

SPECIAL ISSUE REVIEW

Examining the role of micronutrients on improving long COVID sleep-related symptoms

Victoria M. Pak PhD, MS, MTR, FAAN, Assistant Professor^{1,2}  | Jiyun Lee Research Assistant³

¹Emory Nell Hodgson Woodruff School of Nursing, Atlanta, Georgia, USA

²Department of Epidemiology, Emory Rollins School of Public Health, Atlanta, Georgia, USA

³Emory University-College of Arts and Sciences, Atlanta, Georgia, USA

Correspondence

Victoria M. Pak, Emory University, 1520 Clifton Road, Room 243, Atlanta, GA 30322, USA.

Email: victoria.m.pak@emory.edu

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Abstract

Aims and Objectives: Long COVID is defined as the continuation of symptoms for four or more weeks after initial contraction of the virus. This review article examines the role of four select micronutrients (zinc, vitamins C, D and polyphenols) for their anti-inflammatory and therapeutic potential to improve sleep-related symptoms in persons with long COVID.

Background: Evidence suggests a link between long COVID and increased inflammation. There are currently no therapeutic interventions for common sleep-related symptoms associated with long COVID. Micronutrients, due to their antioxidant and anti-inflammatory properties, may have a role in the treatment of sleep-related symptoms in the context of long COVID.

Design: A narrative literature review was conducted and guided by the PRISMA checklist.

Methods: All articles were screened from PubMed, ScienceDirect, NCBI or Google Scholar and were limited to human studies. The following keywords were used: 'COVID-19', 'sleep symptoms', 'zinc', 'vitamin C', 'vitamin D', 'polyphenols' and 'micronutrients'.

Results: There are currently no studies that examine the usage of micronutrients and its impacts on long-term, sleep-related symptoms post-COVID-19 infection. We focussed our review on prior studies that examined micronutrients in the context of sleep symptoms and inflammation, while exploring the potential for micronutrients to help improve sleep-related symptoms associated with long COVID.

Conclusions: There is evidence to suggest that sleep-related symptoms associated with long COVID, such as fatigue and poor sleep quality, are associated with inflammation. Zinc, vitamins C, D and polyphenols all have the potential to improve both inflammation and sleep quality to alleviate symptoms. Future research should further examine these micronutrients in the context of long COVID to improve sleep and quality of life.

Relevance to Clinical Practice: This article provides implications for clinicians to be at the forefront of research on the usage of micronutrients to improve sleep-related symptoms in persons with long COVID.

KEYWORDS

COVID-19, micronutrients, polyphenols, sleep, vitamin C, vitamin D, zinc

1 | INTRODUCTION

'Long COVID' has been frequently used to describe the continuation of symptoms even after recovery from the SARS-CoV-2 virus (Mahase, 2020). The CDC defines this as symptoms lasting for more than four weeks after initial infection (Centers for Disease Control & Prevention, 2021). Although the recent development of vaccines is a grand step towards bringing this pandemic to an end, it has been reported that a considerable proportion of infected persons are still experiencing persistent symptoms, even after more than three and a half months post-discharge (Garrigues et al., 2020). Evidence suggests that a proportion of COVID survivors will continue to have health problems, such as breathing issues, muscle fatigue, mental health problems and difficulty performing everyday tasks (Mahase, 2020). Additionally, long-term, sleep-related symptoms have been especially prevalent in many cases, causing chronic fatigue and worsened sleep quality (Mandal et al., 2021).

Throughout this review, we present research from primary articles on four select micronutrients, namely zinc, vitamins C, D and polyphenols. We focused on these, as they have been studied in the context of improving inflammation and/or sleep and have potential utility in the management of long COVID symptoms. Zinc is an essential mineral that is found to improve sleep and has anti-inflammatory properties (Butters & Whitehouse, 2021; Cherasse et al., 2015). Vitamin C has been found to reduce fatigue in healthy populations (Suh et al., 2012). Vitamin D has anti-inflammatory properties and has been shown to reduce fatigue in vitamin D deficient, but otherwise healthy populations (Nowak et al., 2016). Higher intake of certain polyphenols may be associated with improved sleep quality in otherwise healthy adults (Godos et al., 2020).

