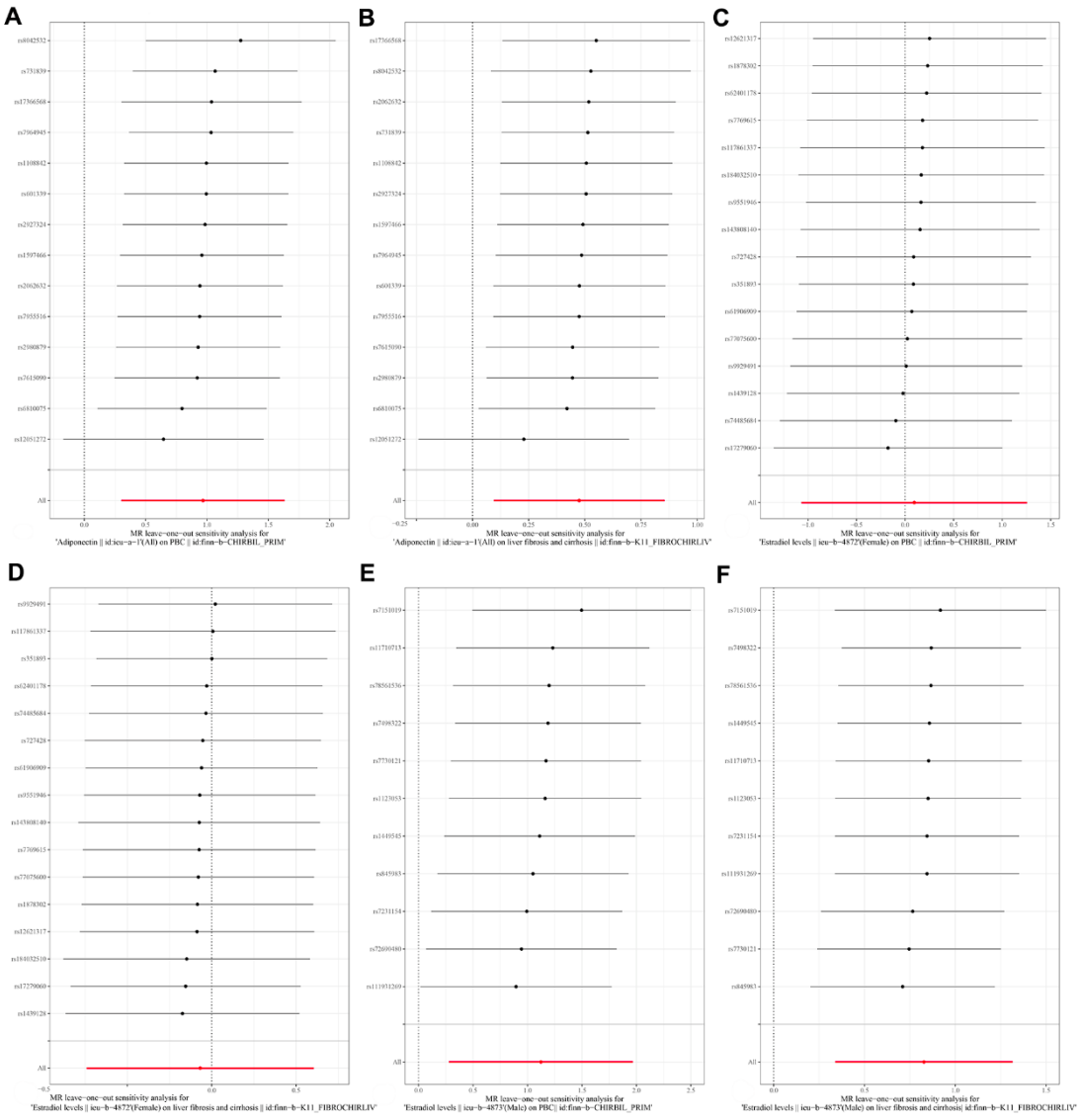
