Original article

The association between dietary intakes of zinc, vitamin C and COVID-19 severity and related symptoms: A cross-sectional study

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SUMMARY

Background: The Coronavirus disease 2019 (COVID-19) pandemic has had a devastating impact on health systems, food supplies, and population health. This is the first study to examine the association between zinc and vitamin C intakes and the risk of disease severity and symptoms among COVID-19 patients.
Methods: This cross-sectional study included 250 recovered COVID-19 patients aged 18—65 years from June to September 2021. Data on demographics, anthropometrics, medical history, and disease severity and symptoms were collected. Dietary intake was evaluated using a web-based, 168-item food frequency questionnaire (FFQ). The severity of the disease was determined using the most recent version of the NIH COVID-19 Treatment Guidelines. Using multivariable binary logistic regression, the association between zinc and vitamin C intakes and the risk of disease severity and symptoms in COVID-19 patients was evaluated.
Results: The mean age of participants in this study was 44.1 ± 12.1, 52.4% of them were female, and 46% had a severe form of the disease. Participants with higher zinc intakes had lower levels of inflammatory cytokines, such as C-reactive protein (CRP) (13.6 vs. 25.8 mg/l) and erythrocyte sedimentation rate (ESR) (15.9 vs. 29.3). In a fully adjusted model, a higher zinc intake was also associated with a lower risk of severe disease (OR: 0.43; 95% CI: 0.21, 0.90, P-trend = 0.03). Similarly, participants with higher vitamin C intakes had lower CRP (10.3 vs. 31.5 mg/l) and ESR serum concentrations (15.6 Vs. 35.6) and lower odds of severe disease after controlling for potential covariates (OR: 0.31; 95% CI: 0.14, 0.65, P-trend = <0.01). Furthermore, an inverse association was found between dietary zinc intake and COVID-19 symptoms, such as dyspnea, cough, weakness, nausea and vomiting, and sore throat. Higher vitamin C intake was associated with a lower risk of dyspnea, cough, fever, chills, weakness, myalgia, nausea and vomiting, and sore throat.
Conclusion: In the current study, higher zinc and vitamin C intakes were associated with decreased odds of developing severe COVID-19 and its common symptoms.
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1. Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by a coronavirus (SARS-CoV-2) with a high rate of transmission and a variety of clinical manifestations, ranging from asymptomatic contamination to severe disease [1]. SARS-CoV-2 typically causes an upper respiratory tract infection, potentially progressing to pneumonia and acute respiratory distress syndrome (ARDS) [2,3]. COVID-19 severity is determined by viral load and the degree of sufficient immune response in patients [4]. Unregulated immune function promotes virus replication and causes a

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destructive inflammatory response, as evidenced by elevated serum levels of inflammatory markers such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), interleukin (IL)-6, and tumor necrosis factor (TNF) [5]. Nutrition is an important factor in maintaining overall health and the integrity of immune function [6]. Nutrient deficiency increases the susceptibility to viral infection, which has a high proclivity for severe clinical manifestation [7]. More specifically, patients suffering from severe and critical COVID-19 have been found to be at an increased risk of malnutrition [8]. Recent studies have also found favorable associations between a number of dietary factors and the severity risk of COVID-19 [9–11].

Zinc, as an essential nutrient, is involved in immunomodulatory functions and regulates inflammatory responses [12,13]. Furthermore, zinc is a critical nutrient in the antioxidant defense system [14,15]. Zinc deficiency is associated with an increased risk of severe diseases in the elderly, obese individuals, those with diabetes mellitus, and those who take immunosuppressive medications [12,16]. Comparatively, vitamin C is another nutrient whose significant antioxidant, anti-inflammatory, and immunomodulatory properties have previously been demonstrated [17]. Moreover, high vitamin C consumption has been linked to reducing the frequency and duration of respiratory infections [18]. In a previous cross-sectional research, Muhammad et al. found that patients with COVID-19 had lower levels of vitamin C than controls [19]. There was no significant correlation between vitamin C concentration and disease severity or lung involvement in patients with COVID-19, however lower zinc concentration was associated with severe disease in these patients in a cross-sectional study by Beigmohammadi et al. [20]. According to Golabi et al., zinc levels in COVID-19 outpatients were significantly lower than those of non-infected participants in a similar study [21]. However, in that study, there was no significant elationship between zinc concentration in the serum and the progression of COVID-19 [21].

Due to the debate surrounding zinc and vitamin C levels and COVID-19 severity, as well as the lack of observational studies examining the association between zinc and vitamin C intake and different COVID-19 symptoms, we conducted this cross-sectional study to examine the association between zinc and vitamin C intake and COVID-19 severity and related symptoms among Iranian adults.