In a systematic review of the prevalence of sleep problems during the pandemic, approximately 74.8% of those with COVID-19 have sleep-related problems (Jahrami et al., 2021). Common sleep-related issues may become longer term problems in COVID-19 patients even after recovery.

There are many similarities between long COVID symptoms and chronic fatigue syndrome (CFS) (Wong & Weitzer, 2021); thus, comparing these may give insight into the pathophysiology of sleep-related symptoms post-COVID-19. CFS is defined as persistent sleep difficulties with various symptoms, such as severe fatigue (Cortes Rivera et al., 2019). Long COVID symptoms have overlaps with the clinical presentation of myalgic encephalomyelitis (ME)/chronic fatigue syndrome (Wong & Weitzer, 2021). The pathophysiological mechanism of ME/CSF is not known, although it may trigger an increase in proinflammatory cytokines and diminished antioxidants (Cortes Rivera et al., 2019).

1.1 | Aims

Sleep symptoms are highly prevalent post-COVID-19, yet there is insufficient research assessing the application of micronutrients as treatment. This review proposes that zinc, vitamins C, D and

What does this paper contribute to the wider global clinical community?

- A large proportion of people infected with COVID-19 continue to have persistent sleep-related symptoms, which lead to a decrease in quality of life. Safe and effective treatment options to manage sleep-related COVID symptoms are needed.
- Underlying inflammation may be a mechanism of persistent sleep related symptoms of long COVID. Zinc, vitamins C, D and polyphenols have been shown in the literature to improve sleep and possess anti-inflammatory properties. These select micronutrients have the potential to decrease inflammation and improve sleep-related symptoms in persons with long COVID symptoms.
- Nurses can be at the forefront of this research to improve sleep-related long COVID symptoms. They can guide clinical trials to explore the potential of micronutrients to improve inflammation and sleep-related symptoms. Nurses are in a unique position to be at the forefront of this area of this research in order to improve sleep-related symptoms in persons with long COVID.

polyphenols could potentially improve long-term sleep-related symptoms, in individuals with past COVID-19 infection.

2 | METHODS

A narrative literature review guided by the PRISMA checklist (File S1) was conducted. The articles were screened from PubMed, ScienceDirect, NCBI and Google Scholar. Our searches were related to three main concepts: micronutrients, sleep-related symptoms and long COVID. Key search terms included 'COVID-19', 'long-term sleep symptoms', 'zinc', 'vitamin C', 'vitamin D', 'polyphenols' and 'micronutrients'. The general criteria for inclusion of data were current, human studies that discuss mechanisms for long COVID and micronutrient usage on sleep-related symptoms. Each micronutrient was searched along with the keywords, 'COVID-19' and/or 'sleep' to find the most relevant primary data studies based on our inclusion criteria.

3 | RESULTS

There are no studies that examine the effects of micronutrient supplementation in, specifically, sleep-related symptoms post-COVID-19. Of the existing studies examined in this review, one article discusses zinc deficiency among COVID patients, while five articles provide information on zinc to relieve sleep symptoms in

other populations. Three other articles provide information on vitamin C's potential to reduce fatigue. Two sources focus on vitamin D reducing fatigue in general populations and another two in vitamin D-deficient COVID patients. Moreover, three sources examine polyphenol supplementation to reduce inflammation and sleep-related symptoms in CFS patients and healthy adults. See [Figure 1](#).

3.1 | Common lingering symptoms of COVID-19

Approximately 67% of participants in a study by Taboada et al., 2021 reported a decreased quality of life six months after ICU discharge due to persistent symptoms (Taboada et al., 2021). As seen in [Table 1](#), multiple published articles have identified continuous symptoms that are experienced after infection of COVID-19.

