Association of 25 Hydroxyvitamin D Concentration with Risk of COVID-19: A Mendelian Randomization Study

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Abstract

Background: Coronavirus disease 2019 (COVID-19) has caused a large global pandemic. In observational studies, 25 hydroxyvitamin D (25OHD) concentration has been associated with an increased risk of Coronavirus disease 2019 (COVID-19). However, it remains unclear whether this association is causal.

Methods: We performed a two-sample Mendelian randomization (MR) to explore the causal relationship between 25OHD concentration and COVID-19, using summary data from the genome-wide association studies (GWASs) and using 25OHD concentration-related SNPs as instrumental variables (IVs).

Results: MR analysis did not show any evidence of a causal association of 25OHD concentration with COVID-19 susceptibility and severity (odds ratio [OR]=1.136, 95% confidence interval [CI] 0.988-1.306, P=0.074; OR=0.889, 95% CI 0.549-1.439, P=0.632). Sensitivity analyses using different instruments and statistical models yielded similar findings, suggesting the robustness of the causal association. No obvious pleiotropy bias and heterogeneity were observed.

Conclusions: The MR analysis showed that there might be no linear causal relationship of 25OHD concentration with COVID-19 susceptibility and severity.

Background

Coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a global pandemic (1). Aimed at delaying disease onset by modulating modifiable risk factors, primary prevention has been proposed as a potentially effective and feasible tool to address the global challenge posed by COVID-19.

Vitamin D is a hormone, produced in the skin during exposure to sunlight, helped regulate the amount of calcium and phosphate in the body, which are needed to keep bones, teeth, and muscles healthy, and played a critical role in the immune system (2–4). Vitamin D deficiency is a candidate risk factor for a range of adverse health outcomes, such as cancer, cardiovascular diseases, metabolic disorders, infectious diseases, as well as autoimmune diseases (5, 6). There were well recognized evidences that vitamin D deficiency contributes to the seasonal increase of virus infections of the respiratory tract, from the common cold to influenza, and now possibly also COVID-19 (7, 8). Some systematic reviews indicated that vitamin D deficiency may increase infection risk of COVID-19 by discussing the biological mechanism of virus infection (2, 9, 10). In addition, numerous population-based studies have evaluated the Vitamin D deficiency in COVID-19 patients relative to controls; however, the findings have been inconsistent. Some studies showed that COVID-19 patients had a lower 25 hydroxyvitamin D (25OHD) concentration compared with healthy controls (8, 11–13), while others found no association (14–16). The inconsistent findings from these epidemiological studies may be due to differences in the study design, study population, assays used for measuring Vitamin D deficiency. It is important to note that as the nature of the above studies is observational, such traditional epidemiological studies are particularly vulnerable to reverse causality and residual confounding.

A promising approach known as Mendelian randomization (MR), which uses inherited genetic variants as instrumental variables, provides stronger evidence for the causal effect of exposure on the diseases largely overcoming the traditional limitations due to confounding and reverse causality (17, 18). Summary based MR is an excellent strategy to evaluate the causality using summary statistics from Genome Wide Association Study (GWAS) data (19, 20). Therefore, we conducted MR analysis to assess whether 25OHD concentration was causally associated with risk of COVID-19.

Methods

Data sources

Genetic association datasets for COVID-19 susceptibility and severity

The summarized data was obtained from the most recent version of GWAS analyses from the COVID-19 host genetics initiative from UK Biobank individuals, which released on July 1, 2020 (https://www.covid19hg.org/results/)(21). Summarized data on COVID-19 included two population, COVID-19 (n = 6,696) vs. general population without the phenotype (n = 1073072) and COVID-19 (n = 3,523) vs. COVID-19 negative (n = 36,634); and summarized data on severe COVID-19 included 536 patients and 329391 control participants from general population without the phenotype. In addition, we used summarized data for severe respiratory confirmed COVID-19 reported by from the Severe Covid-19 GWAS Group(22). The GWAS summarized data can be downloaded at https://ikmb.shinyapps.io/COVID-19_GWAS_Browser/. The study included 1,160 patients who had severe respiratory confirmed COVID-19, and 2,205 participants from the general population without COVID-19 as the control.

Selection of 25OHD concentration -associated single nucleotide polymorphisms (SNPs)

We selected 143 SNPs as instrumental variables (IVs) for 25OHD concentration based on the recent large-scale GWAS (23). In addition, we retained independent variants from each other (Linkage disequilibrium [LD], $r^2 < 0.001$) for sensitivity analysis. When we encountered genetic variants in LD, the SNP with the lowest *p*-value was selected. The LD proxies were defined using 1000 genomes European samples.

MR analysis

In the analyses, the inverse-variance weighted (IVW) method was used to estimate the overall causal association of 25OHD concentration on COVID-19 susceptibility and severity. We additionally conducted the weighted median, penalized weighted median, and MR-Egger regression to account for potential violations of valid instrumental variable assumptions. The MR-Egger analysis was performed to evaluate pleiotropy based on the intercept. We conducted a heterogeneity test in MR analyses using the IVW Q test. Then, sensitivity analyses were performed to examine the stability of the causal estimate. Firstly, we performed a "leave one out" analysis to further investigate the possibility that the causal association was

driven by a single SNP. Then, we retained independent variants from each other (LD, $r^2 < 0.001$) for further sensitivity analysis. Results were presented as odds ratios (OR) with their 95% confidence interval (CI) and beta with standard error (SE) of outcomes per genetically predicted increase in each exposure factor.