2. Methods

2.1. Study design and participants

This retrospective cross-sectional study was conducted from June to September 2021 on 250 recovered COVID-19 patients aged 18–65 years. Patients were selected using a simple random sampling method from Shahid Beheshti Hospital, Kashan, Iran. The ethics committee of Kashan University of Medical Sciences approved the study protocol (Registration No. IR. KAUMS.MEDN-T.REC.1400.048). All participants signed a written informed consent. Participants were drawn from a pool of recovered Covid-19 patients who had been diagnosed at least 3 months before, and their medical records were available in Shahid Beheshti Hospital. Patients with the following conditions were excluded: 1) Patients with other diseases than COVID-19; 2) Patients with a history of chronic diseases, such as heart disease, diabetes, or other diseases that affect the severity of COVID-19; 3) Patients with a BMI greater than 40; 4) Patients who used dietary supplements more than twice a week before being diagnosed with COVID-19; 5) Pregnant or breastfeeding women; 6) Patients who used medicines that affect respiratory function, such as fluticasone, flunisolide, or

others; 7) Patients on specific diets; 8) Current smokers, and 9) Patients with insufficient data in their medical records.

2.2. Assessment of dietary intakes

A web-based 168-item food frequency questionnaire (FFQ) was used to collect data on participants' dietary intakes during the previous year prior to COVID-19 diagnosis. The reliability and validity of this questionnaire has been approved previously [22]. Participants were asked to report their daily, monthly, and annual dietary intakes. Finally, their intakes were converted to grams per day using 'household measures' [23]. We also used Nutritionist 4 (N4) software (First Databank, Hearst Corp, San Bruno, CA, USA) to calculate dietary intakes of micro-and macronutrients.

2.3. Evaluation of COVID-19 severity

The COVID-19 Treatment Guidelines (CTG) [24], which was updated on October 19, 2021, was used to assess COVID-19 severity. According to this guideline, the severity of COVID-19 is classified into five levels. Individuals who have a positive virologic test for SARS-CoV-2 (i.e., a nucleic acid amplification test [NAAT] or an antigen test) but no symptoms of COVID-19 are classified as having an asymptomatic or presymptomatic infection. Mild illness is defined as having any of the signs and symptoms of COVID-19 (e.g., fever, sore throat, cough, headache, malaise, muscle pain, vomiting, nausea, diarrhea, loss of taste and smell) but no shortness of breath, dyspnea, or abnormal chest imaging. Individuals with moderate illness have evidence of lower respiratory disease during clinical assessment or imaging and oxygen saturation (SpO2) of 94% on room air at sea level. Severe illness is defined as SpO2 less than 94% on room air at sea level, a ratio of arterial partial oxygen pressure to fraction of inspired oxygen (PaO2/FiO2) greater than 300 mm Hg, a respiratory rate greater than 30 breaths/min, or lung infiltrates greater than 50%. Individuals suffering from critical illness have respiratory failure, septic shock, and/or multiple organ dysfunction. In our study, mild and moderate illnesses were classified as non-severe.

2.4. Assessment of COVID-19 symptoms

Participants were required to complete a general questionnaire including questions about the presence of common COVID-19 symptoms, including fever, weakness, dyspnea, sore throat, cough, chills, myalgia, nausea, and vomiting.

2.5. Assessment of inflammatory markers

Using medical records, we obtained information on CRP and ESR. The first CRP and ESR firstly measured at the start of the disease.

2.6. Assessment of other variables

Weight was measured using digital scales and recorded to the nearest 100 g, while the participants were minimally clothed and without shoes. Height was measured in the standing position, without shoes, using a measuring tape while the shoulders were in a normal state. We utilized a short version of the International Physical Activity Questionnaire (IPAQ) in order to assess physical activity of the subjects [25]. The IPAQ information was expressed in terms of Metabolic Equivalents per week (METs/week), and participants were divided into three categories: sedentary, moderate, and intense. In addition, participants reported their personal

characteristics, convalescence duration, supplement intake, corticosteroids, and antiviral drug use on a pretested questionnaire.

2.7. Statistical analysis

The Statistical Package for Social Sciences (SPSS) software was used to analyze all data (SPSS Inc, version 25). We considered p-values <0.05 as statistically significant. To investigate normal distribution of the data, we used the Kolmogorov Smirnov test [26]. We estimated energy-adjusted intake of dietary zinc and vitamin C intake using the residual method [27]. We categorized participants by tertile cut-off points of energy-adjusted zinc and vitamin C intake. General characteristics of study participants across tertiles of dietary zinc and vitamin C intake were expressed as means ±SDs for continuous variables and percentages for categorical variables. We used one-way ANOVA to examine differences in continuous variables including dietary and demographic variables across tertiles of dietary zinc and vitamin C intake. In terms of categorical variables, the distribution of participants across tertiles of dietary zinc and vitamin C intake was evaluated using the χ2 test. Dietary intakes of study participants across tertiles of zinc and vitamin C intake were compared using covariance analysis (ANCOVA). We applied binary logistic regression in different models to examine association between dietary zinc and vitamin C intakes with risk of severe disease as well as with risk of COVID-19 symptoms, including depression, anxiety and psychological distress, dyspnea, cough, fever, chills, weakness, myalgia, nausea and vomiting, and sore throat. We included age, sex, and energy intake in the first model. In model 2, further adjustment was conducted for physical activity, supplement use, corticosteroids, and antiviral drugs. Finally, in model 3, we also controlled for BMI.

