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THE ASSOCIATION BETWEEN THE HISTORY OF SUPPLEMENT USE (VITAMIN OR MINERAL) AND COVID-19 DISEASE IN THE PERSIAN COHORT POPULATION

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Abstract. The aim of the study was to examine the association between vitamin and mineral supplement consumption and the possibility of contracting COVID-19 disease in the Persian cohort population in 2020. This retrospective cohort study was conducted on 4241 people who were registered in the Cohort Registration System. A logistic regression was performed to ascertain the multivariate association between demographic, health variables, and supplement use and the likelihood that participants were infected with COVID-19. The software used was IBM SPSS 24.0, and a significance level of 0.05 was considered. Analyze the quantitative variables, if the variable was normal, the independent t-test was used, and if the variable was not normal, the Mann–Whitney test was used. To compare the distribution of qualitative variables in the groups, a chi-square test or, if necessary, a Fisher's exact test was used. The number of participants in this cohort study was 4241. The average age of the participants in the study was 49.22±8.77. The OR value of age variable 0.989 (95% CI: 0.927–1.056); sex variable (95% CI: 0.238–2.743, OR = 0.808); BMI variable (95% CI: 0.927–1.056, OR = 0.953); vitamin D variable (95% CI: 0.333–6.769, OR = 1.502); omega3 variable (95% CI: 0.410–7.688, OR = 1.776); calcium variable (95% CI: 0.041–3.738, OR = 0.391); calcium variable (95% CI: 0.041–3.738, OR = 391); multiVIT variable (95% CI: 0.211–5.645, OR = 1.090); VitC variable (95% CI: 0.000–0.000, OR = 0.000); vitE variable (95% CI: 0.000–0.000, OR = 0.000); were the interval includes. There were no statistically significant multivariate associations (P > 0.05) between the explanatory variables infected with COVID-19. There was only a statistically significant correlation between the use of iron tablets and contracting COVID-19 (P = 0.025). Controlling the variables or identifying causal correlations is not feasible due to the observational nature of the study. The results cannot be safely extrapolated to other regions of the world because the cohort sample was limited to inhabitants of Iran.

Key words: *vitamin, mineral, COVID-19, cohort population, Iran, logistic regression.*

АССОЦИАЦИЯ МЕЖДУ УПОТРЕБЛЕНИЕМ ПИЩЕВЫХ ДОБАВОК (ВИТАМИНОВ ИЛИ МИНЕРАЛОВ) И COVID-19 В ПЕРСИДСКОЙ КОГОРТЕ НАСЕЛЕНИЯ

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Резюме. Цель исследования заключалась в изучении связи между употреблением витаминов и минеральных добавок и возможностью заражения COVID-19 среди населения Ирана в 2020 г. В настоящем ретроспективном когортном исследовании приняли участие 4241 человек, зарегистрированных в Системе регистрации когорт. Была проведена логистическая регрессия для установления многомерной связи между демографи-

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ческими переменными, показателями здоровья, использованием пищевых добавок и вероятностью заражения участников COVID-19. В качестве программного обеспечения использовалось IBM SPSS 24.0, уровень значимости установлен 0,05. Проанализированы количественные переменные: при нормальном распределении — использовался независимый t-критерий, при отклонении от нормального распределения — критерий Манна–Уитни. Для сравнения распределения качественных переменных в группах использовался критерий хи-квадрат или, при необходимости, точный критерий Фишера. Число участников проведенного когортного исследования составило 4241, средний возраст участников — 49,22±8,77. Значение ОШ возрастной переменной 0,989 (95% ДИ: 0,927–1,056); половая переменная (95% ДИ: 0,238–2,743, ОШ = 0,808); переменная ИМТ (95% ДИ: 0,927–1,056, ОШ = 0,953); переменная витамина D (95% ДИ: 0,333–6,769, ОШ = 1,502); переменная омега3 (95% ДИ: 0,410–7,688, ОШ = 1,776); переменная кальция (95% ДИ: 0,041–3,738, ОШ = 0,391); переменная кальция (95% ДИ: 0,041–3,738, ОШ = 391); переменная multiVIT (95% ДИ: 0,211–5,645, ОШ = 1,090); Переменная витамина C (95% ДИ: 0,000–0,000, ОШ = 0,000); переменная витамина E (95% ДИ: 0,000–0,000, ОШ = 0,000); были включены интервалы. Статистически значимых многомерных ассоциаций (P > 0,05) между объясняющими переменными инфицирования COVID-19 не выявлено. Единственная статистически достоверная корреляция обнаружена между употреблением таблеток железа и заражением COVID-19 (P = 0,025). Контроль переменных или выявление причинно-следственных связей невозможно из-за наблюдательного характера исследования. Результаты нельзя строго экстраполировать на другие регионы мира, поскольку когортная выборка была ограничена жителями Ирана.