In terms of various estimates for different measures, we chose the result of main MR method as the following rules:

(1) If no directional pleiotropy in MR estimates (Q statistic: P value > 0.05, MR-Egger intercept: P value > 0.05), the results of the IVW method were reported.

(2) If directional pleiotropy was detected (MR-Egger intercept: P value < 0.05) and P value > 0.05 for the Q test, the results of the MR-Egger method were reported.

(3) If directional pleiotropy was detected (MR-Egger intercept: P value < 0.05) and P value < 0.05 for the Q test, the results of the weighted median method were reported.

All data analyses were performed by the "twosampleMR" package using R version 4.0.0 (https://www.r-project.org/).

Results

As shown in Table 1, the MR analysis showed no significant association of genetically instrumented 25OHD concentration with COVID-19 in the population of COVID-19 vs. population and COVID-19 vs. COVID-19 negative (OR = 1.136, 95% CI 0.988–1.306, P = 0.074; OR = 1.168, 95% CI 0.956–1.427, P = 0.128). The association of 25OHD concentration with COVID-19 was robust in the weighted median and penalized weighted median methods, except in the MR-Egger regression (OR = 1.258, 95% CI 1.053–1.502, P = 0.013; OR = 1.302, 95% CI 1.011–1.676, P = 0.044). Pleiotropy bias and heterogeneity were also not observed. In terms of various estimates for different measures, we reported the results of the IVW method. In addition, the "leave one out" results showed that by omitting the included 89 SNPs one at a time, no individual genetic variants seem to have any significant effect on the overall results (Fig. 1–2). The association of 25OHD concentration with COVID-19 remained robust using SNP instrument (LD, $r^2 < 0.001$) (Table 1, **Figure S1-2**).

Table 1
Causal association of 25OHD concentration with COVID-19[#]

Method	SNP (n)	OR (95% CI)	Beta (SE)	P	SNP (n)	OR (95% CI)	Beta (SE)	P
COVID-19 vs. general population								
IVW	89	1.136 (0.988–1.306)	0.128 (0.071)	0.074	56	1.048 (0.882–1.245)	0.047 (0.088)	0.596
Weighted median	89	1.155 (0.936–1.425)	0.144 (0.107)	0.179	56	1.142 (0.915–1.426)	0.133 (0.113)	0.239
Penalised weighted median	89	1.155 (0.939–1.420)	0.144 (0.106)	0.173	56	1.142 (0.913–1.429)	0.133 (0.114)	0.244
MR_Egger	89	1.258 (1.053–1.502)	0.229 (0.090)	0.013	56	1.149 (0.918–1.439)	0.139 (0.115)	0.230
β (intercept)	89	-	-0.007 (0.004)	0.071	56	-	-0.006 (0.005)	0.214
Q statistic	89	-	-	0.759	56	-	-	0.794
COVID-19 vs. COVID-19 negative								
IVW	89	1.168 (0.956–1.427)	0.156 (0.102)	0.128	57	1.192 (0.945–1.504)	0.176 (0.118)	0.138
Weighted median	89	1.017 (0.750–1.379)	0.017 (0.156)	0.912	57	1.134 (0.810–1.588)	0.126 (0.172)	0.464
Penalised weighted median	89	0.990 (0.737–1.328)	-0.010 (0.150)	0.945	57	1.134 (0.814–1.579)	0.126 (0.169)	0.457
MR_Egger	89	1.302 (1.011–1.676)	0.260 (0.130)	0.044	57	1.265 (0.951–1.682)	0.235 (0.145)	0.112
β (intercept)	89	-	-0.007 (0.005)	0.174	57	-	-0.004 (0.006)	0.485

[#] The summary data are reported by the COVID-19 host genetics initiative.

Beta is the estimated effect size.

25OHD: 25 hydroxyvitamin D; CI: confidence intervals; COVID-19: Coronavirus disease 2019; IVs: instrumental variables; IVW, inverse-variance weighted; MR mendelian randomization; OR: odds ratio; SE, standard error; SNP, single-nucleotide polymorphism.

Method	SNP (n)	OR (95% CI)	Beta (SE)	P	SNP (n)	OR (95% CI)	Beta (SE)	P
Q statistic	89	-	-	0.656	57	-	-	0.925

[#] The summary data are reported by the COVID-19 host genetics initiative.

Beta is the estimated effect size.

25OHD: 25 hydroxyvitamin D; CI: confidence intervals; COVID-19: Coronavirus disease 2019; IVs: instrumental variables; IVW, inverse-variance weighted; MR mendelian randomization; OR: odds ratio; SE, standard error; SNP, single-nucleotide polymorphism.

The MR analysis showed no significant association of genetically instrumented 25OHD concentration with severe COVID-19 in the population of severe respiratory confirmed COVID-19 vs. population reported by two groups (OR = 0.889, 95% CI 0.549–1.439, P = 0.246; OR = 0.894, 95% CI 0.587–1.363, P = 0.603) (Table 2). The result in the weighted median, penalized weighted median, and MR-Egger regression methods were robust. There was limited evidence of heterogeneity and horizontal pleiotropy based on the Q test and MR-Egger intercept test. Sensitivity analyses using different instruments yielded similar findings, suggesting the robustness of the causal association (Table 2, Fig. 3–4, **Figure S3-4**).

