Supplementary Table 1 UVMR estimating the associations of education, intelligence, or cognition with cholelithiasis and cholecystitis

Exposure	Outcome	Method	No.of SNPs	β (95%CI)	OR (95%CI)	*P* value
Education	**Cholelithiasis**	IVW	315	-0.320 (-0.431 to -0.208)	0.726 (0.650 to 0.812)	1.80E-08
		MR Egger	315	-0.280 (-0.694 to 0.134)	0.756 (0.499 to 1.143)	1.86E-01
		Weight Median	315	-0.295 (-0.429 to -0.162)	0.744 (0.651 to 0.851)	1.45E-05
		PRESSO	4*			
	Cholecystitis	IVW	315	-0.374 (-0.621 to -0.126)	0.688 (0.537 to 0.882)	3.11E-03
		MR Egger	315	-0.118 (-1.038 to 0.802)	0.886 (0.354 to 2.230)	8.02E-01
		Weight Median	315	-0.390 (-0.744 to -0.036)	0.677 (0.475 to 0.965)	3.10E-02
		PRESSO	0*			
Cognition	**Cholelithiasis**	IVW	103	-0.224 (-0.337 to -0.112)	0.799 (0.714 to 0.894)	9.24E-05
		MR Egger	103	0.044 (-0.472 to 0.560)	1.045 (0.624 to 1.751)	8.67E-01
		Weight Median	103	-0.173 (-0.308 to -0.039)	0.841 (0.735 to 0.962)	1.14E-02
		PRESSO	3*			
	Cholecystitis	IVW	103	-0.144 (-0.399 to 0.111)	0.866 (0.671 to 0.117)	2.67E-01
		MR Egger	103	-0.365 (-0.806 to 1.536)	1.440 (0.446 to 4.647)	5.43E-01
		Weight Median	103	-0.189 (-0.520 to 0.142)	0.828 (0.595 to 1.152)	2.63E-01

		PRESSO	0*			
		IVW	140	-0.191 (-0.299 to -0.083)	0.826 (0.741 to 0.920)	5.15E-04
	Cholelithiasis	MR Egger	140	-0.410 (-0.931 to 0.111)	0.664 (0.394 to 1.118)	1.25E-01
		Weight Median	140	-0.157 (-0.276 to -0.038)	0.855 (0.759 to 0.963)	9.74E-03
Intelligence		PRESSO	4*			
		IVW	140	-0.040 (-0.272 to 0.193)	0.961 (0.762 to 1.212)	7.37E-01
	Cholecystitis	MR Egger	140	-0.303 (-1.424 to 0.818)	0.739 (0.241 to 2.267)	5.97E-01
		Weight Median	140	-0.011 (-0.305 to 0.326)	1.011 (0.737 to 1.386)	9.48E-01
		PRESSO	1*			

Supplementary Table 2 MR heterogeneity tests of the association of education, cognition, and intelligence with cholelithiasis

Exposure	**Outcome**	**Method**	**Q statistic**	**Q df**	**Q *P* value**
Education	Cholelithiasis	IVW	571.78	313	2.18E-17
		MR Egger	571.85	314	2.92E-17
	Cholecystitis	IVW	378.21	313	6.74E-03
		MR Egger	378.60	314	7.23E-03
Cognition	Cholelithiasis	IVW	144.65	101	5.95E-07
		MR	144.81	102	5.07E-

		Egger			07
	Cholecystitis	IVW	127.96	101	3.62E-02
		MR Egger	128.92	102	3.70E-02
	Cholelithiasis	IVW	295.03	138	1.93E-13
		MR Egger	296.54	139	1.89E-13
Intelligence		IVW	183.86	138	5.51E-03
	Cholecystitis	MR Egger	184.16	139	6.22E-03

Supplementary Table 3 MR directional pleiotropy test (MR Egger) of the correlations of education, cognition, and intelligence

Exposure	**Outcome**	**Egger intercept**	**SE**	***P* value**
Education	Cholelithiasis	0.00027	0.0024	0.91
	Cholecystitis	-0.0033	0.0058	0.57
Cognition	Cholelithiasis	-0.0058	0.0056	0.30
	Cholecystitis	-0.011	0.013	0.38
Intelligence	Cholelithiasis	0.0059	0.0047	0.21
	Cholecystitis	0.0054	0.011	0.64

