Habitual use of vitamin D supplements and risk of coronavirus disease 2019 (COVID-19) infection: a prospective study in UK Biobank

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ABSTRACT

Background: Previous studies have related vitamin D supplementation to a lower risk of acute respiratory tract infection. Emerging evidence suggests that vitamin D insufficiency is related to a higher risk of coronavirus disease 2019 (COVID-19) infection.

Objectives: We aimed to investigate the prospective association between habitual use of vitamin D supplements and risk of COVID-19 infection, and assess whether such an association differed according to the different levels of circulating and genetically predicted vitamin D.

Methods: This study included 8297 adults who have records of COVID-19 test results from UK Biobank (from 16 March 2020 to 29 June 2020). The use of vitamin D supplements, circulating vitamin D levels, and main covariates were measured at baseline (2006–2010). Genetically predicted vitamin D levels were evaluated by genetic risk score.

Results: After adjustment for covariates, the habitual use of vitamin D supplements was significantly associated with a 34% lower risk of COVID-19 infection (OR, 0.66; 95% CI, 0.45–0.97; $P = 0.034$). Circulating vitamin D levels at baseline or genetically predicted vitamin D levels were not associated with the risk of COVID-19 infection. The association between the use of vitamin D supplements and the risk of COVID-19 infection did not vary according to the different levels of circulating or genetically predicted vitamin D (P-interactions = 0.75 and 0.74, respectively).

Conclusions: Our findings suggest that habitual use of vitamin D supplements is related to a lower risk of COVID-19 infection, although we cannot rule out the possibility that the inverse association is due to residual confounding or selection bias. Further clinical trials are needed to verify these results. *Am J Clin Nutr* 2021;113:1275–1281.

Keywords: vitamin D supplement, COVID-19, SARS-CoV-2, circulating vitamin D level, genetic risk score

Introduction

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread into a pandemic worldwide. As of early July, COVID-19 infection has affected more than 11.6 million individuals and caused nearly 539,000 deaths worldwide.

Emerging evidence suggests that vitamin D insufficiency is related to a higher risk of severity of COVID-19 infection (1, 2). Vitamin D is a fat-soluble vitamin that plays a critical role in the prevention of falls and fractures and promotes calcium absorption in the gut (3). Humans obtain vitamin D from exposure to sunlight, diet, and dietary supplements (4). In addition, evidence indicates that vitamin D may also have an important function within the immune system (5, 6), especially in the prevention of acute respiratory tract infections. Previous observational studies have shown a consistent association between low levels of circulating

vitamin D and susceptibility to acute respiratory tract infections ([7], [8]). A body of clinical trials have shown that vitamin D supplementation could significantly decrease the risk of developing an acute respiratory tract infection ([9–11]). Notably, evidence from several studies suggests that the use of vitamin D supplements may be linked to a lower risk of COVID-19 infection ([12–14]); however, no prospective study has evaluated such an association.

In this study, we aimed to prospectively investigate the association between habitual use of vitamin D supplements and risk of COVID-19 infection in a subset of records in UK Biobank. We also assessed whether such an association differed according to the different levels of circulating or genetically predicted vitamin D.

Methods

Study population

The UK Biobank is a large, population-based cohort study comprising more than half a million participants aged 37–73 y living in the United Kingdom. The details of the study design have been described previously ([15]). All participants provided written informed consent and the study was approved by the National Health Service National Research Ethics Service. The current analyses were restricted to participants who have records of COVID-19 test results from 22 assessment centers (between 16 March 2020 and 29 June 2020). We excluded participants with incomplete data on the use of vitamin D supplements, serum vitamin D, and cigarettes ([16], [17]). A total of 8297 participants were included in the final analysis (**Supplementary Figure 1**).

UK Biobank received ethical approval from the North West Multi-Center Research Ethics Committee (REC reference: 11/NW/0,3820). All participants gave written informed consent before enrollment in the study, which was conducted in accordance with the principles of the Declaration of Helsinki.

