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RESEARCH ARTICLE

Associations between self-reported symptoms of SARS-CoV-2 and dietary supplement use over the previous year during the first pandemic wave

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Abstract

During the initial wave of the COVID-19 pandemic, symptoms of infection varied widely among adults younger than 60 years. This cross-sectional investigation of adults ages 18–59 years explored associations between SARS-CoV-2 symptomatology and supplementation of micronutrients involved in immune function, such as multivitamins, vitamin D, vitamin C, vitamin E and zinc. Between August and December 2020, an online survey was completed by 287 respondents, averaging 33·3 ± 10·5 years, who recovered from SARS-CoV-2 infection within the previous 4 months. In regression models, intake of supplements over the previous year was not protective against number of symptoms or symptom severity. Despite higher rates of supplementation over the previous year, smokers experienced more symptoms and greater symptom severity than non-smokers. Micronutrient supplementation did not protect young adults from experiencing symptoms of SARS-CoV-2, but our results suggest that smoking cessation may be a more effective modifiable lifestyle factor.

Key words: **COVID-19: Vitamins dietary supplements: Young adults**

Introduction

The novel coronavirus disease of 2019 (COVID-19), caused by SARS-CoV-2 infection, was declared a global pandemic by the World Health Organization (WHO) in March 2020[1]. During the initial wave of the COVID-19 pandemic, older adults were identified as a vulnerable population at high risk for severe illness[2]. However, symptoms of SARS-CoV-2 infection varied widely among adults younger than 60 years. While some younger adults experienced severe illness, many had only mild symptoms, and as many as 40 % of infected persons remained asymptomatic[3].

Nutrient deficiencies can predispose people to respiratory illnesses and other infections[4,5]. Specific vitamins and minerals are important for immune function, and as COVID-19 will likely become endemic in many areas, the possible protective role of micronutrients is of great interest[6]. Vitamins D, C, E and zinc have garnered particular attention.

Vitamin D receptors are widespread in many tissues[7], including various immune cells[4] and epithelial cells of lung tissue[8]. Vitamin D stimulates production of antimicrobial peptides[9,10], and it may protect against overproduction of cytokines and the so-called cytokine storm[7,8]. Although studies examining vitamin D supplementation to treat COVID-19 infection have shown mixed results[6], low blood concentrations of 25-hydroxyvitamin D are associated with increased risk of infection[11] and more severe illness in those infected with SARS-CoV-2[6]. However, two large studies from Europe recently reported that prophylactic supplementation of vitamin D failed to prevent SARS-CoV-2 infection[12,13].

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Vitamin C is best known for antioxidant function, but it is also important for both innate and adaptive immunity[5]. Vitamin C helps maintain lung epithelium[10], and deficiency is associated with increased risk of respiratory infections[14]. Previous studies have shown that vitamin C supplementation may reduce the severity and duration of the common cold[4,5,9].

Vitamin E is a potent antioxidant. In particular, alpha-tocopherol protects cell membranes against lipid peroxidation[4]. Studies in animals have demonstrated the importance of vitamin E for regulation of both innate and adaptive immunity[8]. Although studies in humans are scarce, a few studies in older individuals suggest vitamin E supplementation may decrease the incidence of respiratory infections[5,8].

Zinc is a trace mineral important for both innate and acquired immune function[15]. Although excessive zinc may actually impair immunity[4], zinc deficiency is known to increase risk of respiratory infections[14,16]. Two studies reported that people with low zinc levels upon hospital admission had more severe COVID-19 symptoms[17,18].

All of these micronutrients are sold over the counter as dietary supplements in the United States[19]. In addition, multivitamin supplements provide a variety of vitamins and minerals in a single pill[20]. Considering the popularity of dietary supplements and the possible protective properties of the aforementioned micronutrients, the present study aimed to determine whether regular supplementation with a multivitamin, vitamin D, vitamin C, vitamin E or zinc during the year prior to SARS-CoV-2 infection was associated with symptoms of adults ages 18–59 during the first pandemic wave.

