

Table S1. The Basic Information and Demographic Characteristics of Each Dataset

Dataset Name	Data Usage	Phenotype	Personal	Numbers of Cases	Numbers of Controls	Link
A2_ALL_eur_leave_23andme	Outcomes of osteoporosis	European	severe covid-19	13,769	1,072,442	COVID19_HGI_A2_ALL_eur_leave23andme_20220403_GRCh37.tsv.gz
B2_ALL_eur_leave_23andme	Outcomes of osteoporosis	European	Hospitalized covid-19	32,519	2,062,805	COVID19_HGI_B2_ALL_eur_leave23andme_20220403_GRCh37.tsv.gz
C2_ALL_eur_leave_23andme	Outcomes of osteoporosis	European	Covid-19 infection	122,616	2,475,240	COVID19_HGI_C2_ALL_eur_leave23andme_20220403_GRCh37.tsv.gz
UKB-A-87	As explosion of covid-19	European	osteoporosis	5,266	337,159	https://gwas.mrcieu.ac.uk/datasets/ukb-a-87/
finn-b-M13_ OSTEOPOROSIS	Outcomes of covid-19	European	osteoporosis	3,203	209,575	https://gwas.mrcieu.ac.uk/datasets/finn-b-M13_ OSTEOPOROSIS/
finn-b- DRUGADVERS_ OSTEOPOROSIS	Outcomes of covid-19	European	Drug-induced osteoporosis	124	218,668	https://gwas.mrcieu.ac.uk/datasets/finn-b- DRUGADVERS_ OSTEOPOROSIS/

Table S2. Summary Table of SNPs That Meet the Working Variable Requirements

Exposures & outcomes	RSID	Coordinate	OA	EA	Alternative allele			F	
					EA	Beta	SE		P value
Severe Covid-19 & Osteoporosis/ DIO	rs11085727	10466123	C	T	0.28	0.163	0.0248	4.84E-11	43.2
	rs13050728	34615210	T	C	0.66	-0.2	0.0241	1.05E-16	68.9
	rs13078854	45861932	G	A	0.07	0.635	0.0384	2.13E-61	273.5
	rs2109069	4719443	G	A	0.31	0.231	0.0241	9.68E-22	91.9
	rs2269899	1.13E+08	C	T	0.65	0.174	0.024	3.88E-13	52.6
	rs72856713	31121958	C	G	0.09	0.275	0.0362	2.96E-14	57.7
	rs77534576	47940666	C	T	0.03	0.369	0.0628	4.37E-09	34.5
	rs10490770	45864732	T	C	0.08	0.5	0.0276	1.44E-73	328.2
	rs13050728	34615210	T	C	0.6	-0.15	0.0162	2.72E-20	85.7
	rs144309607	10492274	C	T	0.04	0.265	0.0461	9.15E-09	33.0
Hospitalized Covid-19 & Osteoporosis/ DIO	rs17659881	44157597	A	G	0.18	-0.12	0.0203	3.30E-09	34.9
	rs1886814	41502683	A	C	0.0424	0.233	0.0382	1.11E-09	37.2
	rs2109069	4719443	G	A	0.31	0.144	0.017	2.76E-17	71.8
	rs2660	113357442	G	A	0.67	0.104	0.0166	4.29E-10	39.3
	rs495828	136154867	T	G	0.79	-0.108	0.018	2.34E-09	36.0
	rs72711165	125336564	T	C	0.0134	0.314	0.0525	2.13E-09	35.8
	rs72856713	31121958	C	G	0.09	0.159	0.0259	7.56E-10	37.7
	rs115478735	136149711	A	T	0.18	0.11	0.0102	1.66E-27	116.3
	rs11919389	101424458	T	C	0.35	-0.0604	0.00768	3.46E-15	61.9
	rs2109069	4719443	G	A	0.32	0.0479	0.00814	4.08E-09	34.6
Covid-19 Infection & Osteoporosis/ DIO	rs2271616	45838013	G	T	0.12	0.144	0.0117	1.79E-34	151.5
	rs35508621	45880481	T	C	0.09	0.151	0.0132	2.73E-30	130.9
	rs6489874	113367895	A	G	0.67	0.0541	0.00854	2.48E-10	40.1
	rs3779381	120966790	A	G	0.26	-0.00258	0.000299	6.60E-18	74.5
	rs34102936	38142840	G	A	0.58	-0.00202	0.000266	3.30E-14	57.7
	rs442115	41118450	T	G	0.56	-0.00186	0.000264	1.70E-12	49.6
	rs10023907	88772535	C	T	0.66	0.001934	0.000277	3.10E-12	48.7
	rs2566755	68635390	T	C	0.21	-0.00221	0.000317	3.30E-12	48.6
	rs851974	151971687	G	A	0.57	0.001566	0.000266	4.10E-09	34.7
	rs1414660	240586695	C	T	0.19	-0.00193	0.000333	6.80E-09	33.6
Osteoporosis & Covid-19(Infection, Hospitalized, Severe)	rs74777717	30965607	C	G	0.07	0.003185	0.000509	3.90E-10	39.2
	rs188810925	41798194	G	A	0.08	-0.00323	0.000498	8.50E-11	42.1
	rs1586274	120026562	A	G	0.48	0.001789	0.000263	1.10E-11	46.3
	rs9594738	42952145	C	T	0.49	0.00217	0.000262	1.20E-16	68.6
	rs9482772	127446790	T	C	0.45	-0.00152	0.000264	7.90E-09	33.1
	rs56312530	68219415	G	A	0.17	0.002225	0.000351	2.30E-10	40.2
	rs6684375	22706434	C	T	0.18	-0.00224	0.000344	6.70E-11	42.4