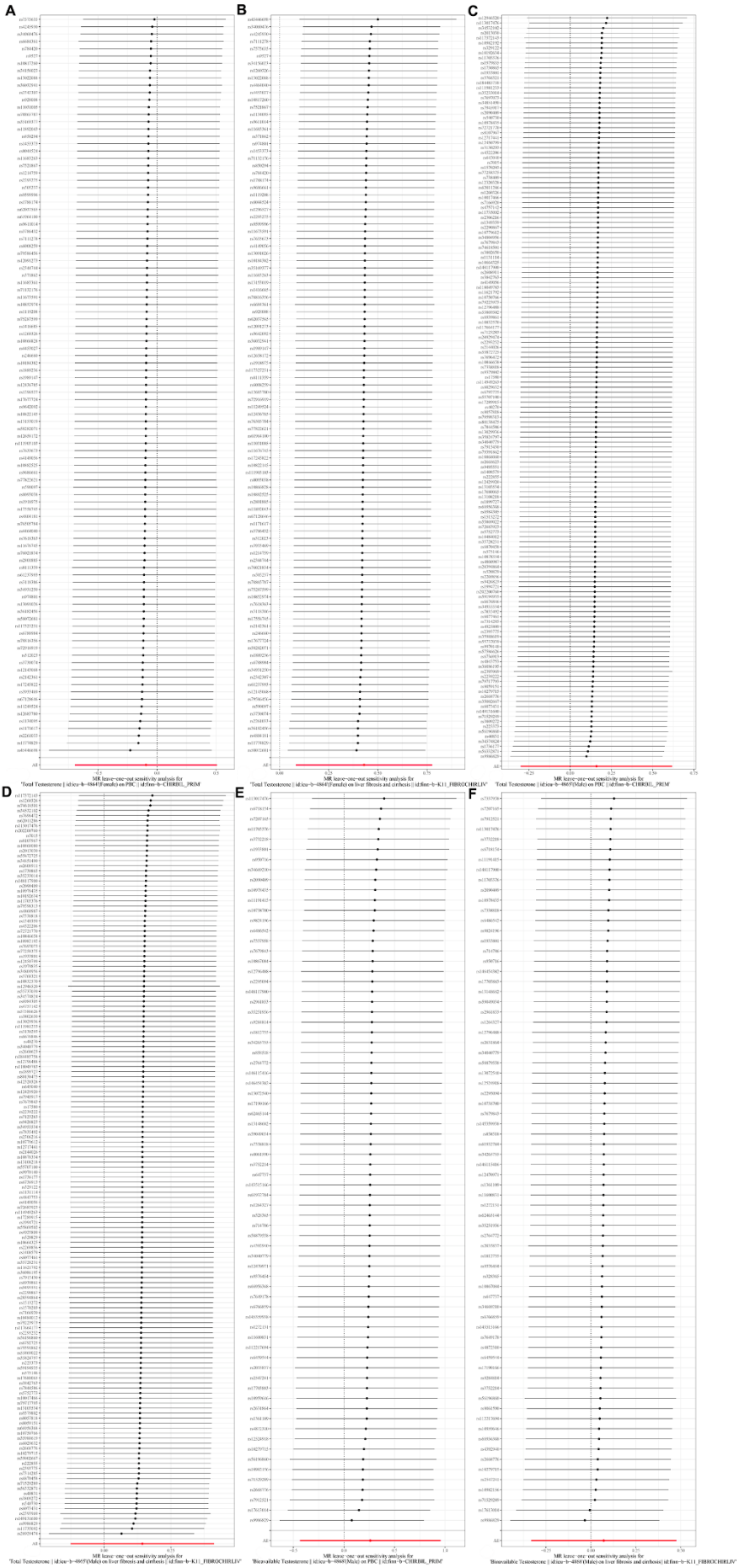
Supplementary material

