British Journal of Nutrition (2023), 130, 155–163 doi:10.1017/S0007114522003075

The association between B vitamins and the risk of COVID-19

Mina Darand[1]†, Shirin Hassanizadeh[1]†, Fahime Martami[2], Shamim Shams[3,4], Masoud Mirzaei[5] and Mahdieh Hosseinzadeh[3,4]*

[1]*Department of Clinical Nutrition, School of Nutrition and Food Science, Food Security Research Center, Isfahan University of Medical Sciences, Isfahan, Iran*

[2]*PhD student in Nutritional Sciences, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences (TUMS), Isfahan, Iran*

[3]*Nutrition and Food Security Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran*

[4]*Department of Nutrition, School of public health, Shahid Sadughi University of Medical Sciences, Yazd, Iran*

[5]*Yazd Cardiovascular Research Centre, Non-communicable Disease Institute, Shahid Sadoughi University of Medical Sciences, Yazd, Iran*

(Submitted 25 January 2022 – Final revision received 27 August 2022 – Accepted 21 September 2022 – First published online 9 November 2022)

Abstract

The fast spread of the coronavirus disease 2019 (COVID-19) epidemic and its high mortality were quickly noticed by the health community. B vitamins are essential micronutrients for the body with antioxidant, anti-inflammatory and immune-regulating properties. The present study can provide a comprehensive picture of the associations between B vitamins and COVID-19 incidence. This study was undertaken on 9189 adult participants of the Yazd Health Study (YaHS) and Taghzieh Mardom-e-Yazd (TAMIZ) study aged 20 to 69 years. Data on dietary intakes were obtained using a validated FFQ. Multivariable logistic regression analysis was used to evaluate the association between B vitamins and COVID-19. Our findings indicated that participants in the fourth quartile of vitamin B_5 intake compared with the first quartile had a protective effect against COVID-19 (OR: 0·53, 95 % CI 0·28, 0·99, *P*-trend = 0·02) after adjustment for all possible confounds in model 3. In addition, participants in the third quartile of vitamin B_{12} intake compared with the first quartile (OR: 0·63, 95 % CI 0·40, 0·98, *P*-trend = 0·11) had fewer odds of COVID-19 after full adjustments for confounders. Our findings indicated no significant relationship between dietary intake of vitamin B_1, B_2, B_3, B_9 and B-complex and COVID-19. A higher intake of vitamin B_5 could reduce the odds of COVID-19 by 47 %, and a moderate intake of vitamin B_{12} had a protective effect on COVID-19. Although our study has promising results, stronger clinical studies are needed.

Key words: Vitamin B: Vitamin B_{12}: Vitamin B_9: COVID-19

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), named after the 2019 novel coronavirus (COVID-19), is a viral disease that was discovered in late 2019 in Wuhan City, Hubei Province of China, and has spread rapidly around the world[1]. As of 4 December 2021, the incidence of coronavirus in the world is 265 million people, and the mortality rate is 5·24 million people. in Iran, almost 130 000 people have lost their lives due to coronavirus[2]. The disease has imposed a heavy economic burden on the health system[3,4] and can cause lifelong damage to the body's organs[5]. The severity of clinical manifestations and mortality rate of COVID-19 varies from person to person[6] and is strongly dependent on the individuals' immune system[7]. Nutrition and dietary components as modifiable factors can play a bilateral role in strengthening or weakening the immune system[8–10]. B vitamins (B_1, B_2, B_3, B_4, B_5, B_6, B_7, B_9 and B_{12}) are a group of water-soluble vitamins that are not synthesised in the human body. So, they must be consumed regularly in the diet. Many body functions, including energy production, methylation, synthesis, DNA repair and enzyme functions, depend on B vitamins' functions[11,12]. The deficiency of B vitamins suppresses immune functions in multiple ways and increases the susceptibility to infection[13,14]. Given the anti-inflammatory, antioxidant and immune enhancement effects of B vitamins, it is hypothesised that an adequate intake of rich sources of vitamin B can reduce the risk of COVID-19[14,15]. Few studies have been conducted on the association between B vitamins and inactivation of the coronavirus[16] and B vitamins and reduction of symptoms and damage

Abbreviations: COVID-19, coronavirus disease 2019; TAMIZ, Taghzieh Mardom-e-Yazd; YaHS, Yazd Health Study.

* **Corresponding author:** Mahdieh Hosseinzadeh, email hoseinzade.mahdie@gmail.com

† These authors are equal in the position of the first name

caused by COVID-19[17–20]. For example, the results of a review study demonstrated that treatment with cobalamin could improve COVID-19 damage. Another study reported that riboflavin and UV light decreased the titre of SARS-CoV-2 in both plasma and platelet products to below the limit of detection in tissue culture[16]. In another study, serum levels of vitamin B_{12} were associated with the clinical outcomes of COVID-19[21]. An observational study in Spain also found that 42·5 % of patients with COVID-19 had low levels of vitamin B_6[22]. This study can provide an association between dietary B vitamins and COVID-19 which may lead to other studies to be conducted in the future. Therefore, the purpose of the present study was to investigate the association between B vitamins and the COVID-19 incident.

Materials & methods

Study population

This study was conducted on the recruitment phase data of the Yazd Health Study (YAHS) and Taghzieh Mardom-e-Yazd (TAMIZ) that were conducted on a large sample of Iranians (www.yahs-ziba.com). YaHS is a population-based prospective cohort study designed to assess the changing incidence of a variety of chronic diseases and their associated risk factors among Iranian adults (aged 20–69 years) in Yazd, Iran. TAMIZ is a population-based prospective cohort study designed to assess the changing dietary habits and intake among Iranian adults (aged 20–69 years) in Yazd, Iran. For the present study, the data from both studies (YaHS and TAMIZ) were merged. Dietary information was extracted from the TAMIZ study, and other data were extracted from the YaHS study. Our survey initially included 10 208 adults, but 1019 were excluded due to unusual dietary intake (more than 6500 kcal and less than 600 kcal), taking dietary supplements containing B vitamins and having any type of cancer. Therefore, we ended up with 9189 adults for the final analysis. Please see the participants' selection algorithm (https://academic.oup.com/ije/article/47/3/697/4658812). The participants were selected from September 2014 to March 2016 based on the two-stage cluster sampling method according to the WHO STEP guidelines. First, 200 clusters were randomly selected based on the postal code of the city of residence. Second, the study was presented to them by interviewers, and they organised a meeting time at their domiciles. Finally, interviewers met fifty participants defined for each cluster (twenty-five men and twenty-five women) to interview based on the study protocol. There are five persons in each 10-year age group (20–29, 30–39, 40–49, 50–59 and 60–69 years). Moreover, due to the cohort nature of the YaHS study, the information is updated every 5 years and the incidence of various diseases is measured. According to the worldwide COVID-19 epidemic, the incidence of COVID-19 among participants was measured.

