

Supplementary Table 1. GWAS statistics

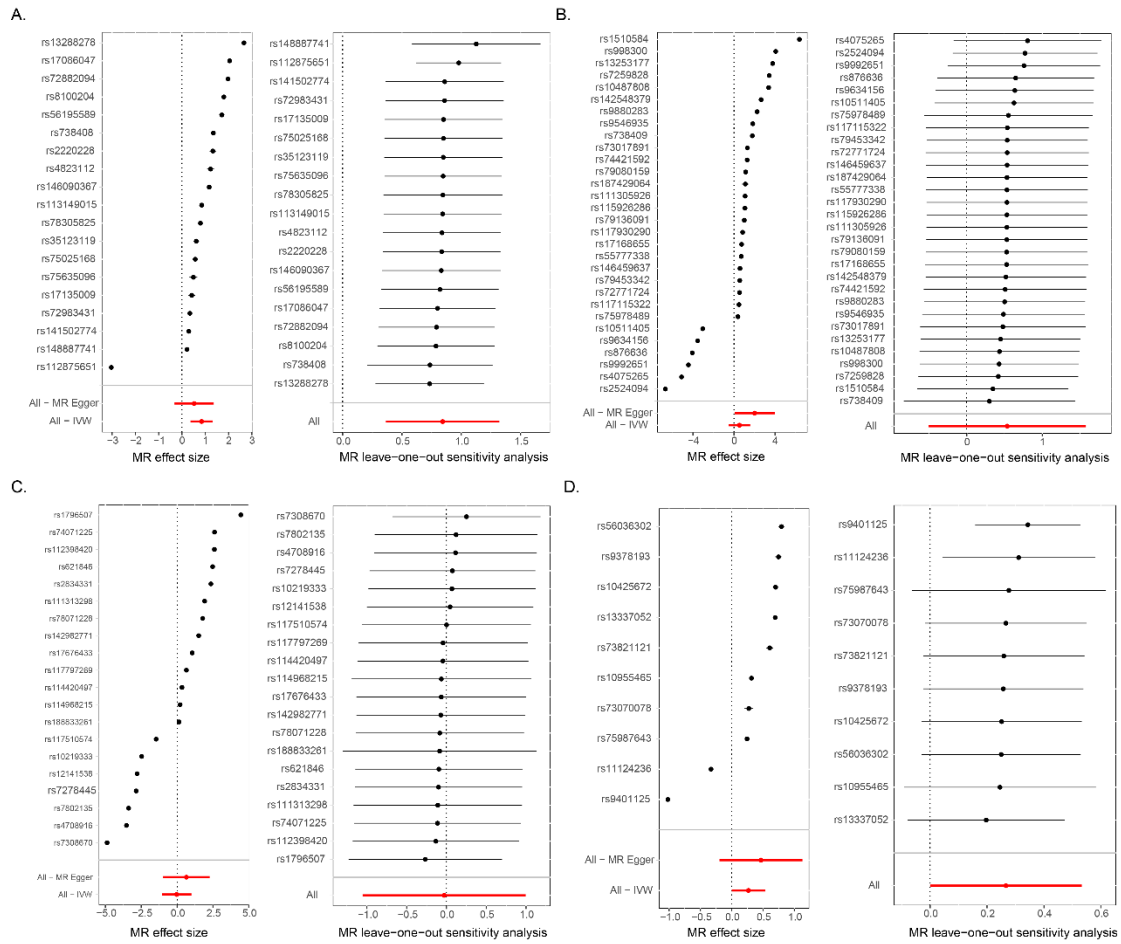
Exposure	genome-wide statistical significance	SNPs	Median R ² [25th–75th Percentile]	Median F [25th–75th Percentile]
Nonalcoholic fatty liver disease	p < 5e-08	2	-	-
	p < 1e-07	3	-	-
	p < 1e-06	6	-	-
	p < 1e-05	19	0.0101[0.0097-0.0106]	32.62[32.18-32.91]
Liver cirrhosis	p < 5e-08	1	-	-
	p < 1e-07	2	-	-
	p < 1e-06	6	-	-
	p < 1e-05	31	0.0099[0.0096-0.0098]	29.02[28.71-29.61]
Viral hepatitis	p < 5e-08	0	-	-
	p < 1e-07	0	-	-
	p < 1e-06	1	-	-
	p < 1e-05	22	0.0097[0.0096-0.0098]	31.74[31.65-31.86]
Autoimmune hepatitis	p < 5e-08	1	-	-
	p < 1e-07	1	-	-
	p < 1e-06	1	-	-
	p < 1e-05	12	0.0110[0.0109-0.0113]	33.43[33.21-33.49]
Breast cancer	p < 5e-08	424	0.0190[0.0186-0.0198]	10.20[10.10-10.27]