3. Results

The general characteristics of study participants across tertiles of dietary zinc and vitamin C intake are depicted in Table 1. Compared with patients in the lowest tertile of dietary zinc, subjects in the highest tertile were younger, had lower BMIs, were more likely to have moderate to intense physical activity, were less likely to be overweight or obese, and had shorter hospitalization and convalescence duration. Participants in the top tertile of vitamin C intake had lower BMIs, were less likely to be overweight or obese, and used supplements, corticosteroids, and antiviral drugs compared to those in the bottom tertile. Furthermore, those

who consumed more vitamin C had shorter hospitalization and convalescence time.

Dietary intakes of selected food groups, as well as nutrient intakes of participants across tertiles of dietary zinc and vitamin C intake, are outlined in Table 2. Compared to those in the bottom tertile of zinc intake, those in the top tertile had significantly higher intakes of some nutrients and food groups. They had higher intakes of carbohydrate, fat, protein, dietary fiber, cholesterol, SFA, MUFA, PUFA, vitamin B1, vitamin B2, vitamin B3, vitamin B6, folate, phosphorus, selenium, magnesium, potassium, vitamin C, zinc, fruit, vegetables, eggs, red meats, fish, poultry, legumes, nuts, low-fat dairy and lower intakes of processed meats, and high-fat dairy compared with those in the lowest tertile. Higher intakes of vitamin C were also associated with higher intakes of total fat, protein, dietary fiber, cholesterol, SFA, MUFA, vitamin B1, vitamin B2, vitamin B6, folate, phosphorus, selenium, magnesium, potassium, vitamin C, zinc, whole grains, fruit, vegetables, fish, poultry, legumes, nuts, low-fat dairy and lower intakes of refined grains, red meats, processed meats, and high-fat dairy.

Table 3 displays inflammatory biomarkers across dietary zinc and vitamin C intake tertiles. Participants who consumed more dietary zinc had significantly lower levels of inflammatory biomarkers, including CRP (13.6 vs. 25.8 mg/l) and ESR (15.9 vs. 29.3) compared to those who had lower intakes. Indeed, participants in the top tertile of vitamin C intake had lower serum levels of CRP (10.3 vs. 31.5 mg/l) and ESR (15.6 vs. 35.6) compared to those in the bottom tertile.

Crude and multivariable-adjusted odds ratios for severe COVID-19 disease based on tertiles of dietary zinc and vitamin C intake are illustrated in Table 4. Higher dietary zinc intake was found to have a significant negative association with severe COVID-19 (OR: 0.34; 95% CI: 0.18, 0.65, P-trend = <0.01). Individuals in the highest tertile of zinc intake had a 57% lower odds of having severe COVID-19 than those in the lowest tertile, even after controlling for potential confounders (OR: 0.43; 95% CI: 0.21, 0.90, P-trend = 0.03). In terms of vitamin C intake, higher vitamin C intake was associated with a lower risk of severe COVID-19 either in the crude model (OR: 0.17; 95% CI: 0.09, 0.34, P-trend = <0.001) or in the fully adjusted model (OR: 0.31; 95% CI: 0.14, 0.65, P-trend = <0.01).

Crude and multivariable-adjusted odds ratios for symptoms of COVID-19 across tertiles of dietary zinc and vitamin C intake are summarized in Table 5. After adjustment for potential confounders, there was a significant inverse association between dietary zinc intake and the odds of having symptoms of COVID-19, including dyspnea (OR: 0.41; 95% CI: 0.19, 0.86), cough (OR: 0.45; 95% CI: 0.22,

Table 1
General characteristics of participants across tertiles of dietary zinc and vitamin C intake.

	Tertiles of zinc intake				Tertiles of vitamin C intake			
	T1 $n = 83$	T2 $n = 84$	T3 $n = 83$	P^a	T1 $n = 83$	T2 $n = 84$	T3 $n = 83$	P^a
Age (years)	45.4 ± 11.6	45.9 ± 12.3	41.2 ± 11.9	0.02	44.3 ± 11.9	45.0 ± 12.2	43.3 ± 12.2	0.66
Females (%)	51.8	48.2	56.6	0.55	55.4	53.0	48.2	0.63
BMI (kg/m²)	27.8 ± 3.8	27.6 ± 4.0	25.3 ± 2.7	<0.001	29.0 ± 3.7	26.0 ± 3.5	25.7 ± 2.9	<0.001
Physical activity				0.02				0.97
sedentary	13.3	20.5	3.6		13.3	13.3	10.8	
moderate	80.7	74.7	88.0		79.5	80.7	83.1	
intense	6.0	4.8	8.4		7.2	6.0	6.0	
Overweight or obese (%)	71.9	69.9	56.6	<0.001	84.2	59.1	55.4	<0.001
Supplements intake (%)	95.2	94.0	95.2	0.92	98.8	95.2	90.4	0.05
Corticosteroids use (%)	94.0	91.6	90.4	0.68	98.8	91.6	85.5	0.007
Antiviral Drugs use (%)	94.0	91.6	90.4	0.68	98.8	91.6	85.5	0.007
Duration of hospitalization (day)	7.2 ± 2.9	6.5 ± 2.7	5.9 ± 3.0	0.01	7.5 ± 2.9	6.4 ± 2.9	5.6 ± 2.6	<0.001
Convalescence duration (day)	9.8 ± 3.6	10.2 ± 4.3	8.1 ± 2.7	<0.001	11.1 ± 4.3	8.7 ± 3.4	8.5 ± 2.8	<0.001

^a Obtained from ANOVA or Chi-square test, where appropriate.

