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Review Article

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# The Role of Some Vitamins in Respiratory-related Viral Infections: A Narrative Review

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## ABSTRACT

This study aimed to find out the effect of vitamins on respiratory-related viral infections, including coronavirus disease 2019 (COVID-19), through the literature reviews. From January 2000 to June 2021, the studies (cohort studies, cross-sectional studies, case-control studies, randomized control trials) related to vitamins (vitamin A, D, E, C, $B_6$, folate, and $B_{12}$) and COVID-19/severe acute respiratory syndrome/Middle East respiratory syndrome/cold/influenza were selected from the PubMed, Embase, and Cochrane libraries and analyzed. The relationship between vitamins and virus-related respiratory diseases was identified. Through the review, 39 studies were selected on vitamin D, one study on vitamin E, 11 studies on vitamin C, and 3 studies on folate. Regarding COVID-19, 18 studies on vitamin D, 4 studies on vitamin C, and 2 studies on folate showed significant effects of the intake of these nutrients in preventing COVID-19. Regarding colds and influenza, 3 studies on vitamin D, 1 study on vitamin E, 3 studies on vitamin C, and 1 study on folate demonstrated that the intake of these nutrients significantly prevents these diseases. Therefore, this review suggested the intake of vitamins D, E, C, and folate is important for preventing respiratory diseases related to viruses, such as COVID-19, colds, and influenza. The relationship between these nutrients and virus-related respiratory diseases should be continuously monitored in the future.

**Keywords:** COVID-19; Vitamins; Respiratory tract infection; Virus

## INTRODUCTION

Since the coronavirus disease 2019 (COVID-19) outbreak in 2019, the global death toll has approached 6 million, and the pandemic, now in its third year, is not over [1]. The new coronavirus, the causative agent of COVID-19, is a family of RNA viruses [2]. RNA viruses are considered to have high mutation rates and frequent mutations [3]. Therefore, it is not easy to manufacture COVID-19-related vaccines or therapeutics. Among the top 10 infectious diseases that have caused the most deaths in the world (Spanish flu, Asian flu, Hong Kong flu, 7th cholera epidemic, swine influenza, Ebola, Congo measles, West African meningitis, and severe acute respiratory syndrome [SARS]), excluding cholera and meningitis, the remaining diseases are infectious diseases caused by RNA viruses. Currently, there is no

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specific treatment for coronavirus infection. In early 2020, the World Health Organization (WHO) declared that SARS-coronavirus 2 had established a pandemic infection and was added to the WHO list of blueprint priority diseases [4].

In 2020, the COVID-19 guidelines published by the WHO, the United Nations Food and Agriculture Organization, the European Food Information Commission, the Centers for Disease Control and Prevention, and the American Nutrition Society identified 4 common nutritional issues. 1) Eat foods that improve immune function, such as vitamins, minerals, dietary fiber, and antioxidants, from fresh, not processed foods. 2) Maintain an adequate intake of minerals (copper, iron, zinc) and vitamins (A, $B_6$, $B_{12}$, C, D, and folate) directly involved in immune function. 3) Eat whole grains and healthy fats, such as omega-3 fatty acids and nuts. 4) Avoid the intake of high-carbohydrate, high-fat, high-salt foods, alcohol, and frozen foods.

Some nutrients were reported to be actively involved in the proper functioning and strengthening of the immune system, including dietary protein, omega-3 fatty acids, vitamins A, D, E, $B_1$, $B_6$, $B_{12}$, and C. Supplementation with some of these dietary components was also reported to be effective in improving the health status of patients with viral infections [5]. Viral infections are characterized by compromised immune function and deficient micronutrient stores, particularly vitamins, including vitamins A, $B_6$, $B_{12}$, C, D, and E [6].

Therefore, based on the studies showing that vitamins are effective in preventing COVID-19, this study attempted to investigate the effects of vitamins on respiratory-related viral infections, including COVID-19, through a review.

## MATERIALS AND METHODS

### Data extraction

Research searches were performed by 4 independent reviewers, focusing on literature published from January 2000 to June 2021 in the PubMed, Embase, and Cochrane libraries. To identify the publications, individual nutrients and COVID-19/SARS/Middle East respiratory syndrome (MERS)/cold/influenza descriptors were adopted. The articles only written in English, Korean, and Japanese were reviewed. The target nutrients were vitamins A, D, E, C, $B_6$, folate, and $B_{12}$.

### Data selection

The selection criteria for literature in this review were cross-sectional studies, cohort studies, case-controlled studies, and randomized clinical trials (RCTs). The exclusion criteria were: in vitro laboratory research, cell experiments, animal experiments, reviews, systematic literature reviews, meta-analysis studies, and conference proceedings. The lists of bibliographical references of the relevant studies were examined to identify potentially eligible studies. The publications were managed in Rayyan to remove duplicates and apply the inclusion criteria. Whether publications met the selection criteria or not was determined by reviewing the titles and abstracts of the searched papers. When it was difficult to judge a paper based on the title and abstract alone, the text was reviewed to decide whether to select the paper. Through this process, the selected articles were re-examined, and the finally selected papers were included in the review.