Supplementary Table 2. Two-way Mendelian randomization analysis of liver disease and breast cancer development

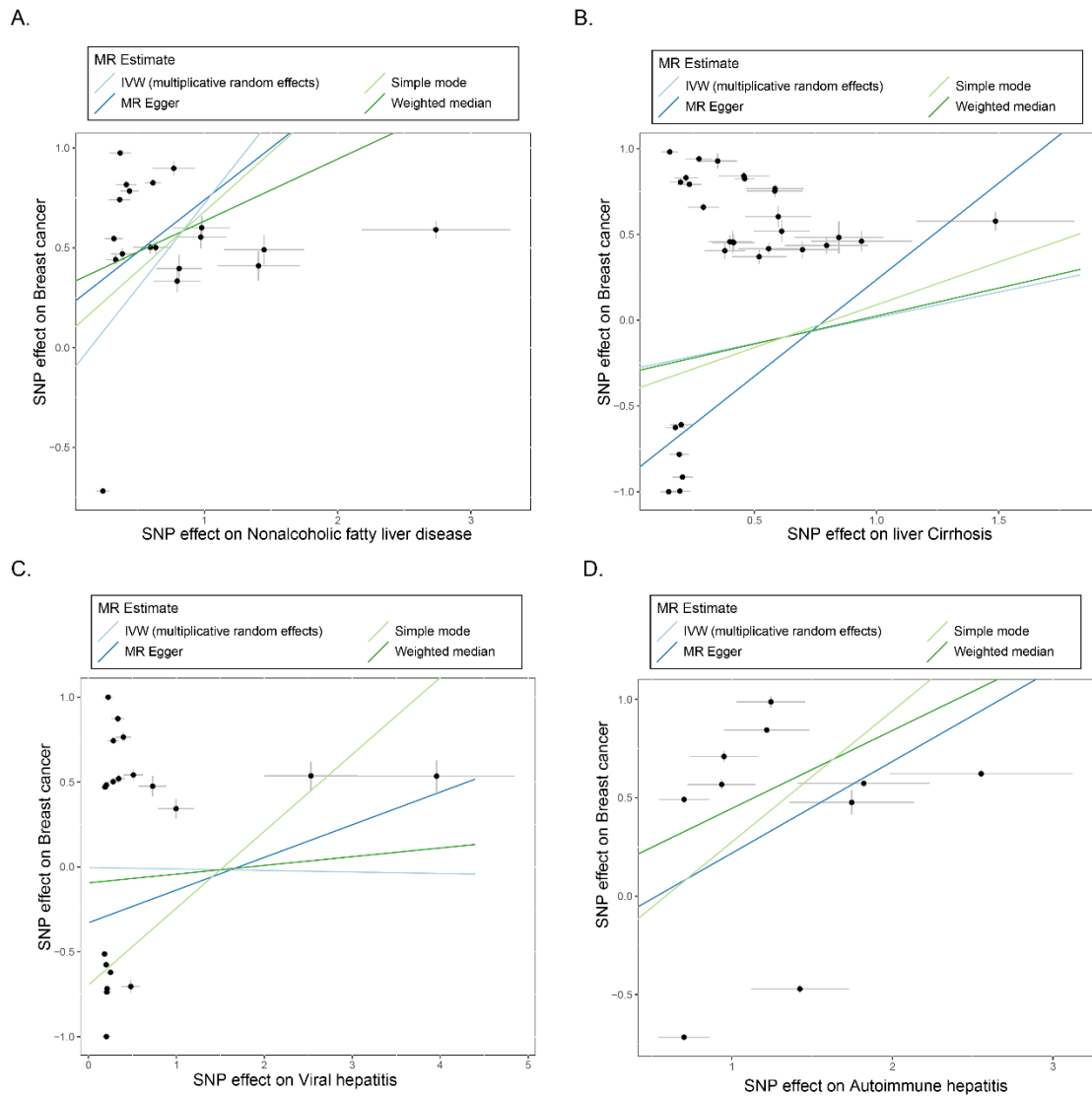
Exposures	method	Beta	se	OR[95%CI]	P-val
Nonalcoholic fatty liver disease (19 SNPs)	MR Egger	-0.1020	0.1017	0.903[0.7398-1.1022]	0.3724
	IVW (multiplicative random effects)	0.8237	0.2923	2.2789[1.2851-4.0413]	0.0048
	Weighted median	0.3372	0.0574	1.401[1.252-1.5678]	4.23e-09
	Simple mode	0.6854	0.3221	1.9846[1.0555-3.7316]	0.0866
	MR-PRESSO (Outlier-corrected)	0.8438	0.1029	2.3251[1.9006-2.8445]	3.64e-05