Table 2
Selected food groups and nutrient intakes of participants across tertiles of dietary zinc and vitamin C intake.

	Tertiles of zinc intake				Tertiles of vitamin C intake			
	T1 (n = 83)	T2 (n = 84)	T3 (n = 83)	P^a	T1 (n = 83)	T2 (n = 84)	T3 (n = 83)	P^a
Nutrients								
Energy (Kcal/day)	2725.1 ± 605.8	2815.6 ± 393.2	2700.7 ± 361.9	0.14	2749.6 ± 607.0	2768.8 ± 414.3	2723.1 ± 344.7	0.73
Carbohydrate (g/d)	397.9 ± 66.5	420.6 ± 46.1	412.1 ± 43.9	0.04	401.8 ± 63.7	412.3 ± 54.3	416.5 ± 40.2	0.20
Fat (g/day)	92.5 ± 35.0	107.8 ± 23.7	102.1 ± 14.4	<0.01	103.6 ± 37.3	104.1 ± 20.7	94.8 ± 15.3	<0.01
Protein (g/day)	94.2 ± 16.3	108.3 ± 11.2	121.6 ± 10.7	<0.001	96.7 ± 15.8	112.5 ± 14.9	114.9 ± 14.7	<0.001
Dietary fiber (g/day)	19.4 ± 3.9	23.3 ± 3.7	26.5 ± 3.4	<0.001	18.4 ± 2.8	23.3 ± 2.9	27.6 ± 2.6	<0.001
Cholesterol	361.0 ± 125.6	458.8 ± 145.4	509.9 ± 157.4	<0.001	403.8 ± 152.0	494.9 ± 152.0	430.9 ± 150.3	<0.001
SOFA	27.3 ± 11.9	31.1 ± 10.3	27.7 ± 5.7	0.02	31.9 ± 13.0	29.6 ± 8.5	24.5 ± 4.3	<0.001
MUFA	27.8 ± 11.8	32.0 ± 9.2	29.3 ± 5.6	0.02	32.0 ± 12.6	30.2 ± 7.6	27.0 ± 6.0	<0.01
PUFA	21.9 ± 9.3	26.8 ± 5.3	25.1 ± 4.5	<0.001	23.7 ± 9.5	26.0 ± 5.3	24.1 ± 5.0	0.03
Vitamin B1 (mg/d)	2.3 ± 0.3	2.5 ± 0.3	2.6 ± 0.3	<0.001	2.3 ± 0.3	2.5 ± 0.3	2.5 ± 0.3	<0.001
Vitamin B2 (mg/d)	1.6 ± 0.3	1.9 ± 0.2	2.2 ± 0.2	<0.001	1.7 ± 0.3	2.0 ± 0.3	2.1 ± 0.3	<0.001
Vitamin B3 (mg/d)	25.7 ± 4.6	27.8 ± 3.7	28.6 ± 3.4	<0.001	26.8 ± 4.6	27.8 ± 3.8	27.6 ± 3.9	0.23
Vitamin B6 (mg/day)	1.4 ± 0.3	1.7 ± 0.2	1.8 ± 0.1	<0.001	1.4 ± 0.3	1.7 ± 0.2	1.9 ± 0.2	<0.001
Folate (μg/day)	339.1 ± 68.6	416.5 ± 63.0	492.6 ± 63.9	<0.001	333.0 ± 60.8	427.0 ± 62.6	488.2 ± 68.6	<0.001
Vitamin E	6.9 ± 2.6	7.4 ± 2.1	7.0 ± 1.4	0.2	7.6 ± 2.9	6.8 ± 1.8	7.0 ± 1.2	0.14
Phosphorus	1241.0 ± 242.2	1474.8 ± 139.7	1641.7 ± 122.6	<0.001	1279.7 ± 237.5	1516.6 ± 214.9	1561.2 ± 162.2	<0.001
Selenium	0.05 ± 0.01	0.06 ± 0.01	0.06 ± 0.01	<0.001	0.05 ± 0.01	0.06 ± 0.01	0.06 ± 0.01	<0.01
Magnesium (mg/d)	281.7 ± 48.9	332.6 ± 29.4	372.3 ± 33.3	<0.001	284.2 ± 46.6	333.3 ± 35.2	369.2 ± 37.9	<0.001
Potassium (mg/d)	3225.4 ± 589.6	3772.7 ± 380.4	4158.9 ± 363.1	<0.001	3182.9 ± 518.7	3745.1 ± 352.1	4228.9 ± 349.1	<0.001
Vitamin C	113.0 ± 29.4	140.9 ± 27.9	163.4 ± 28.5	<0.001	100.8 ± 16.0	137.2 ± 13.7	179.2 ± 14.0	<0.001
Zinc (mg/day)	8.4 ± 1.6	10.4 ± 0.8	11.9 ± 0.8	<0.001	9.0 ± 1.8	10.7 ± 1.6	11.0 ± 1.2	<0.001
Food groups(g/day)								
Refined grains	504.0 ± 155.2	519.1 ± 157.8	488.8 ± 140.1	0.43	558.1 ± 147.4	483.0 ± 155.3	470.8 ± 136.8	<0.001
Whole grains	81.4 ± 86.8	80.0 ± 85.2	85.7 ± 64.0	0.87	60.2 ± 66.8	111.7 ± 96.2	74.9 ± 61.0	<0.01
Fruits	287.1 ± 113.3	358.5 ± 119.1	420.4 ± 83.7	<0.001	232.2 ± 61.4	357.9 ± 79.8	475.9 ± 53.2	<0.001
Vegetables	218.8 ± 66.3	268.0 ± 70.6	346.2 ± 101.5	<0.001	196.7 ± 50.9	264.5 ± 48.9	371.8 ± 85.4	<0.001
Eggs	50.9 ± 24.4	69.2 ± 32.8	78.7 ± 37.2	<0.001	57.7 ± 30.9	76.9 ± 34.8	64.2 ± 33.3	<0.01
Red meats	35.3 ± 22.3	41.8 ± 22.1	43.3 ± 16.3	0.03	44.8 ± 23.1	41.1 ± 22.3	34.5 ± 14.3	<0.01
Processed meats	12.2 ± 15.2	13.3 ± 14.3	8.1 ± 11.2	0.02	18.1 ± 16.9	11.2 ± 11.6	4.4 ± 7.8	<0.001
Fish	15.2 ± 10.3	23.0 ± 13.6	30.8 ± 10.8	<0.001	12.9 ± 6.8	24.3 ± 11.5	31.8 ± 13.1	<0.001
Poultry	45.4 ± 17.4	51.7 ± 16.7	67.6 ± 22.0	<0.001	44.5 ± 13.5	55.5 ± 17.6	64.7 ± 25.2	<0.001
Legumes	108.0 ± 33.4	131.9 ± 40.9	162.1 ± 36.7	<0.001	97.3 ± 26.3	141.8 ± 37.9	162.9 ± 35.0	<0.001
Nuts	22.3 ± 14.1	32.4 ± 12.9	36.2 ± 9.6	<0.001	22.0 ± 13.2	31.8 ± 11.2	37.2 ± 11.8	<0.001
LowLow-fatiry	129.6 ± 70.4	149.4 ± 71.4	188.8 ± 53.2	<0.001	105.7 ± 64.3	180.8 ± 60.9	181.4 ± 55.3	<0.001
HigHigh-fatiry	143.6 ± 88.0	122.3 ± 50.0	133.3 ± 45.3	0.11	158.3 ± 82.9	123.1 ± 47.39	117.8 ± 49.4	<0.01