Ключевые слова: *витамин, минерал, COVID-19, когортная популяция, Иран, логистическая регрессия.*

Introduction

The COVID-19 disease started in December 2019, and in a short period, the coronavirus spread worldwide as a pandemic [12]. By February 26, 2021, it had infected more than 113 million people in 200 countries, of whom 2.5 million had died [4]. The clinical spectrum of SARS-CoV-2 infection appears to be broad and includes asymptomatic infection, mild upper respiratory tract disease, severe viral pneumonia with respiratory failure, gastrointestinal problems, and even death [26].

The SARS-CoV-2 coronavirus enters the cells through the binding of its surface glycoproteins called spikes to the special cell receptor called angiotensin-converting enzyme 2. This enzyme belongs to the group of kinases and is found in different parts of the body. Still, the most common place of its accumulation is in the endothelium of the lungs' capillaries. The mentioned virus enters the respiratory epithelial cells through this receptor [16]. Breathing problems occur when the infection affects the lungs, causing pneumonia, and death is possible due to these symptoms in infected people. Despite the wide spread of this disease, the incidence of different people in different societies is not the same, and even the severity of the conflict is different for different people. The role of various factors, including weight and BMI level, is among the factors that have been considered effective in reducing the possibility of conflict and disease occurrence [19].

In addition, the role of the immune system in preventing conflict or reducing the symptoms of conflict has been mentioned in various studies. Also, the importance of nutritional sufficiency in terms of vitamins and minerals for strengthening the immune system is a very important and controversial issue that has been discussed separately in various studies. For example, Tipas et al. showed that a severe reduction of plasma vitamin A levels is significantly associated with ARDS and mortality in Corona disease [23]. Also, in a meta-analysis conducted by Kaya et al., it was shown that the possibility People who have low serum vitamin D levels are 1.64 times more likely to get COVID-19, and people who have serum 25(OH)D levels less than 20 ng/ml or 50 nmol/l are 2.42 times more likely to get COVID-19 [14]. Regarding vitamin C, several epidemiological studies show that adult patients with COVID-19 who had ARDS criteria according to the Berlin definition (up to 82% in one study) had low amounts of vitamin C [7, 24]. It has been shown that vitamin C increases resistance to infection caused by the coronavirus [2, 7]. In this regard, other studies showed that patients with severe COVID-19 have low levels of omega-3 in their blood [1, 18]. Many epidemiological studies have shown that low consumption of essential minerals in the diet plays an important role in preventing and reducing cardiovascular and cerebrovascular diseases [1, 15]. Therefore, the consumption of vitamin and mineral supplements to prevent infection in the post-corona period has increased to a great extent.

Dietary supplements are one of the widely used products that have been increasingly used in different societies in recent years, especially after the Corona virus. The wide variety and the claims made about the beneficial effects of these products have created a market of more than 30 billion dollars for these products in America. Recent evidence indicates that more than 50% of American people use at least one type of these products. In addition, 10% of people admit to consuming at least four types of these products.