Table 2

Causal association of 25OHD concentration with severe COVID-19[#]

Method	SNP (n)	OR (95% CI)	Beta (SE)	*P*	SNP (n)	OR (95% CI)	Beta (SE)	*P*
Severe respiratory confirmed COVID-19 vs. general population								
IVW	82	0.889 (0.549–1.439)	-0.118 (0.246)	0.632	55	0.936 (0.532–1.647)	-0.067 (0.288)	0.818
Weighted median	82	1.242 (0.618–2.498)	0.217 (0.356)	0.543	55	1.294 (0.605–2.767)	0.257 (0.388)	0.507
Penalised weighted median	82	1.241 (0.620–2.482)	0.216 (0.354)	0.542	55	1.293 (0.585–2.857)	0.257 (0.405)	0.526
MR_Egger	82	0.944 (0.509–1.749)	-0.058 (0.315)	0.855	55	0.998 (0.477)	-0.002 (0.376)	0.996
β (intercept)	82	-	-0.004 (0.012)	0.760	55	-	-0.004 (0.015)	0.790
Q statistic	82	-	-	0.793	55	-	-	0.650
Severe respiratory confirmed COVID-19 vs. general population*								
IVW	82	0.894 (0.587–1.363)	-0.112 (0.215)	0.603	53	0.780 (0.467-1.300)	-0.249 (0.261)	0.340
Weighted median	82	0.638 (0.335–1.215)	-0.450 (0.329)	0.171	53	0.633 (0.322–1.244)	-0.458 (0.345)	0.185
Penalised weighted median	82	0.636 (0.339–1.195)	-0.452 (0.321)	0.160	53	0.633 (0.318–1.261)	-0.457 (0.352)	0.193
MR_Egger	82	0.894 (0.523–1.527)	-0.112 (0.273)	0.682	53	0.711 (0.365–1.387)	-0.341 (0.341)	0.322

[#] The summary data are reported by the COVID-19 host genetics initiative.

* The summary data are reported by the Severe Covid-19 GWAS Group.

Beta is the estimated effect size.

25OHD: 25 hydroxyvitamin D; CI: confidence intervals; COVID-19: Coronavirus disease 2019; IVs: instrumental variables; IVW, inverse-variance weighted; MR mendelian randomization; OR: odds ratio; SE, standard error; SNP, single-nucleotide polymorphism.

Method	SNP (n)	OR (95% CI)	Beta (SE)	P	SNP (n)	OR (95% CI)	Beta (SE)	P
β (intercept)	82	-	0.00003 (0.011)	0.997	53	-	0.006 (0.014)	0.678
Q statistic	82	-	-	0.789	53	-	-	0.555
[#] The summary data are reported by the COVID-19 host genetics initiative.								
* The summary data are reported by the Severe Covid-19 GWAS Group.								
Beta is the estimated effect size.								
25OHD: 25 hydroxyvitamin D; CI: confidence intervals; COVID-19: Coronavirus disease 2019; IVs: instrumental variables; IVW, inverse-variance weighted; MR mendelian randomization; OR: odds ratio; SE, standard error; SNP, single-nucleotide polymorphism.								

Discussion

In the current study, we performed an MR analysis to investigate the causal association of 25OHD concentration with the risk of COVID-19. Our results indicated that there might be no linear causal relationship of 25OHD concentration with COVID-19 susceptibility and severity.

An observational study based on the UK Biobank data claimed that no link between vitamin D concentrations and risk of COVID-19 infection either overall or separated ethnic groups (16). However, one study used causal inference analysis, supported the hypothesis that vitamin D plays a causal role in COVID-19 outcomes via modification of host responses to SARS-CoV-2 (24). In addition, there were also systematic reviews and meta-analyses to explore the association between vitamin D and COVID-19 (9, 10, 25). These studies provided a biological hypothesis and evolving epidemiological data supporting a role for vitamin D in COVID-19. But these results only based on the observational study design, which may be confounder bias. In our study, the SNPs associated with vitamin D as IVs were used to estimate the overall causal association of 25OHD concentration on COVID-19 susceptibility and severity, based on the MR design. The MR study could potentially avoid many biases and confounding issues existing in conventional observational studies and thus help to identify causally related risk factors. Using MR design, we found no evidence supporting that genetically predicted 25OHD concentration was significantly associated with COVID-19 susceptibility and severity.

There are some possible explanations for these negative findings. First, these null findings suggest that the associations of 25OHD concentration with COVID-19 susceptibility and severity could attribute from the reverse causation bias and confounder bias. Vitamin D from environment with across to adequate sunshine or diet was metabolized in the liver to 25OHD, which was used to determine a patient's vitamin D status (23, 26). Vitamin D deficiency may be common in COVID-19 patients, as a consequence of quarantine and reduced outdoor behavior. The observed association between 25OHD concentration with increased risk of COVID-19 could be confounded by outdoor behavior which may be corrected with the

genetic liability to COVID-19 (23). Our findings suggested that COVID-19 susceptibility and severity are expected to decrease the prevalence of vitamin D deficiency, which are needed to be proved by more bi-directional MR studies. Second, it is also important to note that MR study considers the lifelong effect of genetic modification of COVID-19. However, the association between the vitamin D level and the risk of COVID-19 may be not fixed for a lifetime, but perform time-varying (27). The cross-sectional observational nature of all current MR studies limits the evaluation. The future MR studies incorporating follow-up data should be considered the effect of vitamin D level on COVID-19 and how genetic variants effects change with time may impact the interpretability and validity of their results. Third, as shown by previous studies, vitamin D supplementation only shows treatment effects among individuals with baseline 25OHD concentration of no more than 30 nmol/L, indicating that the relationship between the 25OHD concentration and the risk of diseases may be nonlinear (28–30). However, we noted that there is a linearity assumption in our Mendelian randomization analyses (23), then non-linear relationship could not be tested and might equate to the null hypothesis of no effect of the exposure on the outcome. Therefore, our results indicated that there might be no linear causal relationship of 25OHD concentration with COVID-19 susceptibility and severity.

