Celiac Disease and the Susceptibility of COVID-19 and the Risk of Severe COVID-19: A Mendelian Randomization Study

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INTRODUCTION:	**Previous observational studies have found that the susceptibility of coronavirus disease 2019 (COVID-19) and the risk of severe COVID-19 are not increased in patients with celiac disease (CeD). However, the findings of observational studies are prone to bias due to reverse causation and confounding factors, especially in the case of a newly emerged disease. In this study, we aimed to further clarify the underlying relationship by both observational and Mendelian randomization (MR) analysis.**
METHODS:	**This observational study was conducted in the UK Biobank cohort. Univariate and multivariate logistic regression analyses were performed to identify the risk factors of COVID-19 susceptibility and severe COVID-19. To understand the causality between CeD and COVID-19 susceptibility and severe COVID-19, we performed a 2-sample MR analysis.**
RESULTS:	**Our observational study showed that patients with CeD had a lower susceptibility of COVID-19 (odds ratio [OR] = 0.699, *P* = 0.006) while CeD was not significantly associated with severe COVID-19 (*P* > 0.05). The findings from our MR study further demonstrated that both the susceptibility to COVID-19 (OR = 0.963, *P* = 0.006) and severe COVID-19 (OR = 0.919, *P* = 0.049) were lower in patients with CeD, although the former seemed to be specific to the UK Biobank cohort.**
DISCUSSION:	**Our results suggested that it may be unnecessary to take extra COVID-19 precaution in patients with CeD.**

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by the infection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread all over the world, leading to millions of confirmed cases and deaths (1). In a series of observational studies based on COVID-19 patient cohorts, severe COVID-19 was found to be associated with older age (2–4), male sex (2,4), and several comorbidities such as obesity (2,4,5) and diabetes (6,7).

Celiac disease (CeD) is a common autoimmune disease of the small intestine. The prevalence of CeD was estimated to be approximately 1.4% (8). The relationship between CeD and COVID-19 susceptibility has been broadly discussed (9–12). Several observational studies suggested that pediatric and adult patients with CeD are not at increased risk of COVID-19

susceptibility (9–11). Meanwhile, the severity of COVID-19 in patients with CeD had not significantly increased (12,13). The findings of observational studies are prone to bias due to reverse causation and confounding factors, especially in the case of a newly emerged disease.

Mendelian randomization (MR) analysis uses genetic variants to determine the causal effect of the risk factor on the outcome (14,15), which was considered to be advantageous to observational studies because it avoids the confounding factors and reverse causation. In this article, we report the results from an observational study based on the UK Biobank (UKB) cohort and a MR study that we believe will contribute to a further understanding on the susceptibility and severity of COVID-19 in patients with CeD. The results of our work would be informative

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to the clinical management of patients with CeD in the current and future COVID-19 pandemic.

METHODS

Observational study

The UKB released COVID-19 test results and hospital inpatient data, as well as other phenotypes and genome-wide single-nucleotide polymorphism (SNP) genotypes. In our study, COVID-19 susceptibility was defined as a positive PCR test result of SARS-CoV-2 nucleotides. Severe COVID-19 was defined as COVID-19-related death (ICD-10 code: U071) and intensive care unit admission and ventilation machine use from 7 days before and up to 30 days after a patient's first positive test for SARS-CoV-2. Confirmed SARS-CoV-2–negative individuals and SARS-CoV-2–positive patients without intensive care unit admission and ventilation machine use were used as control subjects for COVID-19 susceptibility and severity, respectively. CeD was defined based on ICD-10, ICD-9, and the question "Have you been diagnosed with celiac disease/gluten sensitivity?". The subjects with ICD-10 code K90.0 or ICD-9 code 5790 or those who were told by a doctor that they have CeD were grouped as patients with CeD. Diabetes was defined based on self-reported noncancer code 1223, ICD-10 codes (E110, E111, E112, E113, E114, E115, E116, E117, E118, and E119), ICD-9 codes (25000, 25009, 25010, 25019, 25029, 2503, 2504, 2505, and 25099), random glucose greater than 11.1 mmol/L, and glycated hemoglobin greater than 47.54 mmol/mol. In addition, if a participant was told by a doctor that he has diabetes, he was also defined as a patient with diabetes. Univariate logistic regression analysis was performed to identify the risk factors of COVID-19 susceptibility and severe COVID-19. Multivariate logistic regression models were adjusted for the significant risk factors ($P < 0.05$) identified in our univariate analyses to identify the independent risk factors of COVID-19 susceptibility and severe COVID-19.

