Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Clinical Nutrition ESPEN 43 (2021) 39–48

Contents lists available at ScienceDirect

Clinical Nutrition ESPEN

journal homepage: http://www.clinicalnutritionespen.com

Narrative Review

Strengthening the immunity of the Swiss population with micronutrients: A narrative review and call for action

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ARTICLE INFO

Article history:
Received 7 March 2021
Accepted 8 March 2021

Keywords:
Nutrition
Iron
Selenium
Zinc n-3 PUFA
Vitamin D
Deficiency
Immunity

SUMMARY

Background: The enormous health impact of the COVID-19 pandemic has refocused attention on measures to optimize immune function and vaccine response. Dietary deficiencies of micronutrients can weaken adaptive immunity. The aim of this review was to examine links between micronutrients, immune function and COVID-19 infection, with a focus on nutritional risks in subgroups of the Swiss population.

Methods: Scoping review on the associations between selected micronutrients (vitamins D and C, iron, selenium, zinc, and n-3 PUFAs) and immunity, with particular reference to the Swiss population. These nutrients were chosen because previous EFSA reviews have concluded they play a key role in immunity.

Results: The review discusses the available knowledge on links between sufficient nutrient status, optimal immune function, and prevention of respiratory tract infections. Because of the rapid spread of the COVID-19 pandemic, controlled intervention studies of micronutrients in the context of COVID-19 infection are now underway, but evidence is not yet available to draw conclusions. The anti-inflammatory properties of n-3 PUFAs are well established. In Switzerland, several subgroups of the population are at clear risk of nutrient deficiencies; e.g., older adults, multiple comorbidities, obesity, pregnancy, and institutionalized. Low intakes of n-3 PUFA are present in a large proportion of the population.

Conclusion: There are clear and strong relationships between micronutrient and n-3 PUFA status and immune function, and subgroups of the Swiss population are at risk for deficient intakes. Therefore, during the COVID-19 pandemic, as a complement to a healthy and balanced diet, it may be prudent to consider supplementation with a combination of moderate doses of Vitamins C and D, as well as of Se, Zn and n-3 PUFA, in risk groups.

1. Introduction

Viral infection outbreaks have been and will remain a regular challenge all along human evolution. Currently the annual influenza outbreaks are responsible for 3 to 5 million cases of severe illness requiring hospitalization, and 290,000 to 650,000 deaths. In 2020, the COVID-19 outbreak, caused by the new SARS-CoV-2 virus, has resulted to date in more than 108 million cases globally and 2.4 million deaths [1]. Both virus infections are classified as acute respiratory tract diseases, and are a major cause of morbidity and mortality across the globe [2].

The COVID-19 pandemic resulted in increased focus on public health practices to limit the spread and impact of respiratory viruses, such as regular hand washing, social distancing, covering

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https://doi.org/10.1016/j.clnesp.2021.03.012

coughs, and wearing masks [3]. Considerable efforts enabled the development of COVID-19 vaccines in record time with vaccination starting end of 2020. But nutritional reinforcement of the host immunity enabling fighting the virus has been mostly ignored [4].

This low interest occurred despite the fact that it is scientifically well established and endorsed by expert authorities that selected nutrients, including several micronutrients (we use this term hereafter for vitamins and trace elements) and nutrients such as omega-3 polyunsaturated fatty acids (PUFA), support our immune response [5]. It is thus likely, that depletion of these nutrients is detrimental on the risk of acquiring an infection and on the recovery. Dietary nutrient recommendations for optimal nutrient status in support of a well-functioning immune system have been issued [5,6]. However, due rapid development of the of the COVID-19 pandemic, there is a lack of rigorous evidence that the administration of individual nutrients during an acute COVID-19 infection has beneficial effects [7]. Despite this, there are indications that optimal nutritional status before viral exposure might attenuate the disease severity [8–10].

Over recent months, there has been a call for action to emphasize optimal nutritional status to complement public health measures put in place to manage COVID-19 infection [5,6,11,12]. Considering the absence of focus and specific nutritional measures by the local public health authorities, we took the initiative to perform a scoping review to address whether measures regarding nutritional guidance are likely to improve immunity and health outcomes during the COVID-19 pandemic in Switzerland.

This paper aims to summarize the role of selected nutrients on the immune system, pointing to specific nutritional risks in the Swiss population related to immunity: the review is not aimed at therapy but rather on prevention. As a rapid scoping review, we did not perform a formal systematic search, but relied our data sources on PubMed, Medline, and the Cochrane library.

2. Coronavirus pandemic and the situation in Switzerland

Coronaviruses are single-stranded RNA viruses, common among mammals and birds, that cause mainly respiratory infectious diseases. In December 2019, a new type of coronavirus was identified in Wuhan, China, causing severe pneumonia [2]. The new coronavirus was called SARS-CoV-2. This virus is new to the human immune system with no underlying existing natural immunity against it. The COVID-19 infection is particularly impacting older people and individuals with existing comorbidities like diabetes, cardiovascular disease, respiratory disease, and hypertension, as well as individuals with suppressed immune systems. Most recently more contagious mutations of the SARS-CoV-2 virus have emerged and may further complicate the management of the pandemic.