Investigating the potential impact of sex hormones and adiponectin on the risk of liver fibrosis and cirrhosis: a Mendelian randomization study

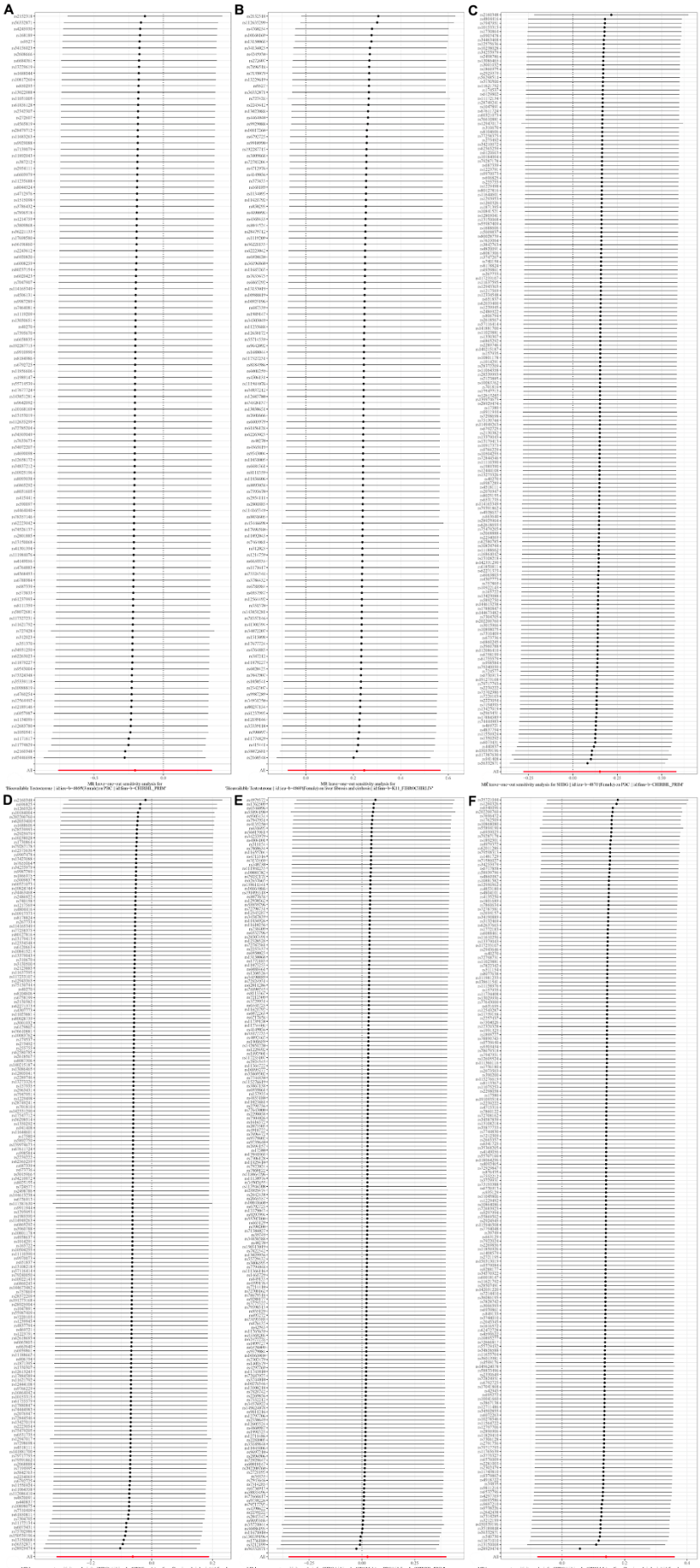
Supplementary Figure S1. Leave-one-out sensitivity tests of the causal relationship between: (**A**) adiponectin and PBC; (**B**) adiponectin and liver fibrosis and cirrhosis; (**C**) estradiol and PBC in females; (**D**) estradiol and liver fibrosis and cirrhosis in females; (**E**) estradiol and PBC in males; (**F**) estradiol and liver fibrosis and cirrhosis in males



Supplementary Figure S2. Leave-one-out sensitivity tests of the causal relationship between: (**A**) total testosterone and PBC in females; (**B**) total testosterone and liver fibrosis and cirrhosis in females; (**C**) total testosterone and PBC in males; (**D**) total testosterone and liver fibrosis and cirrhosis in males; (**E**) bioavailable testosterone and PBC in males; (**F**) bioavailable testosterone and liver fibrosis and cirrhosis in males