Exposure assessment

The use of vitamin D supplements was the primary exposure of interest in this study. Information on vitamin D supplement use was collected through the baseline touch-screen questionnaire (2006–2010). Participants were asked "Do you regularly take any of the following?". Participants selected more than 1 answer from 2 lists of supplements through the touch-screen questionnaire (UK Biobank Field identifier: 6155 and 6179). Individual vitamins, minerals, or other supplements were listed in the questionnaire, and the available options included vitamin A, vitamin B, vitamin C, vitamin D, vitamin E, folic acid, a multivitamin, calcium, zinc, iron, selenium, glucosamine, fish oil, "prefer not to answer," and "none of the above." If a participant selected "prefer not to answer," we treated this as a missing variable and excluded it from our analysis. Whether someone was a vitamin D user was coded as 0 for no or 1 for yes.

We created a genetic risk score (GRS) for circulating vitamin D levels using 6 single-nucleotide polymorphisms (SNPs) that passed quality control measures based on a previous study (**Supplementary Table 1**) ([18]). A weighted method was used to calculate the GRS for vitamin D (GRS-VD). Each SNP was recoded as 0, 1, or 2 according to the number of risk alleles, and each SNP was multiplied by a weighted risk estimate

(β coefficient) on circulating vitamin D obtained from the previous meta-analysis of genome-wide association studies. The genetic risk score was calculated using the equation GRS = ($\beta1 \times$ SNP1+$\beta2 \times$ SNP2+…+$\beta6 \times$ SNP6) $\times$ (6/sum of the β coefficients). The GRS-VD scores ranged from 1.2 to 12.0. Detailed information about genotyping, imputation, and quality control in the UK Biobank study have been described previously ([19]). Genetic data were available for 7549 white participants in this study, after excluding participants with sex discordance or high missingness/heterozygosity on the genetic data.

Serum vitamin D (nmol/L) was measured by chemiluminescence immunoassay analysis on a DiaSorin Ltd. LIASON XL. Calibration and quality control were conducted by the UK Biobank. The blood samples were collected at baseline (2006–2010). In the analysis, we categorized circulating vitamin D levels, in nmol/L, into 3 categories: <25 nmol/L (deficiency), 25–50 nmol/L (insufficiency), and >50 nmol/L (sufficiency) ([20]). Detailed information on these measurements is provided at the UK Biobank website (https://biobank.ctsu.ox.ac.uk/showcase).

Covariates assessment

A touch-screen questionnaire was used to assess the potential confounders at baseline (2006–2010), including age, sex, race (self-identified), assessment centers, education level, Townsend deprivation index [TDI; TDI is a composite measure of deprivation based on unemployment, non–car ownership, non–home ownership, and household overcrowding; a higher Townsend index score implies a greater degree of deprivation ([21])], physical activity, smoking status, alcohol intake, and dietary intakes (red meat intake, vegetable intake, fruit intake, fish intake). Obesity was defined as a BMI [calculated as weight (kg) divided by height in meters squared (m^2)] $\geq$30 kg/m^2. A healthy diet score was evaluated by red meat intake <2 times/wk (median), vegetable intake $\geq$4 times/wk (median), fruit intake $\geq$2.5 times/wk (median), and fish intake $\geq$2 times/wk (median). Each favorable diet factor was assigned 1 point, and the total diet score ranges from 0 to 4. Hypertension was defined as a self-reported history of hypertension, a systolic blood pressure $\geq$140 mmHg or a diastolic blood pressure $\geq$90 mm Hg, or taking antihypertensive medications. High cholesterol was defined as a self-reported history of high cholesterol or taking cholesterol medications. Diabetes was evaluated by a UK Biobank algorithm for the diagnosis of diabetes ([22]). Cardiovascular disease was defined as self-reported history of coronary heart disease or stroke. Cancer was defined as a self-reported history of cancer. Chronic obstructive pulmonary disease (COPD) was evaluated by a UK Biobank algorithm for the diagnosis of COPD (https://biobank.ctsu.ox.ac.uk/showcase/label.cgi?id=42). Asthma was evaluated by a UK Biobank algorithm for the diagnosis of asthma (https://biobank.ctsu.ox.ac.uk/showcase/label.cgi?id=42). For analyses on the genetic data, we also adjusted for the first 10 genetic principal components, a genotyping array, and third-degree relatedness. Detailed information on covariates is also fully described in the **Supplemental Methods**.

Ascertainment of the COVID-19 infection

The primary outcome is the risk of COVID-19 infection. We used the records of COVID-19 test results provided by UK

Biobank (between 16 March 2020 and 29 June 2020). The vast majority of samples tested for COVID-19 are from combined nose/throat swabs that were transported in a medium suitable for viruses (a balanced salt solution) for PCR to be performed. Detailed information on the records of COVID-19 test results in the UK Biobank has been described previously (http://biobank.nd ph.ox.ac.uk/showcase/exinfo.cgi?src=COVID19_availability).