In Switzerland the COVID-19 outbreak started in February 2020 and has to date (February 28th 2021) infected 559′845 people and is responsible for 10′014 deaths [13]. Since the second wave started in autumn 2020, infection and mortality dynamics and numbers have remained high when compared to other European countries with similar socio-economic and healthcare status (Table 1) [13]. Specifically and when compared to Norway, Finland, Germany and Denmark, Swiss incidence is considerably higher. While these differences may be due to many factors such as restriction on movement by authorities and adherence of the population, it is possible that the focus of some Nordic countries on the nutritional status of its inhabitants may have contributed to lower incidence and improved outcomes [11]. In turn, it is possible, that higher mortality rates in Switzerland are at least partly explained by a suboptimal nutrient status of the Swiss population, e.g. regarding selenium and vitamin D [14,15], resulting in suboptimal immune defenses. The aim of this review is to provide a summary of observational and intervention trials linking nutrition status and intake of specific micronutrients to outcomes of viral infections, specifically COVID-19.

3. Nutrition and immune response

The immune system, our first line of defense against infections, is dependent on the host nutritional status. Since the COVID-19 outbreak many scientific papers have been published regarding the role of selected nutrients in support of a well-functioning immune system [12]. Importantly, most nutrients are at low cost and have an excellent safety profile when given in physiological doses.

The important and complementary role of several vitamins (i.e., vitamins A, B6, B9, B12, C, D, and E), trace elements (i.e., zinc, iron, selenium, and copper) as well as omega-3 long-chain polyunsaturated fatty acids (n-3 PUFA) in supporting both the innate and adaptive immune systems is well documented. Deficiencies or suboptimal status in micronutrients can negatively affect immune function and decreases resistance to infections [10–12]. Indeed, except for vitamin E, after rigorous review, each of these micronutrients has been granted health claims in the European Union for contributing to the normal function of the immune system [13]. Other nutrients such as n-3 PUFA also support an effective immune system, specifically by helping to resolve the inflammatory response [14].

3.1. Vitamin D

Vitamin D is of utmost importance for our immune response, a role that is substantiated by authorities such as EFSA [17]. Adequate

Table 1
Incidence and mortality for COVID-19 infection for selected European countries classified according to the incidence of infections (adapted from the Johns Hopkins daily dashboard - Last update on February 28th, 2021 [16]).

Country	Population (millions)	# Infections	Infection incidence (cases/1000)	# Deaths	Mortality rate (deaths/1000)	Country's GDP (nominal)
Belgium	11,460	777′608	67.9	22′169	1.934	$ 43'814
Spain	47,430	3′136′321	66.1	70′247	1.481	$ 26'831
Switzerland	**8,560**	**559′845**	**65.4**	**10′014**	**1.170**	**$ 86'673**
Sweden	10,380	675′292	65.1	12′964	1.249	$ 50'339
Netherlands	17,450	1′116,404	64.0	15′824	0.907	$ 53'016
France	67,410	3′870′144	57.4	87′695	1.301	$ 39'257
Austria	8,930	465′322	52.1	8′625	0.966	$ 50'277
Italy	60,320	2′976′274	49.3	98′635	1.635	$ 33'159
Denmark	5,840	213′486	36.6	2′371	0.406	$ 63'829
Germany	83,170	2′472′913	29.7	71′285	0.857	$ 45'466
Norway	5,380	72′923	13.6	632	0.117	$ 67'987
Finland	5,540	59′442	10.7	759	0.137	$ 48'461

Bold is to higlight the position of Switzerland.

vitamin D status is well known to be a challenge in Europe, insufficiency or even deficiency being widespread [11,18].

Vitamin D supplementation trials in viral infections, in particular upper respiratory tract infections, are not all conclusive [19–21], The latest intervention trials show that the effect is close to zero in case of normal vitamin D status [22,23]. Nevertheless several recent meta-analyses have reported that vitamin D supplementation results in a reduction in the incidence of respiratory tract infections [24–27]. A recent systematic review and meta-analysis of 25 RCTs reported that daily or weekly vitamin D supplementation reduced the incidence of acute respiratory tract infections [20]. The effect was most pronounced in vitamin D deficient subjects (serum 25(OH)D levels <25 nmol/L) for whom supplementation reduced the occurrence of at least one acute episode by 70%. These data are aligned with Brenner et al.'s cohort data, who reported an association of vitamin D insufficiency (blood 25(OH)D levels 30–50 nmol/L) or deficiency (levels < 30 nmol/L) and increased respiratory mortality over a 15-year period in 9548 adults [10]. The authors concluded that 41% of respiratory disease mortality was attributable to inadequate vitamin D status. Non-conclusive clinical outcomes of vitamin D supplementation have been related to a high baseline vitamin D level, a short administration period and low dosage [22].

