce the risks associated with COVID-19. Some of these risk reductions are summarised in Table 1. As noted by Di Pierro et al. [132], despite vaccination efforts, herd immunity appears to be a "distant mirage," and therapeutic interventions, to date, have not stopped the tidal wave of COVID-19-associated mortality. While there is unlikely to be a "magic bullet" for COVID-19, a combination of strategies is more likely to be effective, especially against an ever-evolving virus. All of the strategies and interventions discussed in this review confer health benefits beyond those related directly to COVID-19 and are, in almost all cases, backed by a large body of evidence. In many cases the resulting risk reductions are equivalent to, or even greater than, those associated with currently available vaccines [266,267]. It is suggested that, where the balance of evidence suggests benefits and the risk is extremely minimal to none, it is morally imperative that these interventions are not ignored. It is the view of this author that many lives could be saved if we were willing to embrace lifestyle-centred approaches in our strategies for dealing with COVID-19. Additionally, many of the harms resulting from vaccine mandates could be avoided. Unfortunately, however, most of this research remains largely unknown to the general public, and indeed to many physicians. Even though it could be argued therefore, that people have the ability to take any of the steps discussed here, many of them lack the knowledge and few fully understand the implications of doing so.

Although much has been learned in the previous two years, many of the interventions discussed in this review were already extremely well researched prior to the emergence of SARS-CoV-2, and it was already abundantly clear that the health of populations around the globe needed to improve in order to reduce the disease burden in general. Further, there were signs very early in 2020 that many of the interventions discussed were highly effective in reducing COVID-19 risks. Despite this, none of these strategies have received sufficient attention or been widely employed in public health settings. While vaccine mandates and draconian lockdowns have caused untold amounts of harm and failed to control the pandemic, questions must be asked about why governments have been so unwilling to embrace measures which could have rapidly and inexpensively simultaneously improved the health of nations and bolstered their defences against COVID-19. Even relatively simple steps to present some of the science discussed here alongside other public health measures could have caused enormous change. Notwithstanding the difficulties of getting people to adopt healthier habits, it is suggested that if real effort had gone into encouraging and incentivising

healthier diets and lifestyles, we would not only have saved many more lives from COVID-19, but we would also reduce future mortality from all major causes of death. We are still in a position to make that choice.

Table 1. Summary of relative risk reductions corresponding to interventions discussed.

Intervention/strategy	Risk reduction			Reference
	Infection	Severe disease	Mortality	
Vegan/vegetarian diet		73%		[69]
High diet quality, largely plant-based	10%	40%		[73]
High fruit, vegetable & nut consumption (OR for low)	86% (OR 12.22)			[74]
Normal BMI (compared to obese, OR is for obese)	63% (OR 2.73)	74% (OR 3.81)	38% (OR 1.61)	[29]
		51.9% (OR 2.08)[a]	29.6% (OR 1.42)	[31]
		68.2% (OR 3.14)[b]		
Active/regular exercise (compared to sedentary, OR/aRR for sedentary)	15% (aRR 0.85)	58% (aRR 0.42)	76% (aRR 0.24)	[48]
			94% (aRR 0.16)[c]	
		55.8% (OR 2.26)	59.8% (OR 2.49)	[51]
Sufficient sleep (compared to insufficient sleep)		88.4% (OR 8.61)		[55]
One extra hour of sleep	12% (OR 0.88)	17% (OR 0.83)		[100]
Vitamin D supplements		88% (OR 0.12)[d]		[146]
	9%–24%[e]			[150]
Sufficient vitamin D (compared to deficiency, OR for deficiency)	43.5% (OR 1.77)	61.1% (OR 2.57)	77.1% (OR 4.36)[f]	[145]
			45.1%	[143]
Curcumin (turmeric)			80%[g] and 50%[g]	[112,113]
			82%[h]	[114]
Increased gut health		33%		[219]
Multivitamins	12%–22%[d]			[150]
Omega-3 fatty acid supplements	12%–21%[d]			[150]

aRR; adjusted relative risk; BMI: body mass index; OR: odds ratio. (a) hospitalisation in Western countries; (b) severe disease in Asian populations; (c) over 60 years old; (d) taken after coronavirus disease 2019 diagnosis; (e) depending on country; (f) mean of two models; (g) as nano-curcumin; (h) as standard curcumin with piperine.

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Declaration of competing interest

The author has no competing interest to declare.

References

[1]   World Health Organisation. WHO Coronavirus (COVID-19) Dashboard. [2022-06-23] https://covid19.who.int/.

[2]   Arena R, Lavie CJ; HL-PIVOT Network. The global path forward—healthy living for pandemic event protection (HL-PIVOT). Prog Cardiovasc Dis 2021;64:96–101.

[3]   Dai H, Han J, Lichtfouse E. Smarter cures to combat COVID-19 and future pathogens: a review. Environ Chem Lett 2021;19(4):2759–71.

[4]   Balanzá-Martínez V, Atienza-Carbonell B, Kapczinski F, De Boni RB. Lifestyle behaviours during the COVID-19—time to connect. Acta Psychiatr Scand 2020;141(5):399–400.

[5]   Simon M, Pizzorno J, Katzinger J. Modifiable risk factors for SARS-CoV-2. Integr Med (Encinitas) 2021;20(5):8–14.

[6]   Kompaniyets L, Goodman AB, Belay B, Freedman DS, Sucosky MS, Lange SJ, et al. Body mass index and risk for COVID-19-related hospitalization, intensive care unit admission, invasive mechanical ventilation, and death—United States, March–December 2020. MMWR Morb Mortal Wkly Rep 2021;70(10):355–61

[7]   Kass DA, Duggal P, Cingolani O. Obesity could shift severe COVID-19 disease to younger ages. Lancet 2020; 395(10236):1544–5.

[8]   Sattar N, McInnes IB, McMurray JJV. Obesity is a risk factor for severe COVID-19 infection: multiple potential mechanisms. Circulation 2020;142(1):4–6.

[9]   Kim TS, Roslin M, Wang JJ, Kane J, Hirsch JS, Kim EJ. BMI as a risk factor for clinical outcomes in patients hospitalized with COVID-19 in New York. Obesity (Silver Spring) 2021;29(2):279–84.

[10]   Simonnet A, Chetboun M, Poissy J, Raverdy V, Noulette J, Duhamel A, et al. High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation. Obesity (Silver Spring) 2020;28(7):1195–9.

[11]   Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ 2020;369:m1966.

[12]   Lighter J, Phillips M, Hochman S, Sterling S, Johnson D, Francois F, et al. Obesity in patients younger than 60 years is a risk factor for COVID-19 hospital admission. Clin Infect Dis 2020;71(15):896–7.

[13]   O'Hearn M, Liu J, Cudhea F, Micha R, Mozaffarian D. Coronavirus disease 2019 hospitalizations attributable to cardiometabolic conditions in the United States: a comparative risk assessment analysis. J Am Heart Assoc 2021;10(5):e019259.

[14]   Kompaniyets L, Pennington AF, Goodman AB, Rosenblum HG, Belay B, Ko JY, et al. Underlying medical conditions and severe illness among 540,667 adults hospitalized with COVID-19, March 2020–March 2021. Prev Chronic Dis 2021;18: E66.

[15]   Wise J. COVID-19: highest death rates seen in countries with most overweight populations. BMJ 2021;372:n623.

[16]   de Lusignan S, Dorward J, Correa A, Jones N, Akinyemi O, Amirthalingam G, et al. Risk factors for SARS-CoV-2 among patients in the Oxford Royal College of General Practitioners Research and Surveillance Centre primary care network: a cross-sectional study. Lancet Infect Dis 2020;20(9):1034–42.

[17]   Yang J, Tian C, Chen Y, Zhu C, Chi H, Li J. Obesity aggravates COVID-19: an updated systematic review and meta-analysis. J Med Virol 2021;93(5):2662–74.

[18]   Pettit NN, MacKenzie EL, Ridgway JP, Pursell K, Ash D, Patel B, et al. Obesity is associated with increased risk for mortality among hospitalized patients with COVID-19. Obesity (Silver Spring) 2020;28(10):1806–10.