Methods

Respondents

Between August and December 2020, men and women who had recovered from SARS-CoV-2 infection within the previous 4 months completed an online survey. Inclusion criteria included age between 18 and 59 years and residence in the United States. Respondents were recruited from Amazon Mechanical Turk[21] and advertisements over social media. This study was conducted according to the guidelines laid down in the Declaration of Helsinki. All procedures involving human subjects were approved by the Institutional Review Board at the University of Alabama, and electronic informed consent was obtained from all respondents.

Survey instrument

An online Qualtrics survey was used for data collection. Content validity of the survey questions was assessed by two physicians, a nurse, a dietitian and a nurse/dietitian who were treating COVID-19 patients at that time. Face validity was verified by four adults who met the inclusion criteria of age 18–59 years[22,23].

The survey assessed whether or not respondents experienced common symptoms identified by the Centers for Disease Control and Prevention (CDC) and WHO (i.e. fever, chills, cough, shortness of breath, sore throat, fatigue, body aches, skin rash, red and irritated eyes, headache, diarrhoea, nausea, loss of taste or smell, and congestion or runny nose)[24]. Respondents were asked if they experienced any of the aforementioned symptoms (yes or no). If they responded 'yes', they were asked to rate the severity of each symptom on Likert scale (1 = mild, 2 = moderate, 3 = severe; those who responded 'No' were scored 0 for not experienced). For each participant, the number of symptoms experienced was generated by summing all self-reported symptoms. A composite score of symptom severity was generated by summing severity ratings from the Likert scales for each of the 14 symptoms. The possible range for the composite score of symptom severity was 0–42 with higher scores indicating greater severity.

To assess intake of a one-a-day multivitamin as well as supplementation of vitamin D, vitamin C, vitamin E or zinc not contained in a multivitamin, respondents were asked, 'How often did you take [each supplement] over the past year?' (didn't take, a few days per month, 1 day per week, 2 days per week, 3–4 days per week, 5–6 days per week, or every day). Those who reported taking a supplement at least once per week during the previous year were categorised as 'supplement users' while those who 'didn't take' or took only 'a few days per month' were categorised as 'supplement non-users'.

Participants reported their age in years. Biological sex was self-reported as male or female. For statistical analysis, race was categorised as white, black or other. Smoking status was quantified as non-smokers, occasional smokers (once to several times a month) and frequent smokers (once a week or more frequent smoking). Participants were asked to report concomitant health conditions, including diabetes type 1 and 2, high blood pressure, asthma, chronic pulmonary disease (or emphysema), autoimmune disease, cancer treatment, organ transplant, kidney disease, liver disease or other chronic diseases. Those who reported having at least one pre-existing health problem were categorised as having 'underlying conditions'.

Statistical analysis

In preliminary analyses, we examined bivariate associations between studied variables. Specifically, the associations between supplementation of micronutrients were measured by Cramer's V. Logistic regression was used to examine differences in symptoms and supplementation by age, smoking status and biological sex. Spearman's rho was used to estimate the association between age and symptom severity. Independent t test was used to compare symptom severity between men and women.

In primary analyses, linear regression was used to examine the association between reported symptom severity and supplement intake. Robust standard errors were used to ensure proper inference in case of heteroskedasticity. Negative binomial regression was used to analyse supplement intake and the reported number of symptoms. In both regressions, the set of controlled variables included age, biological sex, race, smoking status and underlying conditions. Data were analysed via SPSS version 28 (IBM SPSS Statistics, Armonk, NY), Stata

17 (StataCorp LLC., College Station, TX), and SAS 9·4 (SAS Institute Inc., Cary, NC) with a *P*-value less than 0·05 was considered statistically significant.