Data are presented as mean ± SD.
[a] Obtained from ANOVA.

Table 3
Inflammatory biomarkers across tertiles of dietary zinc and vitamin C intake.

	Tertiles of zinc intake				Tertiles of vitamin C intake			
	T1 n = 83	T2 n = 84	T3 n = 83	P^a	T1 (n = 83)	T2 (n = 84	T3 (n = 83)	P^a
CRP (mg/L)	25.8 ± 2.1	19.6 ± 2.2	13.6 ± 2.2	<0.01	31.5 ± 2.1	17.2 ± 2.0	10.3 ± 2.0	<0.001
ESR (mm/hr)	29.3 ± 2.4	29.6 ± 2.4	15.9 ± 2.4	<0.001	35.6 ± 2.4	23.6 ± 2.3	15.6 ± 2.3	<0.001

Data are presented as mean ± SE.
[a] Values were adjusted for age, sex, BMI, and physical activity using ANCOVA.

Table 4
Odds ratio (95% CI) of severe disease according to tertiles of dietary zinc and vitamin C intake.

	Tertiles of zinc intake				Tertiles of vitamin C intake			
	T1 (n = 83)	T2 (n = 84)	T3 (n = 83)	P^a	T1 (n = 83)	T2 (n = 84)	T3 (n = 83)	P^a
Crude	1.00	0.78 (0.42, 1.44)	0.34 (0.18, 0.65)	<0.01	1.00	0.20 (0.10, 0.39)	0.17 (0.09, 0.34)	<0.001
Model 1	1.00	0.78 (0.42, 1.48)	0.31 (0.16, 0.62)	<0.01	1.00	0.19 (0.09, 0.38)	0.17 (0.08, 0.34)	<0.001
Model 2	1.00	0.83 (0.43, 1.60)	0.29 (0.15, 0.59)	<0.01	1.00	0.21 (0.10, 0.42)	0.19 (0.09, 0.40)	<0.001
Model 3	1.00	0.89 (0.45, 1.79)	0.43 (0.21, 0.90)	0.03	1.00	0.31 (0.15, 0.66)	0.31 (0.14, 0.65)	<0.01

Model 1: Adjusted for age, sex, and energy intake.
Model 2: Further adjusted for physical activity, supplement use, corticosteroids use, and antiviral drugs use.
Model 3: Further adjusted for BMI.
[a] Obtained from Binary logistic regression.

