

Article

Genetic and biomechanics insights into cathepsins and non-cancerous digestive diseases: A bidirectional two-sample Mendelian randomization study

Supplementary file

Table S1. Information of selected SNPs of 9 cathepsins.

Exposure	SNP	chr. exposure	pos. exposure	other_allele. exposure	effect_allele. exposure	beta. exposure	se. exposure	pval. exposure	eaf. exposure	samplesize. exposure
Cathepsin B	rs75773690	1	24,464,363	G	A	-0.3945	0.08570	4.16869×10^{-6}	0.02192	3301
	rs113646963	2	204,530,789	C	T	0.1996	0.04270	2.95121×10^{-6}	0.09708	3301
	rs76089522	3	140,389,189	G	A	-0.1971	0.04210	2.88403×10^{-6}	0.10475	3301
	rs200518932	3	151,162,527	C	CA	-0.5167	0.11000	2.63027×10^{-6}	0.01693	3301
	rs13152767	4	122,367,502	G	A	0.4158	0.08670	1.62181×10^{-6}	0.02617	3301
	rs36021960	7	47,111,670	G	A	0.1747	0.03740	3.01995×10^{-6}	0.12637	3301
	rs11563944	7	89,816,334	A	G	0.1291	0.02780	3.54813×10^{-6}	0.26799	3301
	rs1692819	8	11,705,448	G	A	0.4246	0.02740	5.24807×10^{-4}	0.29182	3301
	rs148930853	8	114,408,661	T	C	0.5516	0.11810	3.01995×10^{-6}	0.01211	3301
	rs150811995	10	38,633,385	A	C	0.4603	0.10040	4.57088×10^{-6}	0.01878	3301
	rs72863882	10	134,275,165	G	A	-0.2569	0.04750	6.45654×10^{-8}	0.08353	3301
	rs150370599	11	60,718,792	C	T	0.2183	0.04570	1.77828×10^{-6}	0.08341	3301
	rs143557119	11	116,385,842	G	A	0.4327	0.09460	4.7863×10^{-6}	0.02199	3301
	rs117345475	11	131,588,071	A	G	-0.4332	0.09330	3.46737×10^{-6}	0.02062	3301
	rs117486267	15	25,484,738	T	C	-0.4003	0.08340	1.58489×10^{-6}	0.02486	3301
	rs9905973	17	26,735,142	G	A	-0.1405	0.02760	3.54813×10^{-7}	0.27100	3301
	rs147881440	17	80,969,815	G	A	-0.2331	0.05100	4.7863×10^{-6}	0.06428	3301
	rs200652433	18	73,024,506	C	T	0.3389	0.06840	7.24436×10^{-7}	0.04112	3301
	rs7249773	19	18,289,760	G	A	0.1749	0.03510	6.0256×10^{-7}	0.15121	3301
	rs1065853	19	45,413,233	G	T	0.2266	0.04630	1.0×10^{-6}	0.07778	3301

Table S1. (Continued).

Exposure	SNP	chr. exposure	pos. exposure	other_allele. exposure	effect_allele. exposure	beta. exposure	se. exposure	pval. exposure	eaf. exposure	samplesize. exposure
Cathepsin E	rs149553686	2	197,840,502	T	C	0.2425	0.05250	3.89045×10^{-6}	0.06772	3301
	rs13089837	3	5,094,952	T	C	-0.1152	0.02500	4.16869×10^{-6}	0.49848	3301
	rs189009983	4	102,582,604	C	T	0.7055	0.15410	4.67735×10^{-6}	0.00831	3301
	rs57689619	4	189,431,921	A	G	-0.2078	0.04440	2.81838×10^{-6}	0.08618	3301
	rs10900907	6	1,448,387	G	A	0.1188	0.02550	3.23594×10^{-6}	0.41707	3301
	rs112918835	8	109,846,123	C	T	0.7062	0.15260	3.71535×10^{-6}	0.00706	3301
	rs57135345	10	26,671,589	C	T	0.2535	0.05420	2.95121×10^{-6}	0.05697	3301
	rs1936839	10	129,433,747	G	C	0.1562	0.03290	1.99526×10^{-6}	0.16937	3301
	rs74677283	11	19,486,084	C	T	0.4379	0.08820	6.76083×10^{-7}	0.02151	3301
	rs8066936	17	754,600	G	A	-0.1492	0.03250	4.2658×10^{-6}	0.17920	3301
	rs10401027	17	6,858,240	G	A	-0.1225	0.02590	2.23872×10^{-6}	0.45246	3301
Cathepsin F	rs141177481	1	78,678,616	TA	T	-0.1537	0.03160	1.14815×10^{-6}	0.80938	3301
	rs7564167	2	645,190	A	G	-0.2649	0.05260	4.89779×10^{-7}	0.93594	3301
	rs1260326	2	27,730,940	T	C	-0.1642	0.02520	6.91831×10^{-11}	0.59849	3301
	rs115901379	2	106,335,628	T	G	0.4306	0.09270	3.38844×10^{-6}	0.02042	3301
	rs58531759	3	65,827,134	T	G	-0.3722	0.07470	6.30957×10^{-7}	0.03949	3301
	rs186369051	5	93,830,000	C	T	-0.4818	0.10260	2.63027×10^{-6}	0.01504	3301
	rs183683891	6	133,102,456	C	T	-0.5242	0.11230	3.01995×10^{-6}	0.01536	3301
	rs112526544	7	26,300,072	A	G	0.3801	0.07660	6.91831×10^{-7}	0.02831	3301
	rs61866943	10	85,428,041	T	G	0.4969	0.10120	9.12011×10^{-7}	0.01874	3301
	rs1791679	11	66,337,874	C	A	0.2349	0.02690	2.51189×10^{-18}	0.28947	3301
	rs10745925	12	102,218,899	T	C	-0.2874	0.02680	9.12011×10^{-27}	0.29402	3301
	rs143015877	13	23,327,148	C	T	-0.1325	0.02870	3.98107×10^{-6}	0.25734	3301
	rs9796775	16	9,736,917	A	G	-0.1172	0.02490	2.45471×10^{-6}	0.50502	3301

Table S1. (Continued).

Exposure	SNP	chr. exposure	pos. exposure	other_allele. exposure	effect_allele. exposure	beta. exposure	se. exposure	pval. exposure	eaf. exposure	samplesize. exposure
Cathepsin G	rs114418234	2	155,060,275	A	C	0.3077	0.06500	2.23872×10^{-6}	0.03719	3301
	rs35594771	2	167,837,936	C	CT	0.3303	0.07050	2.81838×10^{-6}	0.03753	3301
	rs147099093	3	37,730,576	G	A	0.4271	0.08850	1.38038×10^{-6}	0.02053	3301
	rs192289769	3	134,273,074	C	G	-0.5468	0.10930	5.62341×10^{-7}	0.01364	3301
	rs116142041	4	9,787,836	G	A	-0.3356	0.06650	4.57088×10^{-7}	0.03645	3301
	rs4702448	5	7,295,725	C	A	0.1275	0.02650	1.44544×10^{-6}	0.66583	3301
	rs497459	7	49,838,522	T	C	-0.1752	0.03680	1.94984×10^{-6}	0.86534	3301
	rs62493038	8	12,993,071	C	T	-0.3391	0.07250	2.88403×10^{-6}	0.03503	3301
	rs77893942	8	69,507,645	T	A	-0.376	0.07640	8.70964×10^{-7}	0.03128	3301
	rs72773561	10	9,677,794	T	C	-0.2529	0.05280	1.69824×10^{-6}	0.05703	3301
	rs35241999	12	11,184,504	A	G	0.4059	0.08690	2.95121×10^{-6}	0.02374	3301
	rs117133380	14	107,206,586	C	A	0.5002	0.10650	2.63027×10^{-6}	0.01556	3301
	rs56284011	17	43,079,322	G	C	-0.3136	0.06560	1.7378×10^{-6}	0.03943	3301
	rs35628511	1	24,667,702	C	T	-0.1253	0.02720	4.16869×10^{-6}	0.31160	3301
Cathepsin H	rs147991203	4	140,256,765	C	T	0.3758	0.07730	1.1749×10^{-6}	0.02671	3301
	rs508807	7	152,771,726	G	C	-0.1511	0.03200	2.39883×10^{-6}	0.81025	3301
	rs62474230	8	3,347,249	G	C	-0.2377	0.05060	2.69153×10^{-6}	0.06195	3301
	rs77977134	11	81,603,149	T	C	-0.2721	0.05830	3.01995×10^{-6}	0.04930	3301
	rs12911554	15	51,542,757	C	T	-0.1198	0.02510	1.8197×10^{-6}	0.55027	3301
	rs34843303	15	79,234,470	T	C	-1.1194	0.03440	1.0×10^{-200}	0.11403	3301
	rs62013235	15	79,246,166	G	A	0.402	0.04320	1.34896×10^{-20}	0.09100	3301
	rs60018174	16	5,452,751	C	T	0.1956	0.03950	7.24436×10^{-7}	0.11590	3301
	rs146037740	18	11,507,434	G	A	0.4736	0.09290	3.46737×10^{-7}	0.02292	3301
	rs74342103	19	36,003,934	A	T	0.3766	0.08120	3.46737×10^{-6}	0.02583	3301

Table S1. (Continued).

Exposure	SNP	chr. exposure	pos. exposure	other_allele. exposure	effect_allele. exposure	beta. exposure	se. exposure	pval. exposure	eaf. exposure	samplesize. exposure
Cathepsin O	rs114113108	1	75,257,391	G	C	−0.5922	0.11720	4.36516×10^{-7}	0.01290	3301
	rs1523319	3	2,292,279	C	G	−0.1292	0.02790	3.54813×10^{-6}	0.28541	3301
	rs13068566	3	102,862,667	A	G	0.1157	0.02470	2.88403×10^{-6}	0.46617	3301
	rs151179824	3	173,226,009	G	A	0.4449	0.09430	2.34423×10^{-6}	0.02158	3301
	rs116407656	4	68,099,087	T	C	0.4014	0.08560	2.75423×10^{-6}	0.02439	3301
	rs199544945	4	146,928,659	AT	A	0.1502	0.02740	4.36516×10^{-8}	0.66171	3301
	rs34635662	7	27,220,271	C	CT	0.2286	0.04950	3.89045×10^{-6}	0.07724	3301
	rs10817163	9	99,902,524	T	A	0.1983	0.03040	7.07946×10^{-11}	0.22045	3301
	rs146867532	10	43,225,400	AT	A	−0.3356	0.07080	2.0893×10^{-6}	0.96680	3301
	rs7898416	10	83,700,161	A	G	−0.2277	0.04890	3.23594×10^{-6}	0.07050	3301
	rs117714361	12	109,142,132	A	G	−0.3452	0.07560	4.89779×10^{-6}	0.02685	3301
	rs148608463	12	121,413,027	G	A	−0.1178	0.02570	4.57088×10^{-6}	0.35415	3301
	rs2302837	17	6,014,176	A	G	−0.2541	0.04980	3.31131×10^{-7}	0.92494	3301
	rs146963690	2	156,493,388	T	G	0.6246	0.13220	2.29087×10^{-6}	0.01010	3301
Cathepsin S	rs149159018	3	132,077,351	A	G	0.7034	0.13400	1.54882×10^{-7}	0.01105	3301
	rs17288007	4	159,878,046	A	G	−0.2456	0.05210	2.45471×10^{-6}	0.06381	3301
	rs181844705	5	75,333,560	A	G	0.4412	0.09050	1.09648×10^{-6}	0.02318	3301
	rs4297371	10	11,249,367	A	C	0.1453	0.03130	3.54813×10^{-6}	0.79306	3301
	rs78943701	10	73,736,674	G	A	−0.479	0.10250	2.95121×10^{-6}	0.01536	3301
	rs4076941	11	11,261,567	T	C	−0.1245	0.02620	2.13796×10^{-6}	0.36872	3301
	rs2439803	11	129,083,967	A	G	0.1763	0.03510	5.12861×10^{-7}	0.15304	3301
	rs10902420	12	132,150,183	A	G	−0.2097	0.04320	1.23027×10^{-6}	0.89909	3301
	rs7140599	14	39,942,467	T	C	−0.1219	0.02510	1.1749×10^{-6}	0.57698	3301
	rs1870736	15	88,624,621	C	G	0.1222	0.02490	9.33254×10^{-7}	0.42746	3301
	rs9932172	16	7,642,591	C	T	0.1915	0.04010	1.7378×10^{-6}	0.10769	3301
	rs4843804	16	88,156,187	G	A	−0.3124	0.06730	3.46737×10^{-6}	0.03360	3301

Table S1. (Continued).