Notes: The genetic instrumental variables were filtered with genome-wide significance through $P < 10^{-8}$, and removed Linkage disequilibrium (LD) using a clumping r^2 cutoff of 0.01 within a 10Mb window, using the 1000 Genomes Project Phase 3 (EUR) as the reference panel.

Table S3. Mendelian Randomization Analysis Between Covid-19 and Some Other Osteoporosis GWAS Datasets

Exposures	Outcomes	N. SNPs	OR (95% CI)	P value	Outcomes Datasets
Severe Covid-19	Secondary Osteoporosis	4	1.00 (1.00, 1.00)	0.70	ukb-b-17796
	self-reported osteoporosis	6	1.00 (1.00, 1.00)	0.88	ukb-b-12141
	self-reported osteoporosis	7	1.00 (1.00, 1.00)	0.58	ukb-a-87
	Osteoporosis	6	1.00 (1.00, 1.00)	0.50	bbj-a-137
	Drug-induced osteoporosis with pathological fracture	7	1.02 (0.62, 1.70)	0.25	finn-b-OSTPOPATFRACTURE
	Postmenopausal osteoporosis with pathological fracture	7	0.96 (0.78, 1.18)	0.71	finn-b-OSTEOPOROSIS_FRACTURE_FG
	Postmenopausal osteoporosis with pathological fracture	7	0.95 (0.75, 1.20)	0.67	finn-b-OSTPOPATFRCTURE_POSTEMENO
Hospitalized Covid-19	Secondary Osteoporosis	5	1.00 (1.00, 1.00)	0.65	ukb-b-17796
	self-reported osteoporosis	8	1.00 (1.00, 1.00)	0.74	ukb-b-12141
	self-reported osteoporosis	10	1.00 (1.00, 1.00)	0.97	ukb-a-87
	Osteoporosis	9	1.00 (0.90, 1.11)	0.95	bbj-a-137
	Drug-induced osteoporosis with pathological fracture	10	1.16 (0.61, 2.2)	0.65	finn-b-OSTPOPATFRACTURE
	Postmenopausal osteoporosis with pathological fracture	10	1.03 (0.80, 1.32)	0.83	finn-b-OSTEOPOROSIS_FRACTURE_FG
	Postmenopausal osteoporosis with pathological fracture	10	1.03 (0.77, 1.36)	0.86	finn-b-OSTPOPATFRCTURE_POSTEMENO
Covid-19 Infection	Secondary Osteoporosis	4	1.00 (1.00, 1.00)	0.73	ukb-b-17796
	self-reported osteoporosis	6	1.00 (0.99, 1.00)	0.64	ukb-b-12141
	self-reported osteoporosis	6	1.00 (1.00, 1.00)	0.77	ukb-a-87
	Osteoporosis	5	1.04 (0.81, 1.34)	0.75	bbj-a-137
	Drug-induced osteoporosis with pathological fracture	6	1.14 (0.23, 5.61)	0.87	finn-b-OSTPOPATFRACTURE
	Postmenopausal osteoporosis with pathological fracture	6	1.2 (0.57, 2.51)	0.63	finn-b-OSTEOPOROSIS_FRACTURE_FG
	Postmenopausal osteoporosis with pathological fracture	6	1.16 (0.50, 2.69)	0.73	finn-b-OSTPOPATFRCTURE_POSTEMENO