Data reporting a correlation between inadequate vitamin D status, as measured by circulating 25(OH)D levels, and higher rates of COVID-19 incidence, severity and mortality are rapidly accumulating [9,28–34], although not all agree [35]. Radujkovic et al. found that vitamin D deficiency (<12 ng/mL) was associated with a 6-fold higher risk of invasive mechanical ventilation and/or death, and a near 15-fold increase in mortality, after adjusting for age, gender, and comorbidities [29]. Two studies, one in Ticino and a large study in Israelian adults reported significantly lower 25(OH)D levels in SARS-CoV-2 positive patients [31,36]. In the latter, adjusted odds ratios (age, demographics, comorbidities) of 1.45 and 1.95 were reported for SARS-CoV-2 infection and COVID-19 hospitalization, respectively, in patients with 25(OH)D levels <75 nmol/l vs. >75 nmol/L. The authors concluded that lower serum vitamin D levels appeared to be an independent risk factor for SARS-CoV-2 infection and COVID-19 hospitalization. Finally, a recent systematic review and meta-analysis of 27 publications concluded that individuals with severe COVID-19 symptoms presented vitamin D deficiency 65% more often than those with mild symptoms. In addition, vitamin D inadequacy resulted in increased hospitalization and mortality from COVID-19 [37]. These data have been recently complemented by a dose–response analysis in a cohort with >190,000 patients [9], demonstrating that SARS-CoV-2 positivity rate was higher in 39,190 patients with low 25(OH)D values (<20 ng/mL) as compared to 27,870 patients with "adequate" values (30–34 ng/mL) and 12,321 patients with high values (≥55 ng/mL). Using multivariate analysis the authors concluded that subjects with 25(OH)D levels < 20 ng/mL had a 54% higher infection rate as compared to those with levels at 30–34 ng/mL [9].

A small study in nursing home frail elderly COVID-19 patients found that regular bolus dosing of vitamin D (50,000 IU vitamin D_3/month, or 80,000–100,000 IU vitamin D3 every 2–3 months) over the year prior to infection significantly reduced mortality by 93% [38]. Notwithstanding the small size of this French cohort (57 patients in the intervention group and 9 controls), vitamin D supplementation was strongly associated with enhanced clinical improvement. More pertinently, on follow-up at 5 weeks, 82.5% of the supplemented group had survived vs. just 44.4% of the non-supplemented controls [38]. A pilot intervention study from Spain, examined the clinical course of 76 patients hospitalized with COVID-19 [39], and treated with hydroxychloroquine and azithromycin over the first 5 days of their admission: they were allocated to a supplementation scheme with calcifediol (25(OH)D3) or placebo. One patient of the calcifediol group was admitted to ICU vs. 13 patients from the placebo group Two of these patients died. The authors concluded that the trial provided sufficient evidence to warrant larger clinical trials of early calcifediol administration in COVID-19 patients. Several large-scale trials investigating the effect of vitamin D administration on COVID-19 infection outcomes are currently under way (76 listed on the site of Clinicaltrials.gov, February 15th), with results expected in 2021 [40]. Thus, based on available evidence, it is likely that vitamin D status plays an important role during an infection with COVID-19. Vitamin D deficiency appears to increase risk to acquire the infection and worsens recovery from the infection, and Vitamin D administration in case of deficiency may reduce these risks.

The Finnish authorities implemented a vitamin D fortification program in 2003, with mandatory fortification of dairy products. This policy has increased vitamin D status substantially and has led to adequate vitamin D status (levels >75 nM/l) in the entire population. It is noteworthy that Finland has one of the lowest incidences and COVID-19 mortality data in Europe [14] (Table 1). The Irish Food Safety Authority advices a daily vitamin D supplement for older adults of 10 μg (healthy/during winter) or 15 μg (housebound/all year long). Similarly, the UK government has decided to provide four months of free vitamin D supplements (of 10 μg a day) to the vulnerable elderly population to support their vitamin D status during this winter season [41].

3.2. Vitamin C

Vitamin C, the key water-soluble antioxidant in humans, has an important role in the immune system, as emphasized by expert authorities such as EFSA [42]. In the adaptive immune system, vitamin C is involved in the differentiation and proliferation of both T and B lymphocytes, and supports antibody production [5,42]. Vitamin C deficiency results in impaired immunity, leading to increased rates and severity of infection such as pneumonia, whereas supplementation can reduce the incidence and severity of infection [5,42–44]. A recent review concluded that vitamin C supplementation may reduce symptoms of acute respiratory viral infections, as well as the incidence and duration of hospital stays [43]. Daily vitamin C supplementation at 200 mg or more, was reported to decrease severity and duration (8% in adults, 14–18% in children) of upper respiratory tract infections, including common cold [45]. Daily vitamin C supplementation at 200 mg of elderly patients hospitalized with acute respiratory infections supported recovery, particularly when baseline vitamin C status was low [46]. Leukocyte vitamin C level as well as neutrophil function decline with age [47]. Higher vitamin C intakes are needed to restore blood levels in old adults [48], and these higher intakes and blood levels have been associated with better clinical outcomes [42]. Despite many positive studies especially upper respiratory tract infections, data are not all conclusive [45].