## RESULTS

A search for individual nutrients and respiratory-related viral infections in the PubMed, Embase, and Cochrane libraries found 168 papers on vitamin A, 982 papers on vitamin D, 431 papers on vitamin E, 901 papers on vitamin C, 151 papers on vitamin $B_6$, 220 papers on folate, and 167 papers on vitamin $B_{12}$ (**Figure 1**). Among these publications, only studies related to cohort studies, cross-sectional studies, case-controlled studies, and RCTs were selected.

### Vitamin A

Of the total 168 studies on vitamin A, 156 were not related to COVID-19/SARS/MERS/cold/influenza, and 2 animal studies, 3 systematic reviews, and 7 reviews were excluded. Therefore, no cohort studies, cross-sectional studies, case-control studies, or RCTs of vitamin A were found, so a review of vitamin A could not be performed (**Figure 1A**).

### Vitamin D

A total of 982 articles related to vitamin D were found. Among them, 877 articles were excluded by reviewing the title and abstract, and 2 in vitro research studies, 3 meta-analyses, 21 systemic reviews, and 40 reviews were also excluded (**Figure 1B**). Finally, an article review was conducted on 39 studies, which were classified into 13 cohort studies [7-19], 11 cross-sectional studies [20-30], 6 case-control studies [31-36], and 9 RCTs [37-45] (**Table 1**). The cohort study included 10 COVID-19-related studies and 3 respiratory disease-related studies. The subjects of the study were people infected with COVID-19 in the COVID-19 study and normal people in the study related to respiratory diseases. The cross-sectional study was classified into 9 studies on COVID-19, one study each on influenza, legionella, and pneumonia, and one study each on lung function, respiratory tract infections, and colds. The case-control study consisted of 5 COVID-19-related studies and one influenza-related study. The RCT consisted of 3 studies related to COVID-19 topics, 4 studies related to respiratory diseases, and 2 studies related to influenza. The subjects were divided into a placebo group and an experimental group and took different doses of various forms of vitamin D.

### Vitamin E

We identified 431 studies related to vitamin E in our database. Of these, 415 papers were excluded by reviewing the study titles and abstracts. Only one case was eligible for a literature review, with exclusion of 6 animal experiments, 2 systematic reviews, and 7 reviews (**Figure 1C**, **Table 2**). The eligible study was an RCT study to confirm the efficacy of vitamin E in respiratory infections [46].

### Vitamin C

In vitamin C, 901 papers were searched (**Figure 1D**), and 855 papers were excluded based on the titles and abstracts. A total of 11 documents were used in the study after excluding 2 in vitro studies, 3 animal experiments, 5 meta-analyses, 5 systematic reviews, one mixed meta-analysis and systematic review, and 19 literature reviews (**Table 3**). Of these, 3 cross-sectional studies were COVID-19-related studies [47-49], and 8 RCTs included 3 studies related to COVID-19 [50-52] and 5 studies related to the common cold [53-57].

### Vitamin $B_6$

For vitamin $B_6$, 151 articles were searched, and 147 articles were excluded by reviewing the titles and abstracts. One systematic review and 3 reviews were also excluded (**Figure 1E**). Thus, no articles were eligible for a literature review.


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## Folate

A total of 220 articles on folic acid were searched (**Figure 1F**). As a result of reviewing the titles and abstracts, 217 were excluded. Three papers were classified into 2 cross-sectional studies and one cohort study and underwent literature reviews (**Table 4**).

The cross-sectional studies consisted of one study on COVID-19 [58] and A-H1N1 and one study on respiratory infections [59]. A cohort study related to COVID-19 was conducted [60].

## Vitamin $B_{12}$

The search yielded 167 studies related to vitamin $B_{12}$, and among them, 164 papers were excluded by reviewing the titles and abstracts (**Figure 1G**). No papers underwent a literature review because one systematic review and 2 reviews were excluded.