Considering the prevalence of non-communicable diseases as a global problem, especially types of cancer and cardiovascular diseases, as the main causes of death, it has been proposed that the use

of vitamin-mineral supplements in the prevention of these diseases can be effective.

Previous clinical studies have implied that COVID-19 leads to diverse cardiovascular complications [8, 13, 21]. Preexisting cardiovascular diseases might be more susceptible to COVID-19 — induced heart injury [5].

However, the beneficial effects of preventive consumption of vitamin supplements in the prevention of these diseases have been discussed and doubted a lot in recent years, especially in people with a quality diet [10].

Based on this, due to the high preventive consumption of supplements in society, this study aims to investigate the hypothesis that the history of taking vitamin and mineral supplements for at least 6 months was effective in the initial infection of COVID disease in 2020 or not. Based on this, the present study was designed with the aim of investigating the association between the history of vitamin and mineral supplement consumption and the possibility of contracting the COVID-19 disease in the population of the Sabzevar cohort in Iran in 2020.

Materials and methods

This retrospective cohort study was conducted on 4241 people registered in the Sabzevar cohort system in 2020.

After approving the plan and obtaining the code of ethics, the required variables for the study were obtained from the Sabzevar Persian Cohort Center. Also, information about the patients with Corona until the end of 2020in the Persian cohort population was obtained from the information registration centers of the patients with COVID-19 at the hospital and health center.

Samples of this population who had a history of taking vitamin and mineral supplements (at least for 6 months) (including vitamins D, E, A, and C and minerals including Fe, Ca, and Selenium) in the case group and the control group from the population without history of supplement use were selected. Assimilation of confounding variables such as age, gender, etc. is done with each person in the case group. The rate of infection with COVID-19 until the end of 2019 was compared in two groups.

The method of measuring each variable based on the national cohort protocol was presented on the Persian Cohort Sabzevar website (https://www.medsab.ac.ir/index.aspx?siteid = 1&pageid = 6037). The method of scoring the above variables was stated in the Cohort Country Checklist (Cohort Data Dictionary).

People with a positive PCR test should be considered infected with COVID. Also, inpatients included all patients admitted to the hospital. The obtained data were analyzed based on the objectives of the study using statistical tests. Confidentiality of information and characteristics of people were observed in the research.

The data of the studied population was analyzed statistically after entering software. The description of the variables was based on the type of variable (quantitative-qualitative) using descriptive indicators (mean, standard deviation, frequency, and frequency percentage). To analyze the quantitative variables, the normality of the variables in the groups was determined using the Shapiro-Wilk test. Then, if the variable was normal, the independent t-test was used, and if the variable was not normal, the Mann-Whitney test was used. To compare the distribution of qualitative variables in the groups, a chi-square test or, if necessary, a Fisher's exact test was used. Also, a 95% CI was reported to check the risk factors. The software used was IBM SPSS 24.0, and a significance level of 0.05 was considered.

Results

The number of participants in this cohort study was 4241. The average age of the participants in the study was 49.22±8.77, body mass index (28.19±4.73), education level (9.47±4.89), and blood pressure (71.96±10.537) (Table 1).

There was no statistically significant correlation between the use of supplements and multivitamins and the possibility of contracting the COVID-19 disease ($P > 0.05$). There was only a statistically significant correlation between the use of iron tablets and contracting COVID-19 ($P = 0.025$). (Table 2).