This study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human subjects/patients were approved by the ethics committee of Shahid Sadoughi University of Medical Sciences (Ethical approval code: IR.NIMAD.REC.1395·001, Date: 8 July 2014).

First, all participants signed informed written consent. Data on participants' general characteristics, history of chronic disease, physical activity, smoking history, anthropometric measurements and dietary assessment were collected using validated questionnaires. In order to evaluate the validity and reliability of the questionnaires, a pilot study was conducted on fifty participants before the start of the main study, and the results were reported and published by experts in each section. The reliability of the questionnaires was also confirmed by Cronbach's α of 0·89. More details of YaHS have been published elsewhere[23]. In addition to the previous questionnaires, a specific COVID-19 questionnaire was completed over the phone for all participants who were diagnosed with COVID-19 from February 2020 to February 2021, according to the Yazd Central Health database. In this questionnaire, they were asked whether or not they had undergone a diagnostic test for COVID-19. PCR tests were collected from participants. But our team conducted a PCR test for those without a PCR test or other diagnostic tests.

COVID-19 incidence measurement

The basis of the diagnosis of COVID-19 was PCR tests.[24]. The results of the PCR test were either reported by the participants themselves or the participants came back to the study team if they had symptoms or a COVID-19 suspicion, in which case the PCR test was performed by our research team. Also, serologic assays were used to estimate IgM and IgG antibodies in symptomatic or asymptomatic COVID subjects recovered from the disease. Serologic assays involving IgM and IgG antibodies to detect antibodies against SARS-CoV-2 were used as these antibodies can be detected from the second week of the start of COVID-19 symptoms, where IgM can be detected after the fourth day of infection and IgG has been found after the eighth day of disease onset. Serologic assays provide quick diagnostics by avoiding PCR false-positive or false-negative results. Additionally, these assays provide antibody patterns for the estimation of the strength and duration of humoral immunity[25].

Dietary assessment

Dietary intake was assessed in 2014–2016 using a 178-item semi-quantitative FFQ consisting of 551 questions about dietary intake over the past year[23]. In this FFQ, the intakes of all food groups, such as grains, fruits and vegetables, dairy products, legumes, sweets, and oils, were examined. The FFQ used in TAMIZ was a modified version of a previously validated 168-item FFQ applied to the Tehran Lipid and Glucose Study (TLGS). Ten items commonly consumed by Yazdi adults were added to the original 168-item FFQ, resulting in a 178-item FFQ. Furthermore, the 168-item FFQ used in TLGS was originally designed to be open-ended; however, in TAMIZ, we changed the questionnaire to a multiple-choice one. Also, in order to obtain accurate estimates, we rendered the portion size of food as a unit using a photo book for all participants. Two types of questions were asked of the participants about each food item: (1) the frequency of food consumption (number of times per month, week or day the food was consumed) in the previous year, and (2) the amount of the food that was usually consumed every time (portion size based on the standard serving sizes commonly consumed by Iranians). All reported intakes were converted to g/d by using household measures of consumed foods. Then we used Nutritionist IV software to calculate nutrient intakes[26]. The total B vitamins intake for each person was obtained by summing the content of B vitamins of all food items eaten. Recently, a subgroup of this cohort study's participants was asked if their eating habits had changed over the past few years, and the answer was no. In addition, because the participants live in a city whose people are conservative[27], their dietary patterns have not changed in the last 5 years, and their answers can be generalised to all participants. Also, considering the cohort nature of the data study and the effect of dietary patterns on the immune system over time, the association is justifiable because the immune system has a direct effect on the incidence of the disease. The questionnaire was designed by a trained reviewer.

Anthropometric measurements

Participants' weight was measured using a portable digital scale and the body analyzer (Omron Inc.), with an accuracy of 0·1 kg, with a minimum of clothing and without shoes. Height was measured in a standing position without shoes, with their heads in the Frankfurt position and their shoulder blades touching the straight wall to which the tape was attached. Also, BMI was calculated as weight (kg) divided by height squared (m).

Physical activity assessment

The level of daily PA was assessed using the short form of the International Physical Activity Questionnaire (IPAQ). PA is classified as low, medium and high according to the guidelines of the IPAQ short form[28]. The Persian translation validation of IPAQ was previously confirmed by Moghaddam et al.[29].

Statistical analysis

Study participants were categorised into quartiles based on their B vitamins intake in three models. The first category (the lowest intake) was considered as a reference. The second quartile was considered as the low intake, the third quartile as the moderate intake and the last quartile as the highest intake. Frequency and percentage were used to describe the qualitative variables. Multivariable logistic regression analysis was performed in different models to find the association between B vitamins intake and COVID-19. In model 1, we adjusted only age and total energy intake. In model 2, smoking status, physical activity, marital status, educational level, chronic disease, sex, physical activity, job status, house status (homeowner or tenant) and ethnicity (from Yazd or not from Yazd) were additionally adjusted. Final adjustments were made for BMI. Logistic regression results were reported as the OR and 95 % CI. All analyses were performed using the SPSS software (version 22; SPSS Inc). *P*-values < 0·05 were considered statistically significant.

Results

Characteristics of participants

We studied 9189 Iranian adults (48·4 % were men). Sixty-one per cent of participants were under 50 years old, 85 % were married, 15·5 % graduated from university, 86·9 % had never smoked, and 64·5 % were obese or overweight. In addition, 832 out of 9189 participants were infected with the coronavirus (9·1 %) (Table 1).

Dietary B vitamins intake and coronavirus

Multivariable-adjusted OR and 95 % CI for COVID-19 and B vitamins intake are shown in Table 2. Higher intake of vitamin B_5 (quartile 4) compared with the lowest intake (quartile 1) had a protective effect on COVID-19 after adjusting for model 3 (OR: 0. 53, CI 0·28, 0·99, *P*-trend = 0·02).

The highest intake of B_6 and B_7 (quartile 4) compared with the lowest intake (quartile 1) was associated with a lower odd of COVID-19 after adjusting for model 1 (OR_{B6}:0·60, CI 0·37, 0·96, *P*-trend = 0·006) and model 2, respectively (OR_{B7}:0·62, CI 0·44, 0·87, *P*-trend = 0·002). This significant association disappeared after further adjusting for BMI.