The evidence of findings from MR studies sit at the interface between observational studies and RCTs (31). RCTs provide interventions for disease, while MR studies could therefore not be directly extrapolated for this purpose, but could rather be used to provide evidence of a causal relationship. It should be also focused on the effect of vitamin D supplementation on COVID-19. Making a trade-off between vitamin D deficiency and treatment aims to create an opportunity for prevention and intervention of COVID-19. The previous findings suggest that vitamin D deficiency and treatment has a long-term effect on preventing overall mortality (11, 32). In addition, future research should pay attention to not only the impact of vitamin D deficiency and treatment on the incidence of COVID-19, but also the impact of vitamin D deficiency and treatment on the COVID-19 mortality and lost life in COVID-19.

Some limitations should be noticed. It is important to note that the results of the MR analyses are based on numerous assumptions. First, we selected genetic variants as IVs based on the recent large-scale GWAS (23), which showed a strong association with 25OHD concentration; therefore, the bias of weak instrument might be less likely. Second, the genetic variants are not associated with measured and unmeasured confounders that influence both vitamin D and COVID-19. However, the unmeasured confounders or alternative causal pathways may be still affected our results because of the limitation of the method. Third, the existence of horizontal pleiotropy may distort MR results. In our study, there was limited evidence of heterogeneity and horizontal pleiotropy. In addition, the GWAS of the severe COVID-19 cases included small sample size, which might lead to small effect for the MR estimate and limit the IVs for COVID-19 for reverse MR analysis. The findings were based on European population, which made it difficult to represent the universal conclusions for other ethnic groups. Therefore, the future studies with larger sample size and more ethnic groups are needed to verify and explore the observed associations.

Conclusion

Using 25OHD concentration-related SNPs as IVs from GWAS data, the MR analysis results indicated that there might be no linear causal relationship of 25OHD concentration with COVID-19 susceptibility and severity. In future, the bi-directional MR and non-linear MR study was needed to further prove these results. In addition, we should pay more attention to the randomization control trials about association between vitamin D treatment and the improvement of the COVID-19 in the long-term benefits.

Abbreviations

COVID-19: Coronavirus disease 2019; SARS: Severe acute respiratory syndrome; 25OHD; 25 hydroxyvitamin D; MR: Mendelian randomization; GWAS: Genome Wide Association Study; SNPs: single nucleotide polymorphisms; IVs: instrumental variables; LD: Linkage disequilibrium; IVW: inverse-variance weighted; OR: odds ratios; CI: confidence interval; SE: standard error

Declarations

Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary information files.

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Authors' contribution

YW and QM conceived the study. DL analyzed data. DL and QT wrote the original draft. JZ, HH, and YW reviewed and edited manuscript. All authors commented on and approved the draft and final manuscript.

Ethics declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Both authors read and agreed to the content of the final manuscript, and consented on its publication.

Competing interests

No potential conflicts of interest were disclosed by the authors.

References

1. Thomson B. The COVID-19 Pandemic: A Global Natural Experiment. Circulation. 2020;142:14–6.

2. Aygun H. Vitamin D can prevent COVID-19 infection-induced multiple organ damage. Naunyn Schmiedebergs Arch Pharmacol. 2020;393:1157–60.

3. Kulda V. Vitamin D metabolism. Vnitrni lekarstvi. 2012;58:400–4.

4. DeLuca HF. Vitamin D endocrinology. Ann Intern Med. 1976;85:367–77.

5. Holick MF, Chen TC. Vitamin D deficiency: a worldwide problem with health consequences. Am J Clin Nutr. 2008;87:1080S–1086S.

6. Hossein-nezhad A, Holick MF. Vitamin D for health: a global perspective. Mayo Clin Proc. 2013;88:720–55.

7. Whittemore PB. COVID-19 fatalities, latitude, sunlight, and vitamin D. Am J Infect Control. 2020;S0196-6553:30574–5.

8. Meltzer DO,, et al. (2020) Association of Vitamin D Deficiency and Treatment with COVID-19 Incidence. *medRxiv: the preprint server for health sciences*.

9. Ghasemian R, et al. (2020) The Role of Vitamin D in The Age of COVID-19: A Systematic Review and Meta-Analysis Along with an Ecological Approach. *medRxiv: the preprint server for health sciences*.

10. Munshi R, et al. (2020) Vitamin D insufficiency as a potential culprit in critical COVID-19 patients. *Journal of medical virology*.

11. Pugach IZ, Pugach S. (2020) Strong Correlation Between Prevalence of Severe Vitamin D Deficiency and Population Mortality Rate from COVID-19 in Europe. *medRxiv: the preprint server for health sciences*.

12. De Smet D, De Smet K, Herroelen P, Gryspeerdt S, Martens GA. (2020) Vitamin D deficiency as risk factor for severe COVID-19: a convergence of two pandemics. *medRxiv: the preprint server for health sciences*.