A logistic regression was performed to ascertain the multivariate association between demographic, health variables, and supplement use and the likelihood that participants were infected with COVID-19. We performed multivariate logistic regression analy-

Table 1. Mean, median and standard deviation of age, blood pressure, level pf education, body mass index of people in study

		RightDBP1	RightSBP1	Age	EducationYears	BMI
N	Valid	4184	4184	4241	4241	4202
	Missing	57	57	0	0	39
Mean		71.96	114.50	49.22	9.47	28.19444
Median		70.00	112.00	49.00	9.00	27.92284
Std. Deviation		10.537	17.034	8.770	4.897	4.733909
Minimum		0	0	35	0	14.569
Maximum		140	240	72	22	57.778

Table 2. Correlation between vitamins and supplements with COVID-19

Variable	Value	df	Pearson Chi-Square Asymptotic Significance (2-sided)
Calcium	0.003a	1	0.957
MultiVIT	0.919a	1	0.338
vitD	0.064a	1	0.800
omega3	0.622a	1	0.430
Vit A	0.333a	1	0.564
Vit E	0.342a	1	0.558
zinc	1.029a	1	0.310
Fe	5.027a	1	0.025
Vit C	0.291a	1	0.590
Taking at least one supplement	0.328a	1	0.567

ses to control for the possible confounders such as age, sex, BMI.

The age variable is the 95% CI of 0.927 to 1.056, or decreased odds (OR = 0.989). Exposure is associated with lower odds of being infected with COVID-19 and does not reach statistical significance. A p value of 0.741 is indicated in Table 3. The sex variable's 95% CI of 0.238 to 2.743 spans 1.0, indicating decreased odds (OR = 0.808). Exposure is associated with lower odds of being infected with COVID-19 and does not reach statistical significance. A p value of 0.733. indicated in Table 3.

The BMI variable's 95% CI of 0.927 to 1.056 spans 1.0, indicating decreased odds (OR = 0.953). Exposure is associated with lower odds of being infected with COVID-19 and does not reach statistical significance. A p value of 0.412 is indicated in Table 3. The vitamin D variable's 95% CI of 0.333 to 6.769 spans 1.0, indicating increased odds (OR.502). Exposure to vitamin D was associated with higher odds of being infected with COVID-19, but there was no statistical significance. Table 3 shows a p value of 0.597. The omega3 variable's 95% CI of 0.410 to 7.688 spans 1.0, indicating increased odds (OR = 1.776). Exposure is associated with higher odds of being infected with COVID-19 but does not reach statistical significance. Table 3 shows a p value of 0.442.

The OR value of the vitE variable is 0.000 (95% CI: 0.000–0.000). Exposure does not affect the odds of being infected with COVID-19. Table 3 shows a p value of 0.999. The calcium variable, with a 95% CI of 0.0410 to 3.738, spans 1.0, indicating decreased odds (OR = 0.391). Exposure is associated with lower odds of being infected with COVID-19 and does not reach statistical significance. Table 3 shows a p value of 0.415. The multiVIT variable's 95% CI of 0.211 to 5.645 spans 1.0, indicating increased odds (OR = 1.090). Exposure is associated with higher odds of being infected with COVID-19 but does not reach statistical significance. Table 3 shows a p value of 0.442.

The ferrous variable's 95% CI of 0.166 to 3.398 spans 1.0, indicating decreased odds (OR = 0.750). Exposure is associated with lower odds of being infected with COVID-19 and does not reach statistical significance. Table 3 shows a p value of 0.709. The OR value of the VitC variable is 0.000 (95% CI: 0.000–0.000). Table 3 of the reference article shows a p value of 0.999.

The taking of at least one supplement variable (95% CI of 0.211 to 5.645 spans 1.0) increases the odds (OR = 1.074). Exposure is associated with higher odds of being infected with COVID-19 but does not reach statistical significance. Table 3 shows a p value of 0.932.

There were no statistically significant multivariate associations (p > 0.05) between the explanatory variables and infection with COVID-19 (Table 3).