Moderate intake of vitamin B_{12} (quartile 3) compared with the lowest intake (quartile 1) (OR: 0·63, 95 % CI 0·40, 0·98, *P*-trend = 0·11) could reduce the odds of COVID-19 after adjusting for model 3. Our findings indicated no significant relationship between dietary intake of vitamin B_1, B_2, B_3, B_9 and B-complex and COVID-19.

In addition, there is a significant difference in the intake of B vitamins based on quartiles of consumption ($P < 0·05$). The intakes of our population in the fourth quartile compared with the RDA values for all B vitamins were multi-folded (Table 2).

Subgroup analysis based on BMI

An analysis stratified by BMI indicated that the highest intake of vitamin B_5 (quartile 4) compared with the lowest intake (quartile 1) significantly reduced the odds of COVID-19 in both groups after full controlling for confounders ($OR_{BMI < 25}$:0·45, CI 0·27, 0·77, *P*-trend = 0·003) and ($OR_{BMI \geq 25}$:0·02, CI 0·001, 0·62, *P*-trend = 0·01).

After controlling for confounders, the highest consumption of B_7 (quartile 4) (OR: 0·56, CI 0·38, 0·84, *P*-trend = 0·001) and B_{12} (OR: 0·62, CI 0·41, 0·95, *P*-trend = 0·01) compared with the lowest consumption (quartile 1) could significantly decrease the odds of COVID-19 only in individuals with BMI less than 25. However, the highest intake of vitamin B_6 (quartile 4) compared wih the lowest intake (quartile 1) (OR 0·01, 95 % CI 0·001, 0·74, *P*-trend = 0·02) could significantly decrease the odds of COVID-19 among those with a BMI greater than 25 after controlling for all possible confounders (Table 3).

Subgroup analysis based on chronic disease status

Stratified analysis based on chronic disease status (participants with at least one chronic disease, including high blood pressure, diabetes, CVD and dyslipidemia) indicated that the highest dietary intake of B_9 (quartile 4) (OR: 0·05, CI 0·006, 0·53, *P*-trend = 0·04) and B-complex compared with the lowest intake (quartile 1) (OR: 0·01, CI 0·001, 0·17, *P*-trend = 0·01) could significantly decrease the odds of COVID-19 in participants who have at least one chronic disease. In addition, moderate consumption of B_7 (quartile 3) (OR: 0·60, CI 0·37, 99, *P*-trend = 0·02) and B_{12} (OR: 0·58, CI 0·35, 0·98, *P*-trend = 0·14) compared with

https://doi.org/10.1017/S0007114522003075 Published online by Cambridge University Press

https://doi.org/10.1017/S0007114522003075 Published online by Cambridge University Press

Table 1. The distribution of the Yazd Health Study (YaHS) participants according to general characteristics

	Total (*n* 8728)	
Variables	*n*	%
Sex		
Male	4447	48·4
Female	4742	51·6
Age groups (years)		
20–29	1779	19·9
30–39	1810	20·3
40–49	1858	20·8
50–59	1771	19·8
60–69	1707	19·2
Education level		
Some primary/high school, diploma and graduate diploma	7510	84·5
Bachelors	1146	12·9
Masters and PhD	223	2·6
Smoking		
Never smoker	7565	86·9
Current smoker	964	11·1
Ex-smoker	172	2
Marital status		
Married	7592	85
Single	948	10·6
Widowed or divorced	393	4·4
BMI		
< 25	3152	35·5
≥ 25	5718	64·5
COVID-19 status		
Yes	832	9·1
No	8357	90·9

BMI is calculated as weight in kilograms divided by height in metres squared.

the lowest consumption (quartile 1) could decrease the odds of COVID-19 in participants who have no chronic disease after adjustments for all possible confounders (Table 4).

Subgroup analysis based on sex

Stratified analysis based on sex indicated that the highest intake of vitamin B_6 (quartile 4) in women compared with the lowest intake (quartile 1) could reduce the odds of COVID-19 after adjustments for all possible confounders in model 3 (OR: 0·07, CI 0·006, 0·84, *P*-trend = 0·01), while the moderate intake of vitamin B_6 (quartile 3) (OR: 0·66, CI 0·44, 0·97, *P*-trend = 0·08) in men compared with the lowest intake (quartile 1) was able to reduce the odds of COVID-19 after adjustments for all possible confounders. In addition, men with the highest intake (quartile 4) of vitamin B_5 (OR: 0·55, CI 0·34, 0·88, *P*-trend = 0·009) and B_7 (OR: 0·64, CI 0·45, 0·90, *P*-trend = 0·003) have shown the reduced odds of COVID-19 compared with those with the lowest intake (quartile 1) after full adjustments in model 3.

Discussion

In this relatively large population-based study of Iranian participants, we observed a statistically significant inverse association between dietary intake of B vitamin groups and the risk of COVID-19. The decreased odds of COVID-19 were limited to vitamins B_5, B_6, B_7 and B_{12}, and no significant odds reduction were observed for dietary intake of vitamins B_1, B_2, B_3, B_9 and B-complex.

Previous studies have mainly focused on the effect of dietary supplementation on COVID-19 risk reduction[30–34]. However, a large app-based community survey of 445 850 subjects in the UK, USA and Sweden reported that specific nutrients or dietary supplements are associated with modest reductions in COVID-19 risk (9–14 %)[35]. Our findings are in line with preliminary evidence indicating that optimal nutrition status may reduce the risk of infectious diseases[36–39]. Furthermore, several documents suggest the protective role of a balanced diet in COVID-19[40–43]. The results of a large survey indicated that high-diet quality was associated with lower risk and severity of COVID-19[44]. Another observational study in China investigated the relationship between nutritional status and clinical outcomes in patients with SARS-COV-2 infection. They found that patients with higher nutritional risk had worse outcomes, including a higher risk of mortality and more extended hospital stay[45]. Interestingly, diet is also proposed as a potentially responsible factor for differences in COVID-19 death rates between and within countries[46]. Therefore, based on the available evidence, not only may an appropriate diet containing an optimal amount of micronutrients and macronutrients play a preventive role against COVID-19 but also it can attenuate the clinical consequences in the affected person. Among the B vitamins evaluated in this study, dietary intake of vitamin B_5 showed the highest protective association with COVID-19. Dietary intake of vitamin B_5 was associated with about a 50 % reduction in the odds of COVID-19 when comparing the highest to the lowest quartile of intake. The protective effect of vitamin B_5 may partially be explained by its involvement in immune response as well as its anti-inflammatory properties[47–49]. Vitamin B_5 boosts macrophage maturation, increases macrophage phagocytosis, and promotes Th1 and Th17 cell differentiation[50].