Table 5
Odds ratio (95% CI) for symptoms of COVID-19 according to tertiles of dietary zinc and vitamin C intake.

	Tertiles of zinc intake				Tertiles of vitamin C intake			
	T1 $n = 83$	T2 $n = 84$	T3 $n = 83$	P^a	T1 $n = 83$	T2 $n = 84$	T3 $n = 83$	P^a
Dyspnea								
Crude	1.00	1.00 (0.51, 1.95)	0.37 (0.19, 0.71)	<0.01	1.00	0.20 (0.09, 0.42)	0.17 (0.08, 0.36)	<0.001
Model 1	1.00	0.99 (0.49, 1.99)	0.33 (0.16, 0.65)	<0.01	1.00	0.18 (0.08, 0.39)	0.16 (0.07, 0.36)	<0.001
Model 2	1.00	1.02 (0.49, 2.14)	0.32 (0.16, 0.65)	<0.01	1.00	0.20 (0.09, 0.43)	0.20 (0.09, 0.44)	<0.001
Model 3	1.00	1.06 (0.49, 2.28)	0.41 (0.19, 0.86)	0.01	1.00	0.27 (0.12, 0.63)	0.27 (0.11, 0.63)	<0.01
Cough								
Crude	1.00	2.80 (1.47, 5.34)	1.27 (0.69, 2.34)	<0.01	1.00	0.18 (0.09, 0.38)	0.15 (0.07, 0.31)	<0.001
Model 1	1.00	0.43 (0.22, 0.84)	0.32 (0.16, 0.62)	<0.01	1.00	0.18 (0.08, 0.37)	0.15 (0.07, 0.32)	<0.001
Model 2	1.00	0.42 (0.21, 0.82)	0.33 (0.16, 0.65)	<0.01	1.00	0.18 (0.08, 0.39)	0.15 (0.07, 0.32)	<0.001
Model 3	1.00	0.40 (0.19, 0.83)	0.45 (0.22, 0.94)	0.03	1.00	0.28 (0.13, 0.63)	0.24 (0.11, 0.53)	<0.01
Fever								
Crude	1.00	0.92 (0.42, 2.01)	0.41 (0.2, 0.84)	0.01	1.00	0.29 (0.12, 0.71)	0.18 (0.08, 0.44)	<0.001
Model 1	1.00	0.92 (0.42, 2.04)	0.38 (0.18, 0.8)	<0.01	1.00	0.29 (0.12, 0.7)	0.19 (0.08, 0.45)	<0.001
Model 2	1.00	0.96 (0.43, 2.14)	0.41 (0.19, 0.86)	0.01	1.00	0.31 (0.13, 0.77)	0.20 (0.08, 0.49)	<0.001
Model 3	1.00	1.00 (0.44, 2.28)	0.51 (0.23, 1.10)	0.07	1.00	0.42 (0.16, 1.08)	0.27 (0.1, 0.68)	<0.01
Chilling								
Crude	1.00	0.85 (0.38, 1.87)	0.37 (0.18, 0.78)	<0.01	1.00	0.27 (0.1, 0.68)	0.15 (0.06, 0.37)	<0.001
Model 1	1.00	0.85 (0.38, 1.90)	0.36 (0.17, 0.76)	<0.01	1.00	0.27 (0.1, 0.68)	0.15 (0.06, 0.38)	<0.001
Model 2	1.00	0.87 (0.38, 1.97)	0.38 (0.18, 0.82)	0.01	1.00	0.29 (0.11, 0.74)	0.16 (0.06, 0.41)	<0.001
Model 3	1.00	0.92 (0.40, 2.14)	0.50 (0.22, 1.09)	0.07	1.00	0.41 (0.15, 1.12)	0.23 (0.09, 0.62)	<0.01
Weakness								
Crude	1.00	0.59 (0.31, 1.12)	0.21 (0.09, 0.44)	<0.001	1.00	0.45 (0.24, 0.87)	0.21 (0.1, 0.43)	<0.001
Model 1	1.00	0.58 (0.3, 1.11)	0.20 (0.09, 0.43)	<0.001	1.00	0.44 (0.22, 0.85)	0.21 (0.1, 0.45)	<0.001
Model 2	1.00	0.54 (0.27, 1.05)	0.20 (0.09, 0.44)	<0.001	1.00	0.42 (0.21, 0.83)	0.18 (0.08, 0.4)	<0.001
Model 3	1.00	0.55 (0.27, 1.09)	0.25 (0.11, 0.57)	<0.01	1.00	0.53 (0.25, 1.11)	0.23 (0.1, 0.54)	<0.01
Myalgia								
Crude	1.00	0.90 (0.49, 1.67)	0.63 (0.34, 1.18)	0.15	1.00	0.43 (0.23, 0.81)	0.25 (0.13, 0.48)	<0.001
Model 1	1.00	0.90 (0.48, 1.7)	0.63 (0.33, 1.21)	0.8	1.00	0.41 (0.22, 0.79)	0.25 (0.13, 0.49)	<0.001
Model 2	1.00	0.92 (0.49, 1.75)	0.65 (0.33, 1.25)	0.21	1.00	0.43 (0.22, 0.82)	0.27 (0.13, 0.53)	<0.001
Model 3	1.00	0.97 (0.5, 1.88)	0.86 (0.43, 1.71)	0.67	1.00	0.55 (0.27, 1.11)	0.34 (0.16, 0.72)	<0.01
Nausea and vomiting								
Crude	1.00	0.73 (0.33, 1.59)	0.04 (0.006, 0.33)	<0.001	1.00	0.18 (0.07, 0.46)	0.05 (0.01, 0.25)	<0.001
Model 1	1.00	0.73 (0.33, 1.6)	0.04 (0.005, 0.31)	<0.001	1.00	0.18 (0.06, 0.47)	0.05 (0.01, 0.26)	<0.001
Model 2	1.00	0.75 (0.33, 1.69)	0.03 (0.004, 0.28)	<0.001	1.00	0.19 (0.07, 0.51)	0.06 (0.01, 0.28)	<0.001
Model 3	1.00	0.79 (0.35, 1.8)	0.04 (0.01, 0.36)	<0.01	1.00	0.21 (0.07, 0.60)	0.07 (0.01, 0.33)	<0.001
Sore throat								
Crude	1.00	0.95 (0.5, 1.77)	0.32 (0.15, 0.66)	<0.01	1.00	0.42 (0.22, 0.79)	0.13 (0.06, 0.29)	<0.001
Model 1	1.00	0.94 (0.5, 1.76)	0.32 (0.15, 0.68)	<0.01	1.00	0.41 (0.21, 0.78)	0.13 (0.06, 0.29)	<0.001
Model 2	1.00	0.90 (0.47, 1.71)	0.33 (0.16, 0.7)	<0.01	1.00	0.38 (0.19, 0.74)	0.10 (0.04, 0.25)	<0.001
Model 3	1.00	0.96 (0.49, 1.85)	0.44 (0.2, 0.96)	0.05	1.00	0.50 (0.24, 1.03)	0.14 (0.05, 0.34)	<0.001