Mendelian randomization analysis

We performed a 2-sample MR analysis to examine the causality between CeD and COVID-19 susceptibility and severe COVID-19, respectively. Instrumental variables (IVs) were proposed from CeD-associated SNPs in 2 published genome-wide association studies (GWASs; Table 1). Briefly, 36 independent SNPs (pairwise LD r2 <0.05) achieved genome-wide significance ($P < 5 \times 10^{-8}$) in 12,041 patients with CeD and 12,228 healthy controls of major European ancestry in a 2011 GWAS (16). Another 4 novel independent SNPs were identified after a sample expansion of 4,125 in 2020 (17). For the exposure (i.e., CeD), the association

summary statistics of the IVs were drawn from the respective association studies.

For the proposed IVs, the association summary statistics with COVID-19 susceptibility or severe COVID-19 were obtained from the COVID-19 Host Genetics Initiative (COVID-19 HGI) GWAS (Table 1) (18). The susceptibility of COVID-19 was defined as ever had a positive laboratory test result, clinician diagnosis of COVID-19, or self-reported SARS-CoV-2 infection. Severe COVID-19 was defined by death, hospitalization, or respiratory support because of SARS-CoV-2 infection. Control samples were from individuals who were not confirmed cases. The proposed IVs with minor allele frequency > 0.01, imputation INFO score > 0.6, and heterogeneity P value > 0.05 (Table 2) were used as the IVs in the MR analysis.

The MR analysis was conducted using an inverse-variance weighted model. The intercept of MR-Egger regression and the Cochran Q test were used to detect the pleiotropic effect and the heterogeneity of the IVs, respectively. Owing to the large sample size of the UK Biobank cohort (COVID-19 susceptibility: 6,490 cases [16.6%] and 328,577 controls [20.0%]; severe COVID-19: 309 cases [6%] and 328,577 controls [23.8%]), sensitivity MR analyses were conducted with the COVID-19 summary statistics calculated without the UKB samples.

RESULTS

Sample characteristics of our observational study

As summarized in Table 3, a total of 41,554 unrelated individuals of European ancestry with a SARS-CoV-2 test result were studied (8,267 SARS-CoV-2–positive vs 33,287 SARS-CoV-2–negative). Of these, 535 had a clinical diagnosis of CeD (74 SARS-CoV-2–positive).

The observational relationship between CeD and COVID-19

In our univariate regression analysis (Table 4 and Figure 1), body mass index (BMI) was associated with higher susceptibility of COVID-19 (odds ratio [OR] = 1.022, 95% CI: 1.017–1.027, $P < 0.001$) and severe COVID-19 (OR = 1.071, 95% CI: 1.055–1.087, $P < 0.001$). Male patients had a higher susceptibility of severe COVID-19 (OR = 2.075, 95% CI: 1.733–2.485, $P < 0.001$), but not significant for COVID-19 ($P = 0.132$). Intriguingly, age (OR = 0.942, 95% CI: 0.939–0.945, $P < 0.001$), diabetes (OR = 0.909, 95% CI: 0.841–0.984, $P = 0.018$), and gluten-free diet (OR = 0.365, 95% CI: 0.197–0.677, $P = 0.001$) decreased the susceptibility of COVID-19, while the first 2 were associated with higher risk of severe COVID-19 ($P < 0.001$).

