



Research Article

Association Between COVID-19 and Osteoporosis: A Bidirectional Mendelian Randomization Study

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Abstract

Objective: The prevalence and severity of covid-19 infection were higher in patients with osteoporosis than in healthy controls, and the mean BMD was lower in patients with COVID-19 than in healthy controls, and low vitamin D levels were associated with the development of osteoporosis and the severity of COVID-19. The objective of this study is to understand whether there was indeed a bidirectional causal relationship between osteoporosis and COVID-19.

Methods: Analysis of the causal relationship between the two through a two-way Mendelian pathway. Finding disease-related Single nucleotide Polymorphism as working variables through the Genome-wide association study database. The primary analysis for the Mendelian randomization (MR) study was the inverse variance weighting (IVW) method. The pleiotropy was estimated through the intercept from MR-Egger regression, and heterogeneity was assessed through Cochran's Q test in IVW approach.

Results: In the forward MR analysis, neither exposure to COVID-19 infection, hospitalization or severe infection was significantly associated with osteoporosis or drug-induced osteoporosis outcome ($P>0.05$); in the reverse MR analysis, exposures to osteoporosis was not significantly associated with COVID-19 outcomes (infection, hospitalization, severe case) ($P>0.05$).

Conclusion: There was no significant relationship between COVID-19 patients and osteoporosis or drug-induced osteoporosis by genetic prediction.

Keywords: COVID-19, osteoporosis, Mendelian randomization

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1 INTRODUCTION

The current COVID-19 pandemic has had enormous health^[1] and economic consequences^[1] worldwide due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection^[2]. Glucocorticoid therapy is widely used to treat patients with COVID-19^[3,4]. However, glucocorticoid therapy accelerates the loss of calcium from bone and increases the prevalence of osteoporosis^[5,6]. On

the other hand, SARS-CoV-2 may have direct and indirect effects on osteoclasts and osteoblasts and contribute to osteoporosis^[7,8]. Whether there is a causal relationship between osteoporosis and infection with COVID-19 is therefore difficult to predict.

Vitamin D (VitD) is a key hormone for bone health and vitamin D supplementation may reduce the incidence of osteoporosis^[9], and studies have shown a significant

positive association between vitamin D deficiency and COVID-19 infection and mortality^[10], with vitamin D supplementation reducing COVID-19 infection and mortality^[11]. Patients with osteoporosis combined with COVID-19 infection also have poorer health outcomes compared to those without osteoporosis^[12]. We are therefore interested in whether there is a potential bidirectional relationship between osteoporosis and COVID-19 and the efficacy of vitamin D supplementation improve COVID-19 infection outcomes via the bone density pathway or not.

The Mendelian randomization (MR) framework tests for a potential causal relationship between exposure and outcome by using genetic variation as an instrumental variable^[13]. We analyzed the potential causal relationship between three COVID-19 prevalence states (hospitalized cases, severe cases, infected cases) and osteoporosis or drug-induced osteopenia. Bidirectional MR studies were constructed by comparing genome-wide gene extracts of shared genes reported for each trait^[14,15].

2 MATERIALS AND METHODS

2.1 Study Design and Assumption

Genome-wide association study (GWAS) data were used to conduct bidirectional MR analyses examining the bidirectional association between COVID-19 and osteoporosis. Forward MR analyses used COVID-19 as exposure and osteoporosis as outcome, whereas reverse MR analyses used osteoporosis as exposure and COVID-19 as outcome. [Figure 1](#) shows a brief description and the core assumption of this bidirectional MR design.

2.2 Instrumental Variables Selection Principles

Single nucleotide polymorphism (SNPs) were selected as instrumental variables based on the following principles: (1) SNPs with genome-wide significance ($P < 1.0 \times 10^{-8}$); (2) SNPs were independent, by calculating the linkage disequilibrium based on the European 1,000 Genome reference panel ($r^2 < 0.01$). In reverse MR analysis, to determine whether SNPs are associated with potential risk factors, we searched for all SNPs in PhenoScanner (<http://www.phenoscanter.medschl.cam.ac.uk/>)^[16-18]. SNPs potentially related to factors associated with COVID-19 infection or severity, such as blood cell-related indices^[19], body fat^[20], ulcerative colitis^[21,22], etc., were excluded. Weak instrument variables were evaluated by calculating the F-statistic^[23], with an F-statistic of 10 considered sufficiently robust to mitigate weak instrument bias^[24].