Statistical analysis

A chi-square test for categorical variables and general linear models for continuous variables were applied to compare proportions or means of characteristics between the users and nonusers of vitamin D. Logistic regression models were used to calculate the ORs when comparing COVID-19 infection rates in participants who did and did not use vitamin D supplements. Several potential confounders were adjusted in these models, including research centers, laboratory (laboratory that processed the COVID-19–related sample) and origin (whether the patient was an inpatient when the COVID-19 sample was taken), blood-type haplotype, age (<50, 50–59, or ≥60 y old), sex, race (white, mixed race, Asian, Black, Chinese, and others), years of education (<15 or ≥15 y), TDI, smoking status (never, past, and current), moderate physical activity (≥150 min/wk or <150 min/wk), moderate drinking (women: >0 and ≤14 g/d, men: >0 and ≤28 g/d), any other supplement use (yes or no), healthy diet score, obesity (yes or no), hypertension (yes or no), high cholesterol (yes or no), cardiovascular diseases (yes or no), cancer (yes or no), COPD (yes or no), and asthma (yes or no). Similar logistic regression models were used to compare COVID-19 infection rates in participants who did and did not use other individual supplements (vitamin A, vitamin B, vitamin C, vitamin D, vitamin E, folic acid, a multivitamin, calcium, zinc, iron, selenium, glucosamine or fish oil). Because the missing rates for all covariates were low (all covariates missing ≤3.2%) in the current study, missing data were coded as a missing indicator category for categorical variables and with mean values for continuous variables. To evaluate whether the association between the use of vitamin D supplements and the risk of COVID-19 infection varied according to the different levels of circulating or genetically predicted vitamin D, the interactions between the use of vitamin D supplements and the different levels of circulating or genetically predicted vitamin D were assessed by adding the multiplicative interaction terms to the models. All statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc) and SPSS 22.0. All statistical tests were 2-sided, and we considered $P < 0.05$ to be statistically significant.

Results

Baseline characteristics of participants according to use of vitamin D supplements

Baseline characteristics of study participants according to vitamin D use are shown in **Table 1**. A total of 4.4% of the participants reported regular use of vitamin D. Compared with participants not using vitamin D supplements, the habitual users of vitamin D supplements were older; were more likely to be non-white, female, and non-current smokers; and were more likely to have a healthy diet, a slightly higher TDI, and lower prevalences of obesity and cardiovascular disease but higher prevalences of cancer or COPD at baseline. Users of vitamin D supplements also tended to take more other supplements. In addition, compared with the nonusers, the habitual users of vitamin D had a significantly higher level of circulating vitamin D [56.0 (20.8) vs. 47.0 (21.1), respectively; $P < 0.001$]. Similar genetically predicted vitamin D levels were observed in the vitamin D users and nonusers [7.6 (1.8) vs. 7.5 (1.9), respectively; $P = 0.12$]. The information regarding research centers and laboratories is listed in **Supplementary Table 2**.

The baseline characteristics of study participants according to the status of COVID-19 infection are shown in **Supplementary Table 3**.

The association between habitual use of vitamin D supplements and risk of COVID-19 infection

In 8297 participants who had records of COVID-19 test results, 16.6% (1378/8297) of the total population tested positive for SARS-CoV-2. In the unadjusted model, vitamin D users did not have a significantly lower risk of COVID-19 infection as compared with nonusers (OR, 0.78; 95% CI, 0.57–1.05; $P = 0.105$). However, further adjustment for age, sex, race, research centers, laboratory, origin (outpatient or inpatient), blood-type haplotype, years of education, TDI, smoking, moderate drinking, physical activity, healthy diet score, and use of any other supplements strengthened the association, and a significant, inverse association between habitual use of vitamin D supplements and risk of COVID-19 infection was observed (OR, 0.67; 95% CI, 0.46–0.98; $P = 0.038$). An additional adjustment for baseline disease status (obesity, diabetes, hypertension, high cholesterol, cardiovascular diseases, cancer, asthma, and COPD) and circulating vitamin D did not appreciably alter the results (OR, 0.66; 95% CI, 0.45–0.97; $P = 0.034$; **Table 2**).