Other commonly reported symptoms include difficulty concentrating, brain fog, and continuous fatigue (Ladds et al., 2020). Fatigue was an especially prevalent, long-term symptom that was self-reported by 53.1% of 143 post-acute care COVID patients about two months after first COVID-19 symptom onset (Carfi et al., 2020). Fatigue was similarly reported in approximately 69% of 384 previously hospitalised patients after a median of 54 days post-discharge (Mandal et al., 2021). Moreover, individual narrative interviews found that, in several of the interviewees, fatigue, exhaustion and 'brain fog' limited their daily routines, where one participant noted that '[their] life is just nothing like it was and it's not really the life [they] want' (Ladds et al., 2020).

Studies in persons with suspected and confirmed COVID-19 have demonstrated the majority of subjects (>91%) had a time to recovery lasting over 35 weeks, with fatigue being one of the most prominent symptoms after 6 months (Davis et al., 2021). Another study showed that fatigue was reported by about 97.7% of participants with incident cases of COVID-19, and was most

commonly observed in those with symptoms persisting past 28 days (Sudre et al., 2020).

3.2 | Mechanisms underlying long-term sleep-related symptoms post-COVID-19

As COVID-19 is a new area of study, the mechanisms pertaining to the development of long-term symptoms are still unclear. It is possible that underlying inflammation is a key mechanism in causing persistent sleep-related symptoms. Mandal et al. (2021) studied 384 patients who were followed a median of 54 days post discharge and found that those that were discharged with elevated biomarkers, many cases had persistently elevated C-reactive protein (CRP) and d-dimer (Mandal et al., 2021). In fact, increased levels of CRP and d-dimer, are seemingly characteristic of infected persons due to systemic inflammation (Yael et al., 2020). Furthermore, 34%, 53% and 69% of participants reported coughing, breathlessness and fatigue respectively, and 38% of chest radiographs stayed abnormal and 9% deteriorated (Mandal et al., 2021). Inflammation may persist even 40–60 days after initial infection in asymptomatic and moderately affected patients (Doikov et al., 2020).

Alternatively, Crook et al. (2021) present other possible mechanisms of chronic fatigue in long COVID patients. In particular, cell-mediated immune responses and systemic inflammation have been hypothesized to cause hypometabolism in the frontal lobe and cerebellum, inducing fatigue (Crook et al., 2021). Whether this is related to long COVID remains unknown (Crook et al., 2021). It is important to note that fatigue could also be a result of psychological distress due to social isolation, fear and anxiety from the COVID-19 lockdown (Morgul et al., 2021). Based on results from the Fatigue Assessment Scale questionnaire, Morgul et al. (2021) found that 64.1% of 3672 healthy participants in Istanbul were experiencing

