

**Supplemental Table 1. Characteristics of SNPs included in Instrument C**

Gene	SNP	EA	NEA	EAF	BETA	P-VAL	F STAT	Non-vitamin D GWAS associations
GC	rs11723621	G	A	0.29	-0.19	2.9E-1689	1467	YES
CYP2R1	rs10832289	T	A	0.41	-0.07	2.03E-266	231	YES
NADSYN/DHCR7	rs12803256	G	A	0.78	0.10	1.3E-378	354	YES
CYP24A1	rs6127099	T	A	0.28	-0.04	9.30E-62	55	YES
SEC23A	rs8018720	C	G	0.82	-0.03	4.04E-36	30	NO
AMDHD1/HAL	rs10859995	C	T	0.58	-0.04	7.03E-89	76	YES
RER1	rs6698680	G	A	0.46	-0.01	8.99E-10	7	YES
PADI1	rs3750296	C	G	0.34	-0.02	2.09E-24	19	NO
RP4-657M3.2	rs7519574	A	G	0.18	0.02	2.09E-11	9	NO
FOXO6	rs56044892	T	C	0.21	0.02	2.85E-10	8	YES
DOCK7	rs2934744	A	C	0.64	-0.02	3.96E-26	23	YES
CELSR2	rs7528419	G	A	0.22	0.02	2.41E-16	13	YES
ARNT	rs3768013	A	G	0.37	-0.01	1.37E-13	10	YES
FLG	rs61816761	A	G	0.02	0.13	8.57E-74	71	YES
FDPS	rs11264360	A	T	0.24	0.02	3.34E-15	12	YES
MARC_1	rs867772	G	A	0.68	-0.01	3.64E-11	8	YES
-NA-	rs10127775	T	A	0.60	0.01	3.43E-09	7	YES
TDRD15	rs12997242	A	G	0.44	-0.01	2.23E-10	8	YES
GCKR	rs11127048	A	G	0.62	0.02	6.41E-19	16	YES
NPAS2	rs6724965	G	A	0.17	-0.02	1.29E-10	8	NO
HTR5BP	rs7569755	A	G	0.29	0.01	8.03E-11	8	NO
CPS1	rs1047891	A	C	0.32	-0.01	1.16E-11	9	YES
UGT1A4	rs2011425	G	T	0.08	-0.05	9.66E-38	31	YES
RHOA	rs7650253	A	T	0.69	0.01	1.76E-10	9	YES
CADM2	rs1972994	T	A	0.65	-0.02	7.99E-18	14	YES
MRPL3	rs6438900	G	C	0.26	0.01	9.59E-10	7	YES
TFDP2	rs6773343	T	C	0.72	0.01	5.20E-09	6	YES
DOK7	rs78649910	A	T	0.11	-0.02	4.32E-09	7	YES
UGT2B7	rs7699711	T	G	0.45	-0.03	6.97E-49	41	YES
HSD17B11	rs58073039	G	A	0.30	-0.01	2.16E-11	8	NO
ADH1A	rs28364331	G	A	0.02	0.06	1.31E-17	14	YES
TNFAIP8	rs7718395	G	C	0.32	0.01	1.67E-09	7	NO
MED23	rs3822868	G	A	0.84	0.02	1.41E-15	13	YES
DNAH11	rs111529171	C	G	0.22	-0.02	6.24E-11	8	YES
LINC01004	rs1011468	A	G	0.48	-0.01	1.35E-12	9	YES