[19]   Hernández-Garduño E. Obesity is the comorbidity more strongly associated for COVID-19 in Mexico: a case-control study. Obes Res Clin Pract 2020;14(4): 375–9.

[20]   Dhurandhar NV, Bailey D, Thomas D. Interaction of obesity and infections. Obes Rev 2015;16(12):1017–29.

[21]   Fuhrman C, Bonmarin I, Bitar D, Cardoso T, Duport N, Herida M, et al. Adult intensive-care patients with 2009 pandemic influenza A (H1N1) infection. Epidemiol Infect 2011;139(8):1202–9.

[22]   Huttunen R, Syrjänen J. Obesity and the risk and outcome of infection. Int J Obes (Lond) 2013;37(3):333–40.

[23]   Louie JK, Acosta M, Samuel MC, Schechter R, Vugia DJ, Harriman K, et al. A novel risk factor for a novel virus: obesity and 2009 pandemic influenza A (H1N1). Clin Infect Dis 2011;52(3):301–12.

[24]   Nguyen-Van-Tam JS, Openshaw PJM, Hashim A, Gadd EM, Lim WS, Semple MG, et al. Risk factors for hospitalisation and poor outcome with pandemic A/H1N1 influenza: United Kingdom first wave (May–September 2009). Thorax 2010;65(7):645–51.

[25]   Van Kerkhove MD, Vandemaele KAH, Shinde V, Jaramillo-Gutierrez G, Koukounari A, Donnelly CA, et al. Risk factors for severe outcomes following 2009 influenza A (H1N1) infection: a global pooled analysis. PLoS Med 2011;8(7):e1001053.

[26]   Yu H, Feng Z, Uyeki TM, Liao Q, Zhou L, Feng L, et al. Risk factors for severe illness with 2009 pandemic influenza A (H1N1) virus infection in China. Clin Infect Dis 2011;52(4):457–65.

[27]   Cummings MJ, Baldwin MR, Abrams D, Jacobson SD, Meyer BJ, Balough EM, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. Lancet 2020;395(10239):1763–70.

[28]   Seidu S, Gillies C, Zaccardi F, Kunutsor SK, Hartmann-Boyce J, Yates T, et al. The impact of obesity on severe disease and mortality in people with SARS-CoV-2: a systematic review and meta-analysis. Endocrinol Diabetes Metab 2021; 4(1):e00176.

[29]   Cai Z, Yang Y, Zhang J. Obesity is associated with severe disease and mortality in patients with coronavirus disease 2019 (COVID-19): a meta-analysis. BMC Public Health 2021;21(1):1505.

[30]   Chang TH, Chou CC, Chang LY. Effect of obesity and body mass index on coronavirus disease 2019 severity: a systematic review and meta-analysis. Obes Rev 2020;21(11):e13089.

[31]   Yang Y, Wang L, Liu J, Fu S, Zhou L, Wang Y. Obesity or increased body mass index and the risk of severe outcomes in patients with COVID-19. Medicine (Baltimore) 2022;101(1):e28499.

[32]   Cameron NA, Petito LC, McCabe M, Allen NB, O'Brien MJ, Carnethon MR, et al. Quantifying the sex-race/ethnicity-specific burden of obesity on incident diabetes mellitus in the United States, 2001 to 2016: MESA and NHANES. J Am Heart Assoc 2021; 10(4):e018799.

[33]   Després JP. Health consequences of visceral obesity. Ann Med 2001;33(8):534–41.

[34]   Sanchis-Gomar F, Lavie CJ, Mehra MR, Henry BM, Lippi G. Obesity and outcomes in COVID-19: when an epidemic and pandemic collide. Mayo Clin Proc 2020;95(7):1445–53.

[35]   Lavie CJ, Coursin DB, Long MT. The obesity paradox in infections and implications for COVID-19. Mayo Clin Proc 2021;96(3):518–20.

[36]   Basolo A, Poma AM, Bonuccelli D, Proietti A, Macerola E, Ugolini C, et al. Adipose tissue in COVID-19: detection of SARS-CoV-2 in adipocytes and activation of the interferon-α response. J Endocrinol Invest 2022;45(5):1021–9.

[37]   Kruglikov IL, Scherer PE. The role of adipocytes and adipocyte-like cells in the severity of COVID-19 infections. Obesity (Silver Spring) 2020;28(7):1187–90.

[38]   Sharma A, Garg A, Rout A, Lavie CJ. Association of obesity with more critical illness in COVID-19. Mayo Clin Proc 2020;95(9):2040–2.

[39]   Honce R, Karlsson EA, Wohlgemuth N, Estrada LD, Meliopoulos VA, Yao J, et al. Obesity-related microenvironment promotes emergence of virulent influenza virus strains. mBio 2020;11(2):e03341–19.

[40]   Maier HE, Lopez R, Sanchez N, Ng S, Gresh L, Ojeda S, et al. Obesity increases the duration of influenza A virus shedding in adults. J Infect Dis 2018;218(9):1378–82.

[41]   Yan J, Grantham M, Pantelic J, Bueno de Mesquita PJ, Albert B, Liu F, et al. Infectious virus in exhaled breath of symptomatic seasonal influenza cases from a college community. Proc Natl Acad Sci U S A 2018;115(5):1081–6.

[42]   Darvall KAL, Sam RC, Silverman SH, Bradbury AW, Adam DJ. Obesity and thrombosis. Eur J Vasc Endovasc Surg 2007;33(2):223–33.

[43]   Dixon AE, Peters U. The effect of obesity on lung function. Expert Rev Respir Med 2018;12(9):755–67.

[44]   Green WD, Beck MA. Obesity impairs the adaptive immune response to influenza virus. Ann Am Thorac Soc 2017;14(Supplement_5):S406–9.

[45]   Honce R, Schultz-Cherry S. Impact of obesity on influenza A virus pathogenesis, immune response, and evolution. Front Immunol 2019;10:1071.

[46]   Bray GA, Kim KK, Wilding JPH, Federation WO. Obesity: a chronic relapsing progressive disease process. A position statement of the World Obesity Federation. Obes Rev 2017;18(7):715–23.

[47]   Bakaloudi DR, Barazzoni R, Bischoff SC, Breda J, Wickramasinghe K, Chourdakis M. Impact of the first COVID-19 lockdown on body weight: a combined systematic review and a meta-analysis. Clin Nutr 2021;S0261-5614(21)00207-7.

[48]   Lee SW, Lee J, Moon SY, Jin HY, Yang JM, Ogino S, et al. Physical activity and the risk of SARS-CoV-2 infection, severe COVID-19 illness and COVID-19 related mortality in South Korea: a nationwide cohort study. Br J Sports Med 2021;bjsports-2021-104203.

[49]   Roviello V, Gilhen-Baker M, Vicidomini C, Roviello GN. Forest-bathing and physical activity as weapons against COVID-19: a review. Environ Chem Lett 2022;20(1):131–40.

[50]   Nieman DC, Wentz LM. The compelling link between physical activity and the body's defense system. J Sport Health Sci 2019;8(3):201–17.

[51]   Sallis R, Young DR, Tartof SY, Sallis JF, Sall J, Li Q, et al. Physical inactivity is associated with a higher risk for severe COVID-19 outcomes: a study in 48 440 adult patients. Br J Sports Med 2021;55(19):1099–105.

[52]   Laddu DR, Lavie CJ, Phillips SA, Arena R. Physical activity for immunity protection: inoculating populations with healthy living medicine in preparation for the next pandemic. Prog Cardiovasc Dis 2021;64:102–4.

[53]   Meyer J, McDowell C, Lansing J, Brower C, Smith L, Tully M, et al. Changes in physical activity and sedentary behavior in response to COVID-19 and their associations with mental health in 3052 US adults. Int J Environ Res Public Health 2020;17(18):6469.