The highest intake of B_6 and B_7 was also associated with a lower odd of COVID-19. However, this significant association disappeared after further adjustment for BMI. Unlike B_5, B_6 and B_7, whose highest intake was associated with the lowest risk of COVID-19, only moderate intake of B_{12} contributed to a significant reduction in the odds of COVID-19.

We also found evidence of a modifying effect of BMI, sex and chronic disease status on the association between B vitamins intake and the risk of COVID-19. A high dietary intake of vitamins B_6 and B_5, compared with the lowest intake, reduced the odds of COVID-19 in subjects with BMI ≥ 25. However, a high intake of vitamins B_5, B_7 and B_{12} compared with the lowest intake reduced the odds of COVID-19 among individuals with a BMI of less than 25. Therefore, it seems that the relationship between dietary intake of B vitamins and the risk of COVID-19 is affected by BMI. In addition, a high dietary intake of vitamins B_5 and B_7 compared with the lowest intake could reduce the odds of COVID-19 only in men. The significance of these findings is that men and subjects with BMI ≥ 25 are at higher risk for COVID-19 and its mortality[49,50]. The association between folic acid and COVID-19 has been suggested by recent studies[51,52]. A recent study demonstrated that folic acid inhibits the proteolytic protein furin, which promotes coronavirus activation[51]. Although in our main analysis, we did not find a

Table 2. Multivariable adjusted OR and 95 % CI for COVID-19 and B vitamin intake across quartiles of consumption in a sample of Iranian adults

Variables	Quartile 1 (lowest intake)	Quartile 2 (low intake)		Quartile 3 (moderate intake)		Quartile 4 (high intake)		*P*-trend
		OR	95 %	OR	95 %	OR	95 %	
Vitamin B_1								
Model 1	1	0·99	0·76, 1·28	0·87	0·65, 1·17	0·99	0·67, 1·47	0·57
Model 2	1	0·91	0·68, 1·24	0·77	0·55, 1·09	0·78	0·49, 1·23	0·14
Model 3	1	0·91	0·60, 1·40	0·84	0·52, 1·36	0·94	0·49, 1·78	0·61
The average intake								
Mean	1·29	1·89		2·50		4·09		0 ≤ 001
SD	0·28	0·34		0·47		1·66		
Cases/non-cases (*n*)	185/1981	212/2046		176/2011		150/1397		
Men/women (*n*)	946/1220	1064/1194		1115/1072		804/743		
Vitamin B_2								
Model 1	1	1·05	0·81, 1·36	0·91	0·66, 1·26	0·84	0·53, 1·34	0·43
Model 2	1	1·01	0·75, 1·37	0·78	0·53, 1·15	0·66	0·39, 1·14	0·09
Model 3	1	1·11	0·73, 1·70	0·89	0·53, 1·52	0·93	0·44, 1·94	0·62
The average intake								
Mean	1·32	1·90		2·79		4·89		
SD	0·24	0·29		0·60		2·17		
Cases/non-cases (*n*)	187/1984	210/2051		186/2042		140/1358		0 ≤ 001
Men/women (*n*)	965/1206	1074/1187		1144/1084		746/752		
Vitamin B_3								
Model 1	1	0·93	0·72, 1·22	0·93	0·68, 1·26	0·93	0·60, 1·45	0·64
Model 2	1	0·99	0·73, 1·33	0·89	0·62, 1·28	0·96	0·58, 1·59	0·62
Model 3	1	1·10	0·72, 1·68	0·95	0·57, 1·58	1·18	0·57, 2·42	0·94
The average intake								
Mean	15·33	22·58		32·73		59·45		
SD	3·27	4·05		7·71		27·27		
Cases/non-cases (*n*)	191/1970	192/2066		188/2022		152/1377		0 ≤ 001
Men/women (*n*)	963/1198	1082/1176		1116/1094		768/761		
Vitamin B_5								
Model 1	1	1·09	0·85, 1·41	0·89	0·66, 1·19	0·71	0·48, 1·04	0·07
Model 2	1	1·15	0·86, 1·54	0·78	0·55, 1·09	0·52	0·33, 0·82	0·003
Model 3	1	1·05	0·69, 1·59	0·73	0·45, 1·17	0·53	0·28, 0·99	0·02
The average intake								
Mean	3·52	5·10		8·03		13·62		
SD	0·78	0·80		3·62		7·20		
Cases/non-cases (*n*)	194/1969	207/2048		189/1995		133/1423		0 ≤ 001
Men/women (*n*)	951/1212	1069/1186		1122/1062		787/769		
Vitamin B_6								
Model 1	1	0·71	0·55, 0·93	0·62	0·45, 0·86	0·60	0·37, 0·96	0·006
Model 2	1	0·83	0·62, 1·12	0·60	0·41, 0·88	0·64	0·37, 1·11	0·02
Model 3	1	1·36	0·63, 2·94	1·09	0·56, 2·12	0·87	0·5, 1·49	0·18
The average intake								
Mean	1·26	1·93		3·11		6·03		
SD	0·46	0·57		0·99		2·76		
Cases/non-cases (*n*)	209/1961	192/2071		187/2074		135/1329		0 ≤ 001
Men/women (*n*)	967/1203	1113/1150		1115/1146		734/730		
Vitamin B_7								
Model 1	1	0·87	0·67, 1·11	0·68	0·52, 0·89	0·61	0·45, 0·81	0 < 001
Model 2	1	0·89	0·66, 1·19	0·71	0·52, 0·97	0·62	0·44, 0·87	0·002
Model 3	1	0·81	0·53, 1·23	0·68	0·44, 1·04	0·66	0·41, 1·04	0·04
The average intake								
Mean	9·19	14·64		21·55		44·46		
SD	4·12	2·45		13·64		29·27		
Cases/non-cases (*n*)	221/1818	188/1852		156/1884		158/1881		0 ≤ 001
Men/women (*n*)	912/1127	983/1057		1018/1022		1016/1023		
Vitamin B_9								
Model 1	1	1·06	0·82, 1·38	0·97	0·71, 1·30	1·02	0·68, 1·52	0·96
Model 2	1	1·11	0·82, 1·50	0·94	0·66, 1·34	0·94	0·59, 1·49	0·64
Model 3	1	1·16	0·76, 1·76	0·99	0·61, 1·60	1·03	0·54, 1·94	0·88
The average intake								
Mean	191·76	287·49		448·08		780·14		
SD	40·30	55·50		144·48		320·40		
Cases/non-cases (*n*)	188/1984	207/2050		185/2011		143/1390		0 ≤ 001
Men/women (*n*)	967/1205	1071/1186		1111/1085		780/753		
Vitamin B_{12}								
Model 1	1	0·89	0·69, 1·15	0·82	0·63, 1·08	0·83	0·60, 1·15	0·17

https://doi.org/10.1017/S0007114522003075 Published online by Cambridge University Press