Exposure	SNP	chr. exposure	pos. exposure	other_allele. exposure	effect_allele. exposure	beta. exposure	se. exposure	pval. exposure	eaf. exposure	samplesize. exposure
Cathepsin L2	rs6657328	1	107,433,954	G	C	-0.1291	0.02830	4.89779×10^{-6}	0.71840	3301
	rs41271951	1	150,737,220	A	G	-0.8605	0.04190	7.07946×10^{-94}	0.08349	3301
	rs13411643	2	60,351,132	T	C	0.1831	0.03640	5.01187×10^{-7}	0.13712	3301
	rs4581957	2	174,866,439	G	A	-0.1775	0.03650	1.14815×10^{-6}	0.13414	3301
	rs7614425	3	98,174,258	G	A	-0.2082	0.04360	1.8197×10^{-6}	0.09254	3301
	rs10516855	4	90,924,478	T	C	-0.1969	0.04210	2.95121×10^{-6}	0.09552	3301
	rs989576	4	127,182,592	C	T	0.1307	0.02780	2.5704×10^{-6}	0.29843	3301
	rs13150189	4	181,239,467	G	A	0.1556	0.03060	3.46737×10^{-7}	0.21113	3301
	rs116623438	5	102,689,283	T	C	-0.43	0.08760	9.12011×10^{-7}	0.02023	3301
	rs113108135	5	166,659,513	G	C	0.2349	0.04910	1.69824×10^{-6}	0.06933	3301
	rs13196989	6	239,373	C	T	-0.1758	0.03740	2.5704×10^{-6}	0.13099	3301
	rs13212873	6	143,059,208	T	C	0.5422	0.11700	3.54813×10^{-6}	0.01160	3301
	rs2470994	7	47,430,626	T	C	0.1304	0.02810	3.38844×10^{-6}	0.28088	3301
	rs529565	9	136,149,500	T	C	-0.1315	0.02660	7.76247×10^{-7}	0.31269	3301
	rs61870690	10	127,523,966	A	G	-0.3386	0.06840	7.24436×10^{-7}	0.04143	3301
	rs12804405	11	24,422,062	G	A	0.612	0.12900	2.0893×10^{-6}	0.01019	3301
	rs1060435	11	68,855,595	A	G	-0.1291	0.02510	2.75423×10^{-7}	0.39793	3301
	rs74804137	12	18,017,954	T	C	-0.5178	0.09870	1.58489×10^{-7}	0.01757	3301
	rs73099998	12	58,633,987	C	T	-0.146	0.03080	2.18776×10^{-6}	0.20811	3301
	rs77792819	12	94,386,245	A	G	0.3147	0.06610	1.94984×10^{-6}	0.04096	3301
	rs1022239	13	65,424,046	A	T	0.1157	0.02500	3.71535×10^{-6}	0.58887	3301
	rs4313886	18	74,370,742	T	C	0.1687	0.03650	3.89045×10^{-6}	0.13446	3301
	rs78767885	19	18,112,020	T	C	0.2238	0.04770	2.69153×10^{-6}	0.08725	3301
	rs118010753	21	18,833,920	T	C	0.5018	0.10810	3.46737×10^{-6}	0.01437	3301

Table S1. (Continued).

Exposure	SNP	chr. exposure	pos. exposure	other_allele. exposure	effect_allele. exposure	beta. exposure	se. exposure	pval. exposure	eaf. exposure	samplesize. exposure
Cathepsin Z	rs36128387	1	235,460,258	C	T	0.439	0.09140	1.54882×10^{-6}	0.02261	3301
	rs148201372	3	32,683,740	A	T	-0.5187	0.10630	1.04713×10^{-6}	0.01546	3301
	rs114675081	3	106,826,623	A	G	0.5153	0.10750	1.65959×10^{-6}	0.01467	3301
	rs1135945	4	516,586	G	A	0.1385	0.03010	4.16869×10^{-6}	0.20839	3301
	rs7656806	4	138,271,322	A	C	-0.1276	0.02450	1.86209×10^{-7}	0.51592	3301
	rs770140	5	19,430,825	A	G	-0.1241	0.02650	2.81838×10^{-6}	0.64195	3301
	rs298724	9	94,023,321	T	C	0.2482	0.05380	3.98107×10^{-6}	0.05507	3301
	rs116920068	10	54,555,095	G	A	-0.3498	0.07490	3.01995×10^{-6}	0.02890	3301
	rs10761760	10	65,179,152	A	C	0.1321	0.02580	3.0903×10^{-7}	0.44944	3301
	rs4761709	12	93,785,170	A	G	0.1218	0.02490	1.0×10^{-6}	0.40882	3301
	rs10745925	12	102,218,899	T	C	-0.3624	0.02660	2.29087×10^{-42}	0.29402	3301
	rs67845377	19	19,275,802	C	T	0.1675	0.03620	3.71535×10^{-6}	0.13855	3301
	rs148370779	20	57,602,212	C	T	-1.7632	0.11050	2.5704×10^{-57}	0.01316	3301

Table S2. The results of forward MR analysis between various cathepsins and digestive disorders.

exposure	outcome	nsnp	MR-Egger				Weighted median				Inverse variance weighted				MR-Egger intercept	MR-PRESS O global	MR-IVW			MR-Egger			
			p_value	OR	OR_LCI_95	OR_UCI_95	p_value	OR	OR_LCI_95	OR_UCI_95	p_value	OR	OR_LCI_95	OR_UCI_95	egger intercept	p_value	p_value	Q	Q_df	Q_pval	Q	Q_df	Q_pval
gastroesophageal reflux (GERD)	cathepsin B	19	0.526	0.979	0.917	1.045	0.305	0.980	0.942	1.019	0.413	0.988	0.962	1.016	0.003	0.746	0.682	13.929	17	0.672	14.037	18	0.727
	cathepsin E	9	0.320	1.033	0.973	1.096	0.531	1.015	0.969	1.064	0.554	1.011	0.976	1.047	-0.007	0.399	0.290	8.609	7	0.282	9.603	8	0.294
	cathepsin F	5	0.096	1.136	1.023	1.262	0.374	1.029	0.966	1.097	0.483	1.023	0.960	1.091	-0.027	0.116	0.158	2.839	3	0.417	7.645	4	0.106
	cathepsin G	7	0.813	1.151	0.380	3.486	0.283	1.271	0.821	1.968	0.252	1.382	0.795	2.405	0.060	0.717	0.069	16.415	5	0.006	16.899	6	0.010
	cathepsin H	4	0.513	1.173	0.788	1.746	0.024	1.209	1.025	1.425	0.140	1.197	0.943	1.521	0.017	0.897	0.579	6.774	2	0.034	6.846	3	0.077
	cathepsin L2	12	0.425	0.942	0.819	1.084	0.982	0.999	0.940	1.062	0.940	0.998	0.946	1.053	0.011	0.405	0.115	16.542	10	0.085	17.794	11	0.086
	cathepsin O	12	0.944	1.004	0.909	1.108	0.301	1.030	0.974	1.090	0.082	1.038	0.995	1.082	0.007	0.477	0.274	12.798	10	0.235	13.496	11	0.262
	cathepsin S	9	0.575	0.848	0.490	1.469	0.118	0.789	0.585	1.062	0.207	0.818	0.598	1.118	-0.018	0.874	0.202	13.721	7	0.056	13.775	8	0.088
	cathepsin Z	13	0.027	1.056	1.013	1.102	0.068	1.034	0.998	1.072	0.370	1.012	0.986	1.039	-0.013	0.026	0.618	3.088	11	0.990	9.665	12	0.645

Table S2. (Continued).

exposure	outcome	nsnp	MR-Egger				Weighted median				Inverse variance weighted				MR-Egger intercept	MR-PRESSO global		MR-IVW			MR-Egger		
			p_value	OR	OR_LCI_95	OR_UCI_95	p_value	OR	OR_LCI_95	OR_UCI_95	p_value	OR	OR_LCI_95	OR_UCI_95	egger intercept	p_value	p_value	Q	Q_df	Q_pval	Q	Q_df	Q_pval
Barrett's esophagus (BE)	cathepsin B	20	0.141	0.801	0.604	1.062	0.251	0.906	0.766	1.072	0.289	0.937	0.832	1.056	0.046	0.244	0.974	7.737	18	0.982	9.188	19	0.970
	cathepsin E	9	0.495	0.881	0.624	1.244	0.396	0.915	0.746	1.123	0.524	0.938	0.771	1.142	0.019	0.669	0.087	14.667	7	0.041	15.084	8	0.058
	cathepsin F	12	0.959	1.011	0.674	1.516	0.098	1.163	0.973	1.391	0.406	1.073	0.908	1.268	0.016	0.756	0.103	16.948	10	0.076	17.122	11	0.104
	cathepsin G	12	0.072	0.690	0.481	0.991	0.852	1.023	0.808	1.294	0.703	1.040	0.849	1.274	0.136	0.031	0.062	11.899	10	0.292	19.387	11	0.054
	cathepsin H	11	0.706	1.023	0.911	1.149	0.588	1.027	0.933	1.130	0.964	1.002	0.921	1.090	-0.013	0.618	0.723	4.861	9	0.846	5.128	10	0.882
	cathepsin L2	12	0.706	1.101	0.677	1.791	0.364	0.882	0.673	1.157	0.859	0.983	0.815	1.186	-0.022	0.631	0.533	9.729	10	0.465	9.974	11	0.533
	cathepsin O	12	0.509	1.146	0.776	1.691	0.659	0.949	0.750	1.200	0.160	0.886	0.749	1.049	-0.056	0.182	0.833	4.561	10	0.919	6.620	11	0.829
	cathepsin S	23	0.558	1.057	0.882	1.266	0.854	1.015	0.866	1.189	0.995	1.000	0.900	1.112	-0.015	0.474	0.741	17.503	21	0.680	18.035	22	0.704
	cathepsin Z	13	0.388	1.098	0.896	1.347	0.430	1.070	0.904	1.267	0.216	1.081	0.955	1.224	-0.005	0.851	0.351	13.190	11	0.281	13.235	12	0.352

Table S2. (Continued).

exposu re	outco me	nsn p	MR-Egger				Weighted median				Inverse variance weighted				MR- Egger interce pt		MR- PRESS O global		MR-IVW			MR-Egger		
			p_val ue	OR	OR_LCI 95	OR_UCI 95	p_val ue	OR	OR_LCI 95	OR_UCI 95	p_val ue	OR	OR_LCI 95	OR_UCI 95	egger interce pt	p_val ue	p_valu e	Q	Q_ df	Q_pv al	Q	Q_ df	Q_pv al	
gastric ulcer (GU)	cathepi sn B	20	0.339	0.93 6	0.821	1.068	0.379	0.96 3	0.885	1.048	0.121	0.95 7	0.905	1.012	0.006	0.723	0.613	17.47 2	18	0.491	17.60 1	19	0.549	
	cathepi sn E	9	0.591	1.03 2	0.924	1.154	0.492	1.03 3	0.942	1.133	0.051	1.06 9	1.000	1.142	0.010	0.474	0.617	5.313	7	0.622	5.886	8	0.660	
	cathepi sn F	12	0.867	0.98 4	0.815	1.187	0.145	1.06 8	0.978	1.166	0.524	1.02 6	0.949	1.108	0.011	0.641	0.135	16.70 5	10	0.081	17.09 2	11	0.105	
	cathepi sn G	12	0.420	0.93 6	0.802	1.092	0.991	1.00 1	0.902	1.110	0.811	0.99 1	0.923	1.065	0.019	0.429	0.759	6.797	10	0.744	7.476	11	0.759	
	cathepi sn H	11	0.754	0.99 1	0.939	1.046	0.525	0.98 6	0.945	1.029	0.618	0.99 0	0.952	1.030	-0.001	0.958	0.904	5.000	9	0.834	5.003	10	0.891	
	cathepi sn L2	11	0.061	1.32 6	1.023	1.718	0.147	1.10 1	0.967	1.255	0.734	1.02 1	0.906	1.150	-0.051	0.060	0.073	11.13 0	9	0.267	16.86 1	10	0.077	
	cathepi sn O	12	0.675	0.95 2	0.760	1.192	0.227	0.93 5	0.838	1.043	0.116	0.92 8	0.845	1.019	-0.005	0.813	0.187	15.34 2	10	0.120	15.43 2	11	0.164	
	cathepi sn S	23	0.186	1.06 6	0.973	1.169	0.458	1.02 8	0.956	1.104	0.405	1.02 3	0.969	1.080	-0.012	0.291	0.256	24.81 9	21	0.255	26.20 4	22	0.243	
	cathepi sn Z	13	0.576	1.03 3	0.925	1.153	0.700	1.01 5	0.941	1.095	0.458	1.02 6	0.959	1.097	-0.002	0.873	0.142	17.78 5	11	0.087	17.82 8	12	0.121	