2.3 Data Sources and Instrumental Variables Selection for Forward MR

In the forward MR analysis, instrumental variables were derived from the top 10k SNPs of COVID19-hg GWAS meta-analyses round 7 (<https://www.covid19hg.org/>

[results/r7/](https://www.covid19hg.org/results/r7/)). For the SNPs with missing RSID, we retrieve the RSID through '<https://www.ncbi.nlm.nih.gov/snp/>' using EA, OA, POF and other indicators. Instrumental variables obtained under different exposure scenarios according to selection principles: 7 SNPs for severe COVID-19; 10 SNPs for hospitalized COVID-19; 6 SNPs for COVID-19 infection. The outcome data were obtained from the following two GWAS datasets: the osteoporosis patient dataset (<https://gwas.mrcieu.ac.uk/datasets/finn-b-M13-OSTEOPOROSIS/>) and the drug-induced osteoporosis patient dataset (<https://gwas.mrcieu.ac.uk/datasets/finn-b-DRUGADVERS-OSTEOPPO/>). [Table S1](#) summarizes the basic information and demographic characteristics of each dataset., [Table S2](#) summarizes those SNPs.

2.4 Data Sources and Instrumental Variables Selection for Reverse MR

In the reverse MR analysis, instrumental variables were derived from the dataset of non-cancer illness code self-reported osteoporosis (ukb-a-87, <https://gwas.mrcieu.ac.uk/datasets/ukb-a-87/>). 12 SNPs were used as instrumental variables according to the selection principles. The outcome data were obtained from the COVID19-hg GWAS meta-analyses round 7 (<https://www.covid19hg.org/results/r7/>). [Table S1](#) summarizes the basic information and demographic characteristics of each dataset.

2.5 Statistical Analysis

The primary analysis for the MR study was the Inverse Variance Weighting (IVW) method^[25-28], which is based on a hypothesis that all core assumptions of MR are valid. However, if there had invalid SNPs, the outcome may be biased. Therefore MR-Egger and weighted median methods were used to performed the sensitivity and estimated the causal relationship accurately^[29,30]. The pleiotropy was estimated through the intercept from MR-Egger regression, and heterogeneity was assessed through Cochran's Q test in IVW and MR egger approach. If the P value of Cochran's Q > 0.05, we will assess whether bias existed due to individual SNP independently affecting the results by leave-one-out analysis.

For the binary outcomes, the odd ratios (OR) and 95% credibility interval (CI) were applied to estimate the degree of causality. Causal estimates for binary outcomes, p-values, β and their standard errors are also given. All p-values are two-tailed. All analyses were performed by applying the TwoSampleMR, MendelianRandomization and data.table packages in R (version 4.2.2, www.r-project.org/).

3 RESULTS

3.1 Forward MR Analysis

There was no significant relationship between COVID-19 patients and osteoporosis or drug-induced osteoporosis by genetic prediction, as shown in [Figure 2](#)