Liver cirrhosis (35 SNPs)	MR Egger	2.01 55	0.99 76	7.5041[1.0619- 53.0281]	0.053 0
	IVW (multiplicative random effects)	0.53 57	0.53 17	1.7086[0.6026- 4.8442]	0.313 7
	Weighted median	0.58 30	0.08 21	1.7913[1.525-2 .1042]	1.26e -12
	Simple mode	0.89 11	0.07 17	2.4378[2.1183- 2.8055]	3.83e -13
	MR-PRESSO (Outlier-corrected)	0.57 59	0.06 24	1.7787[1.5738- 2.0102]	6.98e -06
	MR Egger	0.65 08	0.82 68	1.9171[0.3792- 9.693]	0.441 5
Viral hepatitis (20 SNPs)	IVW (multiplicative random effects)	-0.0 295	0.52 27	0.9709[0.3485- 2.7047]	0.955 0
	Weighted median	0.17 41	0.04 03	1.1902[1.0997- 1.288]	1.58e -05
	Simple mode	1.53 16	0.17 31	4.6257[3.2947- 6.4944]	3.64e -08
	MR-PRESSO (Outlier-corrected)	0.17 83	0.04 52	1.1952[1.0938- 1.306]	0.058 8
	MR Egger	0.46 61	0.33 78	1.5937[0.822-3 .09]	0.205 0
	IVW (multiplicative random effects)	0.26 63	0.13 60	1.3051[0.9997- 1.7038]	0.050 2
Autoimmune hepatitis (10 SNPs)	Weighted median	0.26 61	0.04 85	1.3049[1.1866- 1.435]	4.05e -08
	Simple mode	0.66 64	0.11 80	1.9473[1.5452- 2.4541]	0.000 3
	MR-PRESSO	0.27 85	0.02 49	1.3211[1.2583- 1.3871]	0.007 9
	Outcomes	method	Beta	se	OR[95%CI]
Nonalcoholic fatty liver disease (384 SNPs)	MR Egger	0.01 59	0.01 96	1.0161[0.9778- 1.0559]	0.416 5
	IVW	0.00 26	0.00 36	1.0026[0.9956- 1.0096]	0.465 7
	Weighted median	0.00 21	0.00 54	1.0021[0.9916- 1.0128]	0.690 3
	Simple mode	-0.0 136	0.01 53	0.9865[0.9573- 1.0165]	0.373 7
	MR-PRESSO	0.00 28	0.00 35	1.0028[0.996-1 .0097]	0.415 7