Table S2. (Continued).

exposure	outcome	nsnp	MR-Egger				Weighted median				Inverse variance weighted				MR-Egger intercept	MR-PRESS O global		MR-IVW			MR-Egger		
			p_value	OR	OR_LCI 95	OR_UCI 95	p_value	OR	OR_LCI 95	OR_UCI 95	p_value	OR	OR_LCI 95	OR_UCI 95	egger intercept	p_value	p_value	Q	Q_df	Q_pval	Q	Q_df	Q_pval
duodenal ulcer (DU)	cathepsin B	20	0.790	0.977	0.823	1.159	0.216	0.938	0.848	1.038	0.070	0.935	0.870	1.005	-0.013	0.590	0.844	10.789	18	0.903	11.091	19	0.921
	cathepsin E	9	0.927	0.991	0.816	1.203	0.135	0.900	0.783	1.033	0.392	0.953	0.853	1.064	-0.012	0.638	0.145	12.557	7	0.084	12.990	8	0.112
	cathepsin F	12	0.547	1.062	0.879	1.284	0.805	1.014	0.910	1.130	0.666	1.018	0.939	1.104	-0.011	0.637	0.864	4.969	10	0.893	5.206	11	0.921
	cathepsin G	12	0.873	0.983	0.804	1.202	0.682	0.975	0.862	1.102	0.466	0.966	0.880	1.060	-0.006	0.850	0.921	5.772	10	0.834	5.809	11	0.886
	cathepsin H	11	0.404	1.032	0.962	1.107	0.758	1.009	0.953	1.068	0.926	1.002	0.953	1.055	-0.017	0.273	0.678	7.145	9	0.622	8.511	10	0.579
	cathepsin L2	5	0.527	1.326	0.610	2.883	0.963	1.006	0.791	1.279	0.537	1.078	0.849	1.368	-0.054	0.617	0.290	5.577	3	0.134	6.152	4	0.188
	cathepsin O	12	0.614	1.065	0.841	1.349	0.278	0.925	0.804	1.065	0.894	1.007	0.909	1.116	-0.012	0.619	0.646	8.485	10	0.582	8.749	11	0.645
	cathepsin S	23	0.440	1.046	0.935	1.170	0.272	1.051	0.961	1.150	0.083	1.059	0.993	1.129	0.003	0.794	0.539	21.512	21	0.428	21.583	22	0.485
	cathepsin Z	13	0.062	1.127	1.007	1.262	0.210	1.067	0.964	1.180	0.515	1.026	0.949	1.110	-0.030	0.060	0.262	9.933	11	0.536	14.335	12	0.280

Table S2. (Continued).

exposu re	outco me	nsn p	MR-Egger				Weighted median				Inverse variance weighted				MR- Egger interce pt		MR- PRESS O global		MR-IVW			MR-Egger		
			p_val ue	OR	OR_LCI 95	OR_UCI 95	p_val ue	OR	OR_LCI 95	OR_UCI 95	p_val ue	OR	OR_LCI 95	OR_UCI 95	egger interce pt	p_val ue	p_valu e	Q	Q_ df	Q_pv al	Q	Q_ df	Q_pv al	
acute gastritis (AG)	cathepi sn B	20	0.601	1.05 9	0.857	1.309	0.601	0.98 5	0.862	1.126	0.896	0.99 4	0.910	1.086	-0.019	0.525	0.478	18.82 5	18	0.403	19.26 4	19	0.440	
	cathepi sn E	9	0.468	1.07 1	0.900	1.274	0.301	1.07 4	0.938	1.231	0.212	1.06 9	0.963	1.187	0.000	0.983	0.977	2.202	7	0.948	2.203	8	0.974	
	cathepi sn F	12	0.980	0.99 7	0.792	1.255	0.694	1.02 6	0.903	1.166	0.106	1.08 4	0.983	1.197	0.022	0.446	0.700	4.450	10	0.925	5.078	11	0.927	
	cathepi sn G	12	0.944	0.98 9	0.737	1.328	0.646	1.04 0	0.879	1.231	0.955	1.00 4	0.882	1.143	0.005	0.915	0.750	14.60 2	10	0.147	14.62 0	11	0.201	
	cathepi sn H	11	0.612	0.97 6	0.893	1.067	0.865	0.99 4	0.926	1.066	0.750	1.01 1	0.947	1.079	0.021	0.301	0.638	9.854	9	0.362	11.17 3	10	0.344	
	cathepi sn L2	12	0.631	1.09 5	0.766	1.565	0.437	1.08 0	0.889	1.312	0.379	1.06 4	0.927	1.220	-0.006	0.867	0.228	8.496	10	0.581	8.525	11	0.666	
	cathepi sn O	12	0.138	0.78 8	0.591	1.052	0.784	0.97 6	0.819	1.162	0.198	0.92 0	0.810	1.045	0.034	0.272	0.276	10.20 0	10	0.423	11.57 9	11	0.396	
	cathepi sn S	23	0.791	1.01 9	0.890	1.166	0.359	1.05 2	0.944	1.173	0.324	1.04 0	0.962	1.124	0.006	0.713	0.420	21.59 9	21	0.423	21.74 2	22	0.475	
	cathepi sn Z	13	0.935	0.99 4	0.860	1.148	0.668	0.97 6	0.872	1.092	0.421	0.96 4	0.883	1.053	-0.009	0.609	0.177	12.00 8	11	0.363	12.31 1	12	0.421	

Table S2. (Continued).

exposu re	outco me	nsn p	MR-Egger				Weighted median				Inverse variance weighted				MR- Egger interce pt		MR- PRESS O global		MR-IVW			MR-Egger		
			p_val ue	OR	OR_LCI 95	OR_UCI 95	p_val ue	OR	OR_LCI 95	OR_UCI 95	p_val ue	OR	OR_LCI 95	OR_UCI 95	egger interce pt	p_val ue	p_valu e	Q	Q_ df	Q_pv al	Q	Q_ df	Q_pv al	
chronic gastritis (CG)	cathepi sn B	20	0.168	1.09 2	0.968	1.232	0.633	1.01 7	0.948	1.091	0.853	1.00 5	0.953	1.059	-0.025	0.151	0.140	12.45 1	12	0.410	12.73 0	13	0.469	
	cathepi sn E	12	0.401	1.04 1	0.953	1.139	0.410	1.02 8	0.963	1.098	0.551	1.01 6	0.963	1.072	-0.007	0.525	0.979	6.932	12	0.862	7.237	13	0.890	
	cathepi sn F	12	0.696	1.02 4	0.912	1.150	0.239	1.04 2	0.973	1.115	0.088	1.04 4	0.993	1.098	0.005	0.724	0.823	27.90 0	12	0.006	32.30 8	13	0.002	
	cathepi sn G	12	0.609	0.96 3	0.838	1.107	0.084	0.93 0	0.857	1.010	0.076	0.94 6	0.890	1.006	-0.006	0.778	0.348	13.78 1	12	0.315	14.00 1	13	0.374	
	cathepi sn H	11	0.848	0.99 6	0.954	1.040	0.643	1.00 8	0.974	1.043	0.318	1.01 6	0.985	1.048	0.012	0.216	0.786	8.674	12	0.730	8.750	13	0.792	
	cathepi sn L2	12	0.120	0.84 6	0.697	1.026	0.879	0.99 3	0.904	1.090	0.505	1.03 0	0.945	1.122	0.039	0.056	0.141	6.689	12	0.877	6.699	13	0.917	
	cathepi sn O	12	0.340	1.08 6	0.924	1.277	0.246	1.05 5	0.964	1.155	0.472	1.02 6	0.957	1.099	-0.012	0.458	0.254	15.26 1	12	0.227	15.30 6	13	0.289	
	cathepi sn S	23	0.479	1.02 5	0.958	1.097	0.610	1.01 5	0.959	1.073	0.702	1.00 8	0.969	1.049	-0.005	0.547	0.644	21.96 7	12	0.038	22.00 2	13	0.055	
	cathepi sn Z	13	0.043	1.08 4	1.012	1.161	0.036	1.06 3	1.004	1.125	0.024	1.05 2	1.007	1.099	-0.010	0.293	0.651	15.37 5	12	0.222	17.10 3	13	0.195	

Table S2. (Continued).

exposu re	outco me	nsn p	MR-Egger				Weighted median				Inverse variance weighted				MR- Egger interce pt		MR- PRESS O global		MR-IVW			MR-Egger		
			p_val ue	OR	OR_LCI 95	OR_UCI 95	p_val ue	OR	OR_LCI 95	OR_UCI 95	p_val ue	OR	OR_LCI 95	OR_UCI 95	egger interce pt	p_val ue	p_valu e	Q	Q_ df	Q_pv al	Q	Q_ df	Q_pv al	
irritable bowel syndro me (IBS)	cathepi sn B	18	0.062	1.17 1	1.004	1.366	0.607	1.02 2	0.940	1.112	0.706	1.01 3	0.948	1.081	-0.040	0.062	0.094	20.36 2	16	0.204	20.36 2	16	0.204	
	cathepi sn E	9	0.938	1.00 4	0.921	1.094	0.638	0.98 3	0.913	1.057	0.565	0.98 5	0.935	1.037	-0.006	0.611	0.609	5.196	7	0.636	5.479	8	0.705	
	cathepi sn F	12	0.786	1.02 1	0.884	1.179	0.158	1.05 1	0.981	1.125	0.062	1.05 8	0.997	1.124	0.010	0.597	0.150	16.29 0	10	0.092	16.77 6	11	0.115	
	cathepi sn G	12	0.389	0.93 7	0.814	1.079	0.071	0.93 0	0.859	1.006	0.419	0.97 4	0.915	1.038	0.013	0.557	0.284	13.80 6	10	0.182	14.31 6	11	0.216	
	cathepi sn H	11	0.668	0.98 9	0.943	1.038	0.395	0.98 6	0.954	1.019	0.395	0.98 6	0.954	1.019	-0.002	0.843	0.497	11.81 0	9	0.224	11.86 4	10	0.294	
	cathepi sn L2	12	0.426	0.92 2	0.761	1.117	0.562	1.02 8	0.937	1.127	0.739	0.98 8	0.919	1.062	0.014	0.463	0.381	11.79 9	10	0.299	12.48 7	11	0.328	
	cathepi sn O	12	0.167	0.89 9	0.781	1.034	0.971	0.99 8	0.919	1.085	0.839	0.99 4	0.935	1.056	0.022	0.151	0.499	7.920	10	0.637	10.34 0	11	0.500	
	cathepi sn S	23	0.131	1.05 4	0.987	1.125	0.284	1.03 1	0.975	1.090	0.693	1.00 8	0.970	1.048	-0.013	0.113	0.447	19.71 8	21	0.539	22.45 2	22	0.433	
	cathepi sn Z	13	0.294	1.03 9	0.971	1.111	0.433	1.02 3	0.967	1.082	0.276	1.02 4	0.981	1.069	-0.004	0.603	0.641	9.767	11	0.551	10.05 3	12	0.611	

Table S2. (Continued).