British Journal of Nutrition

https://doi.org/10.1017/S0007114522003075 Published online by Cambridge University Press

Table 2. (*Continued*)

Variables	Quartile 1 (lowest intake)	Quartile 2 (low intake)		Quartile 3 (moderate intake)		Quartile 4 (high intake)		*P*-trend
		OR	95 %	OR	95 %	OR	95 %	
Model 2	1	0·78	0·58, 1·05	0·73	0·53, 1·00	0·73	0·51, 1·06	0·04
Model 3	1	0·64	0·42, 0·97	0·63	0·40, 0·98	0·72	0·43, 1·19	0·11
The average intake								
Mean	2·58	3·91		5·68		13·14		
SD	0·54	0·53		0·86		9·23		
Cases/non-cases (*n*)	192/1933	191/2009		192/1935		148/1558		0 ≤ 001
Men/women (*n*)	963/1162	1069/1131		1033/1094		864/842		
B-complex								
Model 1	1	1·11	0·85, 1·46	1·01	0·74, 1·37	0·95	0·64, 1·41	0·77
Model 2	1	1·11	0·81, 1·52	1·01	0·71, 1·44	0·88	0·55, 1·39	0·50
Model 3	1	1·13	0·72, 1·75	1·01	0·62, 1·65	0·93	0·50, 1·74	0·73
The average intake								
Mean	22·93	31·83		42·18		68·83		
SD	3·89	2·40		4·07		18·57		
Cases/non-cases (*n*)	177/1862	188/1852		176/1864		182/1857		0 ≤ 001
Men/women (*n*)	890/1149	988/1052		1014/1026		1037/1002		

Values are reported as OR and 95 % CI and mean (SD).
All average intakes were reported in mg except for B_7, B_9, and B_{12} which were reported in mcg.
Model 1: Adjusted for age and energy intake.
Model 2: model 1+ further adjustment for smoking status, physical activity, marital status, educational levels, chronic disease, sex, job status, house status (homeowner or tenant), ethnicity (from Yazd or not from Yazd).
Model 3: model 2+ further adjustment for BMI.
The Recommended Dietary Allowance (RDA) of B_1, B_2, B_3, B_5, B_6, B_9, and B_{12} for men ages 19 and older is 1·2 mg, 1·3 mg, 16 mg, 5 mg, 1·3 mg, 400 mcg, and 2·4 mcg daily and for women in the same age range is 1·1 mg, 1·1 mg, 14 mg, 5 mg, 1·3 mg, 400 mcg, and 2·4 mcg daily respectively. An RDA does not exist for B_7. Instead, the AI (Adequate Intake) level, for B_7 for men and women 19 years and older is 30 mcg daily.

Table 3. Multivariable adjusted OR and 95 % CI for COVID-19 based on B vitamins intake quartile stratifying by BMI

Variables	Quartile 1 (lowest intake)	Quartile 2 (low intake)		Quartile 3 (moderate intake)		Quartile 4 (high intake)		*P*-trend
		OR	95 % CI	OR	95 % CI	OR	95 % CI	
Vitamin B_1								
BMI < 25	1	0·84	0·59, 1·20	0·81	0·54, 1·21	0·88	0·51, 1·51	0·45
BMI ≥ 25	1	1·41	0·21, 9·47	0·17	0·01, 2·96	0·66	0·04, 9·16	0·49
Vitamin B_2								
BMI < 25	1	1·04	0·73, 1·47	0·86	0·56, 1·33	0·73	0·39, 1·36	0·22
BMI ≥ 25	1	0·32	0·03, 2·81	0·09	0·005, 1·75	0·12	0·005, 3·12	0·15
Vitamin B_3								
BMI < 25	1	0·85	0·60, 1·20	0·72	0·47, 1·10	0·81	0·44, 1·47	0·23
BMI ≥ 25	1	1·51	0·12, 19·07	2·33	0·17, 31·90	3·01	0·12, 73·50	0·52
Vitamin B_5								
BMI < 25	1	1·02	0·72, 1·43	0·73	0·50, 1·09	0·45	0·27, 0·77	0·003
BMI ≥ 25	1	0·66	0·11, 3·71	0·12	0·01, 1·33	0·02	0·001, 0·62	0·01
Vitamin B_6								
BMI < 25	1	0·70	0·50, 1·00	0·58	0·38, 0·91	0·62	0·32, 1·18	0·04
BMI ≥ 25	1	0·29	0·03, 2·21	0·07	0·005, 0·97	0·01	0·00, 0·74	0·02
Vitamin B_7								
BMI < 25	1	0·81	0·57, 1·14	0·62	0·43, 0·88	0·56	0·38, 0·84	0·001
BMI ≥ 25	1	1·01	0·14, 6·85	0·69	0·09, 5·02	0·37	0·04, 3·18	0·29
Vitamin B_9								
BMI < 25	1	1·02	0·72, 1·44	0·95	0·64, 1·42	0·93	0·54, 1·59	0·69
BMI ≥ 25	1	1·28	0·18, 9·15	0·10	0·005, 2·07	0·11	0·005, 2·78	0·07
Vitamin B_{12}								
BMI < 25	1	0·70	0·50, 0·99	0·67	0·46, 0·97	0·62	0·41, 0·95	0·01
BMI ≥ 25	1	0·28	0·02, 3·13	0·15	0·01, 2·06	1·05	0·13, 8·31	0·88
B-complex								
BMI < 25	1	1·07	0·74, 1·54	1·01	0·67, 1·52	0·87	0·51, 1·47	0·55
BMI ≥ 25	1	0·96	0·12, 7·26	0·23	0·02, 2·83	0·06	0·003, 1·55	0·06

Values are reported as OR and 95 % CI.
All values are adjusted for age, sex, energy intake, smoking status, physical activity, marital status, educational levels, chronic disease, job status, house status (homeowner or tenant) and ethnicity (from Yazd or not from Yazd).