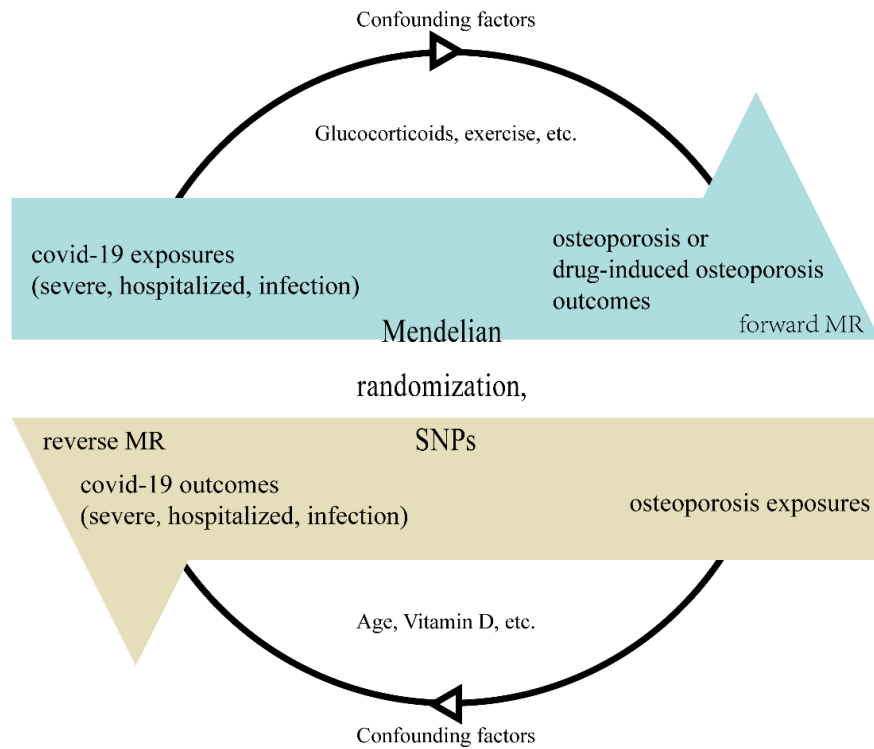


Figure 1. A brief description and the core assumption of this bidirectional MR design. Using SNPs as working variables to exclude confounding factors (age, vitamin D, exercise, etc.) and explore whether COVID-19 and osteoporosis are causally related to each other.

Methods	Used SNPs		OR (95% CI)	P
Exposures & Outcomes: severe COVID-19 & osteoporosis				
IVW	7		0.96 (0.86, 1.06)	0.41
MR Egger	7		1.04 (0.82, 1.34)	0.75
Weighted median	7		0.96 (0.84, 1.09)	0.48
Weighted modemode	7		1.03 (0.90, 1.19)	0.67
Exposures & Outcomes: hospitalized COVID-19 & osteoporosis				
IVW	10		0.96 (0.85, 1.09)	0.67
MR Egger	10		1.18 (0.92, 1.50)	0.54
Weighted median	10		1.05 (0.89, 1.26)	0.23
Weighted mode	10		1.03 (0.86, 1.22)	0.58
Exposures & Outcomes: COVID-19 infection and osteoporosis				
IVW	6		0.91 (0.61, 1.34)	0.63
MR Egger	6		0.92 (0.32, 2.60)	0.88
Weighted median	6		0.88 (0.57, 1.36)	0.57
Weighted mode	6		0.93 (0.56, 1.54)	0.79

Figure 2. Effect of exposure to COVID-19 (infection, hospitalization, and severe disease) on the outcomes of osteoporosis. IVW: Inverse Variance Weighting; Used SNPs: Number of SNPs used as working variables when performing MR. SNPs inclusion criteria: $P < 1 \times 10^{-8}$, $r^2 < 0.01$. There was no significant relationship between COVID-19 patients and osteoporosis by MR.

and Figure 3. Neither exposure to severe COVID-19 (OR: 0.96; 95% CI: 0.86-1.06; $P=0.41$) nor hospitalized COVID-19 (OR: 0.96; 95% CI: 0.85-1.09; $P=0.67$) nor COVID-19 infection (OR: 0.91; 95% CI: 0.61-1.34; $P=0.63$) had a genetically determined responsibility for the outcome of osteoporosis (Figure 2). There was also no genetically determined liability between drug-induced osteoporosis outcomes and exposure to COVID-19 infection (OR: 1.61; 95% CI: 0.35-7.33; $P=0.54$), COVID-19 hospitalization (OR: 0.76; 95% CI: 0.38-1.53;

$P=0.44$), and severe COVID-19 (OR: 0.97; 95% CI: 0.61-1.53; $P=0.89$) (Figure 3). All p-values were greater than 0.05 in heterogeneity analysis (Table 1) and pleiotropic effect test (Table 2). Therefore, it was concluded that there was no heterogeneity or pleiotropic effect.