Gene	SNP	EA	NEA	EAF	BETA	P-VAL	F STAT	Non-vitamin D GWAS associations
COG5	rs1858889	C	A	0.50	0.01	3.85E-11	8	YES
GATA4	rs804280	A	C	0.58	0.01	4.43E-11	8	YES
EBF2	rs34726834	T	C	0.25	0.01	6.65E-10	7	YES
LINC00536	rs7828742	G	A	0.60	-0.02	3.06E-28	23	YES
DNAH11	rs10818769	G	C	0.86	-0.02	3.35E-09	7	YES
ABO	rs532436	A	G	0.18	-0.02	2.17E-09	7	YES
MAT1A	rs10887718	T	C	0.53	-0.01	1.44E-10	8	YES
PLEKHA7	rs567415847	G	A	1.00	0.28	1.03E-14	32	YES
TMEM151A	rs523583	C	A	0.47	0.01	5.58E-10	7	YES
RP11-21L23.4	rs1149605	C	T	0.17	0.02	7.34E-14	11	YES
ZPR1	rs964184	C	G	0.86	0.04	5.11E-44	37	YES
SLCO1B1	rs12317268	G	A	0.15	-0.02	9.15E-12	9	YES
FAM166AP9	rs9668081	T	C	0.47	0.01	5.38E-09	7	YES
LIPC	rs1800588	T	C	0.21	-0.03	2.65E-36	30	YES
AC007950.2	rs17765311	C	A	0.34	-0.02	1.35E-13	10	YES
PEAK1	rs62007299	A	G	0.71	-0.01	1.69E-11	9	YES
BCAR4	rs8063706	T	A	0.27	0.01	3.64E-09	7	NO
PDILT	rs77924615	A	G	0.20	-0.02	1.46E-10	8	YES
FBXL19	rs71383766	T	C	0.42	0.01	1.15E-09	8	YES
CETP	rs1800775	A	C	0.49	-0.02	1.56E-17	14	YES
RP11-120M18.2	rs2909218	T	C	0.79	0.02	2.81E-12	9	YES
DSG1	rs8091117	A	C	0.07	-0.02	1.03E-09	7	NO
SERPINB11	rs2037511	A	G	0.17	0.02	9.29E-10	7	YES
STAP2	rs57631352	G	A	0.30	-0.01	1.48E-09	7	YES
LDLR	rs73015021	G	A	0.12	0.02	1.15E-14	11	YES
TM6SF2	rs58542926	T	C	0.08	0.03	8.57E-19	15	YES
NPHS1	rs3814995	T	C	0.31	-0.01	2.83E-12	9	NO
APOC1	rs157595	G	A	0.61	-0.02	2.95E-14	12	YES
SULT2A1	rs112285002	T	C	0.16	0.06	1.77E-110	98	YES
KLK10	rs10426	A	G	0.21	0.03	3.31E-26	21	YES
ZNF808	rs8103262	C	T	0.31	0.01	3.18E-09	7	NO
NRIP1	rs2229742	C	G	0.10	-0.03	7.13E-16	12	YES
PLA2G3	rs2074735	C	G	0.06	0.03	6.55E-12	9	YES
SCUBE1	rs960596	T	C	0.34	0.01	2.23E-09	7	YES

BETA=beta coefficient for association with vitamin D in UKBB; P-VAL=p-value for SNP—vitamin D association in UKBB; F-stat= measure of instrument strength, calculated as described in the methods, shown for sample size of 100,000; Non-vitamin D GWAS associations = indicator of whether SNP has known genome-wide significant associations with traits other than vitamin D, identified as described in methods using LDlink webtool

Supplemental Table 2) P-values for associations of vitamin D SNPs with BMI and smoking phenotypes

Vitamin D SNP	Locus	BMI (continuous) <sup>a</sup>	Waist Circumference <sup>a</sup>	Obesity (case/control) <sup>a</sup>	Smoking (ever vs never) <sup>b</sup>	Smoking (former vs current) <sup>b</sup>	Smoking (cigarettes per day) <sup>b</sup>
rs11723621	GC	0.500	0.720 <sup>c</sup>	0.6376	0.869	0.645	0.751
rs10832289	CYP2R1	0.00017	0.0023	0.3962	0.462	0.701	0.165
rs12803256	DHCR7	0.590	0.470	0.9025	0.152	0.369	0.353
rs6127099	CYP24A1	0.490	0.440 <sup>c</sup>	0.5857	0.707	0.302	0.517
rs8018720	SEC23A	0.390	0.680	0.2976	0.294	0.133	0.0123
rs10859995	AMDHD1	0.830	0.760	0.2801	0.169	0.17	0.517

<sup>a</sup> P-values for associations with BMI, waist circumference, and obesity accessed through MR-Base platform using the following study IDs: “ebi-a-GCST006368” (BMI) ; “ieu-a-60” (waist circumference); “finn-a-E4\_OBESITY” (obesity).