Results

Sample description

Complete data were available for 287 men and women who completed the survey. Participant characteristics are shown in Table 1. Average age was 33·3 ± 10·5 years. The majority of the sample (72 %) were white. Men accounted for about 56 % of the sample. Approximately 44 % of the participants did not smoke during the past year, another 44 % smoked occasionally and 13 % smoked frequently. Approximately 64 % of the sample reported having at least one concomitant health condition. On average, participants experienced nine symptoms (±4·2). The top three most experienced symptoms were fever (81 %), cough (79 %) and headache (76 %). The three least experienced symptoms were rash (35 %), diarrhoea (46 %) and red and irritated eyes (46 %). Symptom severity scores averaged 15·9 ± 8·3 (range 0–42) with higher scores indicative of greater symptom severity.

Table 1. Respondent characteristics (*n* 287)

Characteristic	Mean ± SD	Range
Age (years)	33·3 ± 10·5	18–59
Composite Score of Symptom Severity* (Range 0–42)	15·9 ± 8·3	0–35
	Number	**Percentage**
Biological sex		
Male	160	55·7 %
Female	127	44·3 %
Race		
White	207	72·1 %
Asian	30	10·5 %
African American	27	9·4 %
Other	23	8·0 %
Smoking status		
Non-smokers	125	43·5 %
Occasional smokers	126	44·0 %
Frequent smokers	36	12·5 %
Dietary supplements taken at least once per week the year prior to infection		
One-a-day multivitamin	153	53·3 %
Vitamin D	136	47·4 %
Vitamin C	137	47·7 %
Vitamin E	116	40·4 %
Zinc	113	39·4 %
Reported symptom		
Fever	232	80·8 %
Chills	208	72·5 %
Cough	227	79·1 %
Shortness of breath	194	67·6 %
Fatigue	214	74·6 %
Sore throat	183	63·8 %
Body aches	193	67·2 %
Red Eyes	133	46·3 %
Headache	217	75·6 %
Diarrhoea	133	46·3 %
Nausea	144	50·2 %
Loss of taste or smell	187	65·2 %
Rash	101	35·2 %
Congestion	184	64·1 %

* Composite score represents the sum of severity ratings from the Likert scales for each of the fourteen symptoms.

Supplementation of micronutrients

Table 1 also shows habitual use of each dietary supplement in the year prior to infection. Approximately 53 % of the sample reported taking multivitamin at least once a week. Not counting what was contained in multivitamin, about 48 % reported taking vitamin C, 47 % supplemented vitamin D, 40 % supplemented vitamin E and 39 % supplemented zinc. The associations between supplement variables were considered strong as suggested by Cramer's V values (Supplementary Table S1), meaning that participants tended to take more than one supplement. For example, among multivitamin users, 78 % reported also taking vitamin C, 80 % took vitamin D, 74% took vitamin E and 71 % took zinc. Among vitamin C users, 87 % also reported taking multivitamin, 88 % took vitamin D, 80 % took vitamin E and 74 % took zinc.

Differences in symptoms and supplementation by age, smoking status and biological sex

Age was associated with the composite symptom severity score ($r = 0·171$, $P = 0·004$). Older age was associated with higher odds of experiencing fever ($P = 0·001$), chills ($P = 0·009$), shortness of breath ($P = 0·017$), sore throat ($P = 0·028$), aches ($P = 0·048$), irritated and red eyes ($P < 0·001$) and rash ($P < 0·001$). Multivitamin supplementation also increased with age ($P < 0·001$). Not counting what was contained in multivitamin, older respondents were also more likely to use vitamin C ($P = 0·027$), vitamin D ($P = 0·004$), vitamin E ($P < 0·001$) and zinc ($P < 0·001$).

Smokers experienced greater symptom severity than non-smokers ($P < 0·001$). Compared with non-smokers, occasional and frequent smokers were more likely experience fever ($P < 0·01$), chills ($P < 0·01$), cough ($P < 0·03$), shortness of breath ($P < 0·02$), red and irritated eyes ($P < 0·001$), diarrhoea ($P < 0·05$), nausea ($P < 0·03$) and rash ($P < 0·001$). Compared to non-smokers, occasional smokers and frequent smokers were more likely to use multivitamin ($P < 0·02$), vitamin D ($P < 0·04$), vitamin E ($P < 0·001$) and zinc ($P < 0·001$.