In our multivariate regression analysis (Table 4 and Figure 1) adjusted for age, BMI, gluten-free diet, and diabetes, COVID-19

Table 1. Sources of data for the analysis

Trait	First author/consortium	Year	Patients, N	Controls, N
Celiac disease	Gosia Trynka	2011	12,041	12,228
Celiac disease	Isis Ricaño-Ponce	2020	13,177	15,217
COVID-19 susceptibility	COVID-19 HGI	2021	38,984	1,644,784
COVID-19 severity	COVID-19 HGI	2021	5,101	1,383,241
COVID-19 susceptibility[a]	COVID-19 HGI	2021	32,494	1,316,207
COVID-19 severity[a]	COVID-19 HGI	2021	4,792	1,054,664

COVID-19, coronavirus disease 2019; UKB, UK Biobank.
[a]The UKB samples were excluded in the sensitivity analysis.

Table 2. The association of instrumental variables with celiac disease and COVID-19

SNP	EA/AA	Celiac disease		COVID-19 susceptibility		Severe COVID-19		COVID-19 susceptibility[a]		Severe COVID-19[a]	
		Beta (SE)	P	Beta (SE)	P	Beta (SE)	P	Beta (SE)	P	Beta (SE)	P
rs1018326	C/T	0.15 (0.02)	3.06E-16	−0.01 (0.01)	0.33	−0.04 (0.03)	0.11	0.00 (0.01)	0.73	−0.04 (0.03)	0.13
rs1050976	T/C	−0.11 (0.02)	1.84E-09	0.01 (0.01)	0.28	−0.02 (0.03)	0.47	−0.01 (0.01)	0.53	−0.03 (0.04)	0.44
rs10800746	T/C	−0.11 (0.02)	2.57E-08	0.00 (0.01)	0.65	0.01 (0.03)	0.73	0.00 (0.01)	0.96	0.01 (0.03)	0.69
rs10892258	A/G	−0.15 (0.02)	1.73E-11	0.02 (0.01)	0.12	NA	NA	0.02 (0.01)	0.19	NA	NA
rs11851414	C/T	0.12 (0.02)	4.71E-08	−0.03 (0.01)	0.02	−0.02 (0.03)	0.48	−0.02 (0.01)	0.10	−0.01 (0.03)	0.70
rs11875687	C/T	0.16 (0.03)	1.92E-10	−0.02 (0.01)	0.09	−0.02 (0.04)	0.55	−0.02 (0.02)	0.26	−0.02 (0.04)	0.61
rs12068671	C/T	−0.16 (0.02)	1.40E-10	0.00 (0.01)	0.73	0.00 (0.03)	0.98	0.00 (0.01)	0.91	0.00 (0.04)	0.94
rs13003464	G/A	0.15 (0.02)	4.34E-16	−0.02 (0.01)	0.10	−0.03 (0.03)	0.22	−0.02 (0.01)	0.13	−0.03 (0.03)	0.37
rs13132308	G/A	−0.35 (0.03)	1.88E-38	0.01 (0.01)	0.28	0.04 (0.04)	0.30	0.02 (0.02)	0.20	0.05 (0.04)	0.19
rs1353248	T/C	−0.17 (0.02)	9.80E-09	0.00 (0.01)	0.79	−0.04 (0.04)	0.26	−0.01 (0.01)	0.54	−0.07 (0.04)	0.07
rs182429	A/G	0.15 (0.02)	8.49E-16	0.00 (0.01)	0.95	0.01 (0.03)	0.80	0.01 (0.01)	0.34	0.02 (0.03)	0.49
rs2030519	G/A	−0.28 (0.02)	3.00E-49	0.00 (0.01)	0.76	0.06 (0.04)	0.11	0.01 (0.01)	0.40	0.09 (0.04)	0.03
rs4445406	C/T	−0.14 (0.02)	5.42E-12	0.00 (0.01)	0.79	−0.01 (0.03)	0.72	0.00 (0.01)	0.73	−0.01 (0.03)	0.71
rs4821124	C/T	0.15 (0.02)	5.72E-11	−0.01 (0.01)	0.62	NA	NA	−0.01 (0.01)	0.63	NA	NA
rs55743914	T/C	0.19 (0.02)	1.15E-18	−0.01 (0.01)	0.46	0.00 (0.04)	0.99	−0.01 (0.01)	0.44	−0.02 (0.04)	0.58
rs61579022	A/G	0.11 (0.02)	9.92E-09	−0.01 (0.01)	0.56	−0.05 (0.03)	0.05	−0.01 (0.01)	0.48	−0.06 (0.03)	0.05
rs61907765	T/C	0.16 (0.02)	3.43E-13	0.02 (0.01)	0.15	0.04 (0.03)	0.17	0.02 (0.01)	0.10	0.03 (0.03)	0.41
rs6715106	G/A	−0.24 (0.04)	8.38E-09	0.01 (0.02)	0.53	0.05 (0.06)	0.37	0.01 (0.02)	0.74	0.06 (0.06)	0.28
rs6806528	T/C	0.17 (0.03)	9.10E-09	−0.03 (0.02)	0.07	−0.10 (0.05)	0.02	−0.03 (0.02)	0.12	−0.11 (0.05)	0.02
rs7616215	C/T	0.11 (0.02)	8.60E-09	−0.01 (0.01)	0.15	0.01 (0.03)	0.82	−0.01 (0.01)	0.48	0.00 (0.03)	0.99
rs79758729	G/A	0.16 (0.03)	2.12E-08	0.02 (0.02)	0.18	0.01 (0.04)	0.84	0.03 (0.02)	0.08	−0.03 (0.04)	0.54
rs9610686	C/T	0.10 (0.02)	3.28E-08	0.00 (0.01)	0.71	−0.02 (0.03)	0.59	0.00 (0.01)	0.99	−0.02 (0.04)	0.61
rs990171	A/C	0.18 (0.02)	1.23E-16	0.00 (0.01)	0.95	0.01 (0.03)	0.71	0.00 (0.01)	0.77	0.02 (0.03)	0.45