Notes: N.SNPs: Number of SNPs used as working variables when performing Mendelian randomization, In other GWAS databases, exposure to covid-19 was also not associated with osteoporosis outcomes. Statistical method is Inverse Variance Weighting (IVW).

Table S4. The Forward MR Analysis Results After Reducing the Inclusion

Exposures	Outcomes	Method	N.SNPs	OR (95% CI)	P value
Severe Covid-19	Osteoporosis	IVW	59	1.02 (0.07, 1.08)	0.51
Severe Covid-19	Drug-induced osteoporosis	IVW	59	-0.84 (0.16, 1.15)	0.28
Hospitalized Covid-19	Osteoporosis	IVW	10	0.96 (0.10, 1.09)	0.54
Hospitalized Covid-19	Drug-induced osteoporosis	IVW	10	0.76 (0.26, 1.53)	0.44
Covid-19 Infection	Osteoporosis	IVW	13	0.94 (0.13, 1.21)	0.65
Covid-19 Infection	Drug-induced osteoporosis	IVW	13	0.61 (0.35, 2.06)	0.43

Notes: Notes: IVW: Inverse Variance Weighting; N.SNPs: Number of SNPs used as working variables when performing Mendelian randomization. SNPs were filtered with genome-wide significance through $P < 1 \times 10^{-7}$, and removed Linkage disequilibrium (LD) using a clumping r^2 cutoff of 0.1 within a 10Mb window, using the 1000 Genomes Project Phase 3 (EUR) as the reference panel. Exposure to covid-19 was also not associated with osteoporosis outcomes. Statistical method is Inverse Variance Weighting (IVW).

Table S5. Excluded SNPs and Reasons in the Reverse MR

RSID	Other Related Diseases (P value)
rs9482772	Hematocrit (1.48e-11); Birth weight (7.19e-07); Red blood cell count (2.00e-10); Varicose veins of lower extremities (1.16e-06); Reticulocyte count (4.05e-06)
rs56312530	Whole body water mass (1.92e-28); Whole body fat-free mass (6.02e-28); Basal metabolic rate (1.02e-24); Arm fat-free mass right (2.51e-23); etc.
rs6684375	Red cell distribution width (3.14e-14); Ulcerative colitis (8.16e-11); High light scatter percentage of red cells (2.85e-12); High light scatter reticulocyte count (4.18e-11), etc.

Notes: Based on this website (<http://www.phenoscanter.medschl.cam.ac.uk/>). In the reverse MR, SNPs were excluded from working variants, if two or more diseases had a genome-wide significance with this SNP ($P < 1 \times 10^{-5}$) and $r^2 < 0.8$. 3 SNPs were excluded from 14 working variants in the reverse MR

Table S6. Results of the Reverse MR Analysis After SNPs Exclusion

Exposes	Outcomes	Methods	N.SNPs	OR (95% CI)	P value
Osteoporosis	Severe covid-19	IVW	10	2.71, (0.02, 320.77)	0.68
Osteoporosis	Hospitalized covid-19	IVW	10	0.63 (0.02, 15.90)	0.78
Osteoporosis	Covid-19 infection	IVW	10	0.45 (0.10, 2.09)	0.31

Notes: IVW: Inverse Variance Weighting; N.SNPs: Number of SNPs used as working variables when performing Mendelian randomization. After excluding SNPs, the association between exposure to osteoporosis and covid-19 outcomes remained non-significant and the 95% confidence interval for OR remains wide.