We did not find a significant association between baseline circulating vitamin D levels and the risk of COVID-19 infection. Compared with participants with vitamin D deficiency (<25 nmol/L), the adjusted ORs were 1.04 (95% CI, 0.84–1.28) for participants with vitamin D insufficiency (25–50 nmol/L) and 1.05 (95% CI, 0.84–1.31) for those with vitamin D sufficiency (>50 nmol/L; **Supplementary Table 4**). Genetically predicted vitamin D levels (GRS-VD) were not associated with the risk of COVID-19 infection, with an adjusted OR comparing the highest with the lowest quarters of 1.15 (95% CI, 0.92–1.44; **Supplementary Table 5**). The association between the use of vitamin D supplements and the risk of COVID-19 infection did not vary according to the different levels of circulating or genetically predicted vitamin D (P-interactions = 0.75 and 0.74, respectively; **Supplementary Figure 2**).

The association between habitual use of other supplements and risk of COVID-19 infection

We also analyzed the associations between the risk of COVID-19 infection and habitual use of other individual supplements, including vitamin A, vitamin B, vitamin C,

TABLE 1   Characteristics of participants at baseline according to use of vitamin D supplements

	Nonusers	Vitamin D users	P value
Number of participants	7934	363	
Age, y	57.4 ± 8.6	59.1 ± 8.1	<0.001
Male	3964 (50.0)	141 (38.8)	<0.001
Whites[1]	7335 (92.8)	316 (87.5)	<0.001
Socio-economic factors			
Years of education, y	14.3 ± 5.2	14.4 ± 5.3	0.77
TDI	−0.8 ± 3.3	−0.4 ± 3.6	0.03
Lifestyle factors			
Physical activity time ≥150 min/wk[1]	4655 (60.6)	216 (61.0)	0.89
Current smoker	1028 (13.0)	34 (9.4)	0.045
Moderate drinker	3412 (43.0)	156 (43.0)	0.99
Healthy diet score (SD)	2.2 (1.1)	2.6 (1.1)	<0.001
Disease factors			
Obesity	2471 (31.1)	86 (23.7)	0.003
Diabetes	766 (9.7)	31 (8.5)	0.48
Hypertension	4871 (61.4)	225 (62.0)	0.82
High cholesterol	2158 (27.2)	94 (25.9)	0.59
Cardiovascular disease	861 (10.9)	26 (7.2)	0.03
Cancer	812 (10.2)	55 (15.0)	0.003
COPD	281 (3.5)	21 (5.8)	0.03
Asthma	1137 (14.3)	55 (15.2)	0.66
Others			
Any other supplements use[1]	3752 (47.4)	342 (94.5)	<0.001
Circulating vitamin D, nmol/L	47.0 ± 21.1	56.0 ± 20.8	<0.001
GRS-VD[2]	7.5 ± 1.9	7.6 ± 1.8	0.12
Origin			0.09
Non-inpatient	2406 (30.3)	95 (26.2)	
Inpatient	5528 (69.7)	268 (73.8)	
Blood groups (blood-type haplotype)[1]			0.68
A (AA, AO)	3471 (44.3)	151 (42.5)	
B (BB, BO)	820 (10.5)	40 (11.3)	
AB (AB)	271 (3.5)	16 (4.5)	
O (OO)	3282 (41.8)	148 (41.7)	

Data are mean ± SD or N (%). Chi-square test for categorical variables and general linear models for continuous variables were applied to compare proportions or means of characteristics between the users of vitamin D and non-users. Abbreviations: TDI, Townsend deprivation index; COPD, Chronic obstructive pulmonary disease; GRS-VD, genetic risk score for vitamin D.

[1] Numbers may not sum to n=8297 owing to missing data.

[2] Genetic data were available for 7549 white participants.

vitamin E, folic acid, a multivitamin, calcium, zinc, iron, selenium, glucosamine, or fish oil. However, we did not observe any other significant association between the use of other individual supplements and the risk of COVID-19 infection (**Figure 1**).

