Supplementary Information

Table S1. Information of data source and candidate genetic instruments.

(a) CNS-regulated Hormones. We were not able to find any LD proxy SNPs. The sample size was the maximum number indicated in the published source. All hormone traits except TSH was obtained from IEU open GWAS project (https://gwas.mrcieu.ac.uk/) and GWAS ID was the ID number of these exposure on the website. TSH was obtained from study of Porcu E. et al.

Exposure	Sample Size	Number of SNPs			Variable adjusted	GWAS ID/Data source
		Severity	Hospitalization	Susceptibility		
IGF-1	468,343	613	604	611	age, age^2, sex, age sex, age^2, sex, PCs	ukb-d-30770_irnt
Estradiol	427,024	1	1	1		ukb-d-30800_irnt
Testosterone	77,700	130	130	129		ukb-d-30850_irnt
DHEA-S	50,000	2	2	2	age, sex, batch effects	met-a-478
TSH	26,420	12	13	12	age, age^2, sex	A meta-analysis[1]
TRH	26,420	1	1	1	age, sex, time duration, PCs	prot-a-3102t
LH	50,000	1	1	1		prot-a-529
FSH	1,000	1	1	1	age, sex, body mass index	prot-c-3032_11_2

Note: PC is the abbreviation of principal component. [1]Porcu, Eleonora, et al. "A meta-analysis of thyroid-related traits reveals novel loci and gender-specific differences in the regulation of thyroid function." PLoS genetics 9.2 (2013): e1003266.

(b). COVID-19. The candidate genetic instruments were used in reverse direction of MR analysis. There were no matched SNPs with TSH.

Exposure	Sample size	Number of SNPs							
		Total	DHEA-S	Estradiol	LH	Testosterone	FSH	IGF-1	TRH
Very severe respiratory syndromes	714,592	9,856,861	6	8	8	8	4	8	8
Hospitalization	1,828,485	8,152,576	4	5	5	5	3	5	5
Susceptibility	2,298,674	8,738,878	6	7	7	7	3	7	7

Table S2. Estimated variance explained by SNPs and F statistics.

Exposure	Very severe respiratory syndromes		Hospitalization		Susceptibility	
	Estimated variance explained (%)	F statistics	Estimated variance explained (%)	F statistics	Estimated variance explained (%)	F statistics
DHEA-S	1.44	53.75	1.44	53.75	1.44	53.75
Estradiol	0.07	37.66	0.07	37.66	0.07	37.66
LH	6.30	221.77	6.30	221.77	6.30	221.77
Testosterone	3.33	82.65	3.31	82.06	3.27	81.14
FSH	17.88	215.92	17.88	215.92	17.88	215.92
IGF-1	13.72	88.67	13.60	87.78	13.68	89.67
TSH	2.95	66.88	2.95	61.73	2.95	66.88
TRH	1.01	33.61	1.01	33.61	1.01	33.61

Note: Estimated variance explained (%) was calculated as: R^2 = (reported GWAS effect)^2 × 2 × minor allele frequency × (1 – minor allele frequency) / variance of trait. F statistics per variant was calculated as: (Sample size – 2) × R^2 / (1 – R^2).

Table S3. MR analyses of CNS-regulated hormone SNPs and COVID-19 very severe respiratory syndromes, hospitalization, and susceptibility.