We analyzed other osteoporosis GWAS datasets from 'ieu open gwas project' (<https://gwas.mrcieu.ac.uk/>), but the results all suggested no significant genetic link between COVID-19 exposures and osteoporosis outcomes

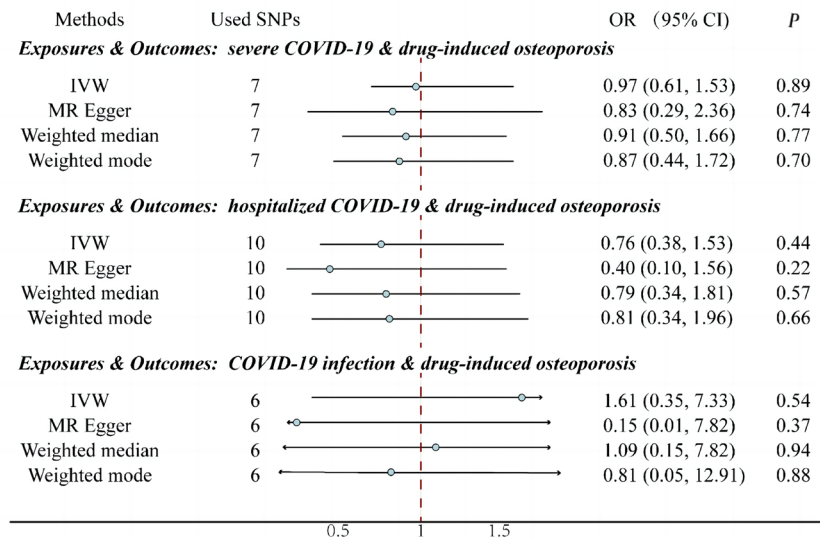


Figure 3. Effect of exposure to COVID-19 (infection, hospitalization, and severe disease) on the outcomes of drug-induced osteoporosis. IVW: Inverse Variance Weighting; Used SNPs: Number of SNPs used as working variables when performing MR. SNPs inclusion criteria: $P < 1 \times 10^{-8}$, $r^2 < 0.01$. There was no significant relationship between COVID-19 patients and drug-induced osteoporosis by MR.

Table 1. MR Heterogeneity Test

Exposures	Outcomes	Methods	Q	Q_df	Q_pval
Forward MR					
Severe COVID-19	Osteoporosis	MR Egger	7.02	5	0.22
		IVW	7.88	6	0.25
	Drug-induced osteoporosis	MR Egger	5.28	5	0.38
		IVW	5.39	6	0.5
Hospitalized COVID-19	Osteoporosis	MR Egger	5.61	8	0.69
		IVW	9.08	9	0.43
	Drug-induced osteoporosis	MR Egger	10.31	8	0.24
		IVW	11.78	9	0.23
COVID-19 infection	Osteoporosis	MR Egger	7.91	4	0.09
		IVW	7.91	5	0.16
	Drug-induced osteoporosis	MR Egger	2.54	4	0.64
		IVW	4.50	5	0.48
Reverse MR					
Osteoporosis	Severe COVID-19	MR Egger	13.93	11	0.24
		IVW	13.94	12	0.3
	Hospitalized COVID-19	MR Egger	10.49	11	0.49
		IVW	12.61	12	0.40
	COVID-19 infection	MR Egger	11.48	11	0.40
		IVW	13.30	12	0.35

Notes: Q: Cochran's Q; Q_df: The freedom of Cochran's Q; Q_pval: P for Cochran's Q were derived from Cochran's Q test and $P < 0.05$ indicates a possible heterogeneity. There was no heterogeneity between COVID-19 to osteoporosis.

(Table S3). We also performed a secondary analysis by selecting SNPs with a significance level of $P < 1 \times 10^{-7}$ and $r^2 < 0.1$, and the results were still not statistically different (Table S4).

3.2 Reverse MR Analysis

There was no significant relationship between osteoporosis exposition and COVID-19 outcomes by genetic prediction, as shown in figure 4. Patients with

osteoporosis compared to non-osteoporotic patients had no genetically determined responsibility outcome of severe COVID-19, hospitalized COVID-19, COVID-19 infection (Figure 4). By pleiotropic effect test (Table 2) as well as heterogeneity analysis (Table 1), all P-values were greater than 0.05. It was concluded that there was no heterogeneity as well as pleiotropic effect.