<sup>b</sup> P-values for associations with smoking phenotypes from Liu et al, 2019, (<https://www.nature.com/articles/s41588-018-0307-5>).

<sup>c</sup> Data were not available for rs11723621 and rs6127099 for the waist circumference outcome. P-values shown are for the GC and CYP24A1 SNPs identified in the SUNLIGHT Consortium (rs3755967 and rs17216707)

**Supplemental Table 3. Studies contributing to different COVID-19 outcomes in the COVID-19 Host Genetics Initiative**

Study	Percent of COVID-19 outcome sample				
	COVID vs. Population	Hosp COVID vs. Population	Sev Resp COVID vs. Population	COVID Pos vs. COVID Neg	Hosp vs. non-hosp COVID
Amsterdam UMC COVID study group	0.11%	0.16%	0.24%		
Ancestry	1.25%	0.23%		13.57%	20.32%
Genetic modifiers for COVID-19 related illness (BelCovid)	0.11%	0.16%			
BoSCO		0.04%	0.05%		3.68%
Biobanque Quebec COVID19 (BQC19)	0.04%	0.06%	0.09%	0.42%	1.89%
Genetic determinants of COVID-19 complications in the Brazilian population	0.17%	0.25%	0.33%		
Genetics of COVID-related Manifestation (Corea)	0.48%	0.68%			
deCODE	19.82%	28.30%		24.17%	17.39%
Estonian Biobank	9.98%			9.64%	
FinnGen	17.19%	24.62%	38.00%		2.81%
GEN-COVID	0.23%	0.31%	0.47%		
genomiCC	0.72%	1.04%	1.60%		
Genomics England (genomicsengland100kcp)	4.50%			1.43%	
Genes & Health (GNH)	1.97%	2.83%		0.29%	0.94%
Helix Exome+ COVID-19 Phenotypes	0.40%				
COVID19-Host(a)ge	0.27%	0.39%			
UK Blood Donors Cohort	3.01%			1.00%	
Italy COVID19-Host(a)ge			0.31%		
Lifelines	1.84%			1.26%	
Michigan Genomics Initiative	3.71%			0.49%	

Study	Percent of COVID-19 outcome sample				
	COVID vs. Population	Hosp COVID vs. Population	Sev Resp COVID vs. Population	COVID Pos vs. COVID Neg	Hosp vs. non-hosp COVID
Million Veterans Program	1.40%	0.56%		32.96%	29.69%
Netherlands Twin Register	0.39%			0.20%	
Partners Healthcare Biobank	2.53%			3.16%	
Penn Medicine Biobank	0.62%	0.89%		0.86%	1.52%
Qatar Genome Program	1.01%	1.38%			6.42%
Spain COVID19-Host(a)ge			0.20%		
Determining the Molecular Pathways and Genetic Predisposition of the Acute Inflammatory Process Caused by SARS-CoV-2	0.05%	0.06%	0.06%		3.32%
Genomic epidemiology of SARS-Cov-2 and host genetics in Coronavirus Disease 2019 (COVID-19)	0.02%				
The genetic predisposition to severe COVID-19	0.28%	0.40%	0.61%		
UK Biobank	27.87%	37.65%	58.05%	12.28%	12.01%

**Supplemental Table 4. Minimum detectable odds ratios for COVID-19 outcomes**

COVID-19 outcome	N cases	N controls	Case prevalence	Min detectable Odds Ratio*
COVID vs population	17,965	1,370,547	0.013	0.88
Hosp COVID vs pop	7,885	961,804	0.008	0.82
Severe resp COVID vs pop	4,336	623,902	0.007	0.73
COVID pos vs COVID neg	110,85	116,794	0.087	0.84
Hosp COVID vs non-hosp COVID	2,430	8,478	0.223	0.66