Discussion

In this prospective study, we observed that habitual use of vitamin D supplements was associated with a lower risk of COVID-19 infection, independent of lifestyle, socio-economic

TABLE 2   Association between vitamin D supplement use and risk of coronavirus disease 2019 infection

	Nonusers, n = 7934	Vitamin D users, n = 363	P value
Cases, n (%)	1329 (16.8%)	49 (13.5%)	
Unadjusted	1 (reference)	0.78 (0.57–1.05)	0.105
Model 1	1 (reference)	0.67 (0.46–0.98)	0.038
Model 2	1 (reference)	0.67 (0.46–0.98)	0.040
Model 2 + baseline circulating vitamin D levels	1 (reference)	0.66 (0.45–0.97)	0.034

Logistic regression models were used to calculate the ORs and 95% CIs ($n = 8297$). Model 1 was adjusted for age group, sex, race, research centers, laboratory, origin (outpatient or inpatient), blood-type haplotype, years of education, Townsend deprivation index, smoking, moderate drinking, physical activity, healthy diet score, and any other supplements. Model 2 was further adjusted for obesity, diabetes, hypertension, high cholesterol, cardiovascular diseases, cancer, asthma, and chronic obstructive pulmonary disease on the basis of Model 1.
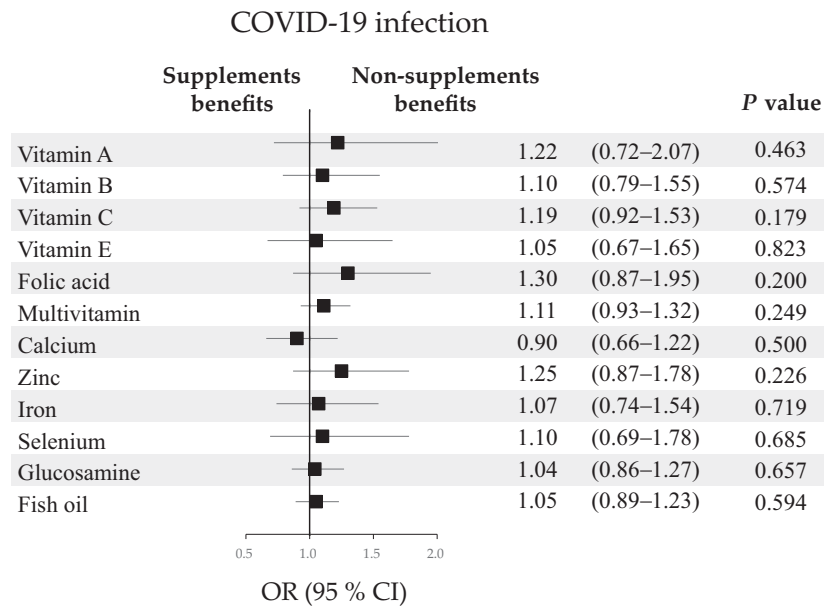
COVID-19 infection

FIGURE 1. ORs of other supplement use for risk of COVID-19 infection. Logistic regression models were used to calculate the ORs and 95% CIs. Results were adjusted for age group, sex, race, research centers, laboratory, origin (outpatient or inpatient), blood-type haplotype, years of education, Townsend deprivation index, smoking, moderate drinking, physical activity, healthy diet score, obesity, diabetes, hypertension, high cholesterol, cardiovascular diseases, cancer, asthma and chronic obstructive pulmonary disease, circulating vitamin D level, and use of vitamin D supplements. $n = 8281$. COVID-19, coronavirus disease 2019.

status, prevalent chronic diseases, and circulating vitamin D levels. Circulating vitamin D levels at baseline or genetically predicted vitamin D levels were not associated with the risk of COVID-19 infection. The association between the use of vitamin D supplements and the risk of COVID-19 infection did not vary according to the different levels of circulating or genetically predicted vitamin D.

To the best our knowledge, this is the first prospective epidemiology study to investigate the association between habitual use of vitamin D supplements and risk of COVID-19 infection. Our findings are supported by the previously reported beneficial effects of vitamin D supplements on the risks of other acute respiratory tract infections (9–11). Several recent studies lend evidence to a potential relationship between the use of vitamin D supplements and COVID-19 infection (12–14, 23). A recent population-based study showed that a low plasma 25(OH) vitamin D level was significantly associated with a higher risk of COVID-19 infection (12). Another study showed that a Northerly latitude was associated with higher mortality rates and hospitalization rates for COVID-19 worldwide (23). A possible explanation for such results was that the prevalence of vitamin D deficiency is much higher in these Northern areas than in Southern areas (23, 24). In addition, a retrospective observational study showed a link between vitamin D insufficiency and severity of COVID-19 infection (1). Another study showed that vitamin D might reduce COVID-19 severity by suppressing cytokine storms in COVID-19 patients (2).