The SNPs in COVID-19 GWAS with the heterogeneity P value less than 0.05 were excluded in this study.

AA, alternative allele; COVID-19, coronavirus disease 2019; EA, effect allele; GWAS, genome-wide association study; NA, not available; SNP, single-nucleotide polymorphism; UKB, UK Biobank.

[a]The UKB samples were excluded in the sensitivity analysis.

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Table 3. Sample characteristics of our observational study

| Sample characteristics | COVID-19 susceptibility | | Severe COVID-19 | |
	Negative (n = 33,287)	Positive (n = 8,267)	Nonsevere (n = 7,711)	Severe (n = 556)
Age (yr) [±SD]	70.37 [7.80]	66.34 [8.64]	65.80 [8.51]	73.87 [6.65]
Male (%)	15,915 (47.81)	4,029 (48.74)	3,666 (47.54)	363 (65.29)
BMI (kg/m^2) [±SD]	27.71 [4.89]	28.25 [5.04]	28.11 [4.96]	30.13 [5.65]
Diabetes (%)	3,760 (11.30)	858 (10.38)	718 (9.31)	140 (25.18)
Gluten-free diet (%)	121 (0.36)	11 (0.13)	9 (0.12)	2 (0.36)
CeD (%)	461 (1.38)	74 (0.90)	71 (0.92)	3 (0.54)

BMI, body mass index; CeD, celiac disease; COVID-19, coronavirus disease 2019.

susceptibility in patients with CeD was lower than that in the control subjects (OR = 0.699, 95% CI: 0.542–0.901, P = 0.006). With the adjustment of age, sex, BMI, and diabetes, the risk of severe COVID-19 in patients with CeD was not significantly different from that in the control subjects (OR = 0.873, 95% CI: 0.256–2.975, P = 0.431).

The causal relationship between CeD and COVID-19

Among the total 40 SNPs associated with CeD, 23 and 21 SNPs were used as IVs in the MR analysis to examine their causal association between CeD and COVID-19 susceptibility or severe COVID-19, respectively. None of the IVs were associated with COVID-19 at the Bonferroni corrected significance level (P < 0.002) (Table 2). As shown in Figure 2 (Table 5), we found that CeD was causally associated with a significantly lower risk of both COVID-19 susceptibility (OR = 0.963, P = 0.006) and severe COVID-19 (OR = 0.919, P = 0.049). The former association became insignificant (P = 0.126) in the sensitivity MR analysis, suggesting that the decreased susceptibility of COVID-19 could be primarily driven by the UKB cohort. However, the decreased risk of severe COVID-19 in patients with CeD was not dominated by the UKB sample (P = 0.037). We did not

observe significant heterogeneity or pleiotropic effects of the IVs in these analyses. The forest plot of the causal effects of CeD-associated IVs on COVID-19 is presented in the Supplementary Figure (see Supplementary Digital Content 1, http://links.lww.com/CTG/A788).