Model 1: Adjusted for age, sex, and energy intake.
Model 2: Further adjusted for physical activity, supplement use, corticosteroids use, and antiviral drugs use.
Model 3: Further adjusted for BMI.
 [a] Oobtained from Binary logistic regression.

0.94), weakness (OR: 0.25; 95% CI: 0.11, 0.57), nausea and vomiting (OR: 0.04; 95% CI: 0.01, 0.36), and sore throat (OR: 0.44; 95% CI: 0.20, 0.96). In terms of vitamin C intake, patients in the highest tertile had significantly lower odds of dyspnea (OR: 0.27; 95% CI: 0.11, 0.63), cough (OR: 0.24; 95% CI: 0.11, 0.53), fever (OR: 0.27; 95% CI: 0.10, 0.68), chills (OR: 0.23; 95% CI: 0.00, 0.62), weakness (OR: 0.23; 95% CI: 0.10, 0.54), myalgia (OR: 0.34; 95% CI: 0.16, 0.72), nausea and vomiting (OR: 0.07; 95% CI: 0.01, 0.33), and sore throat (OR: 0.14; 95% CI: 0.05, 0.34).

4. Discussion

This cross-sectional study found a significant inverse association between higher dietary zinc and vitamin C intakes and lower inflammatory biomarkers, such as CRP and ESR, duration of hospitalization and convalescence, as well as odds of COVID-19 severity. Patients in the highest tertile of zinc and vitamin C intake had a 57% and 69% lower odds of having severe COVID-19 compared to those in the lowest tertile, respectively. Furthermore, we investigated the relationship between dietary zinc and vitamin C intake and the likelihood of having COVID-19 symptoms. The findings revealed a significant negative association between dietary zinc intake and the likelihood of experiencing dyspnea, cough, weakness, nausea and vomiting, and sore throat. In addition, higher vitamin C intake was linked to a lower risk of dyspnea, cough, fever, chills, weakness, myalgia, nausea and vomiting, and sore throat. To the best of our knowledge, this was the first study that examined association between dietary zinc and vitamin C intake and COVID-19 severity and symptoms.