Several potential mechanisms have been proposed to explain the observed inverse association between habitual use of vitamin D supplements and the risk of COVID-19 infection. First, viruses may affect humans by disturbing the integrity of cell junction integrity (25), while vitamin D may maintain cell

junctions and therefore lower the risk of infection (6). Second, vitamin D enhances cellular innate immunity, partly through the induction of multiple antimicrobial peptides, which may lower viral replication rates (26–28); vitamin D also strengthens cellular immunity through reducing the cytokine storm with impacts on the pro-inflammatory cytokines and anti-inflammatory cytokines (29–31). Third, a previous study showed that vitamin D deficiency induced lung fibrosis through the renin-angiotensin system (RAS) (32). SARS-CoV-2 may downregulate the ACE 2 function (33), and thereby dysregulate the RAS and cause acute respiratory distress syndrome. Therefore, it is possible that vitamin D may play a role in balancing RAS and reducing lung damage.

Similar to the previous results from UK Biobank (34), we did not find a significant association between circulating vitamin D levels and the risk of COVID-19 infection in this study. Notably, this may be because the circulating vitamin D levels were largely affected by diet changes and season changes (4). Therefore, after a median of 10.0 y of follow-up, it is not surprising to observe a null association between baseline circulating vitamin D levels and the risk of COVID-19 infection. In addition, we also did not find a significant association between genetically predicted vitamin D levels and the risk of COVID-19 infection, and such null association of GRS-VD might be partly explained by the fact that genetic factors only account for a small proportion of circulating vitamin D (18).

The major strengths of this study include the prospective design and the availability of lifestyle, socio-economic status, and social psychological factors. Several potential limitations should be carefully considered in this study. First, this study might be subjected to selection bias. If COVID-19 testing was more likely in vitamin D users than nonusers, this might introduce

a selection bias. However, we did not find a significant association between the use of vitamin D supplements and receiving COVID-19 tests in the study population (**Supplementary Table 6**), suggesting such a selection bias was unlikely to have affected the observed inverse association between the use of vitamin D supplements and the risk of COVID-19 infection. Despite this, we acknowledge that COVID-19 tests were largely restricted to participants with symptoms in hospitals during the spring period, who might not represent the whole population in the United Kingdom. Therefore, caution should be taken in interpreting the observations. Second, the information about vitamin D supplement use was collected a median of 10 y before the COVID-19 tests, meaning our results might only reflect the association between "ever" use of vitamin D supplements and the risk of COVID-19 infection. We cannot rule out potential effects of changes in the use of vitamin D supplements during the follow-up period on the results. The assessment of the stability of vitamin D supplement use is lacking in this study. Third, because a previous study has shown that the preventive effect of vitamin D supplements on the acute respiratory tract infections appeared to be better in participants with lower circulating vitamin D levels than in those with higher circulating vitamin D levels, the lack of current circulating vitamin D level data is another limitation in this study. Fourth, use of vitamin D supplements might be a marker for a healthier lifestyle or a higher socio-economic level, as compared with nonuse. Fifth, almost all the vitamin D users also took other supplements. However, no significant inverse association between use of other individual supplements and a risk of COVID-19 infection was observed; thus, the higher prevalence of use of other supplements in the vitamin D users as compared with nonusers might not affect the results. And last, a previous study also showed that low circulating vitamin D levels were associated with the severity of COVID-19 ([1]). Therefore, the lack of data on the severity of COVID-19 is another limitation in this study.

In conclusion, an inverse association between habitual use of vitamin D supplements and the risk of COVID-19 infection was observed in the current study. However, we cannot rule out the possibility that the observed inverse association was due to residual confounding or selection bias, since we did not find a consistent inverse association between baseline circulating vitamin D levels or genetically predicted vitamin D levels and the risk of COVID-19 infection. Further clinical trials are needed to verify such an inverse association between the habitual use of vitamin D supplements and the risk of COVID-19 infection.

Data Availability

Data used in this study are available through the UK Biobank (www.ukbiobank.ac.uk) upon request. Analytical methods and study materials will be available to other researchers from the corresponding authors on reasonable request for purposes of reproducing the results or replicating the procedure.

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