DISCUSSION

Observational studies concluded that there is no difference in COVID-19 susceptibility or severe COVID-19 between patients with CeD and control individuals. In this work, our observational study in the UKB cohort showed that COVID-19 susceptibility was lower in patients with CeD, while the risk of severe COVID-19 was not significant. The association between CeD and COVID-19 susceptibility was further supported by the causal association inferred by using genetic instrumental variables. Notably, we also showed that the risk of severe COVID-19 was causally lower in patients with CeD in our MR analysis.

The potential mechanism underlying the lower risk of severe COVID-19 in patients with CeD is unclear. Patients with CeD may have a higher standard of behavior hygiene as compared with other individuals, which may lead to a lower virus load. On the other hand, we speculate that CeD-associated genetic variations that

Table 4. The association between the risk factors and COVID-19 susceptibility and severe COVID-19

| Phenotype | COVID-19 susceptibility | | | Severe COVID-19 | | |
	OR	95% CI	P value	OR	95% CI	P value
Age	0.942	0.939–0.945	<0.001	1.134	1.119–1.148	<0.001
Age[a]	0.941	0.938–0.944	<0.001	1.129	1.114–1.144	<0.001
Male	1.038	0.989–1.089	0.132	2.075	1.733–2.485	<0.001
Male[a]	NA	NA	NA	1.793	1.484–2.165	<0.001
BMI	1.022	1.017–1.027	<0.001	1.071	1.055–1.087	<0.001
BMI[a]	1.026	1.021–1.031	<0.001	1.061	1.042–1.080	<0.001
Gluten-free diet	0.365	0.197–0.677	0.001	3.089	0.666–14.334	0.150
Gluten-free diet[a]	0.374	0.199–0.701	0.002	NA	NA	NA
Diabetes	0.909	0.841–0.984	0.018	3.278	2.667–4.029	<0.001
Diabetes[a]	0.978	0.898–1.064	0.601	1.566	1.241–1.976	<0.001
CeD	0.643	0.503–0.823	<0.001	0.584	0.183–1.859	0.362
CeD[a]	0.699	0.542–0.901	0.006	0.873	0.256–2.975	0.431