13. Merzon E, et al. (2020) Low plasma 25(OH) vitamin D3 level is associated with increased risk of COVID-19 infection: an Israeli population-based study. *The FEBS journal*.

14. Raisi-Estabragh Z, et al. Greater risk of severe COVID-19 in Black, Asian and Minority Ethnic populations is not explained by cardiometabolic, socioeconomic or behavioural factors, or by 25(OH)-vitamin D status: study of 1326 cases from the UK Biobank. J Public Health. 2020;42:451–60.

15. Panagiotou G, et al. (2020) Low serum 25-hydroxyvitamin D (25[OH]D) levels in patients hospitalised with COVID-19 are associated with greater disease severity. *Clinical endocrinology*.

16. Hastie CE, et al. Vitamin D concentrations and COVID-19 infection in UK Biobank. Diabetes metabolic syndrome. 2020;14:561–5.

17. Davey Smith G, Hemani G. Mendelian randomization: genetic anchors for causal inference in epidemiological studies. Hum Mol Genet. 2014;23:R89–98.

18. Sekula P, Del Greco MF, Pattaro C, Köttgen A. Mendelian Randomization as an Approach to Assess Causality Using Observational Data. Journal of the American Society of Nephrology: JASN. 2016;27:3253–65.

19. Burgess S, Butterworth A, Thompson SG. Mendelian randomization analysis with multiple genetic variants using summarized data. Genet Epidemiol. 2013;37:658–65.

20. Dimou NL, Tsilidis KK. A Primer in Mendelian Randomization Methodology with a Focus on Utilizing Published Summary Association Data. Methods Mol Biol. 2018;1793:211–30.

21. Initiative C-HG. The COVID-19 Host Genetics Initiative, a global initiative to elucidate the role of host genetic factors in susceptibility and severity of the SARS-CoV-2 virus pandemic. European journal of human genetics: EJHG. 2020;28:715–8.

22. Ellinghaus D, et al. (2020) Genomewide Association Study of Severe Covid-19 with Respiratory Failure. *N Engl J Med*.

23. Revez JA, et al. Genome-wide association study identifies 143 loci associated with 25 hydroxyvitamin D concentration. Nature communications. 2020;11:1647.

24. Davies G, Garami AR, Byers JC. (2020) Evidence Supports a Causal Role for Vitamin D Status in COVID-19 Outcomes. *medRxiv: the preprint server for health sciences*.

25. Laird E, Rhodes J, Kenny RA. Vitamin D and inflammation: Potential implications for severity of Covid-19. Irish medical journal. 2020;113:81.

26. Holick MF. Vitamin D deficiency. N Engl J Med. 2007;357:266–81.

27. Meng JE,, et al. Intraindividual variation in plasma 25-hydroxyvitamin D measures 5 years apart among postmenopausal women. Cancer epidemiology biomarkers prevention: a publication of the American Association for Cancer Research cosponsored by the American Society of Preventive Oncology. 2012;21:916–24.

28. Crowe FL,, et al. Non-linear associations of 25-hydroxyvitamin D concentrations with risk of cardiovascular disease and all-cause mortality: Results from The Health Improvement Network (THIN) database. J Steroid Biochem Mol Biol. 2019;195:105480.

29. Esteghamati A, et al. Non-linear contribution of serum vitamin D to symptomatic diabetic neuropathy: A case-control study. Diabetes Res Clin Pract. 2016;111:44–50.

30. Zittermann A. Vitamin D Status, Supplementation and Cardiovascular Disease. Anticancer research. 2018;38:1179–86.

31. Davies NM, Holmes MV, Smith GD. Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. Bmj Clinical Research. 2018;362:k601.