A
B
C
D
E
F
All
MR leave−one−out sensitivity analysis for
'Total Testosterone || id:ieu−b−48643||Female|| on PBC || id:finn−b−CHIRBIL_PRIM'
MR leave−one−out sensitivity analysis for
'Total Testosterone || id:ieu−b−48643||Female|| on liver fibrosis and cirrhosis || id:finn−b−K11_FIBROCHIRLIV'
MR leave−one−out sensitivity analysis for
'Total Testosterone || id:ieu−b−48659||Male|| on PBC || id:finn−b−CHIRBIL_PRIM'
MR leave−one−out sensitivity analysis for
'Total Testosterone || id:ieu−b−48659||Male|| on liver fibrosis and cirrhosis || id:finn−b−K11_FIBROCHIRLIV'
MR leave−one−out sensitivity analysis for
'Bioavailable Testosterone || id:ieu−b−48683||Male|| on PBC || id:finn−b−CHIRBIL_PRIM'
MR leave−one−out sensitivity analysis for
'Bioavailable Testosterone || id:ieu−b−48698||Male|| on liver fibrosis and cirrhosis|| id:finn−b−K11_FIBROCHIRLIV'

Supplementary Figure S3. Leave-one-out sensitivity tests of the causal relationship between: (**A**) bioavailable testosterone and PBC in females; (**B**) bioavailable testosterone and liver fibrosis and cirrhosis in females; (**C**) sex hormone-binding globulin and PBC in females; (**D**) sex hormone-binding globulin and liver fibrosis and cirrhosis in females; (**E**) sex hormone-binding globulin and PBC in males; (**F)** sex hormone-binding globulin and liver fibrosis and cirrhosis in males


A
B
C
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F

Supplementary Table SI. GWAS summary data regarding exposure and outcomes

Phenotype	Populations	Sample size (case)	Consortium	GWAS ID
Exposures				
Estradiol	Males	17134	IEU GWAS database	ieu-b-4873
Bioavailable testosterone		184205	IEU GWAS database	ieu-b-4868
Total testosterone		199569	IEU GWAS database	ieu-b-4865
SHBG		185221	IEU GWAS database	ieu-b-4871
Estradiol	Females	53391	IEU GWAS database	ieu-b-4872
Bioavailable testosterone		180386	IEU GWAS database	ieu-b-4869
Total testosterone		199569	IEU GWAS database	ieu-b-4864
SHBG		214989	IEU GWAS database	ieu-b-4870
Adiponectin	All	39883	ADIPOGen	ieu-a-1
Outcomes				
Liver fibrosis and cirrhosis	All	214403 (811)	FinnGen R10	finn-b-K11_FIBROCHIRLIV
PBC		176861 (271)	FinnGen R10	finn-b-CHIRBIL_PRIM

GWAS – genome-wide association studies, FIBROCHIRLIV – liver fibrosis and cirrhosis, CHIRBIL_PRIM – primary biliary cholangitis, PBC – primary biliary cirrhosis, SHBG – sex hormone-binding globulin

Supplementary Table SII. Other MR method about the causal effect of genetically predicted sex hormones, adiponectin and the risk of liver fibrosis, cirrhosis and PBC

Outcome	Exposure	Populations	Methods	SNPs	OR (95% CI)	*p*
Liver fibrosis and cirrhosis	Estradiol	Males	MR Egger	11	1.488 (0.403–5.503)	0.566
			Weighted median	11	1.835 (0.944–3.566)	0.073
			Simple mode	11	1.747 (0.684–4.457)	0.27
			Weighted mode	11	1.775 (0.801–3.938)	0.188
	Total testosterone		MR Egger	148	1.108 (0.638–1.923)	0.717
			Weighted median	148	1.106 (0.693–1.765)	0.672
			Simple mode	148	0.971 (0.378–2.489)	0.95
			Weighted mode	148	0.971 (0.606–1.555)	0.901
	Bioavailable testosterone		MR Egger	72	1.008 (0.371–2.736)	0.988
			Weighted median	72	1.134 (0.603–2.133)	0.697
			Simple mode	72	0.885 (0.258–3.038)	0.846
			Weighted mode	72	0.885 (0.371–2.109)	0.783
	SHBG		MR Egger	186	0.990 (0.651–1.505)	0.963
			Weighted median	186	0.953 (0.643–1.414)	0.812
			Simple mode	186	1.037 (0.460–2.337)	0.931
			Weighted mode	186	0.840 (0.539–1.310)	0.443
	Estradiol	Females	MR Egger	16	1.168 (0.305–	0.824