Exposure	Method	Very severe respiratory syndromes		Hospitalization		Susceptibility	
		OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
DHEA-S	IVW	4.21 (1.41 - 12.59)	0.010	2.31 (1.13 - 4.72)	0.021	1.09 (0.76 - 1.56)	0.655
Estradiol	Wald Ratio	1.73 (0.32 - 9.37)	0.524	1.20 (0.64 - 2.24)	0.571	1.15 (0.34 - 3.83)	0.822
LH	Wald Ratio	0.83 (0.71 - 0.96)	0.013	0.91 (0.82 - 1.00)	0.061	0.96 (0.92 - 1.00)	0.115
Testosterone*	IVW	0.94 (0.60 - 1.47)	0.794	1.10 (0.84 - 1.45)	0.482	0.92 (0.81 - 1.05)	0.237
	MR-Egger	1.54 (0.71 - 3.35)	0.275	1.37 (0.85 - 2.22)	0.205	1.16 (0.91 - 1.47)	0.243
	WM	1.46 (0.75 - 2.84)	0.266	1.30 (0.85 - 1.99)	0.219	1.04 (0.85 - 1.28)	0.691
FSH	Wald Ratio	0.83 (0.59 - 1.16)	0.268	0.87 (0.69 - 1.09)	0.221	0.92 (0.82 - 1.04)	0.174
IGF-1*	IVW	0.97 (0.86 - 1.10)	0.652	1.00 (0.92 - 1.09)	0.987	0.99 (0.95 - 1.03)	0.580
	MR-Egger	0.95 (0.73 - 1.24)	0.731	1.02 (0.86 - 1.21)	0.828	1.01 (0.93 - 1.10)	0.758
	WM	0.94 (0.76 - 1.15)	0.524	1.00 (0.87 - 1.15)	0.972	0.98 (0.92 - 1.05)	0.594
TSH	IVW	0.96 (0.77 - 1.20)	0.729	0.93 (0.79 - 1.09)	0.368	0.99 (0.90 - 1.08)	0.777
	MR-Egger	1.66 (0.80 - 3.34)	0.199	1.20 (0.73 - 1.98)	0.479	1.11 (0.84 - 1.47)	0.475
	WM	0.86 (0.63 - 1.17)	0.327	1.00 (0.81 - 1.23)	0.979	1.05 (0.94 - 1.16)	0.362
TRH	Wald Ratio	1.36 (0.84 - 2.21)	0.212	1.08 (0.81 - 1.44)	0.589	1.09 (0.95 - 1.25)	0.223

Note: * indicated the estimator was outlier corrected by the MR-PRESSO method. The associations between IGF-1 and hospitalization and susceptibility were outlier corrected. The association between testosterone and susceptibility was outlier corrected.

Table S4. Bidirectional MR Analysis using COVID-19 very severe respiratory syndromes, hospitalization, and susceptibility as exposures.

| Outcome | Method | Very severe respiratory syndromes | | Hospitalization | | Susceptibility | |
		OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
DHEA-S	IVW	1.00 (0.98 - 1.02)	0.771	1.01 (0.98 - 1.03)	0.658	1.01 (0.94 - 1.08)	0.419
	MR Egger	0.99 (0.93 - 1.05)	0.704	1.00 (0.94 - 1.06)	0.899	0.97 (0.80 - 1.18)	0.263
	WM	1.00 (0.98 - 1.03)	0.732	1.00 (0.97 - 1.03)	0.874	1.01 (0.93 - 1.10)	0.985
Estradiol	IVW	1.01 (0.99 - 1.03)	0.335	1.01 (0.97 - 1.05)	0.669	0.98 (0.93 - 1.03)	0.458
	MR Egger	1.02 (0.97 - 1.06)	0.582	1.02 (0.93 - 1.11)	0.771	1.01 (0.88 - 1.16)	0.919
	WM	1.01 (0.99 - 1.03)	0.443	1.01 (0.98 - 1.04)	0.603	0.98 (0.93 - 1.05)	0.612
LH	IVW	0.97 (0.88 - 1.05)	0.409	0.98 (0.85 - 1.12)	0.737	1.08 (0.85 - 1.54)	0.526
	MR Egger	0.95 (0.77 - 1.18)	0.677	0.97 (0.72 - 1.29)	0.828	0.79 (0.38 - 1.39)	0.524
	WM	0.97 (0.87 - 1.09)	0.618	0.98 (0.84 - 1.15)	0.834	1.09 (0.79 - 1.63)	0.596
Testosterone *	IVW	1.00 (0.98 - 1.01)	0.338	1.00 (0.98 - 1.01)	0.748	1.05 (1.03 - 1.06)	<0.001
	MR Egger	0.98 (0.95 - 1.11)	0.355	0.98 (0.94 - 1.01)	0.296	0.97 (0.92 - 1.04)	0.440
	WM	0.99 (0.98 - 1.00)	0.077	0.99 (0.98 - 1.00)	0.027	1.04 (1.01 - 1.06)	0.002
FSH	IVW	1.06 (0.90 - 1.25)	0.498	1.04 (0.82 - 1.32)	0.728	0.85 (0.53 - 1.38)	0.517
	MR Egger	0.98 (0.68 - 1.42)	0.940	0.95 (0.56 - 1.60)	0.873	1.13 (0.36 - 3.57)	0.836
	WM	1.02 (0.88 - 1.19)	0.839	1.00 (0.82 - 1.22)	0.978	0.86 (0.50 - 1.48)	0.584
IGF-1 *	IVW	1.01 (1.00 - 1.02)	0.040	1.01 (0.99 - 1.02)	0.339	0.99 (0.94 - 1.03)	0.793
	MR Egger	0.96 (0.86 - 1.06)	0.431	0.99 (0.96 - 1.02)	0.498	0.96 (0.83 - 1.09)	0.530
	WM	1.01 (1.00 - 1.02)	0.271	1.00 (0.99 - 1.02)	0.716	0.99 (0.95 - 1.02)	0.461
TSH	/	/	/	/	/	/	/
TRH	IVW	1.06 (0.97 - 1.15)	0.203	1.08 (0.94 - 1.24)	0.290	0.93 (0.73 - 1.19)	0.559
	MR Egger	1.10 (0.88 - 1.37)	0.448	1.03 (0.73 - 1.44)	0.890	0.82 (0.40 - 1.67)	0.608
	WM	1.04 (0.93 - 1.16)	0.523	1.04 (0.88 - 1.23)	0.642	1.00 (0.73 - 1.35)	0.974