While the potential beneficial role of vitamin C in reducing outcomes of viral infections, and thus COVID-19, may be an area of interest, few data are available. A small study found that 94% of COVID-19 patients with sepsis-related ARDS had undetectable plasma vitamin C levels [49]. In a small pilot study in China, a high dose of vitamin C given intravenously reduced the risk of development of cytokine storm during the late stage of COVID-19 infection [50]. Early administration of high dose of vitamin C has been recommended for COVID-19 pneumonia [51,52]. Several vitamin C intervention studies are ongoing, and results are expected during 2021 (www.clinicaltrials.gov, e.g. NCT04323514). Based on the available evidence, vitamin C may have a role in the

management of COVID-19 infection in both in-patient and out-patient settings [53].

3.3. Selenium

Selenium, best known as a cofactor in glutathione peroxidase and selenoprotein P, functions as cellular antioxidant and supports the body's immune response, a role recognized by authorities such as EFSA [5,54]. While data for selenium supplementation and infectious diseases are not all conclusive [55], most papers link selenium administration to improved outcomes in a variety of viral infections in humans [56,57]. Selenium supplementation increases the production of IFN-γ, a cytokine that inhibits viral replication, as well as other cytokines in response to alive, attenuated poliovirus vaccination in selenium inadequate adults: cellular responses are improved, and virus clearance is more rapid than in absence of supplementation [57,58]. Additionally selenium deficiency has been reported to mutate RNA viruses, such as coxsackievirus and influenza A, into more virulent variants [59–61]. A recent study found a significant correlation between selenium status and outcome of COVID-19 cases in China [8]. In cities known to have a low selenium status, death rates from COVID-19 were significantly higher, and recovery rates significantly lower compared to normal selenium status areas [56,62]. In a small study, lower selenium status was reported in COVID-19 non-survivors compared to survivors [63]. In recently deceased COVID-19 patients, 64.7% and 70.6% showed selenium and selenoprotein deficiency, respectively, whereas 39.3% and 32.6% of survivors were classified deficient. Another study found an association between recovery rates for COVID-19 and selenium status [64]: Sodium selenite can oxidize thiol groups in the virus protein disulfide isomerase rendering it unable to penetrate the healthy cell membrane [64].

Low selenium status is widespread on the European continent [65]. Public health measures such as selenium fortification [15] and supplementation trials [66] have improved global health outcomes. This may be relevant for Switzerland considering its low selenium status, as discussed below.

3.4. Zinc

Zinc is involved in numerous innate and adaptive immune functions as well as defense against oxidative stress: these functions have been substantiated by expert authorities such as EFSA [67–69]. The antiviral property of zinc has been studied extensively, including coronavirus, hepatitis C virus, and HIV infections [70,71]. Pre-existing zinc deficiency may pre-dispose patients to a severe progression of COVID-19 [72,73]. Zinc supplementation may reduce the incidence of acute lower respiratory infection [74]. In institutionalized older adults, a high zinc status (≥70 mg/dL vs. <70 mg/dL) was associated with lower incidence of and faster recovery from pneumonia, and fewer days of antibiotic use [48,75].

A number of association and intervention studies have investigated the role of zinc in COVID-19 infection [71,73,76,77]. In a small study of COVID-19 patients, 27 of 45 (57.4%) were found to be zinc deficient, and these patients exhibited higher rates of complications compared to zinc sufficient patients, including higher rates of acute respiratory distress syndrome (18.5% vs 0%, $p = 0.06$), corticosteroid therapy ($p = 0.02$), prolonged hospital stay, and increased mortality (18.5% vs 0%, $p = 0.06$). The odds ratio of developing complications was 5.54 for zinc deficient COVID-19 patients compared to zinc sufficient patients [71]. In another study (50 mg elemental zinc given twice daily for 5 days) increased the frequency of COVID-19 patients being discharged, decreased the need for ventilation, admission to the ICU, mortality and transfer to hospice for patients who were admitted to the ICU [78]. Zinc supplementation is also currently being used in clinical trials in COVID-19 patients [76]. While limited data regarding zinc and COVID-19 infection are available it seems prudent to achieve adequate zinc intake during the current pandemic.