32. Ouchetto O, Drissi Bourhanbour A. (2020) Risk Factors for Mortality of COVID-19 Patients. *medRxiv: the preprint server for health sciences*.
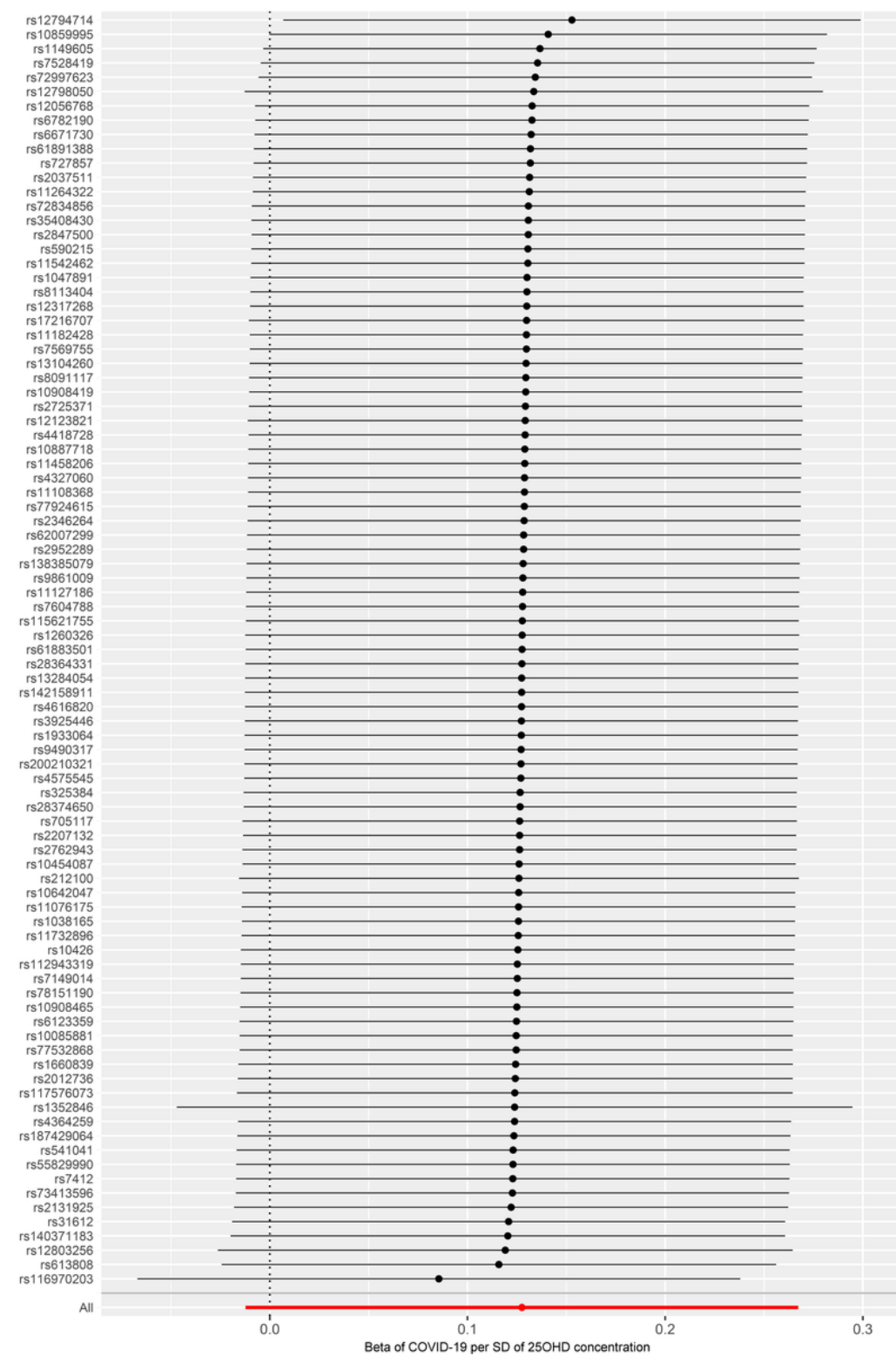
Figures

Figure 1

MR leave-one-out sensitivity analysis for '25OHD concentration' on 'COVID-19' in the population of COVID-19 vs. population Leave-one-out analysis: each row represents a MR analysis of 25OHD concentration on COVID-19 using all instruments expect for the SNP listed on the y-axis. The point represents the beta with that SNP removed and the line represents 95% confidence interval. The summary data are reported by the COVID-19 host genetics initiative. COVID-19: Coronavirus disease 2019; MR: mendelian randomization; SNP, single-nucleotide polymorphism; 25OHD: 25-hydroxyitamin D; SD, standard deviation
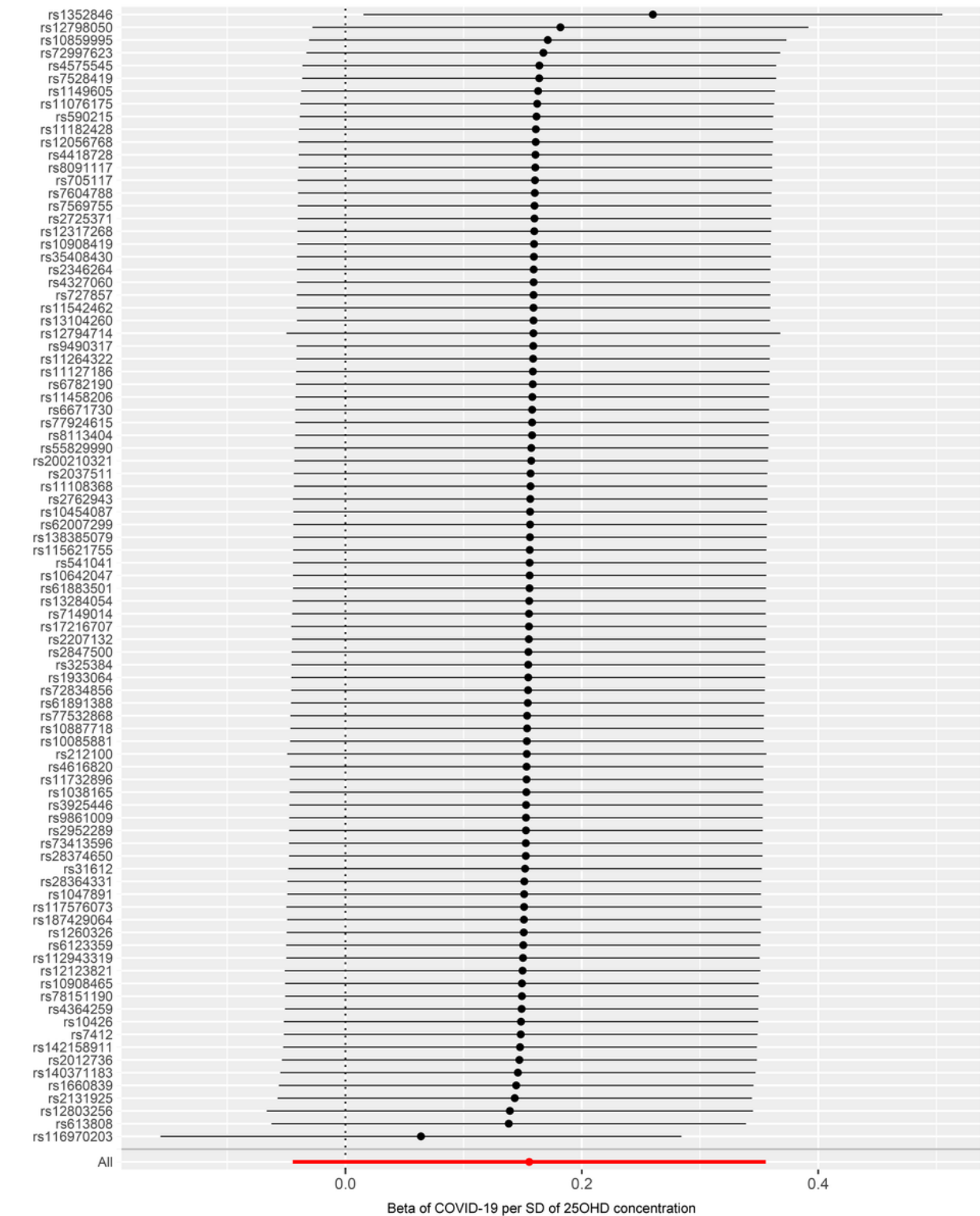
Figure 2