Note: * indicated the estimator was outlier corrected by MR-PRESSO. The associations between IGF-1 and hospitalization and susceptibility were outlier corrected. The association between testosterone and susceptibility was outlier corrected.

Table S5. MVMR analysis using COVID-19 as exposures

Exposure	IGF-1		Testosterone	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Very severe respiratory syndromes	1.05 (0.95 - 1.17)	0.359	1.11 (1.03 - 1.19)	0.003
Hospitalization	0.94 (0.86 - 1.02)	0.150	0.89 (0.84 - 0.94)	<0.001
Susceptibility	1.00 (0.74 - 1.36)	0.990	0.94 (0.77 - 1.15)	0.564

Table S6. Cochran Test of heterogeneity, Measurement Error test, and MRPRESSO Test for horizontal pleiotropy of forward direction MR analysis

(a) Very severe respiratory syndromes as outcome

	MR-Egger Intercept test	Cochran test of Heterogeneity	Measurement Error Test	MRPRESSO Test		
	p	p	I^2_{GX}	Globe Test p	Corrected IVW OR	p
IGF-1	0.885	0.001	0.936	0.001	/	/
Testosterone	0.129	<0.001	0.946	<0.001	/	/
TSH	0.098	0.820	0.808	0.579	/	/

(b) Hospitalization as outcome

	MR-Egger Intercept test	Cochran test of Heterogeneity	Measurement Error Test	MRPRESSO Test		
	p	p	I^2_{GX}	Globe Test p	Corrected IVW OR	p
IGF-1	0.801	< 0.001	0.931	< 0.001	1.00	0.987
Testosterone	0.288	0.028	0.941	0.026	/	/
TSH	0.280	0.313	0.844	0.323	/	/

(c) Susceptibility as outcome

	MR-Egger Intercept test	Cochran test of Heterogeneity	Measurement Error Test	MRPRESSO Test		
	p	p	I^2_{GX}	Globe Test p	Corrected IVW OR	p
IGF-1	0.547	0.007	0.928	0.007	0.99	0.580
Testosterone	0.057	0.050	0.940	0.037	0.96	0.237
TSH	0.379	0.110	0.858	0.122	/	/

Table S7. Cochran Test of heterogeneity, Measurement Error test and MRPRESSO Test for horizontal pleiotropy of bidirectional MR analysis

(a) Very severe respiratory syndrome as exposure

	MR-Egger Intercept test	Cochran test of Heterogeneity	Measurement Error Test	MRPRESSO Test		
	p	p	I^2_{GX}	Globe Test p	Corrected IVW OR	p
IGF-1	0.204	<0.001	0.847	<0.001	1.01	0.040
Estradiol	0.820	0.264	0.846	0.437	/	/
Testosterone	0.392	<0.001	0.847	<0.001	1.00	0.388
DHEA-S	0.550	0.091	0.941	0.206	/	/
TSH	/	/	/	/	/	/
TRH	0.725	0.368	0.828	0.525	/	/
LH	0.907	0.770	0.838	0.848	/	/
FSH	0.646	0.117	0.826	0.354	/	/