Table 4. Multivariable adjusted OR and 95 % CI for COVID-19 based on B vitamins intake quartile stratifying by chronic disease status

Variables	Quartile 1 (lowest intake)	Quartile 2 (low intake)		Quartile 3 (moderate intake)		Quartile 4 (high intake)		*P*-trend
		OR	95 % CI	OR	95 % CI	OR	95 % CI	
Vitamin B_1								
Yes	1	0·72	0·25, 2·07	0·47	0·13, 1·66	0·51	0·09, 2·81	0·24
No	1	1·07	0·65, 1·76	0·94	0·54, 1·64	1·06	0·50, 2·23	0·88
Vitamin B_2								
Yes	1	1·00	0·36, 2·75	0·29	0·06, 1·37	0·21	0·02, 1·85	0·10
No	1	1·12	0·68, 1·85	1·06	0·58, 1·94	1·13	0·49, 2·60	0·94
Vitamin B_3								
Yes	1	1·18	0·40, 3·46	0·98	0·24, 3·92	1·62	0·19, 13·32	0·94
No	1	1·09	0·67, 1·78	0·99	0·55, 1·79	1·18	0·52, 2·67	0·89
Vitamin B_5								
Yes	1	0·94	0·34, 2·58	0·72	0·200, 2·59	0·09	0·008, 1·17	0·10
No	1	1·05	0·65, 1·70	0·74	0·43, 1·29	0·57	0·28, 1·15	0·09
Vitamin B_6								
Yes	1	0·56	0·18, 1·68	0·51	0·12, 2·12	0·32	0·03, 3·48	0·27
No	1	0·80	0·49, 1·29	0·65	0·35, 1·20	0·75	0·31, 1·82	0·32
Vitamin B_7								
Yes	1	1·34	0·45, 4·00	1·36	0·42, 4·37	1·21	0·31, 4·66	0·87
No	1	0·73	0·45, 1·19	0·60	0·37, 0·99	0·59	0·35, 1·00	0·02
Vitamin B_9								
Yes	1	0·92	0·33, 2·5	0·36	0·09, 1·39	0·05	0·006, 0·53	0·04
No	1	1·22	0·74, 1·99	1·12	0·64, 1·95	1·34	0·64, 2·77	0·55
Vitamin B_{12}								
Yes	1	0·78	0·28, 2·15	0·81	0·26, 2·50	0·57	0·14, 2·30	0·40
No	1	0·59	0·36, 0·96	0·58	0·35, 0·98	0·70	0·39, 1·25	0·14
B-complex								
Yes	1	0·68	0·23, 2·01	0·47	0·13, 1·66	0·01	0·001, 0·17	0·01
No	1	1·21	0·72, 2·03	1·14	0·64, 2·01	1·35	0·66, 2·76	0·51

Values are reported as OR and 95 % CI.
All values are adjusted for age, sex, energy intake, smoking status, physical activity, marital status, educational levels, job status, house status (homeowner or tenant), ethnicity (from Yazd or not from Yazd) and BMI.

significant relationship between dietary intake of vitamin B_9 and B-complex and risk of COVID-19, stratified analysis based on chronic disease status revealed a protective effect on COVID-19 in the highest quartile in participants who have at least one chronic disease. In the present study, the average consumption of folic acid in participants who have at least one chronic disease in comparing those without chronic disease was less. These findings may be attributed to the fact that B vitamins, including vitamin B_9, contribute to the healthy balance of the immune system. Additionally, vitamin B_9 is involved in the production of nucleic acids, protein synthesis, and involvement in crucial metabolic processes, such as methylation and the serine, glycine, and purine cycles. Inefficient methylation can result in hyperhomocysteinemia, which contributes to the pathogenesis of many diseases[48]. Hence, a high intake of B vitamins, especially B_9 in the chronic diseases group, may alleviate these conditions.

Interestingly, in the case of B_7 and B_{12}, significant inverse associations were observed only across moderate consumption in participants who had no chronic disease. This can indicate that each micronutrient in its optimal amount can have protective effects, and not necessarily the higher the intake, the lower the risk of disease. In addition, a previous study revealed that there is a positive association between vitamin intake and plasma concentrations. However, determinants such as sex, age and energy intake should be considered[53].

The observed inverse associations between B vitamins intake and COVID-19 risk may be explained by their influence on a variety of biological functions. B vitamins are involved in cell functioning, energy metabolism and proper immune function[48]. B vitamins play an important role in the proper activation of both the innate and adaptive immune responses; they suppress the secretion of pro-inflammatory cytokines; they enhance respiratory function; they support endothelial integrity; besides, they can shorten hospital stays[14,54,55]. Some evidence suggests B vitamins deficiency can significantly impair cell and immune system function and contribute to inflammation resulting from hyperhomocysteinemia[48,55].

Notably, the B vitamins have been shown to have an intestinal bacterial source and a food source, suggesting that the normal intestinal microbiome may have always been the primary source of B vitamins[56]. However, several factors, including lifestyle changes following lockdown and vitamin D deficiency, change the intestinal microbiome, reducing B vitamin production in the gut[57,58]. Considering the beneficial effects of B vitamins in reducing COVID-19 risk and the possibility of disruption in intestinal production of B vitamins, dietary intake of these vitamins needs more attention. Therefore, considering enough intake of rich foods of B vitamin within a healthy diet could lead to attenuating the odds of COVID-19

In this study, no association was found between the intake of vitamins B_1, B_2 and B_3 with the odds of COVID-19, neither in the total analysis nor in the subgroup analyses. These results align with the Deschasaux-Tanguy et al. study[59]. These results are unclear but may be explained by the fact that COVID-19 patients may not suffer from these vitamin deficiencies. Our study investigated the association between dietary intake of B vitamins and the risk of COVID-19 in a large sample of Iranian adults. However, several limitations should be considered in this study. First, recall bias may not be exactly excluded because of the retrospective nature of dietary assessment by FFQ. Second, as an observational study, we are unable to show a causal relationship between B vitamins and COVID risk. Third, we could not assess the correlations between B vitamins intake and plasma levels. Fourth, no information on COVID-19 severity was available. In addition, although we considered the most important confounding variables, there would be some residual confounders that we failed to assess

Conclusion

In conclusion, an inverse association between dietary intake of B vitamins and the risk of COVID-19 was observed in the current study. Results from this study could expand previous findings on nutrition implication in COVID-19 risk and highlight the potential protective effects of dietary intake of B vitamins. Our data support the hypothesis that individuals should not only rely on dietary supplements and adherence to a healthy diet consisting of an optimal amount of macronutrients and micronutrients, especially B vitamins, which could be beneficial in preventing COVID-19. Although the protective role of nutrients against COVID-19 seems promising, further research is needed to better understand the different nutrient implications in both prevention and treatment of COVID-19.