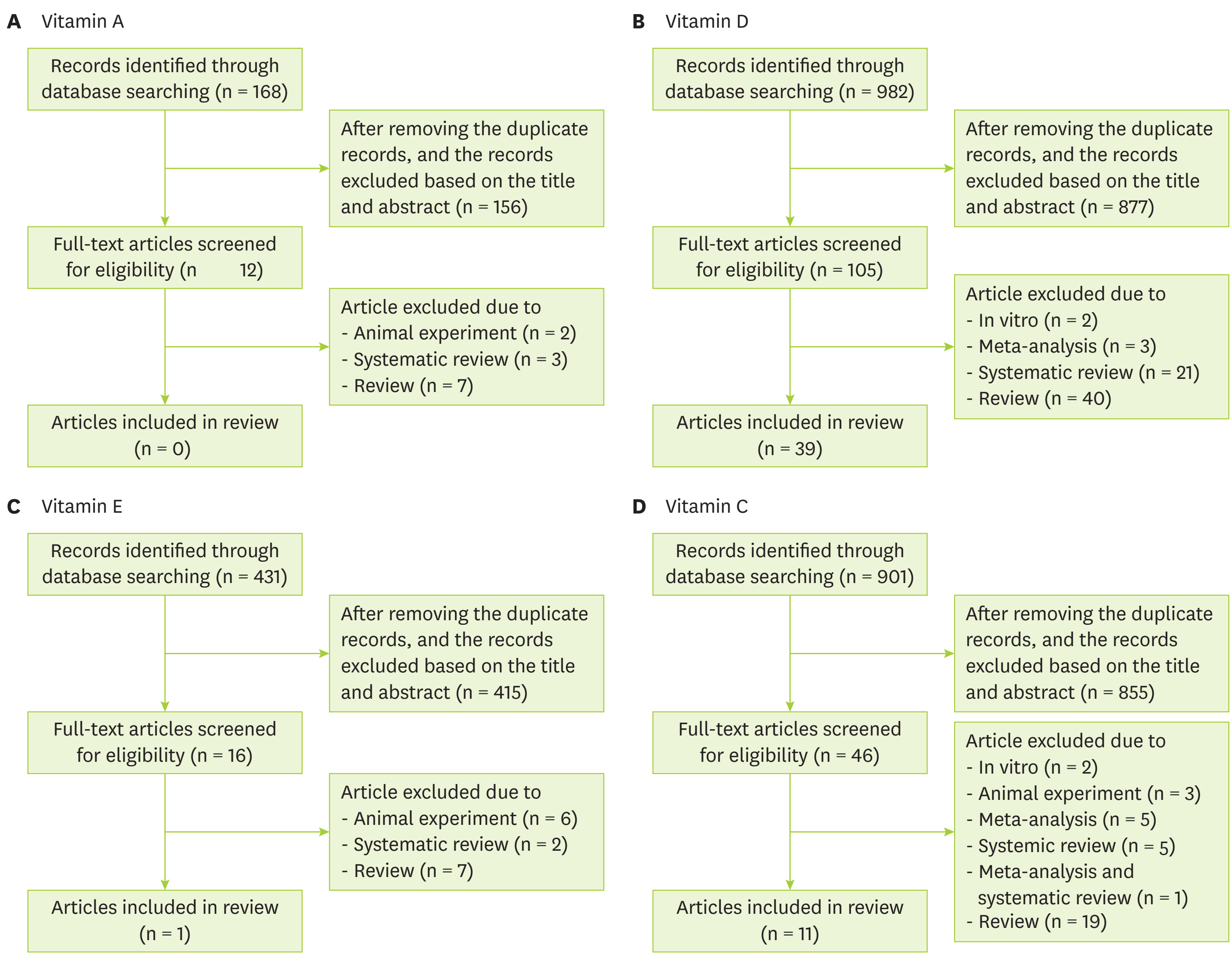


**Figure 1.** Flow diagram of study selection for systematic review of each nutrient.

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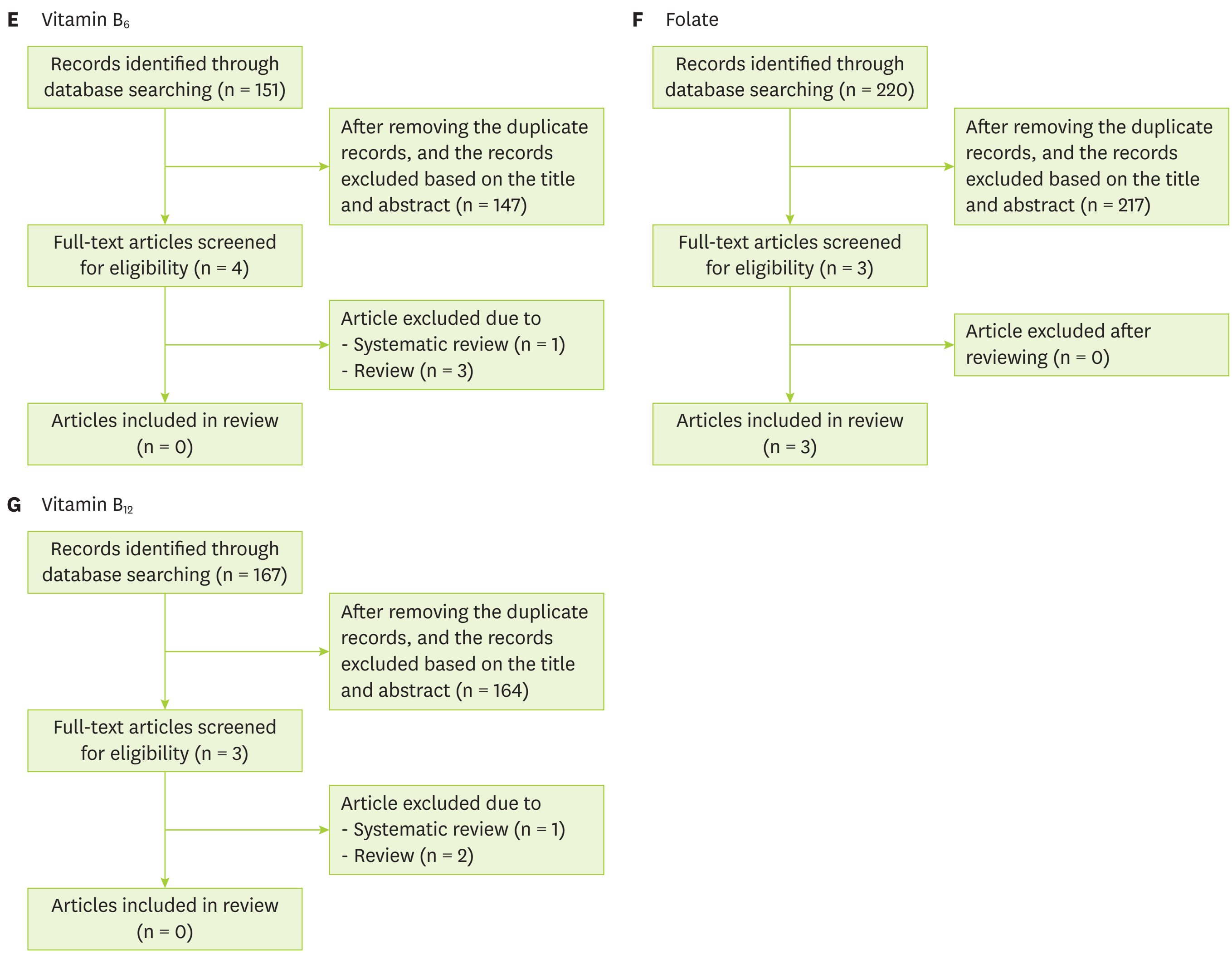


**Figure 1.** (Continued) Flow diagram of study selection for systematic review of each nutrient.

## DISCUSSION

This review was conducted to investigate the effects of vitamins on COVID-19/SARS/MERS/cold/influenza-related viral infections.

Eighteen of the 27 studies related to vitamin D and COVID-19 reported the effect of low levels of vitamin D in the blood on the occurrence of COVID-19. The 25-hydroxyvitamin D (25(OH)D) blood levels of COVID-19-positive patients were reported to be lower than 10–11.1 ng/mL [8,11]. Patients with vitamin D deficiency have seemed more than 5 times higher to be infected with COVID-19 than patients without vitamin D deficiency [23]. In addition, it was reported that for every 1% increase in the prevalence of vitamin D deficiency, the number of deaths from COVID-19 increases by 55 per million [27]. Serum 25(OH)D concentrations in COVID-19-positive patients were 25.95 ± 14.56 ng/mL [20]. Ye et al. [35] identified a potential threshold of serum 25(OH)D of 41.19 nmol/L for COVID-19 prevention. COVID-19-positive patients were hospitalized for a prolonged period if they had low vitamin D levels at the time of admission [25]. It has been reported that the normalization of serum 25(OH)D levels


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**Table 1.** Main characteristics of the articles evaluating the association between vitamin D and respiratory-related viral infection