[54]   Ammar A, Brach M, Trabelsi K, Chtourou H, Boukhris O, Masmoudi L, et al. Effects of COVID-19 home confinement on eating behaviour and physical activity: results of the ECLB-COVID19 international online survey. Nutrients 2020; 12(6):1583.

[55]   Huang B, Niu Y, Zhao W, Bao P, Li D. Reduced sleep in the week prior to diagnosis of COVID-19 is associated with the severity of COVID-19. Nat Sci Sleep 2020;12:999–1007.

[56]   Hamrouni M, Roberts MJ, Thackray A, Stensel DJ, Bishop N. Associations of obesity, physical activity level, inflammation and cardiometabolic health with COVID-19 mortality: a prospective analysis of the UK BioBank cohort. BMJ Open 2021;11(11):e055003.

[57]   Af Geijerstam A, Mehlig K, Börjesson M, Robertson J, Nyberg J, Adiels M, et al. Fitness, strength and severity of COVID-19: a prospective register study of 1 559 187 Swedish conscripts. BMJ Open 2021;11(7):e051316.

[58]   Lavie CJ, Sanchis-Gomar F, Arena R. Fit is it in COVID-19, future pandemics, and overall healthy living. Mayo Clin Proc 2021;96(1):7–9.

[59]   World Health Organisation Regional Office for Europe. Stay physically active during self-quarantine. (2020) [2022-04-30]. https://www.euro.who.int/en/health-topics/disease-prevention/physical-activity/publications/2020/stay-physically-active-during-self-quarantine.

[60]   Xiang M, Zhang Z, Kuwahara K. Impact of COVID-19 pandemic on children and adolescents' lifestyle behavior larger than expected. Prog Cardiovasc Dis 2020;63(4):531–2.

[61]   Edwards MK, Loprinzi PD. Effects of a sedentary behavior-inducing randomized controlled intervention on depression and mood profile in active young adults. Mayo Clin Proc. 2016;91(8): 984–98.

[62]   Weinstein AA, Koehmstedt C, Kop WJ. Mental health consequences of exercise withdrawal: a systematic review. Gen Hosp Psychiatry 2017;49:11–8.

[63]   Kerrigan DJ, Brawner CA, Ehrman JK, Keteyian S. Cardiorespiratory fitness attenuates the impact of risk factors associated with COVID-19 hospitalization. Mayo Clin Proc 2021;96(3):822–3.

[64]   Brawner CA, Ehrman JK, Bole S, Kerrigan DJ, Parikh SS, Lewis BK, et al. Inverse relationship of maximal exercise capacity to hospitalization secondary to coronavirus disease 2019. Mayo Clin Proc 2021;96(1):32–9.

[65]   Ostfeld RJ. Definition of a plant-based diet and overview of this special issue. J Geriatr Cardiol 2017;14(5):315.

[66]   Satija A, Hu FB. Plant-based diets and cardiovascular health. Trends Cardiovasc Med 2018;28(7):437–41.

[67]   Craddock JC, Neale EP, Peoples GE, Probst YC. Plant-based eating patterns and endurance performance: a focus on inflammation, oxidative stress and immune responses. Nutr Bull 2020;45(2):123–32.

[68]   Angelidi AM, Kokkinos A, Katechaki E, Ros E, Mantzoros CS. Mediterranean diet as a nutritional approach for COVID-19. Metabolism 2021;114:154407.

[69] Kim H, Rebholz CM, Hegde S, Lafiura C, Raghavan M, Lloyd JF, et al. Plant-based diets, pescatarian diets and COVID-19 severity: a population-based case-control study in six countries. BMJ Nutr Prev Health 2021;4(1):257–66.

[70]   Perez-Araluce R, Martinez-Gonzalez MA, Fernández-Lázaro CI, Bes-Rastrollo M, Gea A, Carlos S. Mediterranean diet and the risk of COVID-19 in the 'Seguimiento Universidad de Navarra' cohort. Clin Nutr 2021;S0261-5614(21)00190-4.

[71]   Greene MW, Roberts AP, Frugé AD. Negative association between Mediterranean diet adherence and COVID-19 cases and related deaths in Spain and 23 OECD countries: an ecological study. Front Nutr 2021;8:591964.

[72]   Vu THT, Rydland KJ, Achenbach CJ, Van Horn L, Cornelis MC. Dietary behaviors and incident COVID-19 in the UK BioBank. Nutrients 2021;13(6):2114.

[73]   Merino J, Joshi AD, Nguyen LH, Leeming ER, Mazidi M, Drew DA, et al. Diet quality and risk and severity of COVID-19: a prospective cohort study. Gut 2021;70(11):2096–104.

[74]   Jagielski P, Łuszczki E, Wnęk D, Micek A, Bolesławska I, Piórecka B, et al. Associations of nutritional behavior and gut microbiota with the risk of COVID-19 in healthy young adults in Poland. Nutrients 2022;14(2):350.

[75]   Gibson A, Edgar JD, Neville CE, Gilchrist SE, McKinley MC, Patterson CC, et al. Effect of fruit and vegetable consumption on immune function in older people: a randomized controlled trial. Am J Clin Nutr 2012;96(6):1429–36.

[76]   Iddir M, Brito A, Dingeo G, Del Campo SSF, Samouda H, La Frano MR, et al. Strengthening the immune system and reducing inflammation and oxidative stress through diet and nutrition: considerations during the COVID-19 crisis. Nutrients 2020;12(6):1562.

[77]   Guilleminault L, Williams EJ, Scott HA, Berthon BS, Jensen M, Wood LG. Diet and asthma: is it time to adapt our message? Nutrients 2017;9(11):1227.

[78]   Storz MA. Lifestyle adjustments in long-COVID management: potential benefits of plant-based diets. Curr Nutr Rep 2021;10(4):352–63.

[79]   Liu RH. Dietary bioactive compounds and their health implications. J Food Sci 2013;78 Suppl 1:A18–25.

[80]   Hosseini B, Berthon BS, Saedisomeolia A, Starkey MR, Collison A, Wark PAB, et al. Effects of fruit and vegetable consumption on inflammatory biomarkers and immune cell populations: a systematic literature review and meta-analysis. Am J Clin Nutr 2018;108(1):136–55.

[81]   Craddock JC, Neale EP, Peoples GE, Probst YC. Vegetarian-based dietary patterns and their relation with inflammatory and immune biomarkers: a systematic review and meta-analysis. Adv Nutr 2019;10(3):433–51.

[82]   Rizzo A, Sciorsci RL, Magrone T, Jirillo E. Exploitation of some natural products for the prevention and/or nutritional treatment of SARS-CoV2 infection. Endocr Metab Immune Disord Drug Targets 2021;21(7):1171–82.

[83]   Hossain KS, Hossain MG, Moni A, Rahman MM, Rahman UH, Alam M, et al. Prospects of honey in fighting against COVID-19: pharmacological insights and therapeutic promises. Heliyon 2020;6(12):e05798.

[84]   Kahleova H, Levin S, Barnard ND. Vegetarian dietary patterns and cardiovascular disease. Prog Cardiovasc Dis 2018;61(1):54–61.

[85]   Esposito K, Ciotola M, Giugliano D. Mediterranean diet, endothelial function and vascular inflammatory markers. Public Health Nutr 2006;9(8A):1073–6.

[86]   Rosato V, Temple NJ, La Vecchia C, Castellan G, Tavani A, Guercio V. Mediterranean diet and cardiovascular disease: a systematic review and meta-analysis of observational studies. Eur J Nutr 2019;58(1):173–91.

[87]   McDougall J, Thomas LE, McDougall C, Moloney G, Saul B, Finnell JS, et al. Effects of 7 days on an ad libitum low-fat vegan diet: the McDougall Program cohort. Nutr J 2014;13:99.

[88]   Turner-McGrievy GM, Wirth MD, Shivappa N, Wingard EE, Fayad R, Wilcox S, et al. Randomization to plant-based dietary approaches leads to larger short-term improvements in Dietary Inflammatory Index scores and macronutrient intake compared with diets that contain meat. Nutr Res 2015;35(2):97–106.