Supplementary Table 4 MVMR estimating the associations of education, cognition and intelligence with cholelithiasis

Outcome	MVMR Instrument validity test			MVMR Heterogeneity test (MV-IVW)		MVMR Heterogeneity test (MVMR Egger)		MVMR directional pleiotropy		
Cholelithiasis	**Exposure**	**F-statistics**	**Q-statistics**	**P value**	**Q-statistics**	**P value**	**Q-statistics**	**P value**	**Egger intercept**	**SE**	***P* value**
	Models with mutual adjustment for education, intelligence, and cognition										
	Education	25.18	683.54	<0.0001	683.945	<0.0001	677.6218	<0.0001	0.004	0.002	0.07
	Cognition										
	Intelligence										
	Models with mutual adjustment for education and cognition										
	Education	10.46	624.42	<0.0001	698.139	<0.0001	682.34	<0.0001	0.004	0.005	0.15
	Cognition										
	Models with mutual adjustment for education and intelligence										
	Education	45.65	676.46	<0.0001	676.7602	<0.0001	675.09	<0.0001	0.002	0.002	0.35
	Intelligence										
	Models with mutual adjustment for education and cognition										

	Cognition Intelligence	61.28	305.50	<0.0001	305.8223	<0.0001	305.39	<0.0001	0.002	0.004	0.61
Cholelithiasis	**Exposure**	**F-statistics**	**Q-statistics**	**P value**	**Q-statistics**	**P value**	**Q-statistics**	**P value**	**Egger intercept**	**SE**	**P value**
	Models with mutual adjustment for education, intelligence, and cognition										
	Education Cognition Intelligence	25.18	413.52	0.013	413.9856	0.014	413.76	0.013	0.002	0.005	0.66
	Models with mutual adjustment for education and cognition										
	Education Cognition	10.39	415.68	0.012	416.1767	0.013	415.94	0.012	0.002	0.005	0.65
	Models with mutual adjustment for education and intelligence										
	Education Intelligence	45.65	520.70	<0.0001	424.1413	0.0061	423.65	0.0058	0.003	0.005	0.52
	Models with mutual adjustment for education and cognition										
	Cognition Intelligence	61.28	191.42	0.34	191.6862	0.3527	191.67	0.334	0.001	0.008	0.90

Supplementary Table 5 MVMR estimating the associations of education, intelligence, or cognition with cholecystitis adjusted for cholelithiasis.

Exposure	Method	β (95%CI)	OR (95%CI)	*P* value
Education	MR	-0.534 (-0.767 to -0.300)	0.292 (0.171 to 0.501)	1.73032E-43
	MV_IVW			
	MR	-0.614 (-0.853 to -0.376)	0.243 (0.140 to 0.421)	<0.001
	MV_Egger			
	MR	-0.608 (-0.942 to -0.275)	0.247 (0.114 to 0.531)	<0.001
	MV_Median			
	MR	-0.513 (-0.738 to -0.288)	0.307 (0.183 to 0.515)	<0.001
	MV_Lasso			
Cognition	MR	-0.026 (-0.222 to 0.222)	0.942 (0.600 to 1.667)	0.839
	MV_IVW			
	MR	-0.894 (-1.590 to -0.197)	0.128 (0.026 to 1.574)	0.012
	MV_Egger			
	MR	0.094 (-0.234 to 0.421)	1.242 (0.583 to 2.636)	0.576
	MV_Median			
	MR	-0.025 (-0.247 to 0.196)	0.944 (0.566 to	0.822

	MV_Lasso		1.570)			
	MR MV_IVW	-0.079 (-0.296 to 0.138)	0.834 1.374)	(0.506	to	0.475
	MR MV_Egger	-0.454 (-1.171 to 0.264)	0.352 1.837)	(0.067	to	0.215
Intelligence	MR MV_Median	-0.105 (-0.414 to 0.203)	0.785 1.596)	(0.385	to	0.504
	MR MV_Lasso	-0.122 (-0.328 to 0.084)	0.755 1.213)	(0.470	to	0.246

Supplementary Table 6 MVMR estimating the associations of education, cognition and intelligence with cholecystitis adjusted for cholelithiasis

MVMR Instrument validity test	**MVMR Heterogeneity test (MV-IVW)**	**MVMR Heterogeneity test (MVMR Egger)**	**MVMR directional pleiotropy**