3.5. Iron

Exciting new evidence points to iron deficiency (ID) as a key modulator of innate and adaptive immune responses. A mutation in transferrin receptor-1 (which transports iron into lymphocytes) causes severe immunodeficiency in humans, with low levels of circulating IgG and decreased T- and B-cell proliferation [79]. ID in mice attenuates T-cell-dependent and -independent antigen-specific antibody responses, and impairs B-cell proliferation [80]. The intensified metabolism of activated lymphocytes requires high amounts of iron, and T-cell and B-cell responses to adenovirus and vaccinia virus are inhibited in ID mice [81]. Imposing hypoferremia blunts T cell, B cell, and neutralizing antibody responses to influenza virus infection in mice, exacerbating lung inflammation and morbidity, and iron repletion improved the response to vaccination in ID mice [81]. A recent birth cohort study in Kenya has shown that ID at time of routine infant vaccination is a strong predictor of vaccine response to diphtheria, pertussis and pneumococcus [82]. In a randomized trial, compared to infants that did not receive iron, those who received iron at time of measles vaccination at 9 months had higher anti-measles-IgG, seroconversion and IgG avidity [82]. Thus, in adults with ID, giving iron at time of vaccination might improve vaccine performance, but this remains to be tested in prospective trials.

Anemia and impaired iron homeostasis are prevalent in hospitalized COVID-19 patients [83]. Prognostic risk factors in COVID-19 disease include older age, inflammation, low serum iron and low hemoglobin [84,85]. Systemic hypoferremia may impair hypoxia sensing and immunity [86] and may be a potential therapeutic target [87]. The association of serum iron with lymphocyte counts could reflect the requirement of the adaptive immune response for iron [88] and may contribute to possible T cell dysfunction reported in COVID-19 [89]. Based on the above evidence, the European Hematology Association recently recommended that ID be treated at time of COVID-19 vaccination [90]. In summary, ID may be a previously unrecognized modulator of adaptive immunity and a contributor to vaccine failure, and this may be particularly important in the context of the COVID-19 pandemic.

Iron deficiency is a major public health problem, and the most prevalent nutritional deficiency worldwide [91]. Switzerland is not spared. A Swiss study including 1010 women with diagnosed iron deficiency showed that iron deficiency caries a significant burden: using a human capital approach, the estimated annual indirect costs for iron deficiency are CHF 33 million [92]. Iron deficiency anemia affects many older adults [93], who are vulnerable to COVID-19 infection.

3.6. Omega-3 polyunsaturated fatty acids

Adequate n-3 PUFA intake mitigates the adverse effects of inflammation [94]. The inflammatory response is fundamental to immunity and the defense against pathogens. An important example of this negative regulation is via DHA and EPA. These fatty acids are present at the site of infection and constitute substrates for the synthesis of highly active lipid mediators important in regulating inflammatory processes and responses, including resolvins, protectins and maresins [95–97]. As a result, they support the resolution of inflammation and consequently support healing, which may be delayed in individuals with deficiencies of DHA and EPA [98]. Although there is little available evidence on the

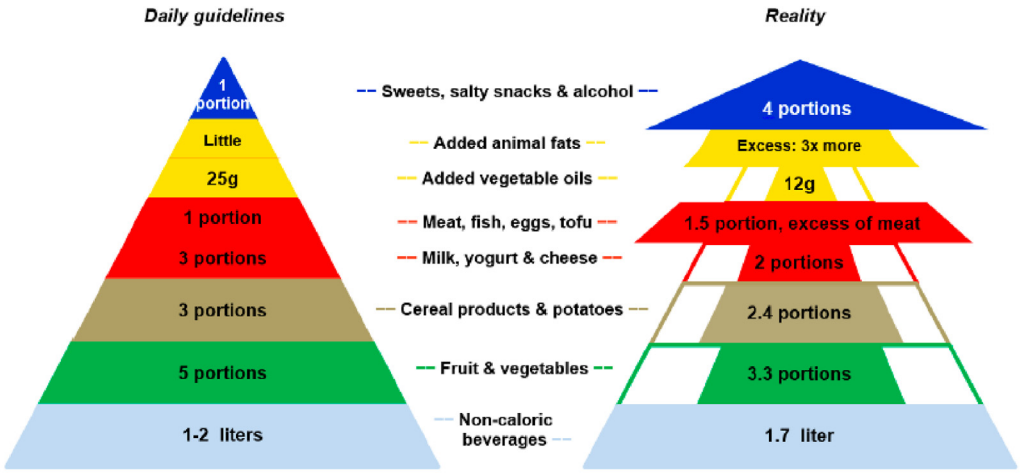

Fig. 1. Comparison of Swiss Dietary recommendations (left) with the actual daily food consumption (right) [107].

role of n-3 PUFA in COVID-19 infection, adequate n-3 PUFA status is important for a well-functioning immune system. The potential benefits of n-3 PUFA to reduce COVID-19 severity are based on well documented in vitro and in vivo studies [99–101].