The role of zinc and vitamin C in strengthening the immune system and improving inflammatory markers has been well investigated. Zinc has been shown to serve as a signaling molecule in the immune system [28]. In addition, serum zinc levels were found to be inversely related to inflammatory markers (IL-6, TNF, and CRP) in a cross-sectional study of 1055 subjects (404 men, 651 women) [29]. Wannamethee et al. [30] studied 3258 men aged 60–79 years with no doctor-diagnosed myocardial infarction, stroke, or diabetes. The findings suggested that vitamin C has anti-inflammatory properties. COVID-19 has been linked to a variety of negative health outcomes, including stroke [31], gastrointestinal bleeding [32], liver dysfunction [33], and kidney injury [34]. Nutritional status was linked to immune function modulation as

well as the development and progression of infectious diseases [35]. Few studies have been conducted to investigate the role of micronutrient deficiencies in COVID-19. Previous research found that serum zinc and vitamin C levels were related to the severity and symptoms of COVID-19. For example, Shakeri et al. [36], revealed that serum zinc levels in patients who died were lower than those who survived, regardless of whether they were admitted to the ICU. As a result, in COVID-19 patients, serum levels of zinc at the time of admission can significantly impact clinical outcomes. Another cross-sectional comparative study on fifty COVID-19 symptomatic patients found that plasma zinc and vitamin C concentrations were lower in COVID-19 patients than in controls [19]. Additionally, a review revealed that zinc and vitamin C deficiency impairs the immune system, predisposing individuals to viral infections and diseases [37]. Concerning the relationship between dietary zinc and vitamin C, a study of 512 subjects diagnosed with chronic obstructive pulmonary disease (COPD) found that dietary vitamin C may protect against COPD [38]. Additionally, Lin et al. [39], demonstrated that zinc consumption is associated with a decreased risk of COPD. In contrast to the aforementioned studies, a study of eighty-four COVID-19 patients revealed no significant correlation between serum zinc and COVID-19 severity [40]. Also, as previously stated, two studies reported contradictory results regarding the relationship between vitamin C and zinc concentrations and the severity and progression of COVID-19, respectively [19,20]. In light of these disagreements, additional research is necessary to determine role of zinc and vitamin C intake in COVID-19 patients.

Several mechanisms could account for the association between zinc and vitamin C intakes and COVID-19 severity and associated symptoms. The primary characteristic of COVID-19 patients is lymphocytopenia [41]. Recently, it was reported that the decline in lymphocyte subsets such as CD4+, CD8+, and CD3+ T cells was related to the severity of COVID-19 [41]. The underlying mechanism is complex, and it primarily contributed to the virus's invasion [42]. Vitamin C was found to be essential for the development, maturation, and proliferation of functional T-lymphocytes in both in vitro and in vivo studies, with epigenetic regulation of gene expression being one of the underlying mechanisms [42]. Another nutritional status that should be considered as a potential cause of COVID-19 severity is zinc deficiency [43]. Zinc bolsters the host cell's antiviral defenses in addition to preventing viral entry and suppressing viral replication [43]. The ciliated epithelium is damaged by the coronavirus infections, and ciliary dyskinesia develops, eventually leading to impaired mucociliary clearance [43]. Zinc may have an effect by increasing the frequency of ciliary beats [44] and having a positive effect on the number and length of bronchial cilia [45]. Disruptions in the integrity of the respiratory epithelium, on the other hand, facilitate the entry of the virus and co-infecting pathogens and can result in pathogens entering the bloodstream [46]. Zinc was discovered to be required for expression of tight junction proteins, such as claudin-1 and zonula occludens (ZO-1) [46]. Furthermore, zinc's inhibitory effect on the lymphocyte function-associated antigen 1 (LFA-1)/intercellular adhesion molecule-1 (ICAM-1) interaction was due to weakened respiratory inflammation by reducing leukocyte recruitment [47]. Overall, zinc could influence several processes, such as preventing viral fusion with the host membrane, decreasing viral polymerase function, interfering with protein translation and processing, preventing particle release, and destabilizing the viral envelope [48—50].

As far as we know, this is the first study to investigate relationship between zinc and vitamin C intake and COVID-19 severity and symptoms. Patients' usual dietary intake was assessed using a validated food frequency questionnaire. In addition, we controlled for several confounders in the final analysis to find an independent association between zinc and vitamin C intakes and COVID-19 severity and related symptoms. However, when interpreting our findings, we must also consider some limitations. The main limitation of our study is its cross-sectional design, which makes it impossible to confer causal interference. It was also a single-center study with a small number of cases which precluded further investigations with additional controlling variables. Thus, the conduction of future prospective studies is warranted to confirm our findings. In addition, the type of dietary supplements used during COVID-19 was not considered in this research, which may have affected the observed results. Furthermore, as with all dietary assessment methods, measurement error is a potential limitation. The FFQ was used to assess usual dietary intake, which raises concerns about participant misclassification. In addition, because data collection occurred three months after the patients' recovery and self-reporting was used in data collection, the present study is particularly prone to recall bias. Finally, despite controlling for a wide range of potential confounders, residual confounders cannot be ruled out.

5. Conclusion

Our findings suggest an inverse association between dietary zinc and vitamin C intakes and hospitalization and recovery duration, serum levels of inflammatory biomarkers (CRP and ESR), and COVID-19 severity and symptoms. Future prospective studies with a large sample size are necessary to further build on our findings.

Ethical standard

We performed our study in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Author contributions

FA, SMM, SMG, NZ, SR and EP contributed to the conception and design of the study, data collection, and statistical analysis and drafting of the manuscript; AE, AM and MT contributed in data collection and manuscript drafting. All authors read and approved the final manuscript.

Declaration of competing interest

The authors have no conflicts of interest to declare.

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