[89]   Glick-Bauer M, Yeh MC. The health advantage of a vegan diet: exploring the gut microbiota connection. Nutrients 2014;6(11):4822–38.

[90]   Storz MA. Is there a lack of support for whole-food, plant-based diets in the medical community? Perm J 2019;23:18–68.

[91]   Kassam S, Freeman L. It's time for healthcare professionals to demand a plant-based food system. Br J Gen Pract 2021;71(713):554.

[92]   Krueger JM, Frank MG, Wisor JP, Roy S. Sleep function: toward elucidating an enigma. Sleep Med Rev 2016;28:46–54.

[93] Mello MT, Silva A, Guerreiro RC, Da-Silva FR, Esteves AM, Poyares D, et al. Sleep and COVID-19: considerations about immunity, pathophysiology, and treatment. Sleep Sci 2020;13(3):199–209.

[94]   Shillington KJ, Vanderloo LM, Burke SM, Ng V, Tucker P, Irwin JD. Not so sweet dreams: adults' quantity, quality, and disruptions of sleep during the initial stages of the COVID-19 pandemic. Sleep Med 2021;91:189–95.

[95]   Walker M. Why we sleep: the new science of sleep and dreams. London：Penguin; 2017.

[96]   Prather AA, Janicki-Deverts D, Hall MH, Cohen S. Behaviorally assessed sleep and susceptibility to the common cold. Sleep 2015;38(9):1353–9.

[97]   Prather AA, Leung CW. Association of insufficient sleep with respiratory infection among adults in the United States. JAMA Intern Med 2016;176(6):850–2.

[98]   Cohen S, Doyle WJ, Alper CM, Janicki-Deverts D, Turner RB. Sleep habits and susceptibility to the common cold. Arch Intern Med 2009;169(1):62–7.

[99]   Patel SR, Malhotra A, Gao X, Hu FB, Neuman MI, Fawzi WW. A prospective study of sleep duration and pneumonia risk in women. Sleep 2012;35(1):97–101.

[100]   Kim H, Hegde S, Lafiura C, Raghavan M, Luong E, Cheng S, et al. COVID-19 illness in relation to sleep and burnout. BMJ Nutr Prev Health 2021;4:132–9.

[101]   Casagrande M, Favieri F, Tambelli R, Forte G. The enemy who sealed the world: effects of quarantine due to the COVID-19 on sleep quality, anxiety, and psychological distress in the Italian population. Sleep Med 2020;75:12–20.

[102]   Huang Y, Zhao N. Generalized anxiety disorder, depressive symptoms and sleep quality during COVID-19 outbreak in China: a web-based cross-sectional survey. Psychiatry Research 2020;288:112954.

[103]   Lin LY, Wang J, Ou-Yang XY, Miao Q, Chen R, Liang FX, et al. The immediate impact of the 2019 novel coronavirus (COVID-19) outbreak on subjective sleep status. Sleep Med 2021;77:348–54.

[104]   Christensen MA, Bettencourt L, Kaye L, Moturu ST, Nguyen KT, Olgin JE, et al. Direct measurements of smartphone screen-time: relationships with demographics and sleep. PLoS One 2016;11(11):e0165331.

[105]   Stevenson S. Sleep smarter: 21 essential strategies to sleep your way to a better body, better health, and bigger success. Emmaus: Rodale; 2016.

[106]   Liu RH. Potential synergy of phytochemicals in cancer prevention: mechanism of action. J Nutr 2004;134(12 Suppl):3479S–85S.

[107]   Liu RH. Health benefits of fruit and vegetables are from additive and synergistic combinations of phytochemicals. Am J Clin Nutr 2003;78(3 Suppl):517S–20S.

[108]   Sahebkar A. Molecular mechanisms for curcumin benefits against ischemic injury. Fertil Steril 2010;94(5):e75–6.

[109]   Zahedipour F, Hosseini SA, Sathyapalan T, Majeed M, Jamialahmadi T, Al-Rasadi K, et al. Potential effects of curcumin in the treatment of COVID-19 infection. Phytother Res 2020;34(11):2911–20.

[110]   Ahmadi R, Salari S, Sharifi MD, Reihani H, Rostamiani MB, Behmadi M, et al. Oral nano-curcumin formulation efficacy in the management of mild to moderate outpatient COVID-19: a randomized triple-blind placebo-controlled clinical trial. Food Sc Nutr 2021;9(8):4068–75.

[111]   Saber-Moghaddam N, Salari S, Hejazi S, Amini M, Taherzadeh Z, Eslami S, et al. Oral nano-curcumin formulation efficacy in management of mild to moderate hospitalized coronavirus disease-19 patients: An open label nonrandomized clinical trial. Phytother Res 2021;35(5):2616–23.

[112]   Tahmasebi S, El-Esawi MA, Mahmoud ZH, Timoshin A, Valizadeh H, Roshangar L, et al. Immunomodulatory effects of nanocurcumin on Th17 cell responses in mild and severe COVID-19 patients. J Cell Physiol 2021;236(7):5325–38.

[113]   Valizadeh H, Abdolmohammadi-Vahid S, Danshina S, Gencer MZ, Ammari A, Sadeghi A, et al. Nano-curcumin therapy, a promising method in modulating inflammatory cytokines in COVID-19 patients. Int Immunopharmacol 2020;89(Pt B):107088.

[114]   Pawar KS, Mastud RN, Pawar SK, Pawar SS, Bhoite RR, Bhoite RR, et al. Oral curcumin with piperine as adjuvant therapy for the treatment of COVID-19: a randomized clinical trial. Front Pharmacol 2021;12: 669362.

[115]   Kow CS, Ramachandram DS, Hasan SS. The effect of curcumin on the risk of mortality in patients with COVID-19: a systematic review and meta-analysis of randomized trials. Phytother Res 2022;10.1002/ptr.7468.

[116]   Hassaniazad M, Eftekhar E, Inchehsablagh BR, Kamali H, Tousi A, Jaafari MR, et al. A triple-blind, placebo-controlled, randomized clinical trial to evaluate the effect of curcumin-containing nanomicelles on cellular immune responses subtypes and clinical outcome in COVID-19 patients. Phytother Res 2021;35(11):6417–27.

[117]   Kannan S, Kolandaivel P. Antiviral potential of natural compounds against influenza virus hemagglutinin. Comput Biol Chem 2017;71:207–18.

[118]   Jena AB, Kanungo N, Nayak V, Chainy GBN, Dandapat J. Catechin and curcumin interact with S protein of SARS-CoV2 and ACE2 of human cell membrane: insights from computational studies. Sci Rep 2021;11(1):2043.

[119]   Pandey P, Rane JS, Chatterjee A, Kumar A, Khan R, Prakash A, et al. Targeting SARS-CoV-2 spike protein of COVID-19 with naturally occurring phytochemicals: an *in silico* study for drug development. J Biomol Struct Dyn 2021;39:6306–16.

[120]   Kishimoto A, Imaizumi A, Wada H, Yamakage H, Satoh-Asahara N, Hashimoto T, et al. Newly developed highly bioavailable curcumin formulation, curcuRouge™, reduces neutrophil/lymphocyte ratio in the elderly: a double-blind, placebo-controlled clinical trial. J Nutr Sci Vitaminol (Tokyo) 2021;67(4):249–52.

[121]   Dourado D, Freire DT, Pereira DT, Amaral-Machado L, Alencar ÉN, de Barros ALB, et al. Will curcumin nanosystems be the next promising antiviral alternatives in COVID-19 treatment trials? Biomedic Pharmacother 2021;139:111578.

[122]   Thimmulappa RK, Mudnakudu-Nagaraju KK, Shivamallu C, Subramaniam KJT, Radhakrishnan A, Bhojraj S, et al. Antiviral and immunomodulatory activity of curcumin: a case for prophylactic therapy for COVID-19. Heliyon 2021;7(2):e06350.

[123]   Han S, Xu J, Guo X, Huang M. Curcumin ameliorates severe influenza pneumonia via attenuating lung injury and regulating macrophage cytokines production. Clin Exp Pharmacol Physiol 2018;45(1):84–93.