Symptom severity did not differ by biological sex, but men were more likely to report taking a multivitamin ($P = 0·021$), vitamin D ($P = 0·029$), vitamin E ($P = 0·004$) and zinc ($P < 0·001$). However, the average age of men was higher than women (35·6 + 10·6 *v.* 30·4 + 9·7, $P < 0·001$).

Associations between supplementation and symptoms

In the linear regression adjusted for age, biological sex, smoking status and underlying conditions, none of the five supplement variables were significantly associated with symptom severity ($P > 0·30$) (Table 2). However, the null hypothesis of their coefficients jointly equal to zero was rejected ($F_{5,274} = 4·83$, $P < 0·001$), implying that at least one of them significantly differed from zero. Similarly, results from the negative binomial regression lent no support to the association between any supplement and the number of symptoms experienced ($P >= 0·20$). The joint significance test, however, resulted in a rejection of the null hypothesis ($F_{5,274} = 5·30$, $P < 0·001$). Variance inflation

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Table 2. Association between supplement intake and COVID-19 symptoms

	Number of symptoms[a]				Symptom severity[b]			
	Model 1		Model 2		Model 1		Model 2	
Variables	β	P	β	P	β	P	β	P
Multivitamin (yes *v.* no)	0·069	0·402	0·095	0·226	0·747	0·524	1·035	0·337
Other supplement use (yes *v.* no)			0·189	0·014			2·827	0·009
Smoking (occasional *v.* no)	0·015	0·824	0·037	0·567	0·713	0·547	1·065	0·351
Smoking (frequent *v.* no)	0·172	0·041	0·180	0·032	4·579	0·003	4·635	0·002
Underlying conditions (yes *v.* no)	0·281	<0·001	0·280	<0·001	4·287	<0·001	4·152	<0·001
Race (black *v.* white)	0·068	0·437	0·090	0·301	0·767	0·517	1·18	0·323
Race (others *v.* white)	0·086	0·205	0·103	0·129	0·668	0·540	0·882	0·417
Biological sex (female *v.* male)	0·043	0·460	0·032	0·572	0·860	0·395	0·783	0·434
Age	0·002	0·476	0·002	0·536	−0·001	0·991	−0·006	0·887
Vitamin C (yes *v.* no)	0·092	0·300			2·376	0·063		
Vitamin D (yes *v.* no)	0·070	0·470			0·762	0·496		
Vitamin E (yes *v.* no)	0·136	0·205			2·152	0·117		
Zinc (yes *v.* no)	−0·057	0·542			−1·811	0·128		

[a] Negative binomial regression.
[b] Linear regression.
Note: Model 1 used the original five supplement variables. Model 2 used of multivitamin and *other supplement use.* Both models included the same set of controlled variables. Test of joint significance: number of symptoms, $F_{5,274} = 5·30$, $P < 0·001$; symptom severity, $F_{5,274} = 4·83$, $P < 0·001$.

factors (VIFs) were 2·46, 2·99, 3·14, 3·54 and 4·00 for multivitamin, vitamin C, zinc, vitamin D and vitamin E, respectively. Johnson and colleagues[25] suggested VIFs ≥2·5 as indicative of considerable multicollinearity, while some authors suggested higher thresholds such as 5 or 10[26,27]. Regressing each supplement variable on the other four produced a R^2 of 59 % for multivitamin, 67 % for vitamin C, 72 % for vitamin D, 75 % for vitamin E and 68 % for zinc. Out of concern that multicollinearity could be at play, we generated the variable *other supplement use* that captured if a participant took any of the individual C, D, E or zinc supplements. Although the association between multivitamin and *other supplement* use remained strong (Cramer's $V = 0·72$), VIFs reduced to about 2·12. With this approach, we attempted to separate the effect of multivitamin from that of the other supplements, if indeed there was an effect. For the set of C, D, E and zinc, the significance test of *other supplement use* amounts to a test of their joint significance.