3.7. Long-term multi-micronutrient administration

Multi-micronutrient trials delivering doses slightly above the DRI for longer periods (years) have generally had other primary endpoints than immunity, except those enrolling HIV patients. A Cochrane review including 33 trials in adult HIV patients showed that routine multiple micronutrient supplementation for up to two years had little or no effect on mortality, and on mean CD4+ cell counts [102]. A meta-analysis of studies conducted in patients with heart failure, showed that micronutrients improved the health outcomes by improving symptoms, work capacity and left ventricular ejection fraction (LVEF), thus increasing the quality of life, without untoward side effects [103]. Several cancer prevention trials conducted in areas of endemic low selenium status have proven beneficial. A very large size trial in Linxian (China) combined Selenium (50 μg), vitamin E (30 mg), and β-carotene (15 mg) [104], and showed that the preventive effect on oesophageal cancer and the reduction of mortality were maintained 10 years after the end of the trial. In France, the SU.VI.MAX trial [105] included 13′017 healthy subjects who ingested a combination of vitamins C (120 mg) and E (30 mg), beta-carotene (6 mg), selenium (100 μg) and zinc (20 mg) for 7.5 years. The authors observed a lower total cancer incidence and mortality in men but not in women [105], and only minor biological benefits (antioxidant sub-study in n = 5220) in this generally well-nourished healthy population [106]. Overall, these studies confirm the high safety profile of multi-micronutrient interventions with doses close to DRI. These are important findings when considering a potential immune enforcement intervention.

Table 2
Evidence level for primary prevention and treatment of COVID-19 in micro-nutrient deficient and non-deficient people (−: no effect; +/−: uncertain, + positive, +++: strong evidence).

Nutrient	Prevention in Deficient	Treatment Deficient	Prevention Non-Deficient	Treatment Non-Deficient
Vitamin C	+++	+/−	−	−
Vitamin D	++	+/−	−	−
Fe	+++	+++	−	−
Se	++	+/−	−	−
Zn	++	+/−	−	−
n-3 PUFA	+++	+/−	+	−

Table 3
Likelihood of deficiency in the Swiss population.

Nutrient	Adults	Older adults 65+
Vitamin C	+ Men	+++
Vitamin D	+	+++
Fe	++ Women	++
Se	+	+++
Zn	+	++
n-3 PUFA	+	++

Table 4
Composition of the proposed nutritional supplements. Correction of iron deficiency requires individualized therapy and is therefore not mentioned.

Nutrient	Dosage/day	Upper intake limits/day
Vitamin C	200 mg	2000 mg
Vitamin D	800–1600 IU (20–40 μg)	4000 IU(100 μg)
Se	100 μg	400 μg
Zn	20 mg	40 mg
n-3 PUFA	500 mg	5000 mg

4. Dietary intake and nutritional status of the Swiss population

Until 2015 Switzerland was one of few high-income countries without national representative data on food consumption or eating behaviors [107]. The first nation-wide survey menuCH conducted in 2014–2015 indicated that the vast majority of the Swiss adult population poorly adhered to the national dietary recommendations (Fig. 1) [108]. The comparison of nutrient intake and/or status to recommendations highlights several nutritional risks [109].

A report by the Federal Office of Public Health on vitamin D status estimated that about 50% of the Swiss population has inadequate serum 25(OH)D concentrations (<50 nmol/L) and that only 30% has optimal levels (>75 nmol/L). A population-based study showed that low serum 25(OH)D levels are common among Swiss adults, in particular during winter months [110]. Also, a recent study found that over 50% of multimorbid Swiss patients had

deficient vitamin D levels at hospital admission, which was associated with higher mortality [111]. The prevalence of vitamin D insufficiency was highest in winter (January–March) with more than nine out of ten men being vitamin D deficient and/or insufficient [112]. Another study using a representative sample of 3191 Swiss adults from three cantons found that 11% were vitamin D deficient (<25 nmol/L) [113]. A recent paper reported that the vitamin D status of the majority (73%) of first trimester pregnant women was inadequate (serum 25(OH)D levels <50 nmol/L) [114]. Most importantly, one third of all pregnant women (34%) had a severe vitamin D deficiency (25(OH)D levels <25 nmol/L), and mean 25(OH)D concentrations in Swiss pregnant women was 37 ± 20 nmol/L, which is insufficient. The CoLaus cohort including 3856 representative participants of Lausanne (mean 51 years)e, demonstrated that mean 25(OH)D levels were insufficient (46 ± 23 and 50 ± 23 nmol/L in those who did and did not develop insulin resistance, respectively) [115]. In 428 Swiss hospitalized patients, aged 85 year on average, 25(OH)D levels were 32 ± 25 nmol/L, and 55% of the hospitalized patients were vitamin D deficient (<25 nmol/L) and 23% insufficient (25–50 nmol/L) [112].

Considering the above, it appears vitamin D status in many segments of the Swiss population is inadequate, and that vulnerable subgroups (e.g., pregnant women, older adults, institutionalized) are at particular high risk for deficiency.