[124] Chen TY, Chen DY, Wen HW, Ou JL, Chiou SS, Chen JM, et al. Inhibition of enveloped viruses infectivity by curcumin. PLoS One 2013;8(5):e62482.

[125] Oso BJ, Adeoye AO, Olaoye IF. Pharmacoinformatics and hypothetical studies on allicin, curcumin, and gingerol as potential candidates against COVID-19-associated proteases. J Biomol Struct Dyn 2022;40(1):389–400.

[126] Tayyem RF, Heath DD, Al-Delaimy WK, Rock CL. Curcumin content of turmeric and curry powders. Nutr Cancer 2006;55(2):126–31.

[127] Siviero A, Gallo E, Maggini V, Gori L, Mugelli A, Firenzuoli F, et al. Curcumin, a golden spice with a low bioavailability. J Herb Med 2015;5(2):57–70.

[128] Wong Y, Chan CH, Venkatakrishnan K, Chiu HF, Shen YC, Glovinskaia O, et al. Impact of dietary nutrients (functional foods/nutraceuticals) and micronutrients on COVID-19: a review. J Food Bioact 2021; 15:29–38.

[129] di Petrillo A, Orrù G, Fais A, Fantini MC. Quercetin and its derivates as antiviral potentials: A comprehensive review. Phytother Res 2022;36:266–78.

[130] Di Pierro F, Iqtadar S, Khan A, Mumtaz SU, Chaudhry MM, Bertuccioli A, et al. Potential clinical benefits of quercetin in the early stage of COVID-19: results of a second, pilot, randomized, controlled and open-label clinical trial. Int J Gen Med 2021;14:2807.

[131] Derosa G, Maffioli P, D'Angelo A, Di Pierro F. A role for quercetin in coronavirus disease 2019 (COVID-19). Phytother Res 2021;35(3):1230–6.

[132] Di Pierro F, Derosa G, Maffioli P, Bertuccioli A, Togni S, Riva A, et al. Possible therapeutic effects of adjuvant quercetin supplementation against early-stage COVID-19 infection: A prospective, randomized, controlled, and open-label study. Int J Gen Med 2021;14:2359–66.

[133] Shohan M, Nashibi R, Mahmoudian-Sani MR, Abolnezhadian F, Ghafourian M, Alavi SM, et al. The therapeutic efficacy of quercetin in combination with antiviral drugs in hospitalized COVID-19 patients: a randomized controlled trial. Eur J Pharmacol 2022;914:174615.

[134] Onal H, Arslan B, Ergun NU, Topuz S, Semerci SY, Kurnaz M, et al. Treatment of COVID-19 patients with quercetin: a prospective, single-centre, randomized, controlled trial. Turk J Biol 2021;45(4):518–29.

[135] Luo E, Zhang D, Luo H, Liu B, Zhao K, Zhao Y, et al. Treatment efficacy analysis of traditional Chinese medicine for novel coronavirus pneumonia (COVID-19): an empirical study from Wuhan, Hubei Province, China. Chin Med 2020;15:34.

[136] Hernández JL, Nan D, Fernandez-Ayala M, Garciá-Unzueta M, Hernández-Hernández MA, López-Hoyos M, et al. Vitamin D status in hospitalized patients with SARS-CoV-2 infection. J Clin Endocrinol Metab 2021; 106(3):eE1343–53.

[137] Seal KH, Bertenthal D, Carey E, Grunfeld C, Bikle DD, Lu CM. Association of vitamin D status and COVID-19-related hospitalization and mortality. J Gen Intern Med 2022 ;37(4):853–61.

[138] Harwood M, Danielewska-Nikiel B, Borzelleca JF, Flamm GW, Williams GM, Lines TC. A critical review of the data related to the safety of quercetin and lack of evidence of *in vivo* toxicity, including lack of genotoxic/carcinogenic properties. Food Chem Toxicol 2007; 45(11):2179–205.

[139] Kamel A, Abdelseed H, Albalawi Y, Aslsalameen E, Almutairi Y, Alkattan A. Evaluation of the effect of zinc, quercetin, bromelain and vitamin C on COVID-19 patients. (2020-12-24) [2022-06-23]. https://doi.org/10.1101/2020.12.22.20245993.

[140] Xu D, Hu MJ, Wang YQ, Cui YL. Antioxidant activities of quercetin and its complexes for medicinal application. Molecules 2019;24(6):1123.

[141] Shah Alam M, Czajkowsky DM, Aminul Islam M, Ataur Rahman M. The role of vitamin D in reducing SARS-CoV-2 infection: an update. Int Immunopharmacol 2021;97:107686.

[142] Kaufman HW, Niles JK, Kroll MH, Bi C, Holick MF. SARS-CoV-2 positivity rates associated with circulating 25-hydroxyvitamin D levels. PLoS One 2020;15(9):e0239252.

[143] Meltzer DO, Best TJ, Zhang H, Vokes T, Arora V, Solway J. Association of vitamin D status and other clinical characteristics with COVID-19 test results. JAMA Netw Open 2020;3(9):e2019722.

[144] Shakeri H, Azimian A, Ghasemzadeh-Moghaddam H, Safdari M, Haresabadi M, Daneshmand T, et al. Evaluation of the relationship between serum levels of zinc, vitamin B12, vitamin D, and clinical outcomes in patients with COVID-19. J Med Virol 2022;94(1):141–6.

[145] Kazemi A, Mohammadi V, Aghababaee SK, Golzarand M, Clark CCT, Babajafari S. Association of vitamin D status with SARS-CoV-2 infection or COVID-19 severity: a systematic review and meta-analysis. Adv Nutr 2021;12(5):1636–58.

[146] Pal R, Banerjee M, Bhadada SK, Shetty AJ, Singh B, Vyas A. Vitamin D supplementation and clinical outcomes in COVID-19: a systematic review and meta-analysis. J Endocrinol Invest 2022;45(1):53–68.

[147] Martineau AR, Jolliffe DA, Hooper RL, Greenberg L, Aloia JF, Bergman P, et al. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. BMJ 2017;356:i6583.

[148] Mithal A, Wahl DA, Bonjour JP, Burckhardt P, Dawson-Hughes B, Eisman JA, et al. Global vitamin D status and determinants of hypovitaminosis D. Osteoporosis Int 2009;20(11):1807–20.

[149] Cereda E, Bogliolo L, Klersy C, Lobascio F, Masi S, Crotti S, et al. Vitamin D 25OH deficiency in COVID-19 patients admitted to a tertiary referral hospital. Clin Nutr 2021;40(4):2469–72.

[150] Louca P, Murray B, Klaser K, Graham MS, Mazidi M, Leeming ER, et al. Modest effects of dietary supplements during the COVID-19 pandemic: insights from 445 850 users of the COVID-19 Symptom Study app. BMJ Nutr Prev Health 2021;4(1):149–57.

[151] Tomasa-Irriguible TM, Bielsa-Berrocal L. COVID-19: up to 82% critically ill patients had low vitamin C values. Nutr J 2021;20(1):66.

[152] Wintergerst ES, Maggini S, Hornig DH. Immune-enhancing role of vitamin C and zinc and effect on clinical conditions. Ann Nutr Metab 2006;50(2): 85–94.

[153] Chiscano-Camón L, Ruiz-Rodriguez JC, Ruiz-Sanmartin A, Roca O, Ferrer R. Vitamin C levels in patients with SARS-CoV-2-associated acute respiratory distress syndrome. Crit Care 2020;24(1): 522.

[154] Arvinte C, Singh M, Marik PE. Serum levels of vitamin C and vitamin D in a cohort of critically ill COVID-19 patients of a North American community hospital intensive care unit in May 2020: a pilot study. Med Drug Discov 2020;8:100064.

[155] Muhammad Y, Kani YA, Iliya S, Muhammad JB, Binji A, El-Fulaty Ahmad A, et al. Deficiency of antioxidants and increased oxidative stress in COVID-19 patients: a cross-sectional comparative study in Jigawa, Northwestern Nigeria. SAGE Open Med 2021;9:2050312121991246.