(b) Hospitalization as exposure

	MR-Egger Intercept test	Cochran test of Heterogeneity	Measurement Error Test	MRPRESSO Test		
	p	p	I^2_{GX}	Globe Test p	Corrected IVW OR	p
IGF-1	0.166	0.6615	0.913	0.525	/	/
Estradiol	0.872	0.069	0.914	0.266	/	/
Testosterone	0.212	0.0035	0.914	0.022	1.00	0.747
DHEA-S	0.679	0.3039	0.949	0.591	/	/
TSH	/	/	/	/	/	/
TRH	0.743	0.2526	0.913	0.509	/	/
LH	0.929	0.4401	0.913	0.687	/	/
FSH	0.660	0.1045	0.960	/	/	/

(c) Susceptibility as exposure

	MR-Egger Intercept test	Cochran test of Heterogeneity	Measurement Error Test	MRPRESSO Test		
	p	p	I^2_{GX}	Globe Test p	Corrected IVW OR	p
IGF-1	0.669	<0.001	0.661	0.003	0.99	0.793
Estradiol	0.694	0.504	0.655	0.643	/	/
Testosterone	0.077	0.057	0.661	0.023	1.05	<0.001
DHEA - S	0.681	0.863	0.903	0.916	/	/
TSH	/	/	/	/	/	/
TRH	0.715	0.650	0.644	0.797	/	/
LH	0.361	0.394	0.644	0.466	/	/
FSH	0.597	0.786	0.755	/	/	/

Table S8. MR analysis of associations of sex stratified hormones with COVID-19 infections

(a) Very severe respiratory syndromes

Sex	Exposure	Significant	Matched	Used	OR (95% CI)	*p*
Female	Estrogen	20	10	1	1.51 (0.43 - 5.33)	0.524
	Testosterone	7909	5075	96	1.16 (0.93 - 1.45)	0.191
	IGF-1	396550	24046	268	0.96 (0.83 - 1.11)	0.553
	TSH	11	8	8	0.87 (0.67 - 1.13)	0.296
Male	Estrogen	236	2	1	0.51 (0.19 - 1.32)	0.163
	Testosterone	27658	14864	157	0.92 (0.79 - 1.08)	0.297
	IGF-1	41186	25510	270	1.03 (0.91 - 1.18)	0.626
	TSH	13	8	8	0.86 (0.69 - 1.06)	0.155

(b) Hospitalization

Sex	Exposure	Significant	Matched	Used	OR (95% CI)	*p*
Female	Estrogen	20	11	1	1.11 (0.45 - 2.73)	0.822
	Testosterone	7909	4940	94	1.11 (0.97 - 1.28)	0.132
	IGF-1	396550	22758	266	1.03 (0.94 - 1.12)	0.535
	TSH	11	8	8	0.97 (0.78 - 1.12)	0.800
Male	Estrogen	236	4	1	1.33 (0.76 - 2.35)	0.333
	Testosterone	27658	14176	156	1.01 (0.91 - 1.13)	0.858
	IGF-1	41186	24641	268	1.03 (0.94 - 1.12)	0.554
	TSH	13	8	8	1.00 (0.86 - 1.15)	0.941

(c) Susceptibility

Sex	Exposure	Significant	Matched	Used	OR (95% CI)	*p*
Female	Estrogen	20	10	1	1.14 (0.72 - 1.83)	0.571
	Testosterone	7909	4990	96	1.03 (0.97 - 1.11)	0.271
	IGF-1	396550	23903	266	0.99 (0.95 - 1.04)	0.774
	TSH	11	8	8	0.89 (0.80 - 0.99)	0.029
Male	Estrogen	236	4	1	0.86 (0.65 - 1.13)	0.274
	Testosterone	27658	13836	157	0.99 (0.94 - 1.04)	0.607
	IGF-1	41186	24873	240	0.99 (0.95 - 1.04)	0.724
	TSH	13	8	8	0.97 (0.90 - 1.04)	0.401