Vitamin C intake in Switzerland is poorly documented. A recent study reported the mean blood vitamin C concentration of Swiss adults was 55.5 ± 17.2 μmol/L, suggesting approximately 12% of adults are below the cutoff for deficiency (<23 μmol/l) [116]. Notably, the data indicate that Swiss men are at higher risk for vitamin C deficiency than Swiss women, with blood values of 11.1–49.7 μmol/L versus 35.4–80.1 μmol/L, respectively. Additionally, blood vitamin C concentrations decline rapidly with increased stress, infections and diseases [117], which suggests vitamin C requirements may be higher during COVID-19 infection.

Population representative dietary intake data for zinc are not available for Switzerland. However, a cross-sectional study reported a plasma zinc concentration of 85 ± 12 μg/dl for omnivorous Swiss adults, with 11% of subjects at risk for deficiency. The percentage of adults at risk of zinc deficiency was even higher for vegetarians (19%) and vegans (47%) [116].

Selenium intake and status may be suboptimal in the European population, including the Swiss population [118–120]. A selenium concentration of 98.7 μg/L in plasma or serum are required to optimize glutathione peroxidase (GPX) activity, a level required for optimal antioxidant defense. A study in the Swiss healthy blood donors from different regions reported a mean plasma selenium 90 μg/L [121], and the data suggested that a substantial portion of the population has a suboptimal selenium status [120]. This may be due to the low selenium content of the Swiss soil which translates in a low selenium content of locally produced foods. These data could be considered for public health strategies [15], although such measures are slow and require several years to yield results [122].

Data for dietary n-3 PUFA intake and status are also limited for Switzerland [123]. In a study in 46 healthy Swiss adults, a food frequency questionnaire (FFQ) for n-3 PUFA intake was performed, and in 152 subjects the erythrocyte n-3 PUFA composition was measured. In the assessments of dietary intake, the EFSA recommendations for EPA + DHA intake were not reached. The median omega-3 index of the study population was 6.1%, which is below the desirable target level of 8–12%. Thus limited data suggest that the n-3 PUFA status of the Swiss population is insufficient [124]. This is in accordance with national menuCH study that reported fatty fish intake below recommendation [123].

In Switzerland the prevalence of obesity (body mass index >30 kg/m^2) is approximately 5% among individuals with higher levels of education, and three times higher (15%) among individuals with lower levels of education [125]. The prevalence of micronutrient deficiencies is higher in obese individuals compared to normal weight people, probably because of inadequate eating habits but also due to increased micronutrient demands of overweight persons [126]. A high prevalence of vitamin D deficiency in obese subjects is a well-documented finding, most probably due to volumetric dilution into the greater volumes of fat, serum, liver, and muscle [127]. Iron deficiency is also more prevalent in overweight and obese subjects as a result of lower dietary iron absorption, as shown in a cohort of Swiss overweight children [128]. Micronutrient deficiencies in obese individuals may not be entirely corrected by a diet containing recommended levels of vitamins and minerals [126].

5. Summary of micronutrients at risk in the Swiss population and recommendations

Considering the evidence (Table 2), a special attention should be paid to optimize nutritional guidance to the Swiss population (Table 3). While there is limited data in Switzerland, it appears that dietary intake is low for vitamin C, vitamin D, iron, selenium, zinc, and n-3 PUFAs, as compared to D-A-CH nutritional recommendations. This is particularly concerning for the vulnerable elderly population, for which inadequate intakes have been reported in several studies [129,130]. The risk of micronutrient deficiencies is increased in older adults due to alterations of the gastro-intestinal tract which reduces the absorption capacity, as well as changes in nutritional habits [131,132]. While the focus on nutritional guidance should be on consuming a well-balanced diet such as that recommended by the Swiss Society for Nutrition, this requires long-term education and advocacy. Supplementing the diet with a combination of specific nutrients which are not sufficient in the diet may be warranted, particularly during wintertime, e.g., for vitamin D. In addition, there is growing evidence that for some vitamins and micronutrients, higher amounts are needed during times of stress and infection that may not be covered by diet alone [130]. While supplements may cover the nutritional gaps, it is important to also focus on the safety of the nutrients in the recommended doses. We feel that nutrient supplements may be needed to fill the nutrient gap for selected micronutrients and n-3 PUFAs in some at-risk subgroups in Switzerland. This nutritional strategy may be particularly relevant for vulnerable groups such as adults 65 years and older, especially for high-risk individuals with underlying health conditions. Ensuring optimal nutritional status in older adults could potentially improve the response to COVID-19 vaccines [12]. The persistent COVID-19 pandemic might be the right moment to introduce such a strategy.