MR leave-one-out sensitivity analysis for '25OHD concentration' on 'COVID-19' in the population of COVID-19 vs. COVID-19 negative Leave-one-out analysis: each row represents a MR analysis of 25OHD concentration on COVID-19 using all instruments expect for the SNP listed on the y-axis. The point represents the beta with that SNP removed and the line represents 95% confidence interval. The summary data are reported by the COVID-19 host genetics initiative. COVID-19: Coronavirus disease 2019; MR: mendelian randomization; SNP, single-nucleotide polymorphism; 25OHD: 25-hydroxyitamin D; SD, standard deviation
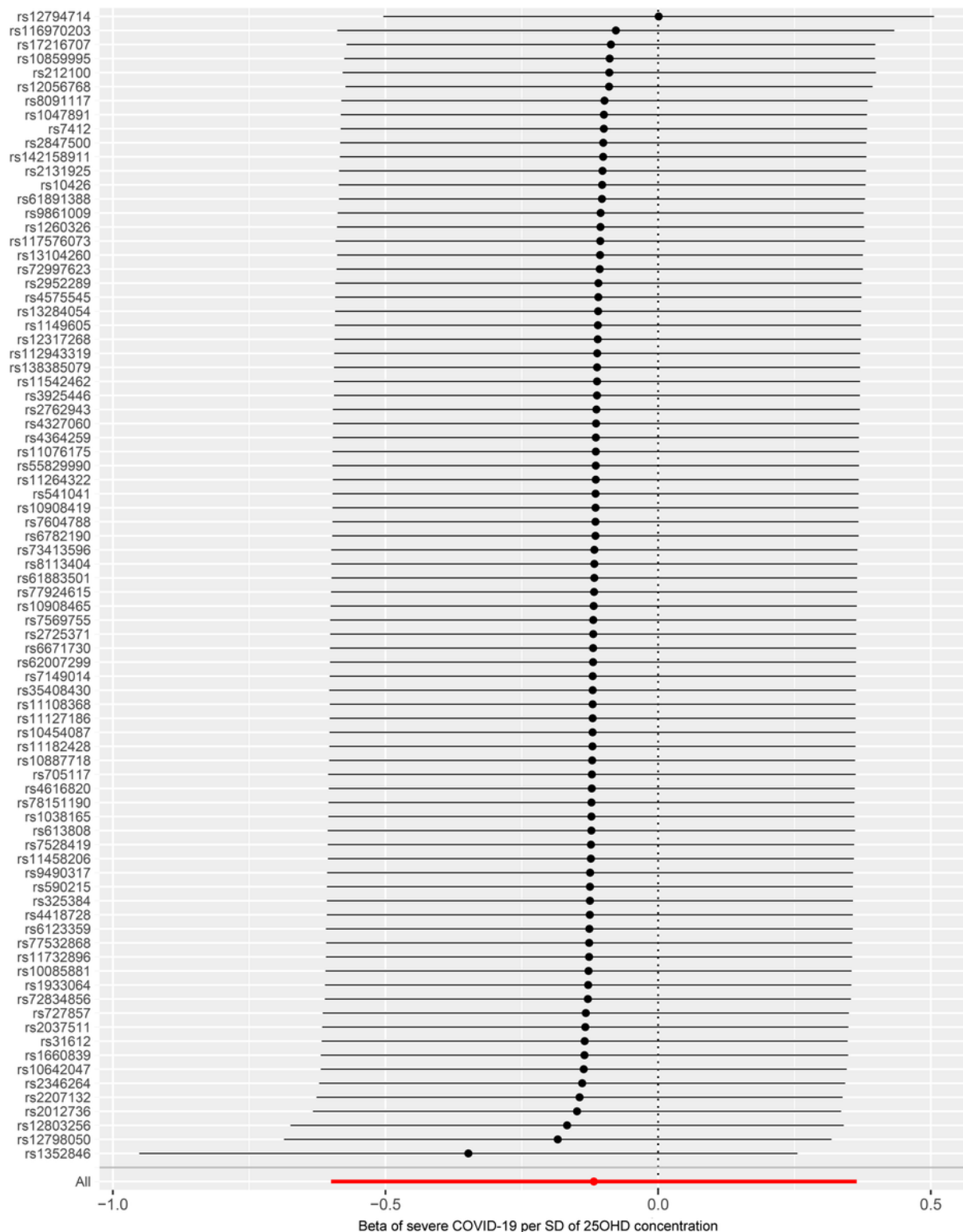
Figure 3