Table 3. Logistic regression vitamin and supplement consumption with COVID-19

Variables in the Equation									
		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I. for EXP(B)	
								Lower	Upper
Step 1*	**age**	–0.011	0.033	0.109	1	0.741	0.989	0.927	1.056
	sex	–0.213	0.623	0.117	1	0.733	0.808	0.238	2.743
	BMI	–0.049	0.059	0.672	1	0.412	0.953	0.848	1.070
	Calcium	–0.938	1.151	0.664	1	0.415	0.391	0.041	3.738
	multiVIT	0.086	0.839	0.011	1	0.918	1.090	0.211	5.645
	vitD	0.407	0.768	0.280	1	0.597	1.502	0.333	6.769
	omega3	0.574	0.748	0.591	1	0.442	1.776	0.410	7.688
	vitE	–18.624	16633.603	0.000	1	0.999	0.000	0.000	0.000
	ferrous	–0.287	0.771	0.139	1	0.709	0.750	0.166	3.398
	vitC	–16.496	24912.129	0.000	1	0.999	0.000	0.000	0.000
	Taking at least one supplement	0.071	0.831	0.007	1	0.932	1.074	0.211	5.474
	Constant	–0.356	2.618	0.018	1	0.892	0.701		

Note. *Variable(s) entered on step 1: age, sex, education, BMI, WSI index, CalciumD, multiVIT, vitD, omega3, vitE, ferrous, vitC, Taking at least one supplement.

Discussion

This study was conducted with the aim of determining the association between the history of vitamin or mineral supplement consumption and the COVID-19 disease in the Iranian cohort population in 2020.

In our study, no correlation was found between age and the incidence of COVID-19, which is not consistent with other studies. In 2021 Irma Yupari-Azabache showed in a study that age is a risk factor for mortality (death) in patients hospitalized for COVID-19 [25].

In our study, no correlation was found between sex and the incidence of COVID-19, which is not consistent with other studies. Leanne Groban in 2020 [11] demonstrates that the intensity of the infection and its complications are more prominent in men. It has been postulated that the potential functional modulation of ACE2 by estrogen may explain the sex difference in morbidity and mortality.

In our study, no correlation was found between BMI and the incidence of COVID-19, which is not consistent with other studies. Naveed Sattar in 2020 [20] demonstrates high BMI is an independent risk factor for susceptibility to infection and requires further research.

In our study, no correlation was found between taking at least one supplement and the incidence of COVID-19, which is not consistent with other studies. RM Nimer, in 2022 [17], states that

there were no significant differences in the frequencies of severe illness and hospitalizations with the consumption of vitamin A, folic acid, vitamin B12, vitamin B complex, vitamin C, zinc, iron, selenium, calcium, magnesium, omega 3, and aspirin before the COVID-19 infection. Among the investigated nutrients, the use of vitamin D prior to the COVID-19 infection was associated with reduced disease severity and hospitalization. However, more studies are required to confirm this finding.

In our study, no correlation was found between the consumption of vitamin A and the incidence of COVID-19, which is not consistent with other studies. Tepasse et al. (2021), in a multicenter prospective observational cross-sectional study entitled "Vitamin A Plasma Levels in COVID-19 Patients: A Prospective Multicenter Study and Hypothesis" conducted on 40 patients, found a decrease in vitamin A levels Plasma was significantly associated with an increase in the level of inflammatory markers (CRP, ferritin and with markers of acute SARS-CoV-2 infection), a decrease in the number of lymphocytes, LDH, and in malignant patients, the level of vitamin A was significantly lower than in moderate patients [18] which is not consistent with our study, in our study there was no statistically significant relationship with the amount of vitamin A consumption and contracting COVID-19.

In our study, no correlation was found between the consumption of vitamin D and the incidence of COVID-19, which is not consistent with other studies. Kaya et al. (2021), in a systematic study and meta-analysis of observational studies entitled 'The role of vitamin D deficiency in COVID-19, showed that the probability of contracting COVID-19 is 1.64 times higher in people who have low serum vitamin D levels, and people whose OH-D25 serum level was less than 20 ng/ml or 50 nmol/l were 42.2 times more likely to suffer from severe COVID [14]. which is not consistent with the results of our study, which can be attributed to the low sample size of Kaya's study. In a cohort study, Cereda et al. examined 129 hospitalized adult patients with COVID-19. In this study, they showed that, although very low levels of vitamin D are likely to be effective in the prognosis of a patient infected with COVID, moderate vitamin D deficiency does not play a role in the prognosis of a person infected with COVID [6].