Acknowledgements

Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

This article has no funding.

M. H.: supervision, study concept and design analysis of data, review and editing; M. D.: drafting the manuscript; S. H.: analysis of data and statistical analysis; A. M.: data collection; M. M.: revising the manuscript; and F. M. and S. S.: writing the manuscript.

The authors declare no conflicts of interest related to this study.

References

1. Khanna RC, Cicinelli MV, Gilbert SS, *et al.* (2020) COVID-19 pandemic: lessons learned and future directions. *Indian J Ophthalmol* **68**, 703.
2. Miller M (2019) Novel Coronavirus COVID-19 (2019-nCoV) Data Repository: Johns Hopkins University Center for Systems Science and Engineering. Bulletin-Association of Canadian Map Libraries and Archives (ACMLA), 30 March 2020, No. 164, pp. 47–51.
3. McArthur L, Sakthivel D, Ataide R, *et al.* (2020) Review of burden, clinical definitions, and management of COVID-19 cases. *Am J Trop Med Hyg* **103**, 625–638.
4. Jin H, Wang H, Li X, *et al.* (2021) Economic burden of COVID-19, China, January–March, 2020: a cost-of-illness study. *Bull World Health Org* **99**, 112.
5. Yelin D, Wirtheim E, Vetter P, *et al.* (2020) Long-term consequences of COVID-19: research needs. *Lancet Infect Dis* **20**, 1115–1117.
6. Baj J, Karakuła-Juchnowicz H, Teresiński G, *et al.* (2020) COVID-19: specific and non-specific clinical manifestations and symptoms: the current state of knowledge. *J Clin Med* **9**, 1753.
7. Paces J, Strizova Z, Smrz D, *et al.* (2020) COVID-19 and the immune system. *Physiol Res* **69**, 379.
8. Venkatraman JT & Pendergast DR (2002) Effect of dietary intake on immune function in athletes. *Sports Med* **32**, 323–337.
9. Watson RR, Zibadi S & Preedy VR (2010) *Dietary Components and Immune Function*. Berlin: Springer Science & Business Media.
10. Darand M, Hassanizadeh S, Marzban A, *et al.* (2022) The association between dairy products and the risk of COVID-19. *Eur J Clin Nutr* **76**, 1583–1589.
11. Herrmann W & Obeid R (2011) *Vitamins in the Prevention of Human Diseases*. Berlin: Walter de Gruyter.
12. LeBlanc JG & de Giori GS (2018) *B Group Vitamins - Current Uses and Perspectives* [Internet]. London: IntechOpen, 154 p. https://www.intechopen.com/books/6709 (accessed November 2022).
13. Maggini S, Pierre A & Calder PC (2018) Immune function and micronutrient requirements change over the life course. *Nutrients* **10**, 1531.
14. Shakoor H, Feehan J, Mikkelsen K, *et al.* (2021) Be well: a potential role for vitamin B in COVID-19. *Maturitas* **144**, 108–111.
15. Manzanares W & Hardy G (2020) Vitamin B12 Pharmaconutrition for COVID-19 Farmaconutrición de la Vitamina B12 Para COVID-19. https://doi.org/10.35454/rncm.v4n1.187 (accessed September 2020).
16. Keil SD, Ragan I, Yonemura S, *et al.* (2020) Inactivation of severe acute respiratory syndrome coronavirus 2 in plasma and platelet products using a riboflavin and ultraviolet light-based photochemical treatment. *Vox Sang* **115**, 495–501.
17. Desbarats J (2020) Pyridoxal 5'-phosphate to mitigate immune dysregulation and coagulopathy in COVID-19. https://doi.org/10.20944/preprints202005.0144.v1 (accessed May 2020).
18. dos Santos LMJ (2020) Can vitamin B_{12} be an adjuvant to COVID-19 treatment? *GSC Biol Pharm Sciences* **11**, 001–005.
19. Sheybani Z, Dokoohaki MH, Negahdaripour M, *et al.* (2020) The role of folic acid in the management of respiratory disease caused by COVID-19. *Preprint* **12034980**, v1.
20. Tan CW, Ho LP, Kalimuddin S, *et al.* (2020) Cohort study to evaluate the effect of vitamin D, magnesium, and vitamin B(12) in combination on progression to severe outcomes in older patients with coronavirus (COVID-19). *Nutrition* **79–80**, 111017.
21. Shakeri H, Azimian A, Ghasemzadeh-Moghaddam H, *et al.* (2021) Evaluation of the relationship between serum levels of zinc, vitamin B_{12}, vitamin D, and clinical outcomes in patients with COVID-19. *J Med Virol* **94**, 141–146.
22. Tomasa-Irriguible T-M, Bielsa-Berrocal L, Bordejé-Laguna L, *et al.* (2021) Low levels of few micronutrients may impact COVID-19 disease progression: an observational study on the first wave. *Metabolites* **11**, 565.
23. Mirzaei M, Salehi-Abargouei A, Mirzaei M, *et al.* (2018) Cohort profile: the Yazd Health Study (YaHS): a population-based study of adults aged 20–70 years (study design and baseline population data). *Int J Epidemiol* **47**, 697–698h.
24. Tahamtan A & Ardebili A (2020) Real-time RT-PCR in COVID-19 detection: issues affecting the results. *Expert Rev Mol Diagnostics* **20**, 453–454.
25. Nakano Y, Kurano M, Morita Y, *et al.* (2021) Time course of the sensitivity and specificity of anti-SARS-CoV-2 IgM and IgG antibodies for symptomatic COVID-19 in Japan. *Sci Rep* **11**, 1–10.