We excluded SNPs associated with both osteoporosis and other diseases due to the large 95% CI of the results

Table 2. MR Pleiotropic Effect Test

Exposures	Outcomes	Methods	Intercept	SE	P
Forward MR					
Severe COVID-19	Osteoporosis	MR Egger	-0.03	0.03	0.47
	Drug-induced osteoporosis	MR Egger	0.05	0.14	0.76
Hospitalized COVID-19	Osteoporosis	MR Egger	-0.04	0.02	0.10
	Drug-induced osteoporosis	MR Egger	0.14	0.13	0.32
COVID-19 infection	Osteoporosis	MR Egger	-0.00	0.04	0.98
	Drug-induced osteoporosis	MR Egger	-0.22	0.16	0.23
Reverse MR					
Osteoporosis	Severe COVID-19	MR Egger	-0.00	0.03	0.97
	Hospitalized COVID-19	MR Egger	-0.03	0.02	0.17
	COVID-19 infection	MR Egger	-0.01	0.01	0.21

Notes: Intercept: The farther the intercept distance 0 is, the greater the pleiotropic effect. *P*-values less than 0.05 are considered to have pleiotropic effect. There was no pleiotropic effect between COVID-19 to osteoporosis.

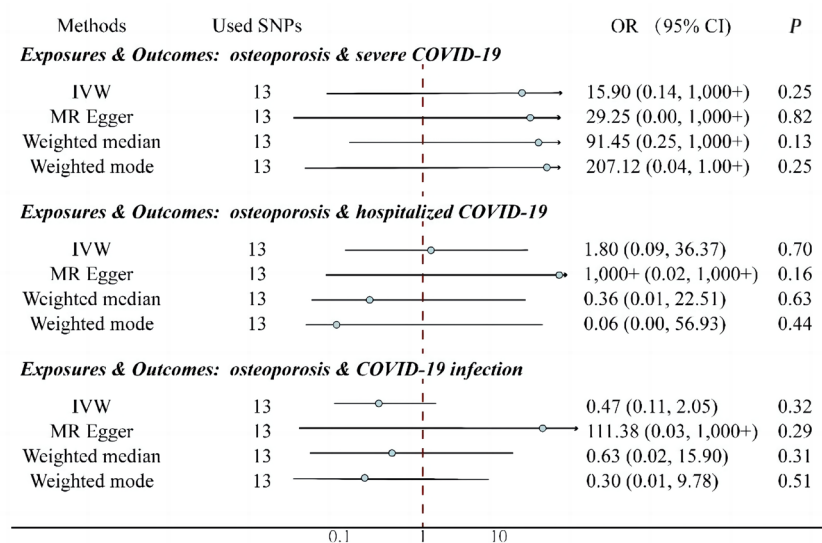


Figure 4. Effect of exposure to osteoporosis on the outcomes of COVID-19 (infection, hospitalization, and severe disease). IVW: Inverse Variance Weighting; Used SNPs: Number of SNPs used as working variables when performing MR. SNPs inclusion criteria: $P < 1 \times 10^{-8}$, $r^2 < 0.01$. There was no significant relationship between osteoporosis exposures and COVID-19 outcomes.

(Figure 4), but the 95% CI range after exclusion was still large and no significant relationship between osteoporosis exposition and COVID-19 outcomes was found by genetic prediction. The excluded SNPs and the reasons are shown in (Table S5). The excluded results are shown in (Table S6). There was no heterogeneity as well as pleiotropic effect.

4 DISCUSSION

A multicenter study showed that patients with COVID-19 requiring intensive care had significantly lower bone mineral density (BMD) than patients treated in a non-intensive care setting^[31]. Some patients report persistent bone pain or burning sensation after COVID-19 infection^[32]. In addition, animal studies have shown that COVID-19 infected C57/b6^[7] or golden Syrian hamsters^[8] activate osteoclast-mediated bone loss. BMD in patients with osteoporosis was decreased after COVID-19 infection^[12]. Based on the above findings we thought that there should be a significant increase in the

global prevalence of osteoporosis after the COVID-19 pandemic in recent years, yet we see no such reports. Using Mendelian regression analysis, we also found no significant association between COVID-19 infection (severe, hospitalized or infection alone) and osteoporosis outcomes.