[156] Holford P, Carr AC, Zawari M, Vizcaychipi MP. Vitamin C intervention for critical COVID-19: a pragmatic review of the current level of evidence. Life (Basel) 2021;11(11):1166.

[157] Calder PC. Nutrition, immunity and COVID-19. BMJ Nutr Prev Health. 2020 May 20;3(1):74–92.

[158] Hemilä H, Carr AC, Chalker E. Vitamin C may increase the recovery rate of outpatient cases of SARS-CoV-2 infection by 70%: reanalysis of the COVID A to Z randomized clinical trial. Front Immunol 2021;12:674681.

[159] Zhang J, Rao X, Li Y, Zhu Y, Liu F, Guo G, et al. Pilot trial of high-dose vitamin C in critically ill COVID-19 patients. Ann Intensive Care 2021;11(1):5.

[160] Fowler AA 3rd, Syed AA, Knowlson S, Sculthorpe R, Farthing D, DeWilde C, et al. Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis. J Transl Med 2014;12:32..

[161] Gao D, Xu M, Wang G, Lv J, Ma X, Guo Y, et al. The efficiency and safety of high-dose vitamin C in patients with COVID-19: a retrospective cohort study. Aging (Albany NY) 2021;13(5):7020–34

[162] Kumari P, Dembra S, Dembra P, Bhawna F, Gul A, Ali B, et al. The role of vitamin C as adjuvant therapy in COVID-19. Cureus 2020; 12(11):e11779.

[163] Zhao B, Liu M, Liu P, Peng Y, Huang J, Li M, et al. High dose intravenous vitamin C for preventing the disease aggravation of moderate COVID-19 pneumonia. a retrospective propensity matched before-after study. Front Pharmacol 2021;12:638556.

[164]   Hemila H, Chalker E. Vitamin C for preventing and treating the common cold. Cochrane Database Syst Rev 2013;2013(1):CD000980.

[165]   Hakamifard A, Soltani R, Maghsoudi A, Rismanbaf A, Aalinezhad M, Tarrahi M, et al. The effect of vitamin E and vitamin C in patients with COVID-19 pneumonia: a randomized controlled clinical trial. Immunopathol Persa 2022;8(1):6.

[166]   Al Sulaiman K, Aljuhani O, Saleh KB, Badreldin HA, Al Harthi A, Alenazi M, et al. Ascorbic acid as an adjunctive therapy in critically ill patients with COVID-19: a propensity score matched study. Sci Rep 2021; 11(1):17648.

[167]   Jothimani D, Kailasam E, Danielraj S, Nallathambi B, Ramachandran H, Sekar P, et al. COVID-19: poor outcomes in patients with zinc deficiency. Int J Infect Dis 2020;100:343–9.

[168]   Razzaque MS. COVID-19 pandemic: can zinc supplementation provide an additional shield against the infection? Comput Struct Biotechnol J 2021;19:1371–8.

[169]   Eby GA 3rd. Zinc lozenges as cure for the common cold—a review and hypothesis. Med Hypotheses 2010; 74(3):482–92.

[170]   Hemilä H. Zinc lozenges may shorten common cold duration. Expert Rev Respir Med 2012;6(3):253-4.

[171]   Hemilä H. Zinc lozenges and the common cold: a meta-analysis comparing zinc acetate and zinc gluconate, and the role of zinc dosage. JRSM Open 2017;8(5):2054270417694291.

[172]   Hunter J, Arentz S, Goldenberg J, Yang G, Beardsley J, Myers SP, et al. Zinc for the prevention or treatment of acute viral respiratory tract infections in adults: A rapid systematic review and meta-analysis of randomised controlled trials. BMJ Open 2021;11(11):e047474.

[173]   Thomas S, Patel D, Bittel B, Wolski K, Wang Q, Kumar A, et al. Effect of high-dose zinc and ascorbic acid supplementation *vs* usual care on symptom length and reduction among ambulatory patients with SARS-CoV-2 infection: the COVID A to Z randomized clinical trial. JAMA Netw Open 2021;4:e210369.

[174]   Yao JS, Paguio JA, Dee EC, Tan HC, Moulick A, Milazzo C, et al. The minimal effect of zinc on the survival of hospitalized patients with COVID-19: an observational study. Chest 2021;159(1):108–11.

[175]   Carlucci PM, Ahuja T, Petrilli C, Rajagopalan H, Jones S, Rahimian J. Zinc sulfate in combination with a zinc ionophore may improve outcomes in hospitalized COVID-19 patients. J Med Microbiol 2020;69(10):1228–34.

[176]   Abd-Elsalam S, Soliman S, Esmail ES, Khalaf M, Mostafa EF, Medhat MA, et al. Do zinc supplements enhance the clinical efficacy of hydroxychloroquine? A randomized, multicenter trial. Biol Trace Elem Res 2021;199(10):3642–6.

[177]   Fenasse R, McEwen B. Impact of the oral contraceptive pill on health and nutritional status. J Aust Trad Med Soc 2019;25:197–203.

[178]   Grant ECG. The contraceptive pill: its relation to allergy and illness. Nutr Health 1983;2(1):33–40.

[179]   Joachimiak MP. Zinc against COVID-19? Symptom surveillance and deficiency risk groups. PLoS Negl Trop Dis 2021;15(1):e0008895.

[180]   Saunders AV, Craig WJ, Baines SK. Zinc and vegetarian diets. Med J Aust 2013;199(S4):S17–21.

[181]   Asher A, Tintle NL, Myers M, Lockshon L, Bacareza H, Harris WS. Blood omega-3 fatty acids and death from COVID-19: a pilot study. Prostaglandins Leukot Essent Fatty Acids 2021;166:102250.

[182]   dos Santos LMJ. Can vitamin B12 be an adjuvant to COVID-19 treatment? GSC Biol Pharmaceut Sci 2020;11(3):1–5.

[1831]   Shakoor H, Feehan J, Mikkelsen K, Al Dhaheri AS, Ali HI, Platat C, et al. Be well: a potential role for vitamin B in COVID-19. Maturitas 2021;144:108–11.

[184]   Watanabe F, Yabuta Y, Bito T, Teng F. Vitamin B12-containing plant food sources for vegetarians. Nutrients 2014;6(5):1861–73.

[185]   Li Q. Effect of forest bathing trips on human immune function. Environ Health Prev Mede 2010;15(1):9–17.

[186]   Li Q, Morimoto K, Nakadai A, Inagaki H, Katsumata M, Shimizu T, et al. Forest bathing enhances human natural killer activity and expression of anti-cancer proteins. Int J Immunopathol Pharmacol 2007;20(2 Suppl 2):3–8.

[187]   Li Q, Morimoto K, Kobayashi M, Inagaki H, Katsumata M, Hirata Y, et al. A forest bathing trip increases human natural killer activity and expression of anti-cancer proteins in female subjects. J Biol Regul Homeost Agents 2008;22(1):45–55.

[188]   Li Q, Morimoto K, Kobayashi M, Inagaki H, Katsumata M, Hirata Y, et al. Visiting a forest, but not a city, increases human natural killer activity and expression of anti-cancer proteins. Int J Immunopathol Pharmacol 2008;21(1):117–27.

[189]   Marketon JIW, Glaser R. Stress hormones and immune function. Cell Immunol 2008;252:16–26.

[190]   Bielinis E, Bielinis L, Krupińska-Szeluga S, Łukowski A, Takayama N. The effects of a short forest recreation program on physiological and psychological relaxation in young Polish adults. Forests 2019;10:34.

[191]   Im SG, Choi H, Jeon YH, Song MK, Kim W, Woo JM. Comparison of effect of two-hour exposure to forest and urban environments on cytokine, anti-oxidant, and stress levels in young adults. Int J Environ Res Public Health 2016;13(7):625.

[192]   Ochiai H, Ikei H, Song C, Kobayashi M, Miura T, Kagawa T, et al. Physiological and psychological effects of a forest therapy program on middle-aged females. Int J Environ Res Public Health 2015;12(12):15222–32.