The models were re-estimated with multivitamin, *other supplement use* and the same set of controlled variables (Table 2). There was absence of evidence supporting an association between multivitamin intake and symptom severity ($P = 0·337$). Results from the negative binomial regression also pointed to an absence of an association between multivitamin intake and the number of symptoms experienced ($P = 0·226$). At this point, the non-significance of multivitamin was unlikely due to multicollinearity. Intake of vitamin C, D, E or zinc was associated with higher number of symptoms ($P = 0·014$) as well as higher symptom severity ($P = 0·009$), on average.

In the exploratory analyses, we ran a series of regressions of symptom severity and number of symptoms against each supplement variable individually (Supplementary Tables S2 and S3). The estimated coefficients all carried a positive sign. In addition, Chi-square tests showed that with the exception of congestion, supplement users were more likely than non-users to report experiencing each of the individual symptoms ($P < 0·05$). So, although such positive associations were unexpected, it was unlikely the repercussion of multicollinearity.

Among controlled variables, smoking status and underlying health conditions were significant (Table 2). Compared with non-smoking, frequent smoking was associated with higher number of symptoms ($P = 0·032$) and higher symptoms severity ($P = 0·002$), on average. Occasional smoking was not significantly different from non-smoking. Having underlying conditions was highly associated with higher number of symptoms ($P < 0·001$) and higher symptoms severity ($P < 0·001$), on average.

Discussion

Results of the present study demonstrated that supplementation of a multivitamin, vitamin D, vitamin C, vitamin E or zinc did not protect adults younger than 60 years from experiencing common symptoms of SARS-CoV-2. Habitual smoking was associated with more symptoms and greater symptom severity. Although adequate intake of micronutrients is important to prevent deficiencies, smoking cessation may be a more impactful modifiable lifestyle factor than use of dietary supplements.

In the United States, vitamins and minerals are classified as 'dietary supplements' under the Dietary Supplement Health and Education Act of 1994. As such, vitamins and minerals are not regulated by the Food and Drug Administration in the same way as medications, and various formulations are readily available over the counter[19]. The prevalence of dietary supplement use is high among American adults. According to the National Institutes of Health, Americans spent approximately $21 billion for dietary supplements containing vitamins or minerals in 2020[20]. Data from large nationwide surveys reveal that 52–57·6 % of adults reported taking at least one dietary supplement on a regular basis, and one-a-day multivitamins were the most commonly used dietary supplement[28,29]. No

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standard definition exists for multivitamin supplements in the United States. Most are intended to be taken once per day to provide the Recommended Dietary Allowance (RDA) for a variety of vitamins and minerals[20]. Similar to nationally representative samples[28,29], a multivitamin was the most commonly used dietary supplement in the present study with 53·3 % of respondents reporting supplementation at least once per week.

The main finding from this analysis was the observation that regular supplementation of a multivitamin, vitamin D, vitamin C, vitamin E or zinc did not appear protective against experiencing common COVID-19 symptoms. In fact, with the exception of congestion, supplement users were more likely than non-users to report experiencing symptoms. Dietary supplement users have been described as the 'worried well'[30], so it is possible that the supplement users in our study were more hyperaware of their symptoms. According to previous studies, common reasons for using dietary supplements are to improve or maintain overall physical health[31,32] and to 'gain peace of mind'[32]. However, a recent review article concluded that current evidence does not support the use of vitamin or mineral supplements to reduce risk of common diseases such as cardiovascular disease and type 2 diabetes[33]. Similarly, a 2022 recommendation statement from the US Preventative Services Task Force reiterated that evidence does not support vitamin or mineral supplementation to protect against cardiovascular disease or cancer[34]. Evidence does, however, support the importance of obtaining adequate amounts of the micronutrient examined in this study for proper immune function. Because deficiencies may predispose individuals to infections, it is important to ingest adequate amounts of these micronutrients within the food matrix[4,5,6]. However, the Office of Dietary Supplements at the National Institutes of Health states, 'current data are insufficient to support recommendations for or against the use of any vitamin, mineral, herb, other botanical, fatty acid, or other dietary supplement ingredient to prevent or treat COVID-19'[35]. Data from our study support current public health statements. Although a nutrient-dense diet should be encouraged to prevent malnutrition and micronutrient deficiencies[4,5,6], no magic bullet vitamin or mineral supplement exists to protect against infection or specific symptoms[16].

