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
		TX 7X A 7	215	-0.320 (-0.431 to	0.726 (0.650 to	1.80E-
		IVW	315	-0.208)	0.812)	08
		MD Eggar	01E	-0.280 (-0.694 to	0.756 (0.499 to	1.86E-
	Cholelithiasis	MR Egger	315	0.134)	1.143)	01
		Weight	315	-0.295 (-0.429 to	0.744 (0.651 to	1.45E-
		Median	313	-0.162)	0.851)	05
Education		PRESSO	4*			
Education		IVW	315	-0.374 (-0.621 to	0.688 (0.537 to	3.11E-
		IV VV	313	-0.126)	0.882)	03
		MP Egger	315	-0.118 (-1.038 to	0.886 (0.354 to	8.02E-
	Cholecystitis	MR Egger	313	0.802)	2.230)	01
		Weight	315	-0.390 (-0.744 to	0.677 (0.475 to	3.10E-
		Median	313	-0.036)	0.965)	02
		PRESSO	0*			
		IVW	103	-0.224 (-0.337 to	0.799 (0.714 to	9.24E-
		1 7 7 7	100	-0.112)	0.894)	05
		MR Egger	103	0.044 (-0.472 to	1.045 (0.624 to	8.67E-
	Cholelithiasis	WIK Egger	100	0.560)	1.751)	01
		Weight	103	-0.173 (-0.308 to	0.841 (0.735 to	1.14E-
		Median	100	-0.039)	0.962)	02
Cognition		PRESSO	3*			
		IVW	103	-0.144 (-0.399 to	0.866 (0.671 to	2.67E-
		1,,,	100	0.111)	0.117)	01
	Cholecystitis	MR Egger	103	-0.365 (-0.806 to	1.440 (0.446 to	5.43E-
	Choiceysticis	WIK LEGET	100	1.536)	4.647)	01
		Weight	103	-0.189 (-0.520 to	0.828 (0.595 to	2.63E-
		Median	100	0.142)	1.152)	01

		PRESSO	0*			
		IVW	140	-0.191 (-0.299 to	0.826 (0.741 to	5.15E-
		1 V V V		-0.083)	0.920)	04
		MR Egger	140	-0.410 (-0.931 to	0.664 (0.394 to	1.25E-
	Cholelithiasis	MR Egger	140	0.111)	1.118)	01
		Weight	140	-0.157 (-0.276 to	0.855 (0.759 to	9.74E-
		Median	140	-0.038)	0.963)	03
Intelligence		PRESSO	4*			
Intelligence		IVW	1.10	-0.040 (-0.272 to	0.961 (0.762 to	7.37E-
		1 V V V	140	0.193)	1.212)	01
		MR Egger	140	-0.303 (-1.424 to	0.739 (0.241 to	5.97E-
	Cholecystitis	WIK Egger	140	0.818)	2.267)	01
		Weight	140	-0.011 (-0.305 to	1.011 (0.737 to	9.48E-
		Median	140	0.326)	1.386)	01
		PRESSO	1*			

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

Evnosura	xposure Outcome		Q	Q df	Q P
Lxposure	Outcome	Method	statistic	Qui	value
		IVW	571.78	313	2.18E-
	Cholelithiasis	1 V V V	371.70	313	17
	Cholentinasis	MR	571.85	314	2.92E-
Education		Egger	371.63	314	17
Education		IVW	378.21	313	6.74E-
		I V VV	370.21	313	03
	Cholecystitis	MR	378.60	01.4	7.23E-
		Egger	370.00	314	03
Cognition		IVW	144.65	101	5.95E-
	Cholelithiasis	1 V VV	144.00	101	07
		MR	144.81	102	5.07E-

		Egger			07
			127.96	101	3.62E-
	Cholecystitis	IVW	127.90	101	02
	Cholecystitis	MR	128.92	102	3.70E-
		Egger	120.92	102	02
	Cholelithiasis	IVW	295.03	138	1.93E-
		1 V V V	293.03	130	13
		MR 296.54		139	1.89E-
Intelligence		Egger	290.34	139	13
intemgence		IVW	183.86	138	5.51E-
	Cholecystitis	1 V V V	105.00	130	03
	Cholecystitis	MR	184.16	139	6.22E-
		Egger	104.10	137	03