As to why the trait appeared in animal experiments, we believe that it was assumed that a large number of COVID-19 pathogens were present for a long time in animal experiments, whereas in humans COVID-19 pathogens are present in much smaller relative numbers and for much less time. This resulted in a different outcome.

Based on relevant research^[33-35], thought that the possible causes of osteoporosis after COVID-19 may come from these confounding factors: (1) the use of glucocorticoids for treat COVID-19; (2) long term stay at indoors and reduce the sun exposure time after infection;

(3) decreased cardiorespiratory fitness and outdoor exercise; (4) inflammatory storm 4. inflammatory storms; (5) a significant decline in the quality of osteoporosis treatment during the COVID-19 pandemic. Therefore, we believe that for COVID-19 patients who are also at high risk for osteoporosis, the use of glucocorticoids should be minimized, and alternative medications should be considered^[36]. Additionally, indoor exercise is crucial for preventing osteoporosis in these patients. We should standardize osteoporosis treatment to better face future public health emergencies^[37].

Some clinical studies have found that patients with lower BMD have significantly higher rates of severe clinical morbidity compared to those with higher BMD, and that BMD can be used as a predictor of COVID-19 clinical outcomes^[38-41]. However, our study showed that exposure to osteoporosis was not related to the COVID-19 infection and the symptoms. The possibility of such outcomes on clinical study may arise from the interference of confounding factors: Osteoporosis is more common in older people^[40], who are more likely to develop COVID-19^[42] and may have more severe COVID-19^[43]; people with osteoporosis often have more comorbidities^[40] and may be in worse health than non-osteoporotic patients. Therefore, the allocation of medical resources during a pandemic should not be based on bone density or prioritize osteoporotic patients for additional resources. Instead, medical resource allocation should consider other relevant indicators, such as age^[44], gender^[44], GDP^[45], etc.

Serum 1,25-dihydroxyvitamin D (1,25(OH)₂D) was significantly decreased in osteoporotic patients ($P < 0.001$) than controls^[46], and COVID-19 outcomes are worse in patients with low serum levels of 1,25(OH)₂D^[10,47]. VitD supplementation may reduce the risk of influenza and COVID-19 infection and death^[11]. However, our findings suggest that COVID-19 infection is not associated with osteoporosis. We therefore conclude that vitamin supplementation improves COVID-19 outcomes should not act by affecting the BMD pathway.

4.1 Limitation

Our study only covers the GWAS dataset for the European population, and it is not possible to conclude whether it is applicable to the Asian and African populations; No MR analysis was performed on whether exposure to secondary infection with COVID-19 had an effect on osteoporosis outcomes; In this study, summary-level data is used to evaluate the causal relationship, not individual-level data; Not Collaboration with experts in the field.

5 CONCLUSIONS

In this bidirectional MR study, non-genetic association was found between osteoporosis and COVID-19. During the COVID-19 pandemic, there were many mildly ill or asymptomatic patients, and our research suggests that

COVID-19 infection alone does not increase the likelihood of developing osteoporosis later in life. There is also no association between simple osteoporosis and COVID-19 infection and secondary attacks.

6 LIMITATION

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Conflicts of Interest

The authors declared no conflict of interest.

Author Contribution

Chen S was responsible for designing the study, interpreting the data, and writing the original draft. Xue S provided supervision and project administration, and contributed to the writing, review, and editing processes. Both of the authors made substantial contributions to the manuscript and approved the final version for submission.

Abbreviation List

BMD, Bone mineral density
 CI, Credibility interval
 GWAS, Genome-wide association study
 IVW, Inverse variance weighting
 MR, Mendelian randomization
 OR, Odd ratios
 SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2
 SNPs, Single nucleotide polymorphism
 VitD, Vitamin D

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