[193]   Ochiai H, Ikei H, Song C, Kobayashi M, Takamatsu A, Miura T, et al. Physiological and psychological effects of forest therapy on middle-aged males with high-normal blood pressure. Int J Environ Res Public Health 2015;12(3):2532–42.

[194]   Peterfalvi A, Meggyes M, Makszin L, Farkas N, Miko E, Miseta A, et al. Forest bathing always makes sense: blood pressure-lowering and immune system-balancing effects in late spring and winter in central Europe. Int J Environ Res Public Health 2021;18(4):2067.

[195]   Yu CP, Lin CM, Tsai MJ, Tsai YC, Chen CY. Effects of short forest bathing program on autonomic nervous system activity and mood states in middle-aged and elderly individuals. Int J Environ Res Public Health 2017;14(8):897.

[196]   Robinson JM, Brindley P, Cameron R, MacCarthy D, Jorgensen A. Nature's role in supporting health during the COVID-19 pandemic: a geospatial and socioecological study. Int J Environ Res Public Health 2021;18(5):2227.

[197]   Wu X, Nethery RC, Sabath MB, Braun D, Dominici F. Exposure to air pollution and COVID-19 mortality in the United States: a nationwide cross-sectional study. medRxiv 2020;2020.04.05.20054502.

[198]   Zoran MA, Savastru RS, Savastru DM, Tautan MN. Assessing the relationship between surface levels of PM2. 5 and PM10 particulate matter impact on COVID-19 in Milan, Italy. Sci Total Environ 2020;738:139825.

[199]   Kim T, Song B, Cho KS, Lee IS. Therapeutic potential of volatile terpenes and terpenoids from forests for inflammatory diseases. Int J Mol Sci 2020;21(6):2187.

[200]   Li Q, Nakadai A, Matsushima H, Miyazaki Y, Krensky AM, Kawada T, et al. Phytoncides (wood essential oils) induce human natural killer cell activity. Immunopharmacol Immunotoxicol 2006;28(2):319–33.

[201]   Roviello V, Roviello GN. Lower COVID-19 mortality in Italian forested areas suggests immunoprotection by Mediterranean plants. Environ Chem Lett 2021;19:699–710.

[202]   Ciupa T, Suligowski R. Green-blue spaces and population density versus COVID-19 cases and deaths in Poland. Int J Environ Res Public Health 2021;18(12):6636.

[203]   Russette H, Graham J, Holden Z, Semmens EO, Williams E, Landguth EL. Greenspace exposure and COVID-19 mortality in the United States: January–July 2020. Environ Res 2021;198:111195.

[204] Chen B, Jia P, Han J. Role of indoor aerosols for COVID-19 viral transmission: a review. Environ Chem Lett 2021;19(3):1953–70.

[205] de Bell S, Graham H, Jarvis S, White P. The importance of nature in mediating social and psychological benefits associated with visits to freshwater blue space. Landsc Urban Plan 2017;167:118–27.

[206] Garrett JK, White MP, Huang J, Ng S, Hui Z, Leung C, et al. Urban blue space and health and wellbeing in Hong Kong: results from a survey of older adults. Health Place 2019;55:100–10.

[207] Pasanen TP, White MP, Wheeler BW, Garrett JK, Elliott LR. Neighbourhood blue space, health and wellbeing: the mediating role of different types of physical activity. Environ Int 2019;131:105016.

[208] Gascon M, Zijlema W, Vert C, White MP, Nieuwenhuijsen MJ. Outdoor blue spaces, human health and well-being: a systematic review of quantitative studies. Int J Hyg Environ Health 2017;220(8):1207–21.

[209] Massey H, Gorczynski P, Harper CM, Sansom L, McEwan K, Yankouskaya A, et al. Perceived impact of outdoor swimming on health: web-based survey. Interact J Med Res 2022;11(1):e25589.

[210] White MP, Pahl S, Ashbullby K, Herbert S, Depledge MH. Feelings of restoration from recent nature visits. J Environ Psychol 2013;35:40–51.

[211] Wheeler BW, White M, Stahl-Timmins W, Depledge MH. Does living by the coast improve health and wellbeing? Health Place 2012;18(5):1198–201.

[212] Roviello V, Gilhen-Baker M, Roviello GN, Lichtfouse E. River therapy. Environ Chem Lett 2022;20(5):2729-34.

[213] Kuo M. How might contact with nature promote human health? Promising mechanisms and a possible central pathway. Front Psychol 2015;6:1093.

[214] Dhar D, Mohanty A. Gut microbiota and COVID-19—possible link and implications. Virus Res 2020;285:198018.

[215] Louis P, Hold GL, Flint HJ. The gut microbiota, bacterial metabolites and colorectal cancer. Nat Rev Microbiol 2014;12(10):661–72.

[216] Brame JE, Liddicoat C, Abbott CA, Breed MF. The potential of outdoor environments to supply beneficial butyrate-producing bacteria to humans. Sci Total Environ 2021;777:146063.

[217] Tuohy KM, Fava F, Viola R. 'The way to a man's heart is through his gut microbiota'—dietary pro- and prebiotics for the management of cardiovascular risk. Proc Nutr Soc 2014; 73(2):172–85.

[218] Zuo T, Zhang F, Lui GCY, Yeoh YK, Li AYL, Zhan H, et al. Alterations in gut microbiota of patients with COVID-19 during time of hospitalization. Gastroenterology 2020;159(3):944–55.e8.

[219] Al Kassaa I, El Omari S, Abbas N, Papon N, Drider D, Kassem II, et al. High association of COVID-19 severity with poor gut health score in Lebanese patients. PLoS One 2021;16(10):e0258913.

[220] Kim HS. Do an altered gut microbiota and an associated leaky gut affect COVID-19 severity? mBio 2021;12(1):e03022–20.

[221] Gu S, Chen Y, Wu Z, Chen Y, Gao H, Lv L, et al. Alterations of the gut microbiota in patients with coronavirus disease 2019 or H1N1 influenza. Clin Infect Dis 2020;71(10):2669–78.

[222] Khalesi S, Bellissimo N, Vandelanotte C, Williams S, Stanley D, Irwin C. A review of probiotic supplementation in healthy adults: helpful or hype? Eur J Clin Nutr 2019;73(1):24–37.

[223] Hamida RS, Shami A, Ali MA, Almohawes ZN, Mohammed AE, Bin-Meferij MM. Kefir: a protective dietary supplementation against viral infection. Biomed Pharmacother 2021;133:110974.

[224] Suez J, Zmora N, Segal E, Elinav E. The pros, cons, and many unknowns of probiotics. Nat Med 2019;25(5):716–29.

[225] David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, et al. Diet rapidly and reproducibly alters the human gut microbiome. Nature 2014;505(7484):559–63.

[226] Makki K, Deehan EC, Walter J, Bäckhed F. The impact of dietary fiber on gut microbiota in host health and disease. Cell Host Microbe 2018;23(6):705–15.

[227] Rishi P, Thakur K, Vij S, Rishi L, Singh A, Kaur IP, et al. Diet, gut microbiota and COVID-19. Indian J Microbiol 2020;60:420–9.

[228] Koeth RA, Wang Z, Levison BS, Buffa JA, Org E, Sheehy BT, et al. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. Nat Med 2013;19(5):576–85.

[229] Trompette A, Gollwitzer ES, Yadava K, Sichelstiel AK, Sprenger N, Ngom-Bru C, et al. Gut microbiota metabolism of dietary fiber influences allergic airway disease and hematopoiesis. Nat Med 2014;20(2):159–66.

[230] Johnson AJ, Vangay P, Al-Ghalith GA, Hillmann BM, Ward TL, Shields-Cutler RR, et al. Daily sampling reveals personalized diet-microbiome associations in humans. Cell Host Microbe 2019;25(6):789–802.e5.