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

Evnosimo	Outcome	Egger	SE	P
Exposure	Outcome	intercept	SE	value
Education	Cholelithiasis	0.00027	0.0024	0.91
	Cholecystitis	-0.0033	0.0058	0.57
Cognition	Cholelithiasis	-0.0058	0.0056	0.30
Cognition	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 Inst	rument val	lidity test		MVMR		MVMR		MVMR	d	lirectional
					Heterogeneity H		Heteroge	Heterogeneity		y	
					test (MV-IVW)		test	(MVMR			
							Egger)				
Cholelithiasis	Exposure	F-	Q-	P	Q-	P	Q-	P	Egger	SE	P
		statistics	statistics	value	statistics	value	statistics	value	intercept		value
	Models with mutual adjustment for education, intelligence, and						nd 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	n mutual ac	ljustment f	or educat	ion and co	gnition					
	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					telligence	!				
	Education	45.65	676.46	<0.0001	676.7602	<0.0001	675.09	< 0.0001	0.002	0.002	0.35
	Intelligence										
	Models with	n mutual ac	ljustment f	or educat	ion and co	gnition					

	Cognition	61.28	305.50	<0.0001	305.8223	<0.0001	305.39	<0.0001	0.002	0.004	0.61
	Intelligence										
Cholelithiasis	Exposure	F-	Q-	P	Q-	P	Q-	P	Egger	SE	P
		statistics	statistics	value	statistics	value	statistics	value	intercept		value
	Models with	n mutual ac	djustment f	or educat	tion, intelli	gence, an	d cognitio	n			
	Education	25.18	413.52	0.013	413.9856	0.014	413.76	0.013	0.002	0.005	0.66
	Cognition										
	Intelligence										
	Models with	n mutual ac	djustment f	or educat	tion and co	gnition					
	Education	10.39	415.68	0.012	416.1767	0.013	415.94	0.012	0.002	0.005	0.65
	Cognition										
	Models with	n mutual ac	djustment f	or educat	tion and in	telligence	!				
	Education	45.65	520.70	<0.0001	424.1413	0.0061	423.65	0.0058	0.003	0.005	0.52
	Intelligence										
	Models with	n mutual ac	djustment f	or educat	tion and co	gnition					
	Cognition	61.28	191.42	0.34	191.6862	0.3527	191.67	0.334	0.001	0.008	0.90
	Intelligence										

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)		
	MR	0.524 (0.767 to .0.200)	0.292 (0.171	to	1.73032E-
	MV_IVW	-0.534 (-0.767 to -0.300)	0.501)		43
	MR	0.614 (0.952 to . 0.276)	0.243 (0.140	to	~ 0.001
Education	MV_Egger	-0.614 (-0.853 to -0.376)	0.421)		<0.001
Education	MR	0 (00 (0 042 to 0 275)	0.247 (0.114	to	~ 0.001
	MV_Median	-0.608 (-0.942 to -0.275)	0.531)		<0.001
	MR	0.512 / 0.520 / 0.200	0.307 (0.183	to	-0.001
	MV_Lasso	-0.513 (-0.738 to -0.288)	0.515)		<0.001
	MR	0.00(/ 0.000 / 0.000)	0.942 (0.600	to	0.839
	MV_IVW	-0.026 (-0.222 to 0.222)	1.667)	1.667)	
	MR	0.004 / 1.500 (- 0.105)	0.128 (0.026	to	0.012
Cognition	MV_Egger	-0.894 (-1.590 to -0.197)	1.574)	1.574)	
	MR	0.004 (0.204 (0.421)	1.242 (0.583	to	0.577
	MV_Median	0.094 (-0.234 to 0.421)	2.636)		0.576
	MR	-0.025 (-0.247 to 0.196)	0.944 (0.566	to	0.822

	MV_Lasso		1.570)			
	MR	-0.079 (-0.296 to 0.138)	0.834	(0.506	to	0.475
	MV_IVW	-0.079 (-0.290 to 0.130)	1.374)			0.475
	MR	-0.454 (-1.171 to 0.264)	0.352	(0.067	to	0.215
Intalliganca	MV_Egger	-0.434 (-1.171 to 0.204)	1.837)			0.215
Intelligence	MR	-0.105 (-0.414 to 0.203)	0.785	(0.385	to	0.504
	MV_Median	-0.103 (-0.414 to 0.203)	1.596)			0.304
	MR	-0.122 (-0.328 to 0.084)	0.755	(0.470	to	0.246
	MV_Lasso	1.213)		0.240		

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

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

Exposure	F-	Q-	P	Q-	P	Q-	P	Egger	SE	P
	statistics	statistics	value	statistics	value	statistics	value	intercept		value
Models with	mutual adj	ustment for	r educatio	n and chol	elithiasi	is				
Education	56.44	613.45	<0.0001	324.1752	0.15	315.08	0.24	-0.002	0.003	0.56
Cholelithiasis										
Models with	Models with mutual adjustment for cognition and cholelithiasis									
Cognition	59.22	178.97	0.025	191.582	0.0058	182.95	0.016	0.005	0.007	0.40
Cholelithiasis										
Models with	mutual adj	ustment fo	r intellige	ence and ch	olelithia	nsis				
Intelligence	56.45	579.44	<0.0001	192.5592	0.1133	191.26	0.12	0.007	0.007	0.28
Cholelithiasis										