| Authors | Study design | Sample size | Biomarker | Dose | Result* | Mean or range of age (yr) | Target |
|---|---|---|---|---|---|---|---|
| Baktash et al. (2020) [7] | Cohort | 70 (66.7%), COVID-19-positive group<br>35 (33.3%), COVID-19-negative group | 25(OH)D | - | + | 81 (79.46–81.16) | COVID-19 |
| D'Avolio et al. (2020) [8] | Cohort | 107, patients who underwent a nasopharyngeal swab PCR analysis for SARS-CoV-2 and a 25(OH)D measurement | 25(OH)D | - | + | 73 | COVID-19 |
| Meltzer et al. (2020) [9] | Cohort | 489, patients with a 25-hydroxycholecalciferol or 1,25-dihydroxycholecalciferol level measured within 1 year before being tested for COVID-19 from March 3 to April 10, 2020 | 25(OH)D or 1,25(OH)$_2$D | - | + | 49.2 | COVID-19 |
| Cereda et al. (2021) [10] | Cohort | 129, consecutive adult COVID-19 patients hospitalized | 25(OH)D | - | + | 73.6 ± 13.9 | COVID-19 |
| Gavioli et al. (2021) [11] | Cohort | 437, COVID-19 patients | 25(OH)D | - | – | 67 (56–79) | COVID-19 |
| Hastie et al. (2021) [12] | Cohort | 341,184, UK Biobank participants, of which 656 had inpatient confirmed COVID-19 infection and 203 died of COVID-19 infection | 25(OH)D | - | – | 37–73 | COVID-19 |
| Infante et al. (2021) [13] | Cohort | 137, consecutive patients with SARS-CoV-2 infection | 25(OH)D | - | + | 34–89 | COVID-19 |
| Lohia et al. (2021) [14] | Cohort | 270, patients with confirmed COVID-19 | Vitamin D | - | – | 63.81 ± 14.69 | COVID-19 |
| Orchard et al. (2021) [15] | Cohort | 50, SARS-CoV-2 PCR positive hospitalizations | Vitamin D | - | +/– | 60 (51.2–67.0) | COVID-19 |
| Osman et al. (2021) [16] | Cohort | 445, hospitalized patients | Vitamin D | - | + | 50.8 (15–94) | COVID-19 |
| Sabetta et al. (2010) [17] | Cohort | 198, healthy adults | 25(OH)D | - | + | 20–88 | Acute viral respiratory tract infections |
| Berry et al. (2011) [18] | Cohort | 6,789, participants in the nationwide 1958 British birth cohort | 25(OH)D | - | + | 45 | Respiratory infections and lung function |
| Brenner et al. (2020) [19] | Cohort | 9,940, recruited by their general practitioners during a routine health check-up between 2000 and 2002 | 25(OH)D | - | + | 50–75, 62.1 | Respiratory disease |
| Ling et al. (2020) [20] | Cross-sectional | 444, patients had symptoms and signs suggestive of SARS-CoV-2 infection | Cholecalciferol<br>Serum 25(OH) D | Approximately ≥ 280,000 IU in a time period of up to 7 wk) | +<br>– | 63–83 | COVID-19 |
| Abdollahi et al. (2021) [21] | Cross-sectional | 118, patients with COVID-19 who were hospitalized in ICU | 25(OH)D | - | + | 65.05 ± 15.75 | COVID-19 |
| De Smet et al. (2021) [22] | Cross-sectional | 186, severe acute respiratory syndrome coronavirus 2 infected individuals hospitalized | 25(OH)D | - | Male, +<br>Female, – | 52–80 | COVID-19 |
| Katz et al. (2021) [23] | Cross-sectional | 884, patients positively diagnosed with COVID-19<br>31,950, patients had vitamin D deficiency<br>87, patients had both vitamin D deficiency and COVID-19 | Vitamin D | - | + | All ages | COVID-19 |
| Luo et al. (2021) [24] | Cross-sectional | 560, individuals who underwent the physical examination program<br>335, COVID-19 patients | 25(OH)D | - | + | Control, 49–60<br>COVID-19, 43–64 | COVID-19 |
| Nasiri et al. (2021) [25] | Cross-sectional | 329, confirmed cases of COVID-19 | Vitamin D | - | +/– | 64.7 ± 18.5 (15–99) | COVID-19 |
| Meoli et al. (2021) [26] | Cross-sectional | 735, adolescents enrolled during the compulsory military fitness-for-duty evaluation | 25(OH)D | - | – | 18–19 | COVID-19 |
| Pugach and Pugach (2021) [27] | Cross-sectional | 10 countries | 25(OH)D | - | + | 37.8–47.8 | COVID-19 |
| Yadav et al. (2021) [28] | Cross-sectional | 37 countries | Vitamin D | - | + | - | COVID-19 |

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**Table 1.** (Continued) Main characteristics of the articles evaluating the association between vitamin D and respiratory-related viral infection