exposu re	outco me	nsn p	MR-Egger				Weighted median				Inverse variance weighted				MR- Egger interce pt	MR- PRESS O global		MR-IVW			MR-Egger		
			p_val ue	OR	OR_LCI 95	OR_UCI 95	p_val ue	OR	OR_LCI 95	OR_UCI 95	p_val ue	OR	OR_LCI 95	OR_UCI 95	egger interce pt	p_val ue	p_valu e	Q	Q_ df	Q_p val	Q	Q_ df	Q_p val
celiac disease (CD)	cathepi sn B	20	0.031	1.22 2	1.033	1.444	0.042	1.11 1	1.004	1.231	0.313	1.04 0	0.963	1.124	-0.048	0.052	0.155	19.25 3	18	0.376	23.86 9	19	0.201
	cathepi sn E	9	0.186	1.10 8	0.966	1.270	0.818	1.01 4	0.904	1.137	0.878	1.00 6	0.927	1.093	-0.029	0.129	0.484	5.111	7	0.646	8.067	8	0.427
	cathepi sn F	12	0.858	0.98 1	0.801	1.202	0.173	1.08 1	0.966	1.209	0.137	1.06 7	0.979	1.163	0.022	0.389	0.232	12.61 4	10	0.246	13.63 7	11	0.254
	cathepi sn G	12	0.517	0.93 6	0.773	1.134	0.333	0.94 0	0.829	1.066	0.164	0.93 9	0.860	1.026	0.001	0.974	0.654	9.159	10	0.517	9.160	11	0.607
	cathepi sn H	11	0.014	0.90 0	0.842	0.963	0.055	0.94 9	0.900	1.001	0.518	0.97 9	0.916	1.045	0.050	0.007	0.246	5.980	9	0.742	18.28 2	10	0.050
	cathepi sn L2	12	0.519	1.13 4	0.784	1.642	0.335	0.92 6	0.793	1.082	0.916	1.00 7	0.877	1.157	-0.023	0.512	0.087	17.15 4	10	0.071	17.94 9	11	0.083
	cathepi sn O	12	0.799	1.03 7	0.789	1.363	0.827	1.01 6	0.883	1.169	0.187	1.08 0	0.964	1.210	0.009	0.756	0.179	14.96 3	10	0.133	15.11 5	11	0.177
	cathepi sn S	23	0.335	0.95 0	0.858	1.052	0.003	0.88 1	0.809	0.958	0.080	0.94 8	0.892	1.006	-0.001	0.951	0.527	18.67 1	21	0.606	18.67 5	22	0.665
	cathepi sn Z	13	0.611	1.02 9	0.924	1.146	0.243	1.05 5	0.964	1.153	0.264	1.04 0	0.971	1.113	0.003	0.818	0.791	8.235	11	0.692	8.290	12	0.762

Table S2. (Continued).

exposure	outcome	nsnp	MR-Egger				Weighted median				Inverse variance weighted				MR-Egger intercept	MR-PRESSO global	MR-IVW			MR-Egger			
			p_value	OR	OR_LCI_95	OR_UCI_95	p_value	OR	OR_LCI_95	OR_UCI_95	p_value	OR	OR_LCI_95	OR_UCI_95	egger intercept	p_value	p_value	Q	Q_df	Q_pval	Q	Q_df	Q_pval
diverticulosis	cathepsin B	20	0.515	1.022	0.958	1.090	0.789	0.995	0.957	1.034	0.977	1.000	0.974	1.028	-0.006	0.481	0.404	19.975	18	0.334	20.550	19	0.362
	cathepsin E	9	0.161	0.955	0.902	1.012	0.471	0.984	0.942	1.028	0.585	0.990	0.954	1.027	0.011	0.173	0.234	8.612	7	0.282	11.438	8	0.178
	cathepsin F	10	0.150	0.943	0.878	1.014	0.713	0.991	0.947	1.038	0.580	0.990	0.957	1.025	0.012	0.170	0.691	4.570	8	0.802	6.846	9	0.653
	cathepsin G	12	0.453	0.963	0.877	1.058	0.987	1.000	0.950	1.052	0.770	1.007	0.964	1.051	0.015	0.326	0.069	17.089	10	0.072	18.915	11	0.063
	cathepsin H	11	0.650	1.006	0.980	1.033	0.449	1.007	0.988	1.027	0.410	1.008	0.990	1.026	0.001	0.881	0.677	9.625	9	0.382	9.650	10	0.472
	cathepsin L2	12	0.809	0.983	0.861	1.123	0.983	0.999	0.944	1.058	0.896	0.997	0.949	1.047	0.003	0.832	0.166	15.726	10	0.108	15.800	11	0.149
	cathepsin O	12	0.474	0.967	0.884	1.057	0.515	1.017	0.967	1.070	0.867	1.003	0.966	1.042	0.008	0.387	0.361	11.086	10	0.351	11.992	11	0.364
	cathepsin S	23	0.961	0.999	0.960	1.039	0.328	0.984	0.952	1.017	0.096	0.981	0.958	1.003	-0.005	0.267	0.764	16.289	21	0.753	17.587	22	0.730
	cathepsin Z	13	0.291	1.031	0.977	1.089	0.256	1.023	0.984	1.064	0.021	1.040	1.006	1.075	0.003	0.708	0.084	19.693	11	0.050	19.957	12	0.068

Table S2. (Continued).

exposu re	outco me	nsn p	MR-Egger				Weighted median				Inverse variance weighted				MR- Egger interce pt	MR- PRESS O global		MR-IVW			MR-Egger		
			p_val ue	OR	OR_LCI 95	OR_UCI 95	p_val ue	OR	OR_LCI 95	OR_UCI 95	p_val ue	OR	OR_LCI 95	OR_UCI 95	egger interce pt	p_val ue	p_valu e	Q	Q_ df	Q_p val	Q	Q_ df	Q_p val
Crohn's disease of small intestin e (CDSI)	cathepi sn B	20	0.279	1.13 3	0.910	1.412	0.386	0.94 1	0.820	1.080	0.075	0.91 9	0.837	1.009	-0.062	0.054	0.710	11.39 2	18	0.877	15.65 2	19	0.680
	cathepi sn E	9	0.839	0.98 0	0.814	1.180	0.963	0.99 6	0.856	1.159	0.572	1.03 3	0.924	1.154	0.016	0.514	0.696	5.311	7	0.622	5.784	8	0.671
	cathepi sn F	12	0.998	1.00 0	0.724	1.382	0.546	1.04 9	0.899	1.224	0.779	1.01 9	0.893	1.163	0.005	0.903	0.096	17.63 6	10	0.061	17.66 3	11	0.090
	cathepi sn G	12	0.044	1.35 3	1.046	1.750	0.213	1.10 9	0.942	1.306	0.549	1.04 0	0.916	1.180	-0.088	0.047	0.280	7.436	10	0.684	12.56 9	11	0.322
	cathepi sn H	11	0.163	1.07 3	0.980	1.174	0.119	1.05 8	0.986	1.136	0.142	1.05 0	0.984	1.121	-0.013	0.524	0.626	8.907	9	0.446	9.346	10	0.500
	cathepi sn L2	12	0.494	0.83 6	0.509	1.371	0.672	1.04 5	0.851	1.285	0.638	1.04 7	0.866	1.265	0.044	0.358	0.090	17.04 0	10	0.073	18.62 3	11	0.068
	cathepi sn O	12	0.773	0.95 5	0.705	1.294	0.571	1.05 3	0.881	1.257	0.527	1.04 3	0.915	1.189	0.019	0.542	0.681	7.809	10	0.647	8.208	11	0.695
	cathepi sn S	23	0.901	1.00 9	0.877	1.161	0.589	0.96 7	0.856	1.092	0.336	0.96 0	0.884	1.043	-0.014	0.403	0.531	20.79 6	21	0.471	21.52 4	22	0.489
	cathepi sn Z	13	0.166	0.89 6	0.774	1.036	0.585	0.96 6	0.854	1.093	0.475	0.96 7	0.882	1.060	0.024	0.210	0.807	5.413	11	0.910	7.186	12	0.845

Table S2. (Continued).

exposu re	outco me	nsn p	MR-Egger				Weighted median				Inverse variance weighted				MR- Egger interce pt	MR- PRESS O global	MR-IVW			MR-Egger			
			p_val ue	OR	OR_LCI 95	OR_UCI 95	p_val ue	OR	OR_LCI 95	OR_UCI 95	p_val ue	OR	OR_LCI 95	OR_UCI 95	egger interce pt	p_val ue	p_valu e	Q	Q_ df	Q_pv al	Q	Q_ df	Q_pv al
Crohn's disease of large intestin e (CDLI)	cathepi sn B	20	0.397	1.12 0	0.867	1.446	0.025	1.19 0	1.022	1.386	0.086	1.09 8	0.987	1.222	-0.006	0.869	0.485	18.48 8	18	0.424	18.51 6	19	0.488
	cathepi sn E	9	0.898	1.01 8	0.779	1.331	0.331	1.09 7	0.910	1.324	0.063	1.17 2	0.991	1.384	0.042	0.240	0.113	11.13 2	7	0.133	13.74 9	8	0.089
	cathepi sn F	10	0.841	1.03 5	0.751	1.426	0.520	1.06 1	0.885	1.273	0.704	1.02 7	0.897	1.175	-0.002	0.959	0.306	9.979	8	0.266	9.983	9	0.352
	cathepi sn G	12	0.500	1.11 5	0.823	1.510	0.422	1.08 3	0.892	1.315	0.540	1.04 3	0.911	1.195	-0.022	0.642	0.511	10.62 6	10	0.387	10.87 1	11	0.454
	cathepi sn H	11	0.958	0.99 7	0.899	1.106	0.550	0.97 5	0.897	1.060	0.415	0.96 9	0.899	1.045	-0.017	0.460	0.786	6.852	9	0.653	7.448	10	0.683
	cathepi sn L2	12	0.278	0.77 0	0.493	1.203	0.687	1.04 8	0.834	1.317	0.556	1.05 6	0.881	1.264	0.062	0.165	0.394	10.49 3	10	0.398	12.85 1	11	0.303
	cathepi sn O	12	0.377	0.80 8	0.513	1.271	0.774	0.96 9	0.784	1.199	0.504	0.93 8	0.779	1.131	0.032	0.491	0.120	15.68 4	10	0.109	16.48 7	11	0.124
	cathepi sn S	23	0.675	1.03 7	0.876	1.229	0.647	1.03 2	0.902	1.180	0.573	0.97 2	0.880	1.073	-0.018	0.362	0.360	23.30 2	21	0.328	24.26 8	22	0.333
	cathepi sn Z	13	0.055	0.83 3	0.705	0.984	0.173	0.90 4	0.782	1.045	0.145	0.92 5	0.832	1.027	0.033	0.143	0.703	6.461	11	0.841	8.947	12	0.707

Table S2. (Continued).

exposure	outcome	nsnp	MR-Egger				Weighted median				Inverse variance weighted				MR-Egger intercept	MR-PRESS O global		MR-IVW			MR-Egger		
			p_value	OR	OR_LCI_95	OR_UCI_95	p_value	OR	OR_LCI_95	OR_UCI_95	p_value	OR	OR_LCI_95	OR_UCI_95	egger intercept	p_value	p_value	Q	Q_df	Q_pval	Q	Q_df	Q_pval
ulcerative colitis (UC)	cathepsin B	20	0.076	1.153	0.994	1.337	0.943	1.003	0.918	1.097	0.389	0.973	0.914	1.036	-0.050	0.023	0.553	10.810	18	0.902	16.970	19	0.592
	cathepsin E	9	0.746	0.979	0.865	1.108	0.947	0.996	0.896	1.108	0.827	0.992	0.921	1.068	0.004	0.805	0.534	6.883	7	0.441	6.949	8	0.542
	cathepsin F	12	0.506	0.944	0.802	1.112	0.486	1.034	0.941	1.136	0.199	1.048	0.976	1.125	0.027	0.196	0.464	9.524	10	0.483	11.442	11	0.407
	cathepsin G	12	0.307	1.119	0.911	1.375	0.265	1.065	0.953	1.191	0.499	1.033	0.940	1.135	-0.027	0.407	0.233	14.233	10	0.163	15.299	11	0.169
	cathepsin H	11	0.981	1.001	0.942	1.064	0.364	0.978	0.933	1.026	0.142	0.968	0.926	1.011	-0.020	0.151	0.533	6.314	9	0.708	8.772	10	0.554
	cathepsin L2	12	0.445	0.897	0.686	1.173	0.530	1.046	0.910	1.202	0.989	0.999	0.903	1.106	0.021	0.412	0.366	11.003	10	0.357	11.810	11	0.378
	cathepsin O	12	0.631	0.950	0.775	1.164	0.958	0.997	0.886	1.121	0.381	0.961	0.880	1.050	0.003	0.900	0.827	6.536	10	0.768	6.553	11	0.834
	cathepsin S	21	0.512	1.037	0.933	1.153	0.733	1.014	0.937	1.097	0.862	0.994	0.934	1.059	-0.012	0.349	0.242	23.718	19	0.207	24.870	20	0.206
	cathepsin Z	13	0.333	0.945	0.847	1.054	0.339	0.960	0.884	1.043	0.888	1.005	0.936	1.080	0.019	0.183	0.218	13.588	11	0.257	16.088	12	0.187