26. Bodner-Montville J, Ahuja JK, Ingwersen LA, *et al.* (2006) USDA food and nutrient database for dietary studies: released on the web. *J Food Compos Anal* **19**, S100–S107.
27. Abbasi-Shavazi MJ & McDonald P (2007) *Family Change in Iran: Religion, Revolution, and the State. International Family Change*, pp. 191–212. Milton Park: Routledge.
28. Committee IR (2005) Guidelines for Data Processing and Analysis of the International Physical Activity Questionnaire (IPAQ)-Short and Long Forms. http://wwwipaqkise/scoringpdf (accessed November 2005).
29. Moghaddam MB, Aghdam FB, Jafarabadi MA, *et al.* (2012) The Iranian Version of International Physical Activity Questionnaire (IPAQ) in Iran: content and construct validity, factor structure, internal consistency and stability. *World Appl Sci J* **18**, 1073–1080.
30. Khalagi K, Gharibzadeh S, Khalili D, *et al.* (2021) Prevalence of COVID-19 in Iran: results of the first survey of the Iranian COVID-19 Serological Surveillance programme. *Clin Microbiol Infection* **27**, 1666–1671.
31. Grant WB, Lahore H, McDonnell SL, *et al.* (2020) Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. *Nutrients* **12**, 988.
32. Mercola J, Grant WB & Wagner CL (2020) Evidence regarding vitamin D and risk of COVID-19 and its severity. *Nutrients* **12**, 3361.
33. Carr AC & Rowe S (2020) The emerging role of vitamin C in the prevention and treatment of COVID-19. *Nutrients* **12**, 3286.
34. McPherson SW, Keunen JE, Bird AC, *et al.* (2020) Investigate oral zinc as a prophylactic treatment for those at risk for COVID-19. *Am J Ophthalmol* **216**, A5.
35. Louca P, Murray B, Klaser K, *et al.* (2021) Modest effects of dietary supplements during the COVID-19 pandemic: insights from 445 850 users of the COVID-19 Symptom Study app. *BMJ Nutr, Prev Health* **4**, 149.
36. Calder PC (2020) Nutrition, immunity and COVID-19. *BMJ Nutr Prev Health* **3**, 74.
37. Belanger MJ, Hill MA, Angelidi AM, *et al.* (2020) Covid-19 and disparities in nutrition and obesity. *New Engl J Med* **383**, e69.
38. Smith VH, Jones TP & Smith MS (2005) Host nutrition and infectious disease: an ecological view. *Front Ecol Environ* **3**, 268–274.
39. Farhadi S & Ovchinnikov RS (2018) The relationship between nutrition and infectious diseases: a review. *Biomed Biotechnology Res J* **2**, 168.
40. Jayawardena R & Misra A (2020) Balanced diet is a major casualty in COVID-19. *Diabetes Metab Syndrome* **14**, 1085.
41. Ambati K & Sucharitha K (2020) An overview of balanced diet on covid-19. *J Inf Comput Sci* **13**, 7–13.
42. Aman F & Masood S (2020) How nutrition can help to fight against COVID-19 pandemic. *Pak J Med Sci* **36**, S121.
43. Lohi AS & Sawarkar G (2020) Management of diet during COVID-19 pandemic. *Int J Res Pharm Sci* **11**, 154–157.
44. Merino J, Joshi AD, Nguyen LH, *et al.* (2021) Diet quality and risk and severity of COVID-19: a prospective cohort study. *Gut* **70**, 2096–2104.
45. Zhao X, Li Y, Ge Y, *et al.* (2021) Evaluation of nutrition risk and its association with mortality risk in severely and critically ill COVID-19 patients. *J Parenteral Enteral Nutr* **45**, 32–42.
46. Bousquet J, Anto JM, Iaccarino G, *et al.* (2020) Is diet partly responsible for differences in COVID-19 death rates between and within countries? *Clin Transl Allergy* **10**, 16.
47. Jung S, Kim M & Choi B (2017) The long-term relationship between dietary pantothenic acid (vitamin B_5) intake and C-reactive protein concentration in adults aged 40 years and older. *Nutr, Metab Cardiovasc Dis* **27**, 806–816.
48. Mikkelsen K & Apostolopoulos V (2019) Vitamin B1, B2, B3, B5, and B6 and the Immune System. In *Nutrition and Immunity*, pp. 115–125 [M Mahmoudi and N Rezaei, editors]. Cham: Springer International Publishing.
49. Gheita AA, Gheita TA & Kenawy SA (2020) The potential role of B_5: a stitch in time and switch in cytokine. *Phytother Res* **34**, 306–314.
50. He W, Hu S, Du X, *et al.* (2018) Vitamin B_5 reduces bacterial growth via regulating innate immunity and adaptive immunity in mice infected with Mycobacterium tuberculosis. *Front Immunol* **9**, 365.
51. Meisel E, Efros O, Bleier J, *et al.* (2021) Folate levels in patients hospitalized with Coronavirus Disease 2019. *Nutrients* **13**, 812.
52. Wiltshire E, Peña AS, MacKenzie K, *et al.* (2020) High dose folic acid is a potential treatment for pulmonary hypertension, including when associated with COVID-19 pneumonia. *Med Hypotheses* **143**, 110142.
53. Baart AM, Balvers MGJ, de Vries JHM, *et al.* (2021) Relationship between intake and plasma concentrations of vitamin B_{12} and folate in 873 adults with a physically active lifestyle: a cross-sectional study. *J Hum Nutr Diet* **34**, 324–333.
54. Michele CA, Angel B, Valeria L, *et al.* (2020) Vitamin supplements in the era of SARS-Cov2 pandemic. *GSC Biol Pharm Sciences* **11**, 007–019.
55. Mahmoudi M & Rezaei N (2019) *Nutrition and Immunity*. Cham: Springer.
56. LeBlanc JG, Milani C, De Giori GS, *et al.* (2013) Bacteria as vitamin suppliers to their host: a gut microbiota perspective. *Curr Opin Biotechnol* **24**, 160–168.
57. Gominak S (2016) Vitamin D deficiency changes the intestinal microbiome reducing B vitamin production in the gut. The resulting lack of pantothenic acid adversely affects the immune system, producing a ‘pro-inflammatory’ state associated with atherosclerosis and autoimmunity. *Med Hypotheses* **94**, 103–107.
58. Zuo T, Wu X, Wen W, *et al.* (2021) Gut microbiome alterations in COVID-19. *Genomics, Proteomics Bioinformatics* **19**, 679–688.
59. Deschasaux-Tanguy M, Srour B, Bourhis L, *et al.* (2021) Nutritional risk factors for SARS-CoV-2 infection: a prospective study within the NutriNet-Santé cohort. *BMC Med* **19**, 290.