| Authors | Study design | Sample size | Biomarker | Dose | Result* | Mean or range of age (yr) | Target |
|---|---|---|---|---|---|---|---|
| Pletz et al. (2014) [29] | Cross-sectional | 101, control<br>50, influenza<br>49, legionella<br>100, *Streptococcus pneumoniae* | 25(OH)D, 1,25(OH)$_2$D | - | –<br>+ | Control, 59.43<br>Influenza, 60.13<br>Legionella, 62.65<br>*Streptococcus pneumoniae*, 57.41 | Influenza<br>Legionella<br>*Streptococcus pneumoniae* |
| Rafiq et al. (2018) [30] | Cross-sectional | 6,138, participants in the NEO study | 25(OH)D | - | BMI > 30, + | 45–65 | Lung function, airway inflammation, common colds |
| Abdollahi et al. (2021) [31] | Case-control | 201, patients with coronavirus infection<br>201, controls | 25(OH)D | - | + | Case, 48<br>Control, 46.34 | COVID-19 |
| Al-Daghri et al. (2021) [32] | Case-control | 138, RT-PCR-confirmed SARS-CoV-2 positive<br>82, negative controls | 25(OH)D | - | + | 43 ± 15 | COVID-19 |
| Alguwaihes et al. (2021) [33] | Case-control | 150, SARS-CoV-2 (+)<br>72, SARS-CoV-2 (–) | 25(OH)D | - | + | 56.6 ± 16.2 | COVID-19 |
| Hernández et al. (2021) [34] | Case-control | 197, COVID-19 with confirmed COVID-19, COVID-19 patients on oral vitamin D supplements for more than 3 mon, 197 control | 25(OH)D | Cholecalciferol, 25,000 IU/monthly in 10 cases, 5,600 IU/weekly in 1, and calcifediol 0.266 mg/monthly in 8 patients were on | + | COVID-19 patients, 61 (47.5–70.0)<br>COVID-19 patients + vitamin D supplementation, 60 (59.0–75.0)<br>Controls, 61 (56.0–66.0) | COVID-19 |
| Ye et al. (2021) [35] | Case-control | 80, healthy controls and 62 patients diagnosed with COVID-19 | 25(OH)D | - | + | Control, 42 (31–52)<br>Case 43, (32–59) | COVID-19 |
| Nanri et al. (2017) [36] | Case-control | 179, cases who reported influenza diagnosis<br>353, participants who did not reported influenza diagnosis | 25(OH)D | - | – | 37.6 ± 11.6 | Influenza |
| Rastogi et al. (2020) [37] | RCT | 16, vitamin D supplementation group<br>24, control group for asymptomatic and mildly symptomatic SARS-CoV-2 positive individuals | 25 (OH)D | 60,000 IU/day, 7 day | + | Intervention group, 50<br>Control group, 47.5 | COVID-19 |
| Ohaegbulam et al. (2020) [38] | RCT | 2, vitamin D-high dose<br>2, vitamin D-standard dose | Vitamin D | 1,000 IU cholecalciferol, 50,000 IU ergocalciferol, 1 mon | + | Vitamin D-high dose, 41, 57<br>Vitamin D-standard dose, 74, 53 | COVID-19 |
| Murai et al. (2021) [39] | RCT | 119, vitamin D$_3$ group<br>118, placebo group | Mortality rate | 200,000 IU, 4 mon | – | 200,000 IU of vitamin D$_3$ 56.5 or placebo 56 | COVID-19 |
| Rees et al. (2013) [40] | RCT | 399, vitamin D3 group<br>360, placebo group | Cold, influenza prevalence | Vitamin D$_3$ (1,000 IU/day) + Ca (1,200 mg/day) | – | Vitamin D3 group, 57.9<br>Placebo group, 57.8 | Upper respiratory tract |
| Aglipay et al. (2017) [41] | RCT | 354, vitamin D dose 400 IU/d<br>349, vitamin D dose 2,000 IU/d | No. of subjects | Vitamin D 400 IU/d or 2,000 IU/d, 4 mon | – | Vitamin D dose 400 IU/d, 2.76<br>Vitamin D dose 2,000 IU/d, 2.70 | Viral upper respiratory tract infections |
| Shimizu et al. (2018) [42] | RCT | 105, placebo group<br>110, 25(OH)D group | 25(OH)D | 10 μg/, 16 wk | Prevalence, –<br>Duration, + | Placebo, 52.6 ± 6.7<br>25(OH)D group, 52.8 ± 6.2 | Upper respiratory tract infection |
| Loeb et al. (2019) [43] | RCT | 650, vitamin D group<br>650, placebo group | 25(OH)D | 14,000 U/wk, 8 mon | – | Vitamin D, 8.6<br>Placebo, 8.4 | Respiratory infections |
| Urashima et al. (2014) [44] | RCT | 148, vitamin D3 group<br>99, placebo group | Influenza A prevalence | 2,000 IU/day, 2 mon | – | - | Influenza A |
| Zhou et al. (2018) [45] | RCT | 168, low dose vitamin D<br>164, high dose vitamin D | Person infected with influenza A | 400 IU or 1,200 IU, 4 mon | + | Low dose vitamin D, 7.7 ± 2.5<br>High dose vitamin D, 8.0 ± 2.7 | Seasonal influenza A |

COVID-19, coronavirus disease 2019; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; 25(OH)D, 25-hydroxyvitamin D; ICU, intensive care unit; NEO, Netherlands Epidemiology of Obesity; BMI, body mass index; RT-PCR, reverse transcription polymerase chain reaction; RCT, randomized control trial.