Table S2. (Continued).

exposure	outcome	nsnp	MR-Egger				Weighted median				Inverse variance weighted				MR-Egger intercept		MR-PRESS O global	MR-IVW			MR-Egger		
			p_value	OR	OR_LCI_95	OR_UCI_95	p_value	OR	OR_LCI_95	OR_UCI_95	p_value	OR	OR_LCI_95	OR_UCI_95	egger intercept	p_value	p_value	Q	Q_df	Q_pval	Q	Q_df	Q_pval
non-alcoholic fatty liver disease (NAFLD)	cathepsin B	20	0.123	0.832	0.665	1.040	0.835	1.014	0.888	1.159	0.965	1.002	0.907	1.108	0.055	0.088	0.119	22.886	18	0.195	27.032	19	0.104
	cathepsin E	9	0.983	1.002	0.847	1.185	0.617	0.965	0.838	1.110	0.802	0.987	0.893	1.092	-0.004	0.836	0.574	6.772	7	0.453	6.818	8	0.556
	cathepsin F	10	0.590	1.085	0.815	1.445	0.439	1.055	0.922	1.207	0.944	0.996	0.899	1.105	-0.026	0.544	0.412	8.965	8	0.345	9.414	9	0.400
	cathepsin G	12	0.986	1.002	0.794	1.265	0.282	0.920	0.789	1.071	0.047	0.897	0.806	0.999	-0.037	0.318	0.890	5.361	10	0.866	6.468	11	0.840
	cathepsin H	11	0.429	0.963	0.882	1.052	0.924	1.003	0.942	1.068	0.755	1.011	0.944	1.082	0.029	0.156	0.388	10.578	9	0.306	13.388	10	0.203
	cathepsin L2	12	0.373	1.187	0.829	1.699	0.054	1.202	0.997	1.450	0.041	1.147	1.006	1.308	-0.007	0.845	0.388	10.974	10	0.360	11.018	11	0.442
	cathepsin O	12	0.515	0.910	0.692	1.197	0.491	0.947	0.813	1.105	0.445	0.955	0.848	1.075	0.010	0.711	0.958	4.449	10	0.925	4.594	11	0.949
	cathepsin S	23	0.362	0.929	0.797	1.084	0.182	0.929	0.833	1.035	0.262	0.951	0.870	1.039	0.006	0.726	0.127	30.774	21	0.077	30.959	22	0.097
	cathepsin Z	12	0.461	0.938	0.795	1.106	0.845	1.012	0.898	1.141	0.527	0.968	0.874	1.072	0.010	0.636	0.158	15.749	10	0.107	16.125	11	0.137

Table S2. (Continued).

exposure	outcome	nsnp	MR-Egger				Weighted median				Inverse variance weighted				MR-Egger intercept	MR-PRESSO global		MR-IVW			MR-Egger		
			p_value	OR	OR_LCI_95	OR_UCI_95	p_value	OR	OR_LCI_95	OR_UCI_95	p_value	OR	OR_LCI_95	OR_UCI_95	egger intercept	p_value	p_value	Q	Q_df	Q_pval	Q	Q_df	Q_pval
Nonalcoholic Steatohepatitis (NASH)	cathepsin B	20	0.480	0.762	0.365	1.593	0.617	0.884	0.545	1.434	0.609	0.922	0.675	1.259	0.056	0.584	0.435	15.680	18	0.615	15.991	19	0.658
	cathepsin E	9	0.410	1.432	0.641	3.199	0.646	1.117	0.696	1.794	0.875	0.961	0.585	1.578	-0.119	0.263	0.113	11.872	7	0.105	14.382	8	0.072
	cathepsin F	12	0.966	1.023	0.371	2.820	0.439	1.215	0.743	1.987	0.362	1.212	0.801	1.834	0.044	0.724	0.183	15.400	10	0.118	15.603	11	0.157
	cathepsin G	12	0.031	0.331	0.140	0.786	0.009	0.479	0.275	0.835	0.083	0.703	0.472	1.047	0.249	0.083	0.408	6.735	10	0.750	10.440	11	0.491
	cathepsin H	11	0.119	1.306	0.964	1.769	0.054	1.271	0.996	1.623	0.077	1.218	0.979	1.517	-0.042	0.534	0.847	4.954	9	0.838	5.373	10	0.865
	cathepsin L2	12	0.338	0.522	0.147	1.851	0.347	0.733	0.384	1.400	0.707	0.911	0.560	1.481	0.109	0.373	0.581	8.646	10	0.566	9.517	11	0.574
	cathepsin O	12	0.697	0.814	0.298	2.226	0.314	0.735	0.404	1.337	0.619	0.895	0.578	1.386	0.021	0.842	0.695	7.634	10	0.665	7.676	11	0.742
	cathepsin S	22	0.528	0.822	0.453	1.493	0.918	1.022	0.681	1.532	0.473	0.882	0.627	1.242	0.020	0.778	0.086	31.939	20	0.044	32.070	21	0.058
	cathepsin Z	13	0.889	1.038	0.618	1.744	0.491	1.160	0.761	1.766	0.868	1.027	0.752	1.401	-0.004	0.957	0.435	12.128	11	0.354	12.131	12	0.435

Table S2. (Continued).

exposu re	outco me	nsn p	MR-Egger				Weighted median				Inverse variance weighted				MR- Egger interce pt	MR- PRESS O global	MR-IVW			MR-Egger			
			p_val ue	OR	OR_LCI 95	OR_UCI 95	p_val ue	OR	OR_LCI 95	OR_UCI 95	p_val ue	OR	OR_LCI 95	OR_UCI 95	egger interce pt	p_val ue	p_valu e	Q	Q_ df	Q_pv al	Q	Q_ df	Q_pv al
Alcohol ic liver disease (ALD)	cathepi sn B	20	0.025	0.78 9	0.653	0.955	0.152	0.91 5	0.810	1.033	0.115	0.93 3	0.857	1.017	0.049	0.073	0.345	17.97 8	18	0.457	21.61 8	19	0.304
	cathepi sn E	9	0.400	1.07 6	0.917	1.261	0.559	1.03 9	0.914	1.181	0.590	1.02 7	0.933	1.130	-0.014	0.497	0.587	5.759	7	0.568	6.273	8	0.617
	cathepi sn F	12	0.650	0.95 1	0.770	1.175	0.719	1.02 2	0.907	1.151	0.691	0.98 2	0.898	1.074	0.008	0.747	0.520	10.21 4	10	0.422	10.32 6	11	0.501
	cathepi sn G	12	0.866	0.98 1	0.785	1.224	0.243	1.08 8	0.945	1.252	0.517	1.03 5	0.934	1.146	0.018	0.606	0.770	7.494	10	0.678	7.778	11	0.733
	cathepi sn H	11	0.818	0.99 1	0.917	1.071	0.492	0.97 8	0.919	1.041	0.333	0.97 3	0.920	1.029	-0.011	0.520	0.844	6.102	9	0.730	6.549	10	0.767
	cathepi sn L2	12	0.165	1.31 8	0.918	1.890	0.211	0.88 8	0.737	1.070	0.985	0.99 9	0.861	1.158	-0.054	0.134	0.146	12.19 6	10	0.272	15.43 1	11	0.164
	cathepi sn O	11	0.771	0.94 7	0.662	1.354	0.319	0.91 3	0.764	1.091	0.416	0.93 8	0.803	1.095	-0.002	0.956	0.083	17.27 8	9	0.045	17.28 5	10	0.068
	cathepi sn S	23	0.618	0.96 9	0.858	1.094	0.696	0.98 0	0.883	1.086	0.949	0.99 8	0.929	1.071	0.008	0.569	0.994	8.168	21	0.994	8.504	22	0.996
	cathepi sn Z	13	0.563	1.03 9	0.916	1.179	0.949	0.99 7	0.900	1.103	0.593	1.02 2	0.944	1.106	-0.005	0.744	0.809	8.045	11	0.709	8.157	12	0.773

Table S2. (Continued).

exposu re	outco me	nsn p	MR-Egger				Weighted median				Inverse variance weighted				MR- Egger interce pt	MR- PRESS O global		MR-IVW			MR-Egeer		
			p_val ue	OR	OR_LCI 95	OR_UCI 95	p_val ue	OR	OR_LCI 95	OR_UCI 95	p_val ue	OR	OR_LCI 95	OR_UCI 95	egger interce pt	p_val ue	p_valu e	Q	Q_ df	Q_pv al	Q	Q_ df	Q_pv al
liver cirrhosi s	cathepi sn B	20	0.212	0.82 9	0.624	1.102	0.176	1.13 6	0.944	1.366	0.073	1.13 0	0.988	1.292	0.091	0.030	0.250	17.95 9	18	0.458	23.52 0	19	0.215
	cathepi sn E	9	0.626	0.94 0	0.739	1.194	0.436	0.92 6	0.762	1.124	0.180	0.90 6	0.785	1.046	-0.011	0.724	0.629	6.644	7	0.467	6.779	8	0.561
	cathepi sn F	12	0.206	0.78 4	0.551	1.115	0.610	1.04 8	0.874	1.257	0.643	1.04 0	0.882	1.226	0.074	0.113	0.171	12.69 8	10	0.241	16.53 2	11	0.122
	cathepi sn G	12	0.331	1.18 9	0.853	1.657	0.609	1.05 5	0.859	1.297	0.617	1.04 0	0.892	1.212	-0.045	0.394	0.883	5.623	10	0.846	6.418	11	0.844
	cathepi sn H	11	0.694	0.97 6	0.869	1.097	0.658	0.98 0	0.896	1.072	0.680	0.98 2	0.903	1.069	0.004	0.879	0.741	8.545	9	0.480	8.570	10	0.573
	cathepi sn L2	12	0.644	1.12 6	0.690	1.839	0.128	1.22 0	0.944	1.577	0.038	1.22 1	1.011	1.473	0.016	0.735	0.674	8.529	10	0.577	8.650	11	0.654
	cathepi sn O	12	0.895	0.97 3	0.658	1.439	0.844	0.97 7	0.775	1.231	0.525	0.94 7	0.799	1.121	-0.006	0.880	0.807	7.014	10	0.724	7.038	11	0.796
	cathepi sn S	23	0.082	0.82 8	0.677	1.014	0.032	0.84 3	0.720	0.985	0.151	0.91 6	0.813	1.032	0.028	0.241	0.212	25.70 8	21	0.218	27.49 0	22	0.193
	cathepi sn Z	12	0.336	1.13 4	0.888	1.448	0.625	1.04 3	0.882	1.233	0.114	1.12 8	0.971	1.309	-0.002	0.953	0.167	16.74 4	10	0.080	16.75 0	11	0.115

Table S2. (Continued).