Although the present study only included adults younger than 60 years, age was associated with the composite symptom severity score in bivariate analysis. This is consistent with epidemiological data showing risk of severe illness from SARS-CoV-2 infection increases with age[2,36]. Supplement users were also more likely to be older. This is also consistent with nationally representative data on dietary supplement use in the United States. Across multiple reports, use of dietary supplements has been shown to increase with age[28,29,31,37]. The observation of more frequent supplementation among men in our study was surprising in light of other studies reporting greater supplement use among women[29,37]. However, this observation may also be explained by age as on average, men among this cohort were significantly older than women. However, after controlling for other variables in regression models, age was no longer associated with symptoms or symptom severity.

Although frequent smokers were more likely to supplement micronutrients, smokers reported more symptoms and greater symptom severity. These observations are supported by previous studies showing that younger adults were more susceptible to severe illness from SARS-CoV-2 infection if they were smokers[38,39]. Cigarette smoking is known to increase oxidative stress, damage respiratory epithelium, and disrupt both humoral and cell-mediated immunity[40]. A recent report from the WHO presented evidence relating smoking to risk of respiratory infections and urged more public health efforts for smoking cessation in this pandemic era[41].

In a season when many companies are marketing immune-enhancing dietary supplements[16], the present study provides important insights into associations between micronutrient supplementation and symptomatology of SARS-CoV-2. However, several limitations should be noted. In addition to the relatively small sample size, was a cross-sectional analysis that relied on respondents' self-report of both symptoms and supplementation[42]. Specific dosages of each supplement and blood samples to assess serum levels were not available. Although models were adjusted for comorbid conditions, confounding factors not explicitly considered in this analysis, such as obesity and dietary intake, could also influence the relationship between micronutrient supplementation and symptoms[43]. Selection bias is a possibility because the study was conditioned on those who tested positive for SARS-CoV-2. Those who were asymptomatic or experienced mild symptoms may have been less likely to seek testing. Similarly, perhaps those who are more likely to take dietary supplements for peace of mind may have been more likely to take a COVID-19 test. We only asked respondents to subjectively rate their symptoms as 'mild, moderate or severe', so more granular, objective assessments of symptom severity were not available. The present study included a sample of predominantly white individuals that could also hinder generalizability. Because we only considered adults ages 18–59 years who had recovered from infection during the first wave of COVID-19, results could differ among older adults, vaccinated individuals and those with different variants of SARS-CoV-2.

In summary, although vitamin and mineral deficiencies may compromise immunity and predispose adults infected with SARS-CoV-2 to more severe disease[4,5], habitual self-supplementation of a multivitamin, vitamin D, vitamin C, vitamin E or zinc did not appear protective against common COVID-19 symptoms among this cohort of relatively young adults. A diet rich in micronutrients to prevent deficiencies is advised; however, supplementation of particular micronutrients above the RDA is not supported by these results. Taken together with previous studies, it appears that smoking cessation may be a more effective modifiable lifestyle factor to mitigate COVID-19 symptoms.

Supplementary material

The supplementary material for this article can be found at https://doi.org/10.1017/jns.2022.115.

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A. E. was involved in study design, data collection, analysis and drafting the original manuscript. H. P. was involved in study design, data collection, interpretation of findings and editing of the manuscript. A. E. and H. P. are co-principal investigators who contributed equally to the design and management of this study; as such, they should be considered co-anchor authors on this article. C. B. and D. A. participated in data analysis, interpretation of the findings and editing of the paper. C. F. was involved in study design, data collection, interpretation of the findings and editing of the manuscript.

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