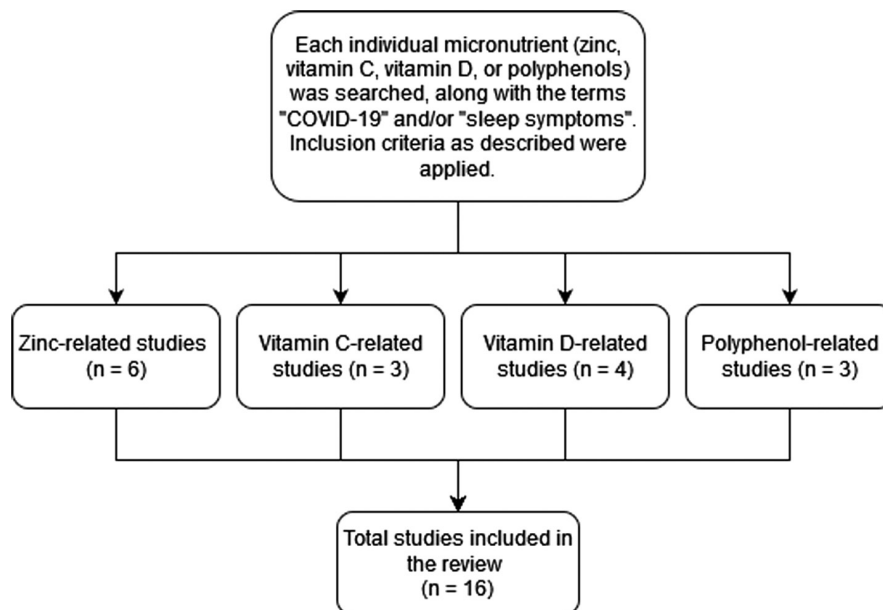


FIGURE 1 Illustrates our search process for the narrative literature review

TABLE 1 Primary articles reporting long-term symptoms of COVID-19

Author and Year	Type of study	Study population	Long-term symptoms	Timeline of the assessment of symptoms/outcomes
Carfi et al. (2020)	Cross-sectional study	143 patients who were discharged from the hospital after recovery from COVID-19	Fatigue (53.1%) Dyspnoea (43.4%) Joint pain (27.3%) Chest pain (21.7%)	The symptoms were assessed a mean of 60.3 (SD, 13.6) days after onset of the first COVID-19 symptom
Davis et al. (2021)	Cross-sectional study	3762 respondents with suspected or confirmed COVID-19 infection	Fatigue (86.7%) Decreased cognition or memory (88%) Relapses in symptoms due to physical/mental activity or stress (85.9%)	>91% of respondents took a time to recovery that exceeded 35 weeks
Garrigues et al. (2020)	Cross-sectional, study	120 patients	Fatigue (55%) Dyspnoea (42%) Memory Loss (34%) Problems concentrating (28%) Sleep disorders (30.8%)	Post-discharge persistent symptoms were assessed more than 100 days after their admission
Ladds et al. (2020)	Qualitative research design (Focus groups and individual interviews)	114 participants	Nerve issues, fatigue, exhaustion, 'brain fog', decreased ability for daily activities	NA
Mandal et al. (2021)	Cross-sectional study	384 patients followed a median 54 days post discharge	Fatigue (69%) Breathlessness (53%) Cough (34%) Depression (15%) 38% of chest radiographs stayed abnormal and 9% deteriorated	4–6 weeks post-discharge
Sudre et al. (2020)	Prospective observational cohort study	4,182 incident cases of COVID-19 were analyzed in which individuals self-reported their symptoms	Most commonly reported symptoms were the following: Fatigue (97.7%) and Intermittent headaches (91.2%)	Data gathered from COVID-19 infected persons using app from March 24–September 2, 2022
Taboada et al. (2021)	Cross-sectional study	91 participants previously admitted to COVID-19 ICU	Difficulty breathing (57%) Physical weakness (37%) Muscle pain (37%) Joint pain (29%) Moderately anxious or depressed (41.8%) Extremely anxious or depressed (4.4%)	6 months after ICU discharge

fatigue. Further research is necessary to clarify the mechanisms that give rise to long-term sleep-related COVID-19 symptoms.

3.3 | Zinc to reduce long-term sleep-related symptoms of COVID-19

Zinc may dose-dependently increase the total amount of nonrapid eye movement sleep and decrease locomotor activity (Cherasse et al., 2015). Zinc has been suggested to be a potential therapeutic for COVID-19 itself, as it promotes antiviral activity and inhibits the production of cytokines such as tumour necrosis factor-alpha and IL-1beta (Butters & Whitehouse, 2021).

Saito et al. (2017) administered zinc supplementation in the form of oysters and yeast extracts, both containing rich amounts

of dietary zinc. A double-blinded experiment was conducted with 120 healthy patients who were randomly assigned to a placebo or a zinc-rich group and measured sleep using an actigraphy sleep monitor for 12 weeks (Saito et al., 2017). The zinc-rich food group had decreased time needed to fall asleep and improved sleep efficiency compared with the placebo group, and the group that ingested zinc-enriched yeast and astaxanthin oil showed improved sleep onset latency (Saito et al., 2017). A nutritional survey administered to 5587 random participants in the general US population found that zinc deficiency was associated with short sleep duration of less than five hours of sleep per night, after adjustment for overall diet (Grandner et al., 2013). Moreover, when zinc sulphate capsules were administered to 54 ICU nurses, they reported improved sleep quality after one month (Gholipour Baradari et al., 2018). Significantly increasing zinc concentrations can aid

in improving sleep latency and sleep efficiency (Saito et al., 2017). While these previous studies were not conducted in COVID-19 patients, the mechanisms underlying sleep-related issues appear to be associated with inflammation. Administering select micronutrients may help to target this pathway and improve symptoms.