[231] McDonald D, Hyde E, Debelius JW, Morton JT, Gonzalez A, Ackermann G, et al. American gut: an open platform for citizen science microbiome research. mSystems 2018;3(3):e00031–18.

[232] Stella C, Beckwith-Hall B, Cloarec O, Holmes E, Lindon JC, Powell J, et al. Susceptibility of human metabolic phenotypes to dietary modulation. J Proteome Res 2006;5(10):2780–8.

[233] Robinson JM, Cando-Dumancela C, Liddicoat C, Weinstein P, Cameron R, Breed MF. Vertical stratification in urban green space aerobiomes. Environ Health Perspect 2020;128(11):117008.

[234] Selway CA, Mills JG, Weinstein P, Skelly C, Yadav S, Lowe A, et al. Transfer of environmental microbes to the skin and respiratory tract of humans after urban green space exposure. Environ Int 2020;145:106084.

[235] Roslund MI, Puhakka R, Grönroos M, Nurminen N, Oikarinen S, Gazali AM, et al. Biodiversity intervention enhances immune regulation and health-associated commensal microbiota among daycare children. Sci Adv 2020;6(42):eaba2578.

[236] Sobko T, Liang S, Cheng WHG, Tun HM. Impact of outdoor nature-related activities on gut microbiota, fecal serotonin, and perceived stress in preschool children: the Play&Grow randomized controlled trial. Sci Rep 2020;10(1):21993.

[237] Haahtela T. A biodiversity hypothesis. Allergy 2019;74(8):1445–56.

[238] Nielsen CC, Gascon M, Osornio-Vargas AR, Shier C, Guttman DS, Becker AB, et al. Natural environments in the urban context and gut microbiota in infants. Environ Int 2020;142:105881.

[239] Parajuli A, Hui N, Puhakka R, Oikarinen S, Grönroos M, Selonen VAO, et al. Yard vegetation is associated with gut microbiota composition. Sci Total Environ 2020;713:136707.

[240] Reddy RK, Charles WN, Sklavounos A, Dutt A, Seed PT, Khajuria A. The effect of smoking on COVID-19 severity: a systematic review and meta-analysis. J Med Virol 2021;93(2):1045–56.

[241] Umnuaypornlert A, Kanchanasurakit S, Lucero-Prisno DEI, Saokaew S. Smoking and risk of negative outcomes among COVID-19 patients: a systematic review and meta-analysis. Tob Induc Dis 2021;19:09.

[242] Zhang H, Ma S, Han T, Qu G, Cheng C, Uy JP, et al. Association of smoking history with severe and critical outcomes in COVID-19 patients: a systemic review and meta-analysis. Eur J Integr Med 2021;43:101313.

[243] Clay JM, Parker MO. Alcohol use and misuse during the COVID-19 pandemic: a potential public health crisis? Lancet Public Health 2020;5(5):e259.

[244] Stockwell T, Andreasson S, Cherpitel C, Chikritzhs T, Dangardt F, Holder H, et al. The burden of alcohol on health care during COVID-19. Drug Alcohol Rev 2021;40(1):3–7.

[245] Capasso A, Jones AM, Ali SH, Foreman J, Tozan Y, DiClemente RJ. Increased alcohol use during the COVID-19 pandemic: the effect of mental health and age in a cross-sectional sample of social media users in the U.S. Prev Med 2021;145:106422.

[246] Ramalho R. Alcohol consumption and alcohol-related problems during the COVID-19 pandemic: a narrative review. Australas Psychiatry 2020;28(5):524–6.

[247] Bailey KL, Samuelson DR, Wyatt TA. Alcohol use disorder: a pre-existing condition for COVID-19? Alcohol 2021;90:11–7.

[248] Samji H, Wu J, Ladak A, Vossen C, Stewart E, Dove N, et al. Mental health impacts of the COVID-19 pandemic on children and youth—a systematic review. Child Adolesc Ment Health 2022;27(2):173–89.

[249] Viner R, Russell S, Saulle R, Croker H, Stansfield C, Packer J, et al. School closures during social lockdown and mental health, health behaviors, and well-being among children and adolescents during the first COVID-19 wave: a systematic review. JAMA Pediatr 2022;176(4):400–9.

[250] Ammar A, Chtourou H, Boukhris O, Trabelsi K, Masmoudi L, Brach M, et al. COVID-19 home confinement negatively impacts social participation and life satisfaction: a worldwide multicenter study. Int J Environ Res Public Health 2020;17(17):6237.

[251] Ammar A, Trabelsi K, Brach M, Chtourou H, Boukhris O, Masmoudi L, et al. Effects of home confinement on mental health and lifestyle behaviours during the COVID-19 outbreak: insights from the ECLB-COVID19 multicentre study. Biol Sport 2021;38(1):9–21.

[252] Di Renzo L, Gualtieri P, Cinelli G, Bigioni G, Soldati L, Attinà A, et al. Psychological aspects and eating habits during COVID-19 home confinement: results of EHLC-COVID-19 Italian online survey. Nutrients 2020;12(7):2152.

[253] Mattioli AV, Sciomer S, Maffei S, Gallina S. Lifestyle and stress management in women during COVID-19 pandemic: impact on cardiovascular risk burden. Am J Lifestyle Med 2021;15(3):356–9.

[254] Wu P, Liu X, Fang Y, Fan B, Fuller CJ, Guan Z, et al. Alcohol abuse/dependence symptoms among hospital employees exposed to a SARS outbreak. Alcohol Alcohol 2008;43(6):706–12.

[255] Liu X, Kakade M, Fuller CJ, Fan B, Fang Y, Kong J, et al. Depression after exposure to stressful events: lessons learned from the severe acute respiratory syndrome epidemic. Compr Psychiatry 2012;53(1):15–23.

[256] Brooks SK, Webster RK, Smith LE, Woodland L, Wessely S, Greenberg N, et al. The psychological impact of quarantine and how to reduce it: rapid review of the evidence. Lancet 2020;395(10227):912–20.

[257] Jeong H, Yim HW, Song YJ, Ki M, Min JA, Cho J, et al. Mental health status of people isolated due to Middle East Respiratory Syndrome. Epidemiol Health 2016;38:e2016048.

[258] Hawryluck L, Gold WL, Robinson S, Pogorski S, Galea S, Styra R. SARS control and psychological effects of quarantine, Toronto, Canada. Emerg Infect Dis 2004; 10(7):1206–12.

[259] Torres SJ, Nowson CA. Relationship between stress, eating behavior, and obesity. Nutrition 2007;23(11–12):887–94.

[260] Roelfs DJ, Shor E, Davidson KW, Schwartz JE. Losing life and livelihood: a systematic review and meta-analysis of unemployment and all-cause mortality. Soc Sci Med 2011;72(6):840–54.

[261] Claussen B. Alcohol disorders and re-employment in a 5-year follow-up of long-term unemployed. Addiction 1999;94(1):133–8.

[262] Fjorback LO, Arendt M, Ørnbøl E, Fink P, Walach H. Mindfulness-based stress reduction and mindfulness-based cognitive therapy: a systematic review of randomized controlled trials. Acta Psychiatr Scand 2011; 124(2):102–19.

[263] Praissman S. Mindfulness-based stress reduction: a literature review and clinician's guide. J Am Acad Nurse Pract 2008; 20(4):212–6.

[264] Shiloh S, Sorek G, Terkel J. Reduction of state-anxiety by petting animals in a controlled laboratory experiment. Anxiety Stress Coping 2003;16(4):387–95.

[265] Wang F, Szabo A. Effects of yoga on stress among healthy adults: a systematic review. Altern Ther Health Med 2020; 26(4):AT6214.

[266]   Leung K, Wu JT. Managing waning vaccine protection against SARS-CoV-2 variants. Lancet 2022;399(10319):2–3.

[267]   Fabiani M, Puopolo M, Morciano C, Spuri M, Alegiani SS, Filia A, et al. Effectiveness of mRNA vaccines and waning of protection against SARS-CoV-2 infection and severe COVID-19 during predominant circulation of the delta variant in Italy: retrospective cohort study. BMJ 2022;376:e069052.