In our study, no correlation was found between the consumption of vitamin C and vitamin E.

Minkyung Bae in 2020 [3] demonstrated that vitamin C increases antiviral cytokines and free radical formation, decreasing viral yield. It also attenuates excessive inflammatory responses and the hyperactivation of immune cells. Amir Dehghani-Samani 2020 [9] in a systematic review showed that among all vitamins, the roles of vitamin A, C, D, and E are more defined and maybe more effective on the immune system, which emphasizes the importance of vitamins in the prevention of several viral infections like COVID-19. Therefore, sufficient vitamin intake can be recommended to prevent viral infections like the COVID-19 infection.

In our study, no correlation was found between the consumption of Omega-3 and the incidence of COVID-19, which is not consistent with other studies. Fadiyah et al., in a systematic review entitled "Potential of Omega-3 Supplementation for Disease" of 211 studies published between January 31, 2020, and September 1, 2021, that focused on omega-3 fatty acids, showed that patients with COVID-19 severely have low levels of omega-3 in their blood, and omega-3 was considered to reduce the risk of CoV-SARS infection and the duration of symptoms, overcome renal and respiratory dysfunction, and increase the survival rate in COVID-19 patients [10].

In our study, no correlation was found between the consumption of vitamin C and the incidence of COVID-19, which is not consistent with other studies. Tomasa et al. (2021), in a prospective study titled "COVID-19: Up to 82% of critically ill patients had low levels of vitamin C", showed that in patients with ARDS related to COVID-19, vitamin C status is very low. In our study, there was no significant correlation between COVID-19 and vitamin C [24].

In our study, people who did not take iron tablets were more likely to be infected with COVID-19,

and iron consumption had a statistically significant relationship with COVID. Erin Suriawinata and colleagues [22] stated in their research titled "Iron and iron-related proteins in COVID-19" that iron-related changes in COVID-19 so far include anemia of inflammation, low serum iron levels (hypoferemia), transferrin saturation, and high levels of serum ferritin (hyperferritinemia), hepcidin, lipocalin-2, catalytic, and soluble iron. Transferrin receptor (in ICU patients). Hemoglobin levels can be low or normal, and compromised hemoglobin function has been suggested. The membrane-bound transferrin receptor may facilitate virus entry, thus serving as a potential target for antiviral therapy.

Serum iron and ferritin levels can predict hospitalization, severity, and mortality from COVID-19. Serum hepcidin and ferritin/transferrin ratio can predict the severity of COVID-19.

Conclusion

Controlling the variables or identifying causal correlations is not feasible due to the observational nature of the study. There is evidence of omitted variable bias, even though a large number of explanatory variables were modeled and adjusted for. Furthermore, simultaneity bias poses a risk in the absence of well managed modifications of the explanatory variables. As stated differently, variance was occurring simultaneously as opposed to separately or in dependence. Additionally, the sample and the population of interest differed because this study used a cohort sample. It is not possible to properly extrapolate the results to Iran due to the cohort sample's limited concentration on Sabzevar inhabitants.

Additional information

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Study registration. N/A.

Disclosure of interests. The authors declare that she has no conflict of interests.

Ethical approval. Ethical approval in this study, all procedures performed on human samples were conducted following the relevant guidelines and regulations of the Helsinki Declaration. The study protocol was approved by the Research Ethics Committee in Iran (IR.MEDSAB.REC.1401.081).

Informed consent. Written informed consent was obtained from the participants for publication of this research.

Data sharing. Data are available under reasonable request to the corresponding author. The data are not publicly available due to their containing information that could compromise the privacy of research participant.

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