In suggesting judicious nutrient supplementation may be beneficial for at risk subgroups during the current COVID-19 pandemic, we acknowledge there is currently a lack of data from prospective interventions that clearly support the concept that nutrient supplementation improves outcomes. However, there is strong evidence that correction of nutrient deficiency is associated with positive effects on patient health and that the potential benefit of supplementation likely depends on the baseline status of the individual or population [20]. This emphasizes the role of micronutrients in prevention rather than therapy. We do feel that, given the prevalence of suboptimal intakes and status of several micronutrients and n-3 PUFA in Switzerland, supplements for some subgroups at risk are warranted, particularly during times of stress, infection and vaccination [12]. Clearly, any recommendations on supplementation need to carefully consider safe intake levels, ensuring that all proposed doses fall within the safety limits established by expert scientific bodies such as D-A-CH, EFSA and

IOM [133–135]. All proposed additional intakes need to comply with Swiss regulations for dietary supplements. Moreover, vitamins C and D, as well as selenium and zinc have health claims for immunity that have been substantiated by EFSA [134,135]. While the doses we propose are safe, we admit there is currently a lack of a conclusive interventional trial data proving this strategy would improve the health of the target population. It would be valuable to test the effects on immunity in a prospective study using a combination of the below nutrients (Table 4).

Finally, it is important to differentiate subjects with a likely normal status from those with insufficient status, as only the latter will benefit of the complements. Diagnosing anemia and iron deficiency, and treating the latter, will be an important verification to increase the effects of a prevention strategy [90].

- **Vitamin D:** an intake of at least 800 IU (20 μg) of vitamin D is currently recommended in Switzerland for persons over the age of 65 years (D-A-CH recommendation). A higher dose of up to 2000 IU (50 μg) of vitamin D may be required however, to raise blood levels of 25-hydroxyvitamin D consistently above 30 ng/ml (>75 nmol/L) in adults and the elderly. This dose is safe and within the tolerable upper safe intake level at 4000 IU/day (100 μg/day) (D-A-CH and EFSA recommendations), and has been proposed by expert groups [6], and by the Endocrine Society [136]. While final proof of causality is yet to be generated, and trials are underway, the authors consider that the evidence is compelling enough to recommend higher vitamin D supplementation [6,10,20,137–139] specifically for vulnerable population groups (e.g., pregnancy, obesity, older adults, and institutionalized) where vitamin D deficiency is endemic [9,36,140].
- **Vitamin C:** supplementing a well-balanced diet with 200 mg vitamin C per day is a prudent precautionary measure, which will enable most healthy individuals to achieve a plasma concentration of 70 μmol/L in healthy people. The dose is higher than the daily intake recommendation (D-A-CH) but in line with international findings [45]. The use of vitamin C at this level is safe and the potential benefit supports its use [6,101].
- **Zinc:** a daily supplement of 20 mg zinc is in the range of the daily intake recommendation: it is safe and potentially beneficial on immunity and well below a recently tested 100 mg/day dose [78].
- **Selenium:** a daily supplement of 50–100 μg selenium is in the range of the daily intake recommendation [133]. The prolonged intake of such selenium doses is safe.
- **Omega-3 PUFA:** a daily supplement of 500 mg DHA and EPA. This amount of DHA and EPA intake is equal to the dose obtained by eating oily fish twice a week. The use of n-3 PUFA at this level is safe [12].

6. Conclusion

Optimal immune function requires sufficient levels of several key micronutrients (Vitamin C and D, Fe, Se, Zn) and of n-3 PUFA (EPA, DHA). There is evidence that subgroups of the Swiss population are at risk of inadequate intakes and suboptimal nutritional status of these nutrients, particularly the multimorbid older adult population. It is possible that poor nutritional status may contribute to greater prevalence and severity of COVID-19 infection in the Swiss population. Although the mainstay of nutritional health is a varied and well-balanced diet, it may be beneficial, in some circumstances, to supplement with specific micronutrients. Such supplements may be a safe, low-cost, and effective way to fill the nutrient gap and improve the immunity of the population. This preventive strategy is clearly an adjunct to other established measures to cope with the COVID-19 pandemic, e.g., social distancing, wearing of masks, and hygiene measures.

Funding disclosure

This research received no external funding.

Declaration of competing interest

M.E. is president of the Gesellschaft für angewandte Vitamin for schung (Germany), member of the scientific boards of PM International and consults companies in the nutrition and supplement field. M.M.B. receives honoraria for lectures from the companies Baxter, B. Braun, DSM, Fresenius Kabi, Nestlé, and Nutricia; has research funding from Fresenius Kabi, ESPEN, Fondation Nutrition 2000, and Swiss Foundation for Research. IHA is currently vice-president of the Swiss Society for Nutrition (SGE). MBZ's spouse is an employee of Burgerstein Vitamins, a nutritional supplement producer. JS is Director of the Swiss Lung Association, Member of the Board of the Swiss Society for Pulmonology, the health associations of Switzerland (GELIKO) and Health Promotion Switzerland.

Acknowledgments

The authors are grateful to Prof. Heike A. Bischoff-Ferrari (Universitätsspital und Universität Zürich) for advice regarding the formulation of vitamin D dosage proposal, and to Prof. Philipp Schütz (Medizinische Universitätsklinik, Kantonsspital Aarau, Switzerland) for helpful scientific discussions.

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