\*Minimum detectable odds ratios for 80% power, represents odds ratio per SD increase in serum vitamin D, assumes 3% variance in vitamin D explained by genetic instruments

Supplemental Table 5. Multivariable MR estimates for direct effect of vitamin D on COVID-19 outcome conditioning on BMI

MR method	Conditioning GWAS		COVID vs. population		Hosp COVID vs. population		Severe Resp COVID vs. population		COVID pos vs. COVID neg		Hosp COVID vs. non-hosp COVID	
	Study ID	Ancestry	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
MVMR	ebi-a-GCST006368	European	1.04	0.93-1.17	1.14	0.96-1.35	1.01	0.79-1.31	1.13	0.97-1.32	1.36	0.90-2.06
MVMR	ieu-a-835	European	1.04	0.91-1.18	1.15	0.93-1.43	0.99	0.74-1.33	1.14	0.97-1.33	1.46	0.92-2.30
MVMR	ieu-a-2	Mixed	1.04	0.92-1.16	1.15	0.95-1.39	1.00	0.76-1.30	1.14	0.96-1.34	1.48	1.01-2.16

OR, odds ratios per unit increase in serum vitamin D in natural log scale; 95% CI, 95% confidence interval

Supplemental Table 6. MR analysis limiting instrument to SNPs with no known associations except with vitamin D

MR method	COVID vs. population		Hosp COVID vs. population		Severe Resp COVID vs. population		COVID pos vs. COVID neg		Hosp COVID vs. non-hosp COVID	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
IVW	0.94	0.55-1.62	0.92	0.34-2.50	0.92	0.27-3.15	0.96	0.51-1.80	0.60	0.12-2.98
MR-Egger intercept test	p-value = 0.32		p-value = 0.62		p-value = 0.89		p-value = 0.17		p-value = 0.92	

OR, odds ratios per SD increase in log-transformed serum vitamin D; 95% CI, 95% confidence interval;

SNPs included in instrument: rs3750296, rs3814995, rs58073039, rs6724965, rs7519574, rs8103262, rs7569755, rs7718395, rs8018720, rs8063706, rs8091117

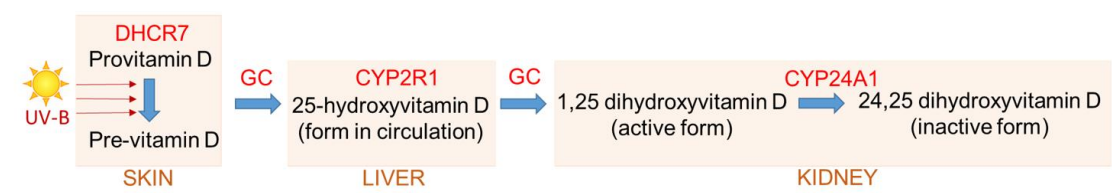
**Supplemental Table 7. Replication of MR estimates of effect of vitamin D on COVID-19 outcomes using SNP-vitamin D association data from SUNLIGHT Consortia**

MR method	COVID vs. population		Hosp COVID vs. population		Severe Resp COVID vs. population		COVID pos vs. COVID neg		Hosp COVID vs. non-hosp COVID	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Instrument A										
IVW	1.04	0.79-1.35	1.04	0.67-1.62	0.72	0.40-1.29	1.16	0.77-1.75	2.39	0.93-6.13
MR-Egger intercept test	p-value = 0.90		p-value = 0.91		p-value = 0.40		p-value = 0.26		p-value = 0.13	