Liver cirrhosis (384 SNPs)	MR Egger	0.00 21	0.01 36	1.0021[0.9757- 1.0292]	0.877 3
	IVW	-0.0 012	0.00 25	0.9988[0.9939- 1.0038]	0.634 4
	Weighted median	0.00 01	0.00 38	1.0001[0.9927- 1.0076]	0.976 0
	Simple mode	0.00 96	0.01 25	1.0096[0.9852- 1.0347]	0.443 6
	MR-PRESSO	-0.0 001	0.00 25	0.9999[0.9951- 1.0047]	0.964 4
	Viral hepatitis (384 SNPs)	MR Egger	0.00 00	0.01 69	1[0.9675-1.033 7]
IVW		-0.0 019	0.00 31	0.9981[0.992-1 .0042]	0.537 7
Weighted median		0.00 17	0.00 47	1.0017[0.9925- 1.011]	0.712 1
Simple mode		0.00 05	0.01 25	1.0005[0.9762- 1.0253]	0.971 3
MR-PRESSO		-0.0 015	0.00 31	0.9985[0.9925- 1.0045]	0.614 4
Autoimmune hepatitis (322 SNPs)		MR Egger	0.04 31	0.07 08	1.044[0.9088-1 .1995]
	IVW	0.00 88	0.01 36	1.0088[0.9823- 1.036]	0.518 0
	Weighted median	0.03 11	0.01 93	1.0316[0.9934- 1.0712]	0.106 5
	Simple mode	0.06 84	0.05 75	1.0707[0.9566- 1.1985]	0.235 3
	MR-PRESSO	0.00 72	0.01 31	1.0073[0.9818- 1.0334]	0.580 6



Supplementary Figure 1. Correlated SNPs and leave-one-out validation results in Mendelian randomization analysis of liver disease on breast cancer development



Supplementary Figure 2. Scatterplots for Mendelian randomization analysis of liver disease on breast cancer development

Supplementary Table 3. Cochran's Q test, horizontal gene pleiotropy and outlier test results in Mendelian randomization analysis

Exposures	method	Cochran's Q			Horizontal pleiotropy			MR-PRESSO outlier test	
		Q	Q_df	Q_pval	intercept	se	p	RSSobs	p-value
Nonalcoholic fatty liver disease	MR Egger	12400.5	17	< 0.0001	-0.5962	0.3217	0.072	15839.7	<0.001
	IVW	13006.6	18	0.0001	-	-	-	-	-
Cirrhosis	MR Egger	56088.7	28	< 0.0001	-0.5060	0.2923	0.094	67286.5	<0.001
	IVW	62091.2	29	< 0.0001	-	-	-	-	-
Viral hepatitis	MR Egger	34639.2	18	< 0.0001	-0.2814	0.2655	0.303	45690.7	<0.001

Exposures	method	Cochran's Q			Horizontal pleiotropy			MR-PRESSO outlier test	
		Q	Q_df	Q_pval	intercept	se	p	RSSobs	p-value
Autoimmune hepatitis	IVW	36800.17	19	< 0.0001	-	-	-	-	-
	MR Egger	9938.651	8	< 0.0001	-0.3045	0.4682	0.5536	18885.17	<0.001
	IVW	10464.287	9	< 0.0001	-	-	-	-	-
Outcomes	method	Q	Q_df	Q_pval	intercept	se	p	RSSobs	p-value
Nonalcoholic fatty liver disease	MR Egger	365.7461	382	0.7165	-0.0116	0.0168	0.4889	381.1361	0.697
	IVW	366.2261	383	0.7227	-	-	-	-	-
	MR Egger	393.9006	382	0.3263	-0.0028	0.0117	0.8050	407.2169	0.374
Cirrhosis	IVW	393.9635	383	0.3386	-	-	-	-	-
	MR Egger	381.9989	382	0.4904	-0.2814	0.2655	0.3033	394.2623	0.548
	IVW	382.0127	383	0.5046	-	-	-	-	-
Viral hepatitis	MR Egger	356.7530	320	0.0768	-0.0299	0.0605	0.6216	369.2335	0.115
	IVW	357.0252	321	0.0811	-	-	-	-	-