MR-Egger	Weighted median	Inverse variance weighted	MR-Egger				Weighted median				Inverse variance weighted				MR-Egger intercept	MR-PRESS O global	MR-IVW			MR-Egger			
			p_value	OR	OR_LCI 95	OR_UCI 95	p_value	OR	OR_LCI 95	OR_UCI 95	p_value	OR	OR_LCI 95	OR_UCI 95			egger intercept	p_value	p_value	Q	Q_df	Q_pval	Q
Cholangitis	cathepsin B	20	0.982	1.003	0.790	1.273	0.861	1.013	0.873	1.177	0.331	1.051	0.950	1.163	0.014	0.672	0.374	17.275	18	0.504	17.460	19	0.559
	cathepsin E	9	0.628	1.054	0.860	1.292	0.131	1.128	0.965	1.320	0.135	1.097	0.972	1.240	0.012	0.642	0.595	5.476	7	0.602	5.712	8	0.679
	cathepsin F	12	0.452	0.877	0.632	1.218	0.754	0.975	0.834	1.141	0.148	0.905	0.791	1.036	0.008	0.839	0.513	15.667	10	0.110	15.735	11	0.151
	cathepsin G	12	0.888	0.979	0.732	1.309	0.656	1.042	0.868	1.252	0.618	1.034	0.908	1.177	0.018	0.688	0.752	10.691	10	0.382	10.874	11	0.454
	cathepsin H	11	0.516	1.042	0.925	1.172	0.594	1.021	0.945	1.104	0.978	1.001	0.920	1.090	-0.024	0.367	0.823	13.089	9	0.159	14.400	10	0.156
	cathepsin L2	12	0.939	0.984	0.651	1.487	0.801	0.973	0.787	1.203	0.508	0.948	0.809	1.111	-0.007	0.853	0.141	8.739	10	0.557	8.776	11	0.643
	cathepsin O	12	0.854	0.969	0.697	1.346	0.503	0.939	0.782	1.128	0.881	1.011	0.876	1.166	0.009	0.784	0.626	7.948	10	0.634	8.027	11	0.711
	cathepsin S	23	0.744	0.971	0.813	1.159	0.581	1.040	0.906	1.193	0.916	0.995	0.898	1.101	0.007	0.742	0.997	27.926	21	0.142	28.074	22	0.173
	cathepsin Z	13	0.598	0.957	0.817	1.121	0.950	0.996	0.871	1.138	0.957	1.003	0.907	1.108	0.015	0.472	0.809	5.788	11	0.887	6.344	12	0.898

Table S2. (Continued).

MR-Egger	Weighted median	Inverse variance weighted	MR-Egger				Weighted median				Inverse variance weighted				MR-Egger intercept		MR-PRESO global	MR-IVW			MR-Egger		
			p_value	OR	OR_LCI_95	OR_UCI_95	p_value	OR	OR_LCI_95	OR_UCI_95	p_value	OR	OR_LCI_95	OR_UCI_95	egger intercept	p_value		p_value	Q	Q_df	Q_pval	Q	Q_df
Cholecystitis	cathepsin B	20	0.015	1.230	1.057	1.431	0.051	1.102	1.000	1.215	0.029	1.074	1.007	1.145	-0.040	0.069	0.533	14.474	18	0.698	18.205	19	0.509
	cathepsin E	9	0.268	0.924	0.813	1.051	0.202	0.934	0.842	1.037	0.233	0.954	0.883	1.031	0.010	0.562	0.773	4.769	7	0.688	5.139	8	0.743
	cathepsin F	12	0.420	1.087	0.895	1.321	0.215	0.936	0.843	1.039	0.454	0.968	0.888	1.055	-0.031	0.224	0.169	13.495	10	0.197	15.766	11	0.150
	cathepsin G	12	0.840	0.978	0.797	1.202	0.307	0.937	0.827	1.062	0.232	0.946	0.864	1.036	-0.011	0.724	0.334	13.285	10	0.208	13.460	11	0.264
	cathepsin H	11	0.455	1.029	0.958	1.104	0.530	1.016	0.967	1.067	0.745	1.008	0.959	1.060	-0.012	0.446	0.437	11.615	9	0.236	12.434	10	0.257
	cathepsin L2	12	0.856	1.032	0.743	1.433	0.376	1.068	0.923	1.236	0.270	1.070	0.949	1.208	0.007	0.818	0.171	15.768	10	0.106	15.856	11	0.147
	cathepsin O	12	0.866	1.019	0.825	1.258	0.666	1.027	0.910	1.159	0.867	1.008	0.920	1.103	-0.002	0.913	0.548	10.137	10	0.429	10.150	11	0.517
	cathepsin S	23	0.371	1.047	0.949	1.154	0.181	1.061	0.973	1.156	0.618	1.015	0.958	1.074	-0.009	0.451	0.440	20.888	21	0.466	21.477	22	0.491
	cathepsin Z	13	0.656	1.027	0.916	1.152	0.862	1.008	0.925	1.098	0.830	1.008	0.939	1.081	-0.006	0.681	0.334	14.457	11	0.209	14.691	12	0.259

Table S2. (Continued).

MR-Egger	Weighted median	Inverse variance weighted	MR-Egger				Weighted median				Inverse variance weighted				MR-Egger intercept	MR-PRESO global	MR-IVW			MR-Egger			
			p_value	OR	OR_LCI_95	OR_UCI_95	p_value	OR	OR_LCI_95	OR_UCI_95	p_value	OR	OR_LCI_95	OR_UCI_95			egger intercept	p_value	p_value	Q	Q_df	Q_pval	Q
Cholelithiasis	cathepsin B	19	0.046	1.077	1.007	1.153	0.005	1.054	1.016	1.093	0.002	1.047	1.017	1.078	-0.009	0.373	0.077	25.194	17	0.090	26.432	18	0.090
	cathepsin E	9	0.911	1.003	0.956	1.052	0.950	1.001	0.963	1.041	0.485	0.990	0.962	1.018	-0.004	0.526	0.612	5.762	7	0.568	6.208	8	0.624
	cathepsin F	11	0.899	0.994	0.911	1.085	0.214	0.975	0.938	1.014	0.116	0.971	0.936	1.007	-0.007	0.570	0.075	16.836	9	0.051	17.485	10	0.064
	cathepsin G	12	0.148	1.054	0.987	1.126	0.311	1.023	0.979	1.068	0.219	1.019	0.989	1.051	-0.011	0.286	0.744	6.698	10	0.754	7.967	11	0.716
	cathepsin H	11	0.245	1.015	0.992	1.038	0.278	1.010	0.992	1.028	0.146	1.012	0.996	1.029	-0.001	0.789	0.839	5.603	9	0.779	5.679	10	0.841
	cathepsin L2	11	0.269	0.939	0.847	1.042	0.971	0.999	0.945	1.057	0.965	0.999	0.961	1.039	0.013	0.242	0.516	7.395	9	0.596	8.963	10	0.536
	cathepsin O	9	0.402	1.046	0.947	1.156	0.368	1.023	0.973	1.075	0.276	1.022	0.983	1.063	-0.005	0.628	0.422	8.361	7	0.302	8.666	8	0.371
	cathepsin S	23	0.061	1.040	1.000	1.082	0.027	1.036	1.004	1.070	0.360	1.011	0.987	1.036	-0.008	0.095	0.151	24.547	21	0.267	28.130	22	0.171
	cathepsin Z	12	0.908	0.998	0.961	1.036	0.494	1.011	0.980	1.043	0.324	1.012	0.988	1.037	0.005	0.353	0.930	3.693	10	0.960	4.643	11	0.947

Table S2. (Continued).

MR-Egger	Weighted median	Inverse variance weighted	MR-Egger				Weighted median				Inverse variance weighted				MR-Egger intercept	MR-PRESS O global	MR-IVW			MR-Egger			
			p_value	OR	OR_LCI 95	OR_UCI 95	p_value	OR	OR_LCI 95	OR_UCI 95	p_value	OR	OR_LCI 95	OR_UCI 95			egger intercept	p_value	p_value	Q	Q_df	Q_pval	Q
acute pancreatitis (AP)	cathepsin B	20	0.639	0.969	0.851	1.103	0.249	1.045	0.969	1.127	0.419	1.023	0.968	1.080	0.016	0.379	0.415	18.955	18	0.395	19.811	19	0.406
	cathepsin E	9	0.645	0.974	0.876	1.084	0.406	1.036	0.953	1.125	0.336	1.032	0.968	1.100	0.017	0.228	0.735	3.515	7	0.834	5.263	8	0.729
	cathepsin F	11	0.263	1.112	0.934	1.322	0.348	1.045	0.953	1.146	0.128	1.059	0.984	1.139	-0.014	0.555	0.196	13.196	9	0.154	13.746	10	0.185
	cathepsin G	12	0.920	0.990	0.812	1.206	0.285	0.948	0.860	1.045	0.868	1.007	0.923	1.099	0.006	0.846	0.103	17.877	10	0.057	17.947	11	0.083
	cathepsin H	11	0.876	1.009	0.969	1.050	0.677	1.009	0.969	1.050	0.623	1.009	0.972	1.048	0.008	0.479	0.608	9.293	9	0.411	9.856	10	0.453
	cathepsin L2	12	0.622	0.945	0.759	1.176	0.950	1.003	0.902	1.117	0.947	1.003	0.922	1.090	0.012	0.576	0.894	5.746	10	0.836	6.080	11	0.868
	cathepsin O	12	0.589	0.951	0.799	1.133	0.715	1.020	0.919	1.131	0.874	0.994	0.922	1.072	0.009	0.599	0.658	8.116	10	0.617	8.411	11	0.676
	cathepsin S	23	0.961	1.002	0.924	1.087	0.224	0.958	0.894	1.027	0.149	0.966	0.921	1.013	-0.010	0.282	0.574	19.582	21	0.548	20.799	22	0.533
	cathepsin Z	13	0.273	1.051	0.966	1.143	0.825	1.009	0.933	1.091	0.418	1.022	0.969	1.078	-0.009	0.425	0.561	8.527	11	0.665	9.212	12	0.685

Table S2. (Continued).

MR-Egger	Weighted median	Inverse variance weighted	MR-Egger				Weighted median				Inverse variance weighted				MR-Egger intercept	MR-PRESS O global	MR-IVW			MR-Egger			
			p_value	OR	OR_LCI 95	OR_UCI 95	p_value	OR	OR_LCI 95	OR_UCI 95	p_value	OR	OR_LCI 95	OR_UCI 95			egger intercept	p_value	p_value	Q	Q_df	Q_pval	Q
chronic pancreatitis (CP)	cathepsin B	20	0.217	1.128	0.938	1.357	0.006	1.165	1.046	1.297	0.238	1.048	0.970	1.133	-0.022	0.398	0.156	21.719	18	0.245	22.624	19	0.254
	cathepsin E	9	0.263	0.907	0.776	1.061	0.981	0.999	0.887	1.124	0.772	1.016	0.914	1.129	0.034	0.121	0.170	8.566	7	0.285	12.381	8	0.135
	cathepsin F	12	0.516	1.088	0.850	1.393	0.377	1.056	0.936	1.191	0.894	1.007	0.908	1.117	-0.020	0.510	0.086	17.580	10	0.062	18.401	11	0.073
	cathepsin G	12	0.500	0.929	0.756	1.141	0.449	0.951	0.835	1.083	0.582	0.975	0.889	1.068	0.016	0.619	0.326	10.922	10	0.364	11.208	11	0.426
	cathepsin H	11	0.773	0.990	0.923	1.060	0.502	0.981	0.928	1.037	0.503	0.983	0.935	1.033	-0.004	0.793	0.933	4.783	9	0.853	4.856	10	0.901
	cathepsin L2	12	0.734	0.944	0.683	1.305	0.991	1.001	0.862	1.162	0.485	0.959	0.852	1.079	0.003	0.921	0.362	12.293	10	0.266	12.305	11	0.341
	cathepsin O	12	0.600	1.066	0.845	1.345	0.590	1.037	0.908	1.185	0.152	1.076	0.973	1.190	0.002	0.933	0.874	6.323	10	0.787	6.331	11	0.850
	cathepsin S	23	0.363	0.942	0.831	1.068	0.379	0.959	0.875	1.052	0.320	0.964	0.896	1.036	0.006	0.664	0.182	28.697	21	0.121	28.962	22	0.146
	cathepsin Z	13	0.348	1.070	0.935	1.224	0.616	1.025	0.930	1.130	0.731	0.984	0.900	1.077	-0.026	0.148	0.115	15.824	11	0.148	19.300	12	0.082

Table S2. (Continued).