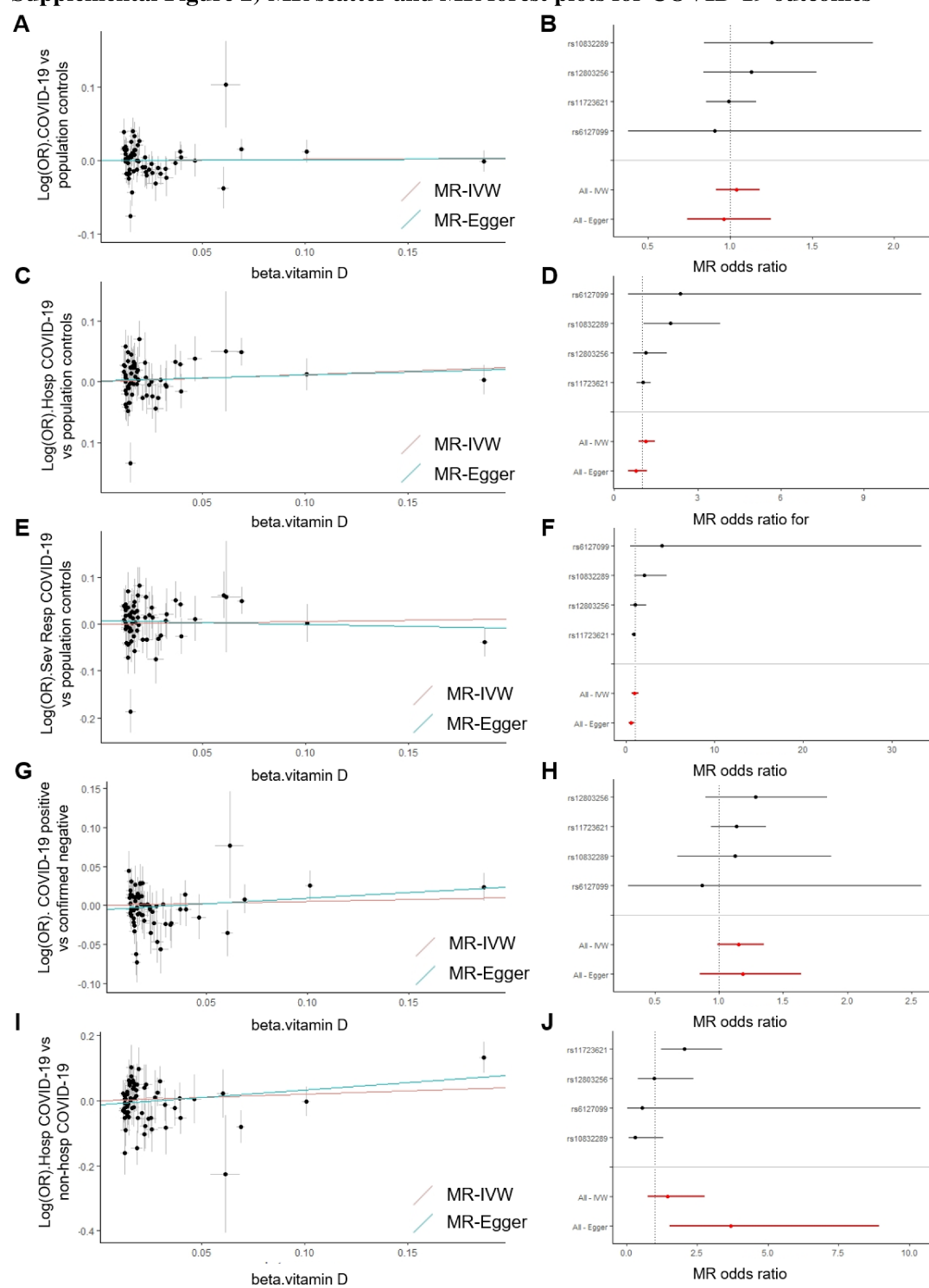
OR, odds ratios per unit increase in serum vitamin D in natural log scale; 95% CI, 95% confidence interval