Greater serum zinc concentrations are negatively associated with the severity of fatigue and depression in CFS, such that decreased zinc causes more severe CFS (Maes et al., 2006). The FibroFatigue scale was used to assess the severity of CFS symptoms, measuring items such as fatigue symptoms, muscular pain and concentration (Maes et al., 2006). It has also been noted that CFS patients had higher oxidative stress in accordance with lower serum zinc levels (Maes et al., 2006). These studies further support the potential for zinc to improve sleep-related long COVID symptoms. It is important that future studies explore this even further, as previous articles have suggested the high likelihood of COVID patients developing CFS in the future.

In one particular double-blind, randomised study in fifteen hospitalized COVID-19 patients, it was observed that hospitalized COVID-19 patients showed a zinc deficiency, which was corrected when given high-dose intravenous zinc (Patel et al., 2021). This study demonstrated that COVID-19 patients appear to have zinc deficiency and that treatment to reverse this appears safe and feasible (Patel et al., 2021)

3.4 | Antioxidants to reduce long-term sleep-related symptoms of COVID-19

Many observations have led to the conclusion that COVID-19 is associated with a substantial increase in cytokines, suggesting that infected persons are at the risk of increased systemic inflammation (Mazza et al., 2021). Thus, increased inflammation may be related to these persistent long COVID symptoms.

3.5 | Vitamin C

Prior studies have examined the effect of vitamin C on fatigue (Jung et al., 2006; Ou et al., 2020; Suh et al., 2012), although none have examined this in the context of COVID-19. As previously demonstrated by Mandal et al. (2021), long COVID is sometimes characterised by elevated CRP and d-dimer levels. An imbalance of essential micronutrients could be an underlying cause of constant fatigue after initial infection. Recent studies have found that COVID-19 and lung cancer have similar biological pathways that suggest a comparable relationship between the two diseases (Nan et al., 2021). Specifically, Nan et al. (2021) discovered ten similar genes involved in cellular communication, as well as common biological pathways, such as IL-17 (pro-inflammatory) signalling. Ou et al. (2020) also examined the use of intravenous vitamin C for a median follow-up of 24 months to help treat lung cancer patients. While the symptoms in the control arm worsened with time, the group that was administered 1 g/kg per day

of intravenous vitamin C concurrent with modulated electrohyperthermia (mEHT) reported significantly decreased patient-reported fatigue post-treatment (Ou et al., 2020). Additionally, Suh et al. (2012) performed a randomised clinical trial to determine whether the administration of intravenous vitamin C would reduce fatigue in healthy office workers. Not only did fatigue scores reported by the experimental group decrease after one day, but oxidative stress levels decreased on average as well, measured by the Free Oxygen Radicals Test (Suh et al., 2012). Another study explored vitamin C treatment in nineteen patients with fatigue and noted a significantly decrease in fatigue score after four weeks (Jung et al., 2006). Based on these studies, vitamin C has anti-inflammatory properties that may potentially help to address persistent fatigue in persons post-COVID-19.

3.6 | Vitamin D

Vitamin D is another essential micronutrient where deficiency is likely to result in impaired cognitive performance and fatigue (Nowak et al., 2016). Nowak et al. suggested that the regulation of dopamine levels by vitamin D receptors in the brain can help to combat central fatigue (Nowak et al., 2016); thus, vitamin D supplementation may be beneficial for those with fatigue associated long COVID.

Vitamin D deficiency is common in persons infected by COVID-19, as 82% of 216 patients from Spain were deficient compared to 47.2% of the control group of 197 healthy individuals (Hernández et al., 2021). Additionally, Demir et al. found vitamin D levels were less than sufficient (<30 ng/mL) in approximately 92% of 227 persons infected with COVID-19. Furthermore, COVID-19 patients with sufficient (>30 ng/ml) vitamin D levels had lower risk of contracting COVID, shorter hospital stay duration, and considerably lower serum levels of CRP and d-dimer than patients with insufficient levels (Demir et al., 2021).