*+: significant effect on the prevention of respiratory-related viral infection; –: no significant effect on the prevention of respiratory-related viral infection.

**Table 2.** Main characteristics of included article evaluated the association between vitamin E and respiratory-related viral infection

| Authors | Study design | Sample size | Biomarker | Dose | Result* | Mean or range of age (yr) | Target |
|---|---|---|---|---|---|---|---|
| Meydani et al. (2004) [46] | RCT | 70 (66.7%), COVID-19-positive group<br>35 (33.3%), COVID-19-negative group | Incidence, No. of subjects and No. of days with respiratory infections (upper and lower), and No. of new antibiotic prescriptions | Vitamin E 200 IU | + | Vitamin E, 84.7 or placebo, 84.3 | Respiratory infection |

COVID-19, coronavirus disease 2019.
*+: significant effect on the prevention of respiratory-related viral infection; –: no significant effect on the prevention of respiratory-related viral infection.

**Table 3.** Main characteristics of included article evaluated the association between VC and respiratory-related viral infection

| Authors | Study design | Sample size | Biomarker | Dose | Result* | Mean or range of age (yr) | Target |
|---|---|---|---|---|---|---|---|
| Xing et al. (2021) [47] | Cross-sectional | 25, COVID-19 patients treated with VC<br>6, COVID-19 patients<br>51, healthy volunteers | VC | Patients with COVID-19: IV VC at a dose of 100 mg/kg/day | + | Patients treated with VC (n = 39)<br>Patients treated without VC (n = 35.63),<br>Healthy (n = 31.42) | COVID-19 |
| Zhao et al. (2021) [48] | Cross-sectional | 6, severe<br>6, critical | Inflammatory response, immune | Severe, 162.7 mg/kg/days<br>Critical, 178.6 mg/kg/days | + | Severe, 56 Critical, 63 | COVID-19 |
| Zhao et al. (2021) [49] | Cross-sectional | 55, HDIVC group<br>55, control group | No. of patients, duration of systemic inflammatory response syndrome | 100 mg/kg/day | – | HDIVC, 36<br>Control, 36 | COVID-19 |
| Zhang et al. (2021) [50] | RCT | 27, severe SARS-CoV-2-related pneumonia. HDIVC group<br>29, placebo group | Mortality, P/F ratio, IL-6 | IV VC 24 g | + | HDIVC, 66.7<br>Control, 66.3 | COVID-19 |
| Thomas et al. (2021) [51] | RCT | 50, usual care<br>48, ascorbic acid<br>58, zinc gluconate<br>58, ascorbic acid + zinc gluconate | 50% reduction in symptoms | Ascorbic acid 8,000 mg, Zinc gluconate 50 mg, Ascorbic acid 8,000 mg + Zinc gluconate 50 mg | – | 45.2<br>Standard of care, 42.0<br>Ascorbic acid only, 45.6<br>Zinc only, 44.1<br>Ascorbic acid with zinc, 48.7 | COVID-19 |
| Kumari et al. (2020) [52] | RCT | 75, intervention (standard of care + IV VC)<br>75, placebo (standard of care) | No. of days required for treatment, hospital stay | VC 50 mg/kg/day | + | Intervention, 52<br>Placebo, 53 | COVID-19 |
| Audera et al. (2001) [53] | RCT | 42, VC 0.03 g<br>47, VC 1 g<br>50, VC3 g<br>45, VC 3 g + additives | Daily symptoms, severity | VC 0.03 g<br>VC 1 g<br>VC 3 g<br>VC 3 g + bioflavenoids 75 mg, rutin 150 mg, hisperidin 150 mg, rose hip extract 750 mg acerola 150 mg | – | VC 0.03 g, 38.6<br>VC 1 g, 40.1<br>VC 3 g, 39.9<br>VC 3 g + additives, 45.1 | Common cold |
| Van Straten and Josling (2002) [54] | RCT | 84, active treatment<br>84, placebo | Recorded any common cold infections and symptoms in a daily diary | VC 500 mg | + | Active treatment, 47.7<br>Placebo, 48.5 | Common cold |
| Sasazuki et al. (2006) [55] | RCT | 120, 50 mg of VC<br>144, 500 mg of VC | Symptom, cold duration | VC 50/500 mg | – | Low dose, 58.7<br>High dose, 56.3 | Common cold |
| Johnston et al. (2014) [56] | RCT | 15, VC<br>13, placebo | Plasma vitamin, cold episodes, duration, cold duration and severity | VC 1,000 mg | + | VC, 23.0<br>Placebo, 23.2 | Cold incidence |
| Kim et al. (2020) [57] | RCT | 695, VC group<br>749, placebo group | Diagnosis of common colds | VC 6,000 mg | + | < 19, 491<br>20–22, 878<br>> 23, 75 | Common cold |

IV, intravenous; VC, vitamin C; COVID-19, coronavirus disease 2019; HDIVC, high-dose intravenous vitamin C; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; P/F, $PaO_2/FiO_2$; IL, interleukin; RCT, randomized control trial.
*+: significant effect on the prevention of respiratory-related viral infection; –: no significant effect on the prevention of respiratory-related viral infection.