Supplemental Figure 1) Genetic Loci integral to the vitamin D metabolic pathway

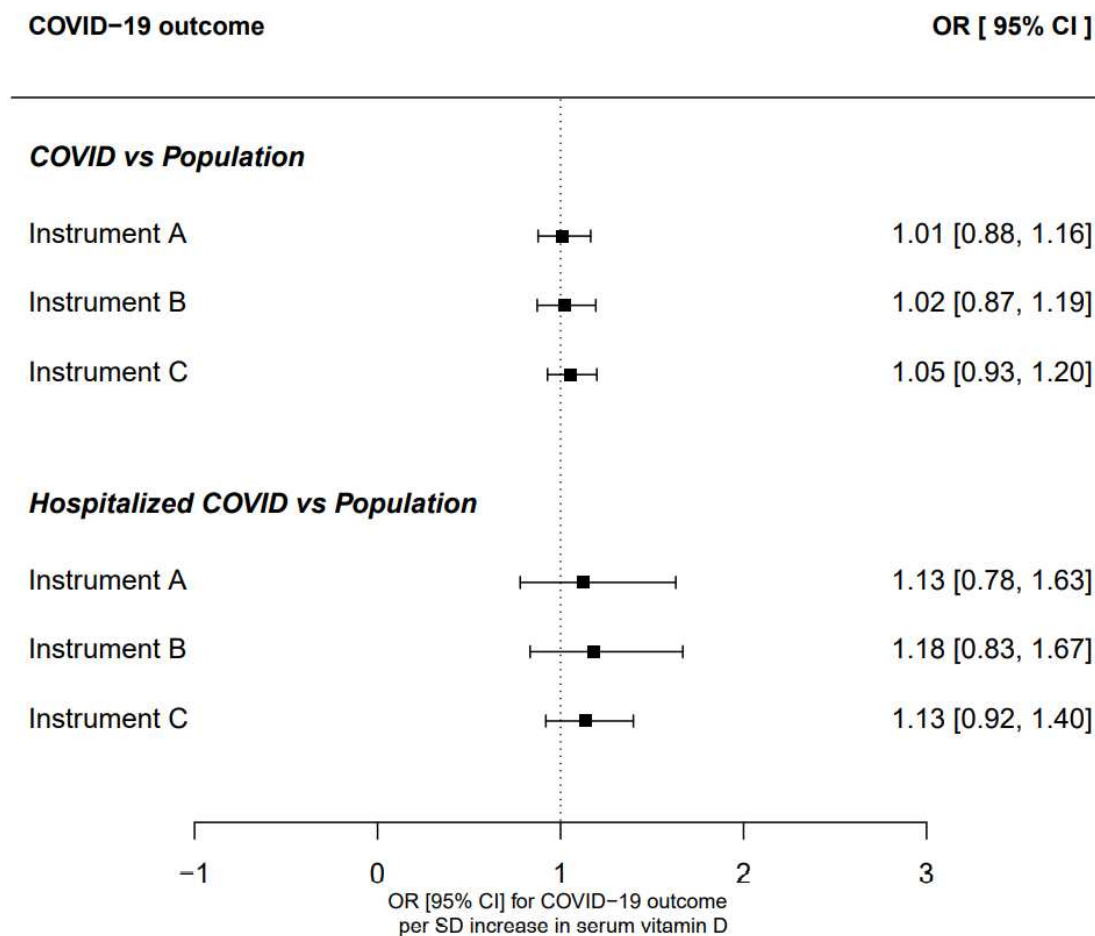


## Supplemental Figure 2) MR scatter and MR forest plots for COVID-19 outcomes

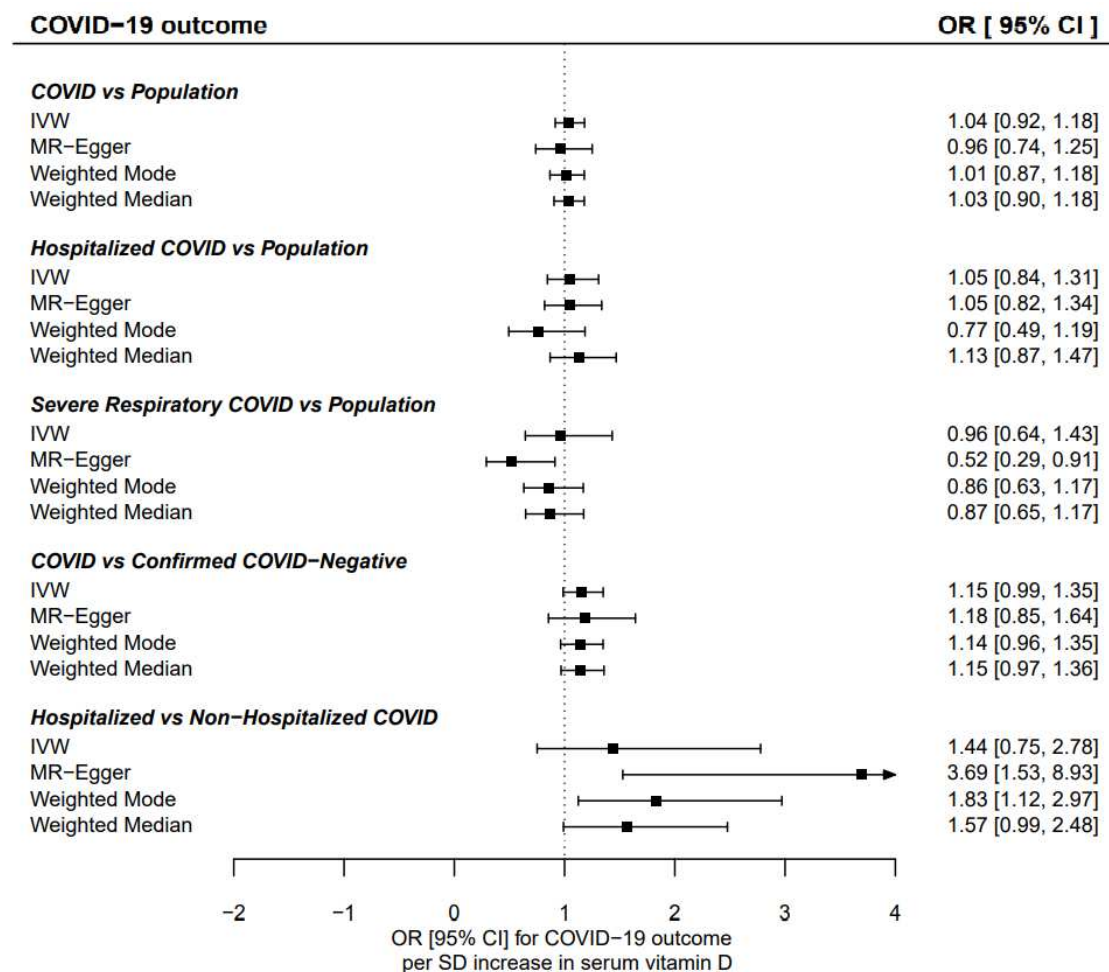


*Supplemental Figure 2 caption: MR scatter and forest plots for (A-B) COVID-19 vs population controls, (C-D) Hospitalized COVID-19 vs population controls, (E-F) Severe respiratory COVID-19 vs population controls, (G-H) COVID-19 vs confirmed negative and (I-J) hospitalized COVID-19 vs non-hospitalized COVID-19. Scatter plots show the SNP—vitamin D associations on the x-axis vs the SNP—log(OR) for COVID-19 case vs comparator on the y axis for all SNPs considered in instruments A,B and C. The MR estimates generated from the IVW (red slope) and MR-Egger (teal slope) MR methods are overlaid. The forest plots show the MR estimates (odds ratios and 95% confidence intervals) generated from instrument A for the effect of 1 SD higher serum vitamin D on risk of COVID-19 case vs comparator. Estimates for each SNP are shown separately (black bars), as well as summarized estimates across all SNPs (red bars).*

**Supplemental Figure 3) Inverse variance weighted MR estimates of effect of vitamin D on risk of COVID-19 infection and hospitalization in European ancestry participants**



**Supplemental Figure 4) MR estimates of effect of vitamin D on COVID-19 outcomes using different MR Methods for instrument A**



**Supplemental Figure 5) Pairwise correlations of beta-coefficients observed for SNP-vitamin D associations stratified by COVID-19 risk subgroup, across all SNPs in instruments A, B and C**