Zhang et al. (2012) also determined that vitamin D inhibits the production of proinflammatory cytokines. A double-blinded clinical trial examined the impact of vitamin D on 120 vitamin D deficient, but otherwise healthy adults with self-reported fatigue (Nowak et al., 2016). At a follow-up of four weeks after baseline testing, the experimental group that received 100,000 IU of vitamin D experienced improved Fatigue Assessment Scale (FAS) scores and increased serum vitamin D levels compared to placebo (Nowak et al., 2016). While not yet studied in the context of COVID-19 patients and long-term sleep-related symptoms, the results demonstrate the use of vitamin D as an effective antioxidant to potentially reduce inflammation and improve fatigue symptoms.

3.7 | Polyphenols

Certain food-derived micronutrients may also mitigate the severity of COVID-19. Polyphenols, namely curcumin, have antioxidant properties that counters inflammation (Kowluru & Kanwar, 2007).

Kowluru and Kanwar, 2007 found that curcumin lowered proinflammatory marker levels and prevented increases in oxidative stress in diabetic rats (Kowluru & Kanwar, 2007). It is possible that changing diets to include more micronutrients could ultimately reduce long-term sleep-related symptoms. Dark chocolate is especially high in polyphenols, specifically various flavonoids which have been found to reduce mortality rates from heart disease, cancer and stroke (Sathyapalan et al., 2010). A double-blind, randomised, clinical pilot study by Sathyapalan et al. (2010) compared the effects of high cocoa liquor/polyphenol rich chocolate with simulated iso-caloric chocolate on fatigue and residual function in ten patients with CFS. Those consuming the 15 g of polyphenol-rich chocolate for eight weeks demonstrated a significant improvement in their fatigue measured by the Chalder Fatigue Scale score (Sathyapalan et al., 2010). Another study reviewed the diets of 1936 adults in southern Italy and showed a relationship between higher dietary intake of certain polyphenols and better sleep quality, assessed using the Pittsburgh Sleep Quality Index (Godos et al., 2020). Subjects who consumed more foods with flavonoid subclasses (flavanones and flavones), phenolic acids (such as hydroxycinnamic acids) and consumed lignans were less likely to have inadequate sleep quality (Godos et al., 2020). It is possible that increasing certain polyphenol intake may help to alleviate sleep-related symptoms of long COVID.

4 | DISCUSSION

Persistent COVID-19 sleep-related symptoms may be associated with increased inflammation. See Figure 2. There are currently no primary data studies that examine micronutrients in the context of sleep-related symptoms, specifically in relation to COVID-19. We have compiled prior research examining select micronutrients in disease states and the general population to show the potential for micronutrients to improve sleep-related symptoms post-COVID-19 infection. Table 2 presents the 16 scholarly articles used in our review to determine how the four aforementioned micronutrients may aid in alleviating long-term symptoms of COVID-19 by targeting inflammation and improving sleep. Six research articles discussed

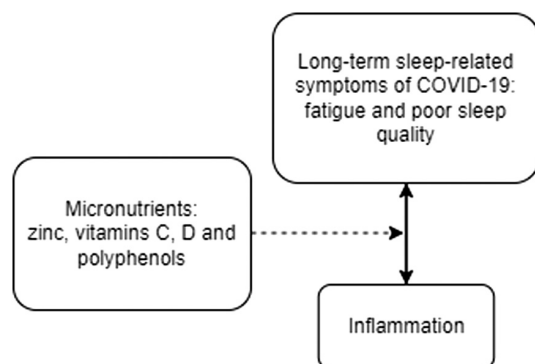


FIGURE 2 Illustrates the connection between inflammation and long-term sleep-related symptoms associated with COVID-19 and the potential use of certain micronutrients to manage symptoms