MR-Egger	Weighted median	Inverse variance weighted	MR-Egger				Weighted median				Inverse variance weighted				MR-Egger intercept	MR-PRESO global	MR-IVW			MR-Egger			
			p_value	OR	OR_LCI_95	OR_UCI_95	p_value	OR	OR_LCI_95	OR_UCI_95	p_value	OR	OR_LCI_95	OR_UCI_95			egger intercept	p_value	p_value	Q	Q_df	Q_pval	Q
acute appendicitis (AA)	cathepsin B	20	0.521	1.025	0.951	1.105	0.014	1.048	1.010	1.088	0.226	1.019	0.988	1.051	-0.002	0.867	0.092	27.633	18	0.068	27.677	19	0.090
	cathepsin E	9	0.441	1.028	0.962	1.099	0.540	1.014	0.970	1.060	0.425	1.016	0.978	1.055	-0.004	0.665	0.184	11.996	7	0.101	12.345	8	0.136
	cathepsin F	12	0.819	1.008	0.943	1.078	0.515	1.012	0.976	1.050	0.364	1.013	0.985	1.043	0.001	0.868	0.961	3.892	10	0.952	3.921	11	0.972
	cathepsin G	12	0.823	1.010	0.929	1.097	0.144	1.036	0.988	1.086	0.399	1.016	0.979	1.054	0.002	0.876	0.274	13.766	10	0.184	13.802	11	0.244
	cathepsin H	11	0.903	0.998	0.974	1.024	0.557	1.006	0.987	1.025	0.557	1.006	0.987	1.025	0.002	0.648	0.766	6.683	9	0.670	6.906	10	0.734
	cathepsin L2	12	0.396	0.954	0.859	1.059	0.644	1.013	0.958	1.071	0.353	1.019	0.979	1.061	0.013	0.208	0.469	9.345	10	0.500	11.162	11	0.430
	cathepsin O	12	0.787	0.988	0.909	1.074	0.257	1.028	0.980	1.079	0.163	1.026	0.990	1.064	0.008	0.351	0.851	5.329	10	0.868	6.285	11	0.854
	cathepsin S	23	0.830	1.005	0.962	1.050	0.706	1.006	0.974	1.039	0.478	1.009	0.984	1.035	0.001	0.817	0.263	26.818	21	0.177	26.888	22	0.216
	cathepsin Z	12	0.287	1.030	0.978	1.084	0.568	1.010	0.976	1.045	0.922	1.002	0.968	1.036	-0.009	0.199	0.107	15.989	10	0.100	19.021	11	0.061

Table S2. (Continued).

MR-Egger	Weighted median	Inverse variance weighted	MR-Egger				Weighted median				Inverse variance weighted				MR-Egger intercept	MR-PRESO global		MR-IVW			MR-Egger		
			p_value	OR	OR_LCI_95	OR_UCI_95	p_value	OR	OR_LCI_95	OR_UCI_95	p_value	OR	OR_LCI_95	OR_UCI_95		p_value	p_value	Q	Q_df	Q_pval	Q	Q_df	Q_pval
other appendicitis (OA)	cathepsin B	20	0.301	1.112	0.915	1.351	0.324	1.058	0.946	1.183	0.364	1.039	0.957	1.129	-0.020	0.463	0.676	14.576	18	0.691	15.138	19	0.714
	cathepsin E	9	0.695	0.957	0.773	1.183	0.465	0.948	0.821	1.094	0.465	0.948	0.821	1.094	-0.006	0.832	0.215	11.592	7	0.115	11.672	8	0.166
	cathepsin F	12	0.906	0.987	0.794	1.226	0.733	1.022	0.901	1.160	0.990	0.999	0.911	1.097	0.003	0.901	0.714	6.840	10	0.740	6.857	11	0.811
	cathepsin G	12	0.836	1.026	0.812	1.295	0.867	1.013	0.873	1.174	0.853	1.010	0.909	1.123	-0.005	0.888	0.528	10.354	10	0.410	10.376	11	0.497
	cathepsin H	11	0.424	1.035	0.955	1.122	0.200	1.042	0.979	1.109	0.183	1.040	0.982	1.103	0.003	0.861	0.820	7.062	9	0.631	7.095	10	0.716
	cathepsin L2	12	0.291	0.825	0.589	1.157	0.637	0.959	0.807	1.140	0.663	0.972	0.853	1.106	0.032	0.329	0.752	6.966	10	0.729	8.020	11	0.711
	cathepsin O	12	0.302	1.185	0.873	1.609	0.539	1.054	0.891	1.246	0.722	1.024	0.897	1.170	-0.032	0.325	0.219	12.855	10	0.232	14.231	11	0.220
	cathepsin S	23	0.432	1.053	0.928	1.193	0.394	1.045	0.944	1.157	0.887	1.005	0.934	1.082	-0.013	0.386	0.753	16.638	21	0.733	17.423	22	0.740
	cathepsin Z	13	0.178	0.909	0.798	1.035	0.260	0.936	0.834	1.050	0.260	0.936	0.834	1.050	0.019	0.259	0.498	9.481	11	0.578	10.898	12	0.538

Table S3. The results of reverse MR analysis between various cathepsins and digestive disorders.

exposure	outcome	nsnp	MR-Egger				Weighted median				Inverse variance weighted				MR-Egger intercept		MR-PRESSO global		MR-IVW			MR-Egeer		
			p_value	OR	OR_LC I95	OR_UC I95	p_value	OR	OR_LC I95	OR_UC I95	p_value	OR	OR_LC I95	OR_UC I95	egger intercept	p_value	p_value	Q	Q_df	Q_p_val	Q	Q_df	Q_p_val	
gastroesophageal reflux (GERD)	cathepsin B	37	0.089	1.080	0.991	1.176	0.156	1.052	0.981	1.128	0.657	1.010	0.965	1.058	−0.018	0.082	0.683	28.320	35	0.781	31.531	36	0.681	
	cathepsin E	37	0.140	1.070	0.980	1.167	0.061	1.074	0.997	1.156	0.050	1.048	1.000	1.098	−0.006	0.584	0.448	36.453	35	0.401	36.771	36	0.433	
	cathepsin F	37	0.712	0.984	0.902	1.072	0.948	0.998	0.928	1.072	0.606	0.988	0.944	1.035	0.001	0.909	0.558	35.385	35	0.450	35.398	36	0.497	
	cathepsin G	37	0.138	1.075	0.979	1.180	0.496	1.028	0.950	1.111	0.121	1.040	0.990	1.093	−0.009	0.418	0.235	41.490	35	0.209	42.285	36	0.218	
	cathepsin H	37	0.748	1.014	0.931	1.105	0.356	1.034	0.963	1.109	0.545	0.986	0.942	1.032	−0.008	0.448	0.553	33.029	35	0.564	33.619	36	0.582	
	cathepsin L2	37	0.940	1.003	0.921	1.093	0.392	0.968	0.898	1.043	0.500	0.984	0.940	1.031	−0.005	0.607	0.589	33.695	35	0.531	33.965	36	0.566	
	cathepsin O	37	0.592	0.977	0.896	1.064	0.623	0.982	0.915	1.055	0.369	0.979	0.935	1.025	0.001	0.944	0.963	22.632	35	0.947	22.637	36	0.960	
	cathepsin S	37	0.252	0.947	0.863	1.038	0.250	0.960	0.894	1.030	0.174	0.967	0.920	1.015	0.006	0.603	0.285	40.560	35	0.239	40.879	36	0.265	
	cathepsin Z	37	0.999	1.000	0.918	1.090	0.227	0.957	0.891	1.028	0.241	0.973	0.929	1.019	−0.008	0.460	0.769	29.305	35	0.739	29.862	36	0.755	

Table S3. (Continued).

exposu re	outco me	nsn p	MR-Egger				Weighted median				Inverse variance weighted				MR-Egger intercept	MR-PRESSO global		MR-IVW			MR-Egger		
			p_val ue	OR	OR_LC I95	OR_UC I95	p_val ue	OR	OR_LC I95	OR_UC I95	p_val ue	OR	OR_LC I95	OR_UC I95	egger intercept	p_val ue	p_value	Q	Q_ df	Q_p val	Q	Q_ df	Q_p val
Barrett' s esopha gus (BE)	cathep isn B	16	0.365	1.1 13	0.889	1.393	0.355	1.0 54	0.943	1.179	0.522	1.0 28	0.944	1.120	-0.021	0.465	0.308	16.5 04	14	0.284	17.1 69	15	0.309
	cathep isn E	16	0.897	1.0 17	0.793	1.304	0.513	1.0 38	0.929	1.159	0.221	1.0 60	0.966	1.163	0.011	0.730	0.181	20.3 10	14	0.121	20.4 91	15	0.154
	cathep isn F	16	0.232	1.1 41	0.928	1.403	0.429	0.9 56	0.856	1.068	0.681	0.9 83	0.908	1.065	-0.039	0.149	0.693	9.24 0	14	0.815	11.5 68	15	0.711
	cathep isn G	16	0.225	1.1 43	0.930	1.406	0.961	0.9 97	0.897	1.109	0.685	1.0 17	0.939	1.101	-0.031	0.248	0.690	10.6 00	14	0.717	12.0 52	15	0.675
	cathep isn H	16	0.963	1.0 05	0.817	1.236	0.557	0.9 68	0.869	1.079	0.262	0.9 55	0.882	1.035	-0.013	0.612	0.740	11.3 89	14	0.655	11.6 58	15	0.705
	cathep isn L2	16	0.737	0.9 62	0.772	1.199	0.781	0.9 85	0.882	1.099	0.456	0.9 69	0.893	1.052	0.002	0.944	0.395	15.8 36	14	0.323	15.8 42	15	0.393
	cathep isn O	16	0.458	0.9 23	0.750	1.135	0.055	0.8 97	0.803	1.003	0.043	0.9 21	0.850	0.997	-0.001	0.984	0.802	10.2 51	14	0.744	10.2 51	15	0.804
	cathep isn S	16	0.439	1.0 88	0.884	1.337	0.611	1.0 27	0.926	1.139	0.896	1.0 05	0.928	1.089	-0.021	0.433	0.949	6.86 8	14	0.940	7.52 0	15	0.942
	cathep isn Z	16	0.994	1.0 01	0.776	1.291	0.800	1.0 15	0.904	1.140	0.499	0.9 68	0.880	1.064	-0.009	0.783	0.127	21.1 95	14	0.097	21.3 15	15	0.127

Table S3. (Continued).

exposure	outcome	nsn	MR-Egger			Weighted median					Inverse variance weighted				MR-Egger intercept	MR-PRESSO global		MR-IVW			MR-Egger		
			p_value	OR	OR_LC I95	OR_UC I95	p_value	OR	OR_LC I95	OR_UC I95	p_value	OR	OR_LC I95	OR_UC I95	egger intercept	p_value	p_value	Q	Q_df	Q_p_val	Q	Q_df	Q_p_val
gastric ulcer (GU)	cathepsin B	15	0.812	1.039	0.762	1.418	0.900	1.013	0.830	1.235	0.265	0.921	0.798	1.064	-0.018	0.405	0.408	13.834	13	0.386	14.621	14	0.405
	cathepsin E	15	0.082	1.336	0.989	1.807	0.709	1.038	0.852	1.264	0.492	1.051	0.912	1.210	-0.037	0.100	0.532	9.996	13	0.694	13.129	14	0.516
	cathepsin F	14	0.884	0.971	0.654	1.440	0.831	0.976	0.785	1.215	0.229	0.895	0.747	1.072	-0.012	0.656	0.106	20.211	12	0.063	20.562	13	0.082
	cathepsin G	14	0.072	1.438	1.003	2.061	0.077	1.209	0.980	1.491	0.041	1.198	1.007	1.425	-0.027	0.281	0.217	15.911	12	0.195	17.598	13	0.173
	cathepsin H	15	0.633	0.920	0.658	1.286	0.126	0.852	0.694	1.046	0.307	0.924	0.795	1.075	0.001	0.975	0.308	16.074	13	0.245	16.075	14	0.309
	cathepsin L3	15	0.462	1.124	0.831	1.519	0.990	1.001	0.834	1.202	0.563	1.042	0.905	1.200	-0.011	0.591	0.816	8.647	13	0.799	8.951	14	0.834
	cathepsin O	15	0.120	1.334	0.950	1.872	0.327	1.103	0.906	1.344	0.480	1.061	0.899	1.253	-0.035	0.160	0.171	16.471	13	0.225	19.292	14	0.154
	cathepsin S	15	0.915	1.017	0.752	1.375	0.650	0.955	0.783	1.165	0.907	0.992	0.861	1.142	-0.004	0.856	0.728	9.876	13	0.704	9.911	14	0.769
	cathepsin Z	15	0.931	0.987	0.730	1.334	0.347	0.913	0.754	1.104	0.432	0.945	0.821	1.088	-0.007	0.757	0.847	8.449	13	0.813	8.549	14	0.859