Table 4. Main characteristics of included article evaluated the association between folate and respiratory-related viral infection

| Authors | Study design | Sample size | Biomarker | Dose | Result* | Mean or range of age (yr) | Target |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Acosta-Elias and Espinosa-Tanguma (2020) [58] | Cross-sectional | 94, pregnant women<br>137, non-pregnant in 2009 A-H1N1 pandemic<br>908 of those patients were non-pregnant women in reproductive age<br>55, pregnant women in COVID-19 pandemic | The likelihood of requiring hospitalization for SARS-CoV-2 infection | - | + | - | COVID-19<br>A-H1N1 pandemic |
| Hamer et al. (2009) [59] | Cross-sectional | 352 | Vitamins and minerals concentration | - | + | Men, 75.8<br>Women, 73.7 | Respiratory infections |
| Itelman et al. (2020) [60] | Cohort | 162 | Blood folate concentration | - | + | 52 | COVID-19 |

COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
*+: significant effect on the prevention of respiratory-related viral infection; −: no significant effect on the prevention of respiratory-related viral infection.

shortened hospital stays and reduced inflammatory biomarkers [37]. Of the 16 subjects who consumed 60,000 IU/d of vitamin D for 7 days, 10 tested negative for COVID-19, and only 5 of the 24 subjects who did not take vitamin D tested negative for COVID-19 [37]. However, 9 studies reported that vitamin D had no significant effect on COVID-19 prevention. Among the 12 studies related to respiratory diseases, 5 studies reported that vitamin D had a significant effect on the prevention of respiratory diseases. Serum 25(OH)D concentrations above 38 ng/mL lowered the risk of developing acute viral respiratory infections by about half [17], and mortality from respiratory diseases increased significantly as 25(OH)D levels fell below 50 nmol/L [19]. The group that consumed 1,200 IU of vitamin D for 4 months (8.0 ± 2.7 years) had a significantly lower number of influenza A infections than the group that consumed 400 IU (7.7 ± 2.5 years) [45].

Vitamin E has not been studied for its effect on COVID-19, and only one study was related to respiratory infections. The number of respiratory infections was significantly lower in the vitamin E intake group (200 IU, 84.7 years) than in the vitamin E non-intake group (84.3 years) [46].

Vitamin C reduced COVID-19-positive diagnoses in 4 out of 6 studies involving COVID-19. The vitamin C concentration in the plasma of COVID-19 patients was 5 times lower than that of healthy people ($p < 0.001$) [47], and C-reactive protein levels were significantly reduced when 162.7–178.6 mg/kg/day of vitamin C was consumed ($p < 0.05$), and lymphocyte counts, CD4+ T-cells, and respiratory function were significantly increased ($p < 0.05$) [48]. The intravenous administration of 24 g of vitamin C reduced COVID-19-induced mortality and interleukin-6 ($p = 0.04$) levels [50], an inflammatory index. The duration of symptoms and duration of hospitalization were significantly reduced when 50 mg/kg/day of vitamin C was supplied in the same way ($p < 0.001$) [52]. In the studies on vitamin C and colds, 3 out of 5 studies showed the effect of reducing the cold diagnosis rate and the duration of cold symptoms by a vitamin C intake of 500–6,000 mg [54,56,57].

Two studies related to folate and COVID-19 found that folate had a positive effect on COVID-19 prevention. Folate supplementation was a factor in protecting patients from COVID-19 infection [58]. The reason is that folate inhibits furin protease, which is necessary for viruses to enter host cells, and folate inactivates protease 3C-like protease, a protein that the virus needs to replicate [58]. Indeed, it has been reported that blood folate levels were low in patients with severe COVID-19 ($p = 0.014$) [60]. A study related to folate and respiratory infections also reported that a deficiency in micronutrients, such as folate, was closely related to the occurrence of pneumonia or cold ($p < 0.001$) [59]. In this study, no publications on the relationship between vitamins and SARS/MERS were found during the study period.

Thus, the results of this study found that maintaining normal blood levels of vitamin D, vitamin E, vitamin C, and folate had a positive effect on the prevention of COVID-19/cold/influenza. This effect is thought to be possible by maintaining normal blood levels through the daily intake of these nutrients. However, due to the limited period of this study, additional research publications related to these vitamins and COVID-19/SARS/MERS/cold/influenza will need to be collected, analyzed and evaluated periodically in the future.

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