the connections related to zinc intake and either inflammation and/or sleep (Cherasse et al., 2015; Gholipour Baradari et al., 2018; Grandner et al., 2013; Maes et al., 2006; Patel et al., 2021; Saito et al., 2017). Ou et al. (2020) and Suh et al. (2012) performed trials with vitamin C on lung cancer patients and healthy office workers respectively and discovered reduced fatigue associated with supplementation. Moreover, Jung et al. observed a decrease in fatigue scores after four weeks of treatment with intravenous vitamin C (Jung et al., 2006). Additionally, COVID-19 patients with vitamin D deficiency have shown elevated d-dimer and CRP levels (Hernández et al., 2021). Persons with adequate Vitamin D levels >30 ng/ml have significantly lower d-dimer and CRP levels (Demir et al., 2021). Vitamin D also inhibits cytokine production (Zhang et al., 2012). Lastly, certain polyphenols may improve symptoms in persons with CSF (Sathyapalan et al., 2010) and higher intake may be associated with better sleep quality (Godos et al., 2020).

In infected persons months after initial infection of COVID-19, long COVID causes persistent muscle pain, weakness and fatigue, and has symptoms that are similar to CFS (Wong & Weitzer, 2021). Studies show improved CFS symptoms with vitamin C (Vollbracht & Kraft, 2021) and polyphenol-rich chocolate (Sathyapalan et al., 2010) supplementation. Thus, supplementation with these micronutrients may help to improve long-term fatigue symptoms of COVID-19.

To alleviate long-term sleep-related issues in those previously infected by SARS-CoV-2, vitamins C, D, zinc and certain polyphenols may serve to be beneficial. In particular, zinc is an essential mineral that has been linked to improved sleep related measures (Cherasse et al., 2015; Gholipour Baradari et al., 2018; Saito et al., 2017). Vitamins C and D may reduce fatigue (Nowak et al., 2016; Suh et al., 2012). The research discussed within this manuscript is important to consider as we take the next steps forward in improving quality of life for long COVID patients with sleep-related symptoms. Fatigue is one of the most common persistent symptoms term after contracting COVID-19 (Carfi et al., 2020); thus, administration of these micronutrients may serve as a safe and low-risk treatment option.

5 | CONCLUSION

It is important to consider the aforementioned select micronutrients as a low-risk supplement treatment for those with long-term sleep-related symptoms due to COVID-19. Micronutrients have the potential to target these symptoms via their effects on inflammation. Furthermore, they may improve quality of life and help to manage long-term sleep-related symptoms. Subsequent research should examine which micronutrients will mitigate long-term sleep-related symptoms. There is a need for double-blind placebo-controlled randomised trial designs in this area in order to more robustly examine the effect of supplementation on sleep-related symptoms. Nurses can play an important role in conducting clinical trials that consider novel combinations of micronutrients on long-term sleep-related symptoms of COVID-19 infection.

TABLE 2 Primary articles relating to COVID-19 and micronutrients, sleep and micronutrients, or inflammation and micronutrients

Author and Year	Micronutrient	Study design	Study population	Result	Length of follow-up period
<i>COVID-related articles</i>					
Patel et al. (2021)	Zinc	Double-blinded, randomized controlled trial	15 participants received IV zinc, 18 patients received placebo	COVID-19 patients showed zinc deficiency which appears to be corrected with high dose IV zinc	Maximum of 7 days, until hospital discharge or death
Demir et al. (2021)	Vitamin D	Retrospective cohort study	227 COVID-positive patients, 260 negative	Low vitamin D levels (<30 ng/ml) in 94.27% of COVID-positive patients. Severe vitamin deficiency (<10 ng/ml) more common in COVID-positive participants (44%); The group of COVID-19 positive patients with vitamin D levels >30 ng/mL showed lower CRP and d-dimer levels	N/A
Hernández et al. (2021)	Vitamin D	Retrospective case-control study	216 COVID patients (with 19 on vitamin D supplements), 197 participants in control group	82.2% of COVID-positive participants had vitamin D deficiency. Serum 25OHD levels were lower in hospitalized COVID-19 patients compared with population controls	N/A
<i>Sleep-related or CSF articles</i>					
Cherasse et al. (2015)	Zinc	Experimental study	Mice administered zinc-containing yeast	Increased NREM sleep and decreased locomotor activity	Locomotor activity tracked each hour after yeast administration, time spent in REM, NREM, and wakefulness tracked 4 hours after yeast administration
Gholipour Baradari et al. (2018)	Zinc	Double-blinded, randomised controlled trial	54 ICU nurses; 27 receiving zinc sulphate capsules, 26 placebo	Sleep quality (measured using Pittsburgh Sleep Quality Index), sleep latency, and serum zinc concentrations improved with zinc supplementation	1 month
Grandner et al. (2013)	Zinc	Observational study	5587 participants	Less than 5 hours of sleep was associated with decreased mineral intake, after adjustment for overall diet	N/A
Maes et al. (2006)	Zinc	Observational study	CFS patients and normal participants	Decreased serum zinc concentrations and increased inflammatory markers/oxidative stress in CFS patients	N/A
Saito et al. (2017)	Zinc	Double-blinded, randomised, controlled, parallel-group trial	120 healthy subjects randomly assigned placebo or zinc-rich group	The zinc-rich food group decreased the time needed to fall asleep and demonstrated improved sleep efficiency. The group that was given zinc-enriched yeast and astaxanthin oil showed significantly improved sleep onset latency.	12 weeks