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% MR Egger 2270.24 331 1.05E-285 Waist IVW 477.87 269 7.03E-14 circumference MR Egger 479.47 270 6.59E-14
MR Egger 2270.24 331 1.05E-285 Waist IVW 477.87 269 7.03E-14
circumference MR Egger 479.47 270 6.59E-14
IVW 342.63 269 1.58E-03 WHR
MR Egger 342.85 270 1.76E-03
Time spent IVW 846.57 330 4.29E-47
watching TV MR Egger 847.23 331 5.63E-47
Time spent IVW 596.70 104 3.39E-70 Cognition
watching TV MR Egger 600.27 105 1.85E-70
Time spent IVW 671.96 134 1.52E-72 Intelligence
watching TV 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	MVMR	MVMR	directional
	Heterogeneity	Heterogeneity	pleiotropy	
	test (MV-IVW)	test (MVMR		
		Egger)		

F-	Q-	P	Q-	P	Q-	P	Egger	SE	P
statistics	statistics	value	statistics	value	statistics	value	intercept		value
mutual adju	stment for	educatio	n and BMI						
52.57	606.96	<0.0001	611.49	<0.0001	611.29	<0.0001	-0.001	0.001	0.702
Models with mutual adjustment for education and BF $\%$									
51.45	539.82	<0.0001	544.48	0.0001	544.48	0.0001	< 0.001	0;001	0.970
mutual adju	stment for	educatio	n and wais	t circumf	erence				
36.48	331.29	0.0005	339.89	0.0002	337.76	0.0002	-0.002	0.003	0.451
:									
mutual adju	stment for	educatio	n and WHI	λ .					
19.58	342.24	<0.0001	347.97	< 0.0001	347.76	<0.0001	-0.001	0.003	0.701
mutual adju	stment for	educatio	n and time	spent wa	tching TV				
10.76	370.26	0.0050	371.40	0.0049	370.55	0.0048	-0.003	0.003	0.405
	statistics mutual adju 52.57 mutual adju 51.45 mutual adju 36.48 mutual adju 19.58 mutual adju 19.58	statistics mutual adjustment for 52.57 606.96 mutual adjustment for 51.45 539.82 mutual adjustment for 36.48 331.29 mutual adjustment for 19.58 342.24 mutual adjustment for 19.58 370.26	statistics statistics value mutual adjustment for education 52.57 606.96 <0.0001 mutual adjustment for education 51.45 539.82 <0.0001 mutual adjustment for education 36.48 331.29 0.0005 mutual adjustment for education 19.58 342.24 <0.0001 mutual adjustment for education 19.58 342.24 <0.0001	statistics statistics value statistics mutual adjustment for education and BMI 52.57 606.96 <0.0001 611.49 mutual adjustment for education and BF% 51.45 539.82 <0.0001 544.48 mutual adjustment for education and wais 36.48 331.29 0.0005 339.89 mutual adjustment for education and WHI 19.58 342.24 <0.0001 347.97 mutual adjustment for education and time 10.76 370.26 0.0050 371.40	statistics statistics value mutual adjustment for education and BMI 52.57 606.96 <0.0001	statistics statistics value statistics mutual adjustment for education and BF% 52.57 606.96 <0.0001	statistics value statistics value statistics value mutual adjustment for education and BF% 51.45 539.82 < 0.0001 544.48 0.0001 544.48 0.0001 mutual adjustment for education and waist circumference 36.48 331.29 0.0005 339.89 0.0002 337.76 0.0002 mutual adjustment for education and WHR 19.58 342.24 <0.0001	statistics value statistics value statistics value intercept mutual adjustment for education and BF% 52.57 606.96 <0.0001	Statistics Sta

watching TV										
Models with	mutual ad	justment fo	or cognitio	n and tim	e spent wa	atching TV	7			
Cognition	30.29	187.64	0.30	188.54	0.30	185.30	0.34	-0.004	0.002	0.078
Time sper	nt									
watching TV										
Models with	mutual ad	ljustment fo	or intellige	ence and ti	me spent	watching [ΓV			
Cognition										
Time sper	nt 26.51	235.33	0.0063	236.44	0.0063	231.92	0.0096	-0.005	0.003	0.058
watching TV										