BMI, body mass index; CeD, celiac disease; CI, confidence interval; COVID-19, coronavirus disease 2019; OR, odds ratio.
[a]Multivariate regression analysis was used to identify the independent risk factors of COVID-19 susceptibility and severe COVID-19. "NA" represents that the phenotype was not adjusted in the multivariate regression analysis.
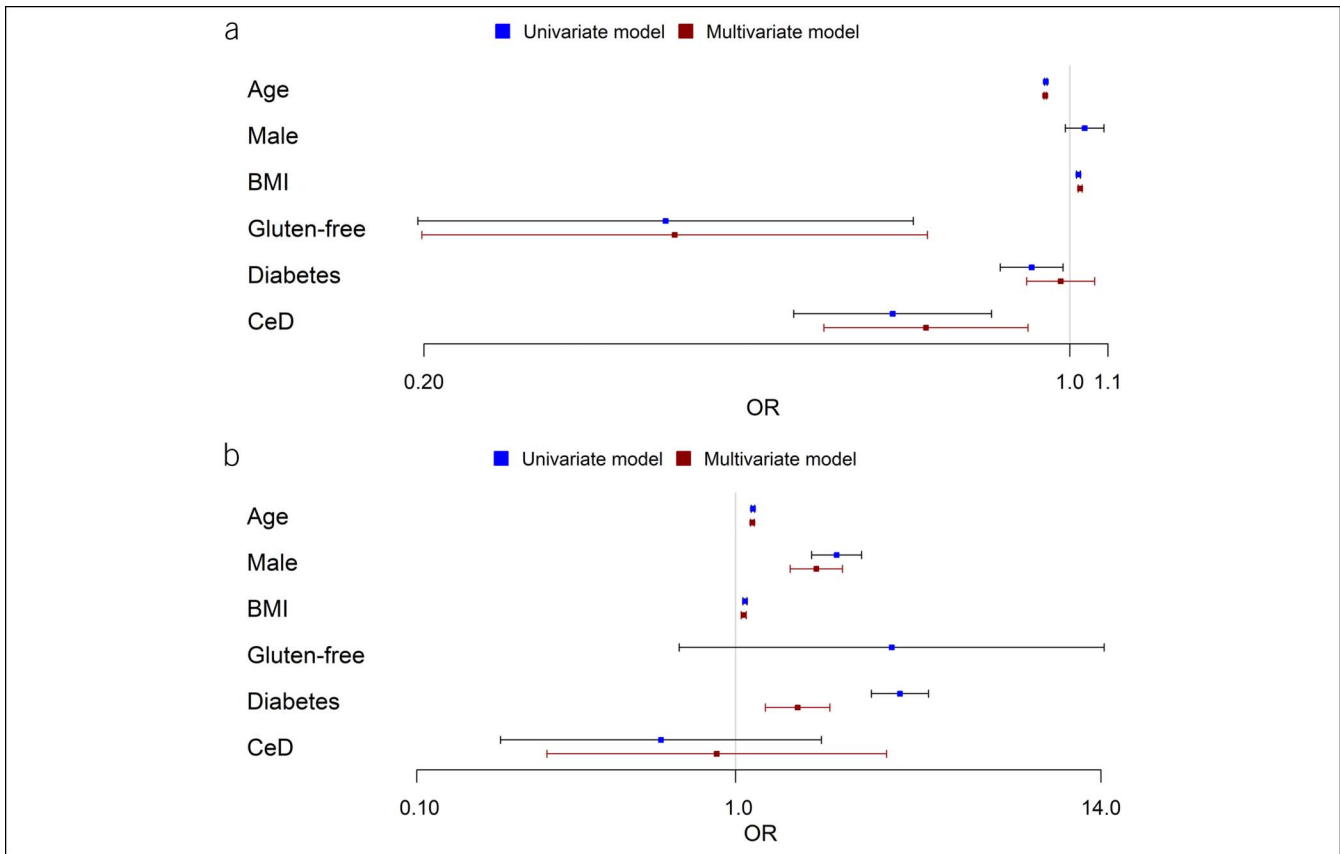
Figure 1. The association between the risk factors and COVID-19 susceptibility and severe COVID-19. (**a**) COVID-19 susceptibility and (**b**) severe COVID-19. Multivariate regression analysis was used to identify the independent risk factors of COVID-19 susceptibility and severe COVID-19. BMI, body mass index; CeD, celiac disease; COVID-19, coronavirus disease 2019; Gluten-free, gluten-free diet; OR, odds ratio.

affect the immunity system may play a significant role as well. The human leukocyte antigen (HLA) gene cluster has been associated with CeD. As reported, the CeD risk allele of rs2187668-A near the *HLA-DQA1* locus was also associated with immunoglobulin A deficiency (19) and decreased white blood cell count and neutrophil count (20), all of which were elevated in patients with severe COVID-19 (3,21). This hypothesis was further supported proven by the works of Luca and Fainareti et al. Luca et al. found that anti–SARS-CoV-2 IgA was lower in patients with CeD compared with healthy individuals (22). Fainareti et al. demonstrated that the high anti–SARS-CoV-2 IgA in patients increased the risk of severe COVID-19 (23). Meanwhile, a missense variant rs3184504-T in *SH2B3* gene was associated with both higher risk of CeD and lower risk of obesity (24). Obesity and concomitant chronic inflammation were independent risk factors for severe COVID-19 (25). We believe that relatively lower BMI in patients with CeD (26) may contribute to the lower risk of severe COVID-19.