(Continues)

TABLE 2 (Continued)

Author and Year	Micronutrient	Study design	Study population	Result	Length of follow-up period
Jung et al. (2006)	Vitamin C	Experimental study	19 patients who reported consistent fatigue, measured before and after IV vitamin C treatment	Decreased fatigue scores after IV vitamin C administration	4 weeks of treatment, then follow-up questionnaire
Suh et al. (2012)	Vitamin C	Double-blinded, randomised, controlled clinical trial	141 healthy volunteers	IV vitamin C decreased fatigue 2 hours post-administration and until next day	Two hours after vitamin C administration, and follow-up one day after
Nowak et al. (2016)	Vitamin D	Double-blind placebo-controlled clinical trial	120 vitamin D-deficient individuals with fatigue; randomised into placebo or vitamin D supplement groups	Decreased fatigue assessment scores in vitamin D group	4 weeks post-vitamin D supplementation
Godos et al. (2020)	Polyphenols	Observational study	1936 participants	Increased polyphenols in the diet is associated with improved sleep quality (measured using Pittsburgh Sleep Quality index)	N/A
Sathyapalan et al. (2010)	Polyphenols (flavonoids)	Double-blinded, randomised, clinical pilot crossover study	Ten CFS patients	Reduced CFS symptoms associated with high-polyphenol chocolate administration	8 weeks of high-polyphenol or low-polyphenol chocolate, then 2 weeks of no treatment; another 8 weeks with other type of chocolate
<i>Inflammation-related articles</i>					
Ou et al. (2020)	Vitamin C	Phase II clinical trial	Total of 97 lung cancer patients receiving intravenous vitamin C, 48 control	Increase in progression-free survival and overall survival with IV vitamin C combined with modulated electrohyperthermia (mEHT) compared to best supportive care alone. Fatigue was decreased significantly between groups post treatment	Follow-up after a median of 24 months
Zhang et al. (2012)	Vitamin D	Experimental study	Blood samples from healthy volunteers and mice	Vitamin D inhibits monocyte/macrophage proinflammatory cytokine production	N/A
Kowluru and Kanwar (2007)	Polyphenols (curcumin)	Controlled, experimental study	Diabetic rats receiving curcumin or placebo diet	A curcumin diet is associated with decreased diabetes-induced pro-inflammatory marker levels	6 weeks

6 | RELEVANCE TO CLINICAL PRACTICE

This review considers the potential use of micronutrients as a low-risk treatment option for persistent sleep-related symptoms of COVID-19. Nurses are in a unique position to be at the forefront of this area of research and can lead to studies examining the impact of supplements on long-term sleep-related symptoms to improve the quality of care within this population.

ACKNOWLEDGEMENT

N/A.

CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are openly available on PubMed, Science Direct, NCBI or Google Scholar.

ORCID

Victoria M. Pak  <https://orcid.org/0000-0002-4081-8347>

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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