				4.468)	
		Weighted median	16	0.977 (0.394–2.423)	0.96
		Simple mode	16	1.067 (0.276–4.128)	0.927
		Weighted mode	16	1.082 (0.327–3.573)	0.899
Total testosterone		MR Egger	101	1.868 (0.988–3.532)	0.057
		Weighted median	101	1.312 (0.717–2.402)	0.379
		Simple mode	101	2.849 (0.736–11.033)	0.133
		Weighted mode	101	1.377 (0.771–2.462)	0.283
Bioavailable testosterone		MR Egger	118	1.454 (0.706–2.993)	0.312
		Weighted median	118	1.366 (0.802–2.326)	0.251
		Simple mode	118	2.374 (0.804–7.014)	0.12
		Weighted mode	118	1.365 (0.764–2.440)	0.295
SHBG		MR Egger	179	1.019 (0.632–1.645)	0.938
		Weighted median	179	0.960 (0.619–1.487)	0.854
		Simple mode	179	0.865 (0.344–2.177)	0.758
		Weighted mode	179	0.907 (0.576–1.428)	0.674
Adiponectin	All	MR Egger	14	2.066 (1.182–3.611)	0.026
		Weighted median	14	1.451 (0.855–2.463)	0.168
		Simple mode	14	1.450 (0.553–	0.463

					3.800)	
			Weighted mode	14	1.796 (1.090–2.958)	0.039
PBC	Estradiol	Males	MR Egger	11	1.747 (0.161–18.949)	0.657
			Weighted median	11	1.450 (0.455–4.620)	0.53
			Simple mode	11	1.507 (0.235–9.673)	0.674
			Weighted mode	11	1.353 (0.374–4.896)	0.655
	Total testosterone		MR Egger	149	1.150 (0.473–2.796)	0.759
			Weighted median	149	1.175 (0.556–2.483)	0.672
			Simple mode	149	1.559 (0.367–6.624)	0.549
			Weighted mode	149	1.031 (0.470–2.262)	0.94
	Bioavailable testosterone		MR Egger	72	1.510 (0.282–8.072)	0.632
			Weighted median	72	2.271 (0.759–6.801)	0.143
			Simple mode	72	1.021 (0.083–12.508)	0.987
			Weighted mode	72	1.983 (0.313–12.551)	0.469
	SHBG		MR Egger	187	1.137 (0.579–2.234)	0.71
			Weighted median	187	1.041 (0.576–1.883)	0.893
			Simple mode	187	1.023 (0.301–3.476)	0.971
			Weighted mode	187	1.023 (0.568–1.841)	0.939
	Estradiol	Females	MR Egger	16	0.904 (0.079–	0.937

				10.408)	
		Weighted median	16	0.718 (0.158–3.263)	0.668
		Simple mode	16	1.047 (0.109–10.058)	0.969
		Weighted mode	16	0.811 (0.124–5.298)	0.829
Total testosterone		MR Egger	101	1.813 (0.605–5.428)	0.29
		Weighted median	101	1.254 (0.421–3.739)	0.685
		Simple mode	101	0.883 (0.105–7.446)	0.909
		Weighted mode	101	1.090 (0.384–3.096)	0.872
Bioavailable testosterone		MR Egger	118	1.677 (0.526–5.346)	0.384
		Weighted median	118	0.942 (0.374–2.372)	0.899
		Simple mode	118	0.929 (0.151–5.715)	0.937
		Weighted mode	118	1.023 (0.368–2.839)	0.966
SHBG		MR Egger	180	1.919 (0.894–4.120)	0.096
		Weighted median	180	1.122 (0.545–2.309)	0.754
		Simple mode	180	0.884 (0.213–3.674)	0.866
		Weighted mode	180	1.178 (0.527–2.632)	0.69
Adiponectin	All	MR Egger	14	2.832 (0.924–8.682)	0.094
		Weighted median	14	2.514 (0.973–6.492)	0.057
		Simple mode	14	4.429 (0.816–	0.108

			24.045)	
	Weighted mode	14	2.650 (1.200–5.854)	0.031

SHBG – sex hormone-binding globulin, PBC – primary biliary cirrhosis, MR – mendelian randomization, SNPs – single-nucleotide polymorphisms, OR – odds ratio, CI – confidence intervals.