The impacts of rheumatoid arthritis, another common autoimmune disease, on severe COVID-19 have also been broadly concerning (27–29). Contrary to CeD, patients with rheumatoid arthritis are at a higher risk of severe COVID-19 (27–29). Interestingly, rs2187668-A was negatively associated with rheumatoid arthritis (30). Given the role of rs2187668-A in the immunity system, we hypothesized that the opposite risks of severe COVID-19 in patients with CeD and rheumatoid arthritis may be attributed to the different immune statuses of the patients. The mechanisms need to be investigated in future studies to

clearly explain the opposite risks of severe COVID-19 in patients with CeD and rheumatoid arthritis.

Of course, our study could also be biased by a few intrinsic limitations, which may lead to confounded results. These may include unknown confounding factors, uncontrolled mask wearing, pleiotropic effects of selected IVs or shewed GWAS summary statistics if adjusted insufficiently, or included control subjects without a SARS-CoV-2 test result. Therefore, the attention should still be paid to the physical status of patients with CeD during the COVID-19 pandemic. The proposals from Luca et al. (31) may help clinicians in managing patients with CeD during the COVID-19 pandemic.
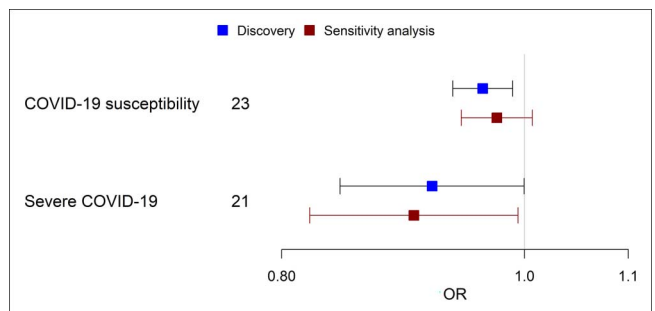

Figure 2. The causal association between CeD and COVID-19 susceptibility and severe COVID-19. CeD, celiac disease; COVID-19, coronavirus disease 2019; OR, odds ratio.

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Table 5. The causal association between celiac disease and COVID-19 susceptibility and severe COVID-19

Stage	Outcome	Nsnp	OR	95% CI	P value	Het-p	Ple-p
Discovery	COVID-19 susceptibility	23	0.963	0.937–0.989	0.006	0.523	0.400
	Severe COVID-19	21	0.919	0.844–0.999	0.049	0.522	0.676
Sensitivity analysis	COVID-19 susceptibility[a]	23	0.975	0.943–1.008	0.126	0.574	0.577
	Severe COVID-19[a]	21	0.903	0.820–0.994	0.037	0.321	0.396

CI, confidence interval; MR, Mendelian randomization; Nsnp, the number of instrumental variables used in MR; OR, odds ratio, calculated as the natural exponential of beta; P value, the P value of the 2-sample MR analysis; Het-p, the P value of heterogeneity; Ple-p, the P value of the pleiotropic effect; UKB, UK Biobank.
[a]The UKB samples were excluded in the sensitivity analysis.

In conclusion, our study observed a potentially protective effect of CeD on the susceptibility of COVID-19 and severe COVID-19 in cohorts of major European ancestry. Our study suggested that it may be unnecessary to take extra COVID-19 precaution in patients with CeD. The relationship underlying this inverse association between CeD and severe COVID-19 warrants further investigations.

Study Highlights

WHAT IS KNOWN
✔ Observational studies did not draw a clear conclusion on the association between celiac disease (CeD) and COVID-19.
✔ A Mendelian randomization study could be used to detect the association without the effects of the risk factors that could confound observational studies.

WHAT IS NEW HERE
✔ A significant decreased susceptibility of COVID-19 and the risk of severe COVID-19 could be observed in patients with CeD.
✔ The CeD risk allele rs2187668-A near HLA-DQA1 is associated with decreased white blood cell count and neutrophil count. This pleiotropic effect may explain the decreased risk of severe COVID-19 in patients with CeD.

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