Exposure	F-statistics	Q-statistics	P value	Q-statistics	P value	Q-statistics	P value	Egger intercept	SE	*P* value
Models with mutual adjustment for education and cholelithiasis										
Education Cholelithiasis	56.44	613.45	<0.0001	324.1752	0.15	315.08	0.24	-0.002	0.003	0.56
Models with mutual adjustment for cognition and cholelithiasis										
Cognition Cholelithiasis	59.22	178.97	0.025	191.582	0.0058	182.95	0.016	0.005	0.007	0.40
Models with mutual adjustment for intelligence and cholelithiasis										
Intelligence Cholelithiasis	56.45	579.44	<0.0001	192.5592	0.1133	191.26	0.12	0.007	0.007	0.28

Supplementary Table 7 MR heterogeneity test of the association of education with each mediator

Exposure	Mediator	Method	Q statistic	Q df	Q *P* value
Education	**BMI**	**IVW**	2534.99	330	7.03E-300
		MR Egger	2538.2	331	2.05E-299

	BF%	**IVW**	2268.61	330	8.02E-286
		MR Egger	2270.24	331	1.05E-285
	Waist circumference	**IVW**	477.87	269	7.03E-14
		MR Egger	479.47	270	6.59E-14
	WHR	**IVW**	342.63	269	1.58E-03
		MR Egger	342.85	270	1.76E-03
	Time spent watching TV	**IVW**	846.57	330	4.29E-47
		MR Egger	847.23	331	5.63E-47
Cognition	**Time spent watching TV**	**IVW**	596.70	104	3.39E-70
		MR Egger	600.27	105	1.85E-70
Intelligence	**Time spent watching TV**	**IVW**	671.96	134	1.52E-72
		MR Egger	681.06	135	8.81E-74

Supplementary Table 8 MR directional pleiotropy test (MR Egger) of the correlation of education, cognition or intelligence with each mediator

Exposure	**Mediator**	**Egger intercept**	**SE**	***P* value**
Education	BMI	-0.00080	0.0012	5.19E-01

	BF%	-0.00045	0.00091	6.27E-01
	WHR	0.0014	0.0015	3.43E-01
	Waist circumference	0.00052	0.0013	6.80E-01
	Time spent watching TV	0.00029	0.00058	6.13E-01
Cognition	Time spent watching TV	0.0014	0.0017	4.32E-01
Intelligence	Time spent watching TV	0.0021	0.0016	1.80E-01

Supplementary Table 9 MVMR estimating the associations of education, cognition and intelligence with cholelithiasis adjusted for relevant mediator

MVMR Instrument validity test	**MVMR Heterogeneity test (MV-IVW)**	**MVMR Heterogeneity test (MVMR Egger)**	**MVMR directional pleiotropy**

Exposure	F-statistics	Q-statistics	P value	Q-statistics	P value	Q-statistics	P value	Egger intercept	SE	*P* value
Models with mutual adjustment for education and BMI										
Education	52.57	606.96	<0.0001	611.49	<0.0001	611.29	<0.0001	-0.001	0.001	0.702
BMI										
Models with mutual adjustment for education and BF%										
Education	51.45	539.82	<0.0001	544.48	0.0001	544.48	0.0001	<0.001	0;001	0.970
BF%										
Models with mutual adjustment for education and waist circumference										
Education	36.48	331.29	0.0005	339.89	0.0002	337.76	0.0002	-0.002	0.003	0.451
Waist circumference										
Models with mutual adjustment for education and WHR										
Education	19.58	342.24	<0.0001	347.97	<0.0001	347.76	<0.0001	-0.001	0.003	0.701
WHR										
Models with mutual adjustment for education and time spent watching TV										
Education	10.76	370.26	0.0050	371.40	0.0049	370.55	0.0048	-0.003	0.003	0.405
Time spent										

watching TV										
Models with mutual adjustment for cognition and time spent watching TV										
Cognition	30.29	187.64	0.30	188.54	0.30	185.30	0.34	-0.004	0.002	0.078
Time spent watching TV										
Models with mutual adjustment for intelligence and time spent watching TV										
Cognition										
Time spent watching TV	26.51	235.33	0.0063	236.44	0.0063	231.92	0.0096	-0.005	0.003	0.058