MR leave-one-out sensitivity analysis for '25OHD concentration' on 'severe COVID-19' in the population of severe respiratory confirmed COVID-19 vs. population Leave-one-out analysis: each row represents a MR analysis of 25OHD concentration on severe COVID-19 using all instruments expect for the SNP listed on the y-axis. The point represents the beta with that SNP removed and the line represents 95% confidence interval. The summary data are reported by the COVID-19 host genetics initiative. COVID-19: Coronavirus

disease 2019; MR: mendelian randomization; SNP, single-nucleotide polymorphism; 25OHD: 25-hydroxyitamin D; SD, standard deviation
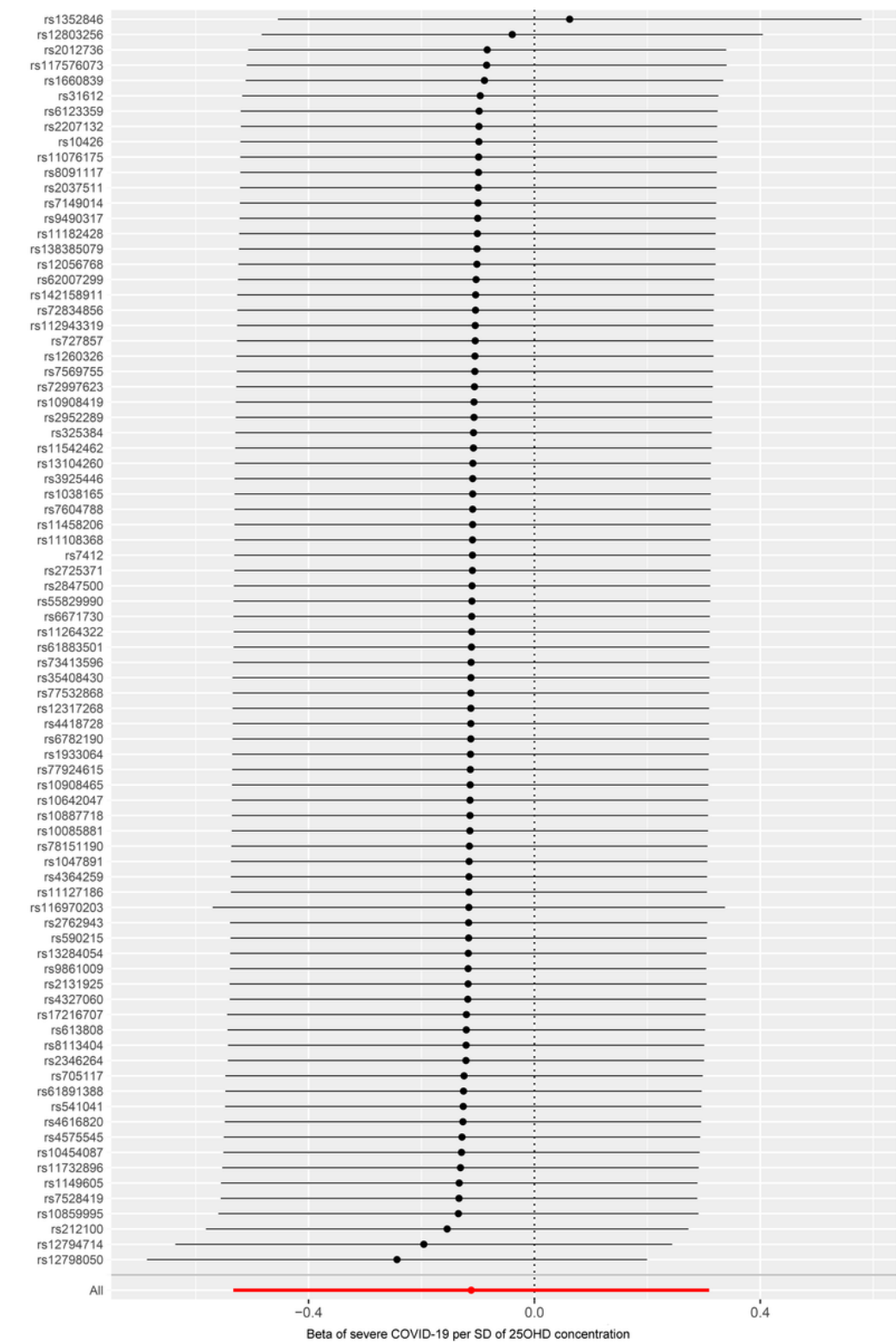

Figure 4

MR leave-one-out sensitivity analysis for '25OHD concentration' on 'severe COVID-19' in the population of severe respiratory confirmed COVID-19 vs. population Leave-one-out analysis: each row represents a MR analysis of 25OHD concentration on severe COVID-19 using all instruments expect for the SNP listed on

the y-axis. The point represents the beta with that SNP removed and the line represents 95% confidence interval. The summary data are reported by the severe COVID-19 GWAS Group. COVID-19: Coronavirus disease 2019; MR: mendelian randomization; SNP, single-nucleotide polymorphism; 25OHD: 25-hydroxyitamin D; SD, standard deviation; GWAS, genome wide association study