Table S3. (Continued).

exposure	outcome	nsnp	MR-Egger				Weighted median				Inverse variance weighted				MR-Egger intercept	MR-PRESSO global		MR-IVW			MR-Egeer		
			p_value	OR	OR_LC I95	OR_UC I95	p_value	OR	OR_LC I95	OR_UC I95	p_value	OR	OR_LC I95	OR_UC I95	egger intercept	p_value	p_value	Q	Q_df	Q_p val	Q	Q_df	Q_p val
duodenal ulcer (DU)	cathepsin B	12	0.779	0.980	0.852	1.127	0.373	0.949	0.846	1.065	0.710	0.983	0.896	1.078	0.001	0.954	0.266	14.594	10	0.148	14.600	11	0.202
	cathepsin E	15	0.691	0.971	0.843	1.119	0.658	1.024	0.921	1.139	0.657	1.021	0.932	1.117	0.015	0.383	0.144	20.045	13	0.094	21.301	14	0.094
	cathepsin F	15	0.527	0.955	0.833	1.096	0.888	1.008	0.906	1.120	0.941	1.003	0.919	1.096	0.015	0.378	0.181	18.904	13	0.126	20.114	14	0.127
	cathepsin G	15	0.556	0.961	0.844	1.094	0.483	0.962	0.864	1.072	0.778	0.988	0.911	1.072	0.009	0.586	0.284	16.837	13	0.207	17.241	14	0.244
	cathepsin H	15	0.582	1.037	0.914	1.177	0.700	1.022	0.916	1.140	0.882	1.006	0.929	1.090	-0.009	0.549	0.323	16.090	13	0.244	16.559	14	0.280
	cathepsin L2	15	0.745	1.023	0.895	1.169	0.731	1.019	0.915	1.136	0.474	1.031	0.949	1.120	0.002	0.885	0.286	17.900	13	0.161	17.930	14	0.210
	cathepsin O	15	0.233	0.911	0.787	1.054	0.033	0.891	0.802	0.991	0.274	0.950	0.866	1.042	0.013	0.480	0.083	21.361	13	0.066	22.232	14	0.074
	cathepsin S	12	0.645	1.028	0.916	1.155	0.873	0.991	0.891	1.103	0.934	0.997	0.920	1.080	-0.011	0.478	0.624	9.364	10	0.498	9.908	11	0.539
	cathepsin Z	15	0.575	0.967	0.863	1.084	0.490	0.964	0.868	1.070	0.286	0.961	0.893	1.034	-0.002	0.886	0.633	12.622	13	0.477	12.643	14	0.555

Table S3. (Continued).

exposure	outcome	nsnp	MR-Egger				Weighted median				Inverse variance weighted				MR-Egger intercept	MR-PRESSO global		MR-IVW			MR-Egger		
			p_value	OR	OR_LC I95	OR_UC I95	p_value	OR	OR_LC I95	OR_UC I95	p_value	OR	OR_LC I95	OR_UC I95	egger intercept	p_value	p_value	Q	Q_df	Q_p_val	Q	Q_df	Q_p_val
acute gastritis (AG)	cathepsin B	9	0.052	0.781	0.634	0.961	0.113	0.879	0.749	1.031	0.268	0.924	0.804	1.063	0.046	0.093	0.155	8.256	7	0.311	12.725	8	0.122
	cathepsin E	9	0.709	0.948	0.724	1.242	0.063	1.156	0.992	1.346	0.283	1.092	0.930	1.284	0.039	0.247	0.061	13.888	7	0.053	17.051	8	0.030
	cathepsin F	9	0.580	1.058	0.874	1.282	0.587	1.043	0.896	1.214	0.171	1.080	0.967	1.207	0.006	0.805	0.700	5.059	7	0.653	5.125	8	0.744
	cathepsin G	9	0.938	1.008	0.832	1.221	0.337	0.931	0.805	1.077	0.324	0.946	0.847	1.056	−0.018	0.452	0.750	4.396	7	0.733	5.031	8	0.754
	cathepsin H	9	0.821	0.977	0.807	1.184	0.993	0.999	0.859	1.162	0.545	0.966	0.865	1.079	−0.003	0.892	0.638	6.374	7	0.497	6.393	8	0.603
	cathepsin L2	9	0.485	1.087	0.871	1.355	0.376	0.929	0.789	1.093	0.915	1.007	0.888	1.141	−0.021	0.435	0.288	9.324	7	0.230	10.237	8	0.249
	cathepsin O	9	0.343	0.900	0.734	1.103	0.584	1.045	0.892	1.225	0.712	1.024	0.902	1.163	0.036	0.171	0.276	7.892	7	0.342	10.521	8	0.230
	cathepsin S	9	0.185	0.865	0.713	1.049	0.188	0.906	0.782	1.049	0.484	0.959	0.854	1.077	0.029	0.239	0.421	7.127	7	0.416	8.812	8	0.358
	cathepsin Z	9	0.572	1.078	0.841	1.382	0.753	1.026	0.875	1.202	0.456	1.053	0.920	1.205	−0.007	0.824	0.177	11.801	7	0.107	11.890	8	0.156

Table S3. (Continued).

exposure	outcome	nsnp	MR-Egger				Weighted median				Inverse variance weighted				MR-Egger intercept	MR-PRESSO global		MR-IVW			MR-Egeer		
			p_value	OR	OR_LC I95	OR_UC I95	p_value	OR	OR_LC I95	OR_UC I95	p_value	OR	OR_LC I95	OR_UC I95	egger intercept	p_value	p_value	Q	Q_df	Q_p_val	Q	Q_df	Q_p_val
chronic gastritis (CG)	cathepsin B	14	0.859	0.948	0.532	1.690	0.235	1.174	0.901	1.529	0.338	1.095	0.909	1.319	0.018	0.614	0.454	23.603	18	0.168	26.546	19	0.116
	cathepsin E	14	0.342	1.332	0.755	2.348	0.204	1.168	0.919	1.485	0.154	1.145	0.951	1.379	-0.019	0.591	0.900	1.931	7	0.964	2.380	8	0.967
	cathepsin F	13	0.028	2.186	1.194	4.004	0.871	0.978	0.748	1.279	0.973	1.004	0.788	1.280	-0.095	0.022	0.085	11.829	11	0.377	19.472	12	0.078
	cathepsin G	14	0.864	0.947	0.516	1.740	0.145	0.830	0.647	1.066	0.064	0.833	0.687	1.011	-0.016	0.670	0.401	12.649	10	0.244	12.755	11	0.310
	cathepsin H	14	0.439	1.261	0.715	2.224	0.148	1.200	0.937	1.535	0.099	1.169	0.971	1.408	-0.009	0.788	0.823	3.054	9	0.962	4.824	10	0.903
	cathepsin L2	14	0.634	0.492	0.868	1.531	0.080	0.804	0.630	1.026	0.076	0.845	0.702	1.018	-0.003	0.924	0.907	11.456	10	0.323	16.808	11	0.114
	cathepsin O	14	0.636	0.853	0.450	1.619	0.386	0.888	0.678	1.162	0.331	0.905	0.740	1.107	0.007	0.853	0.301	12.501	10	0.253	13.245	11	0.278
	cathepsin S	14	0.894	1.055	0.489	2.273	0.386	1.129	0.858	1.484	0.986	1.002	0.787	1.276	-0.006	0.892	0.059	19.115	21	0.578	19.490	22	0.615
	cathepsin Z	14	0.164	1.625	0.855	3.090	0.495	1.099	0.838	1.440	0.247	1.134	0.916	1.404	-0.045	0.268	0.187	8.842	11	0.637	10.059	12	0.611

Table S3. (Continued).

exposure	outcome	nsnp	MR-Egger				Weighted median				Inverse variance weighted				MR-Egger intercept	MR-PRESSO global		MR-IVW			MR-Egeer		
			p_value	OR	OR_LC I95	OR_UC I95	p_value	OR	OR_LC I95	OR_UC I95	p_value	OR	OR_LC I95	OR_UC I95	egger intercept	p_value	p_value	Q	Q_df	Q_p_val	Q	Q_df	Q_p_val
irritable bowel syndrome (IBS)	cathepsin B	18	0.525	0.928	0.740	1.163	0.541	1.063	0.875	1.291	0.845	0.986	0.857	1.134	0.009	0.510	0.796	10.963	16	0.812	11.417	17	0.834
	cathepsin E	18	0.742	1.050	0.790	1.395	0.841	0.979	0.795	1.205	0.485	1.063	0.896	1.261	0.002	0.915	0.092	25.203	16	0.066	25.221	17	0.090
	cathepsin F	18	0.388	0.903	0.720	1.132	0.790	0.974	0.801	1.184	0.482	1.052	0.914	1.210	0.023	0.111	0.458	13.973	16	0.601	16.811	17	0.467
	cathepsin G	18	0.398	1.105	0.882	1.386	0.213	1.139	0.928	1.397	0.418	1.060	0.921	1.219	−0.006	0.648	0.898	9.931	16	0.870	10.148	17	0.897
	cathepsin H	18	0.338	0.892	0.712	1.119	0.663	1.048	0.850	1.292	0.695	1.028	0.894	1.183	0.022	0.137	0.595	12.346	16	0.720	14.804	17	0.610
	cathepsin L2	18	0.722	0.959	0.765	1.203	0.916	1.011	0.829	1.232	0.968	0.997	0.867	1.147	0.006	0.674	0.618	14.302	16	0.576	14.486	17	0.632
	cathepsin O	18	0.956	0.994	0.792	1.246	0.977	0.997	0.826	1.205	0.713	1.027	0.892	1.181	0.005	0.722	0.737	12.982	16	0.674	13.114	17	0.729
	cathepsin S	18	0.784	0.968	0.772	1.214	0.443	1.079	0.888	1.312	0.312	1.075	0.934	1.237	0.016	0.266	0.850	9.814	16	0.876	11.145	17	0.849
	cathepsin Z	18	0.964	1.006	0.792	1.276	0.752	0.968	0.794	1.182	0.723	0.974	0.844	1.125	−0.005	0.744	0.419	17.748	16	0.339	17.870	17	0.397

Table S3. (Continued).

exposure	outcome	nsnp	MR-Egger				Weighted median				Inverse variance weighted				MR-Egger intercept	MR-PRESSO global		MR-IVW			MR-Egeer		
			p_value	OR	OR_LC I95	OR_UC I95	p_value	OR	OR_LC I95	OR_UC I95	p_value	OR	OR_LC I95	OR_UC I95	egger intercept	p_value	p_value	Q	Q_df	Q_p_val	Q	Q_df	Q_p_val
celiac disease (CD)	cathepsin B	52	0.550	0.991	0.962	1.021	0.520	1.009	0.981	1.038	0.618	1.006	0.983	1.030	0.011	0.114	0.094	63.084	50	0.101	66.350	51	0.073
	cathepsin E	52	0.687	1.005	0.979	1.032	0.928	0.998	0.966	1.032	0.383	0.991	0.971	1.012	-0.010	0.086	0.731	36.656	50	0.920	39.728	51	0.874
	cathepsin F	52	0.007	0.962	0.936	0.988	0.294	0.984	0.956	1.014	0.011	0.973	0.952	0.994	0.008	0.185	0.330	52.758	50	0.368	54.666	51	0.337
	cathepsin G	52	0.364	0.988	0.962	1.014	0.407	1.015	0.979	1.053	0.701	1.004	0.984	1.025	0.012	0.056	0.589	40.411	50	0.832	44.249	51	0.737
	cathepsin H	52	0.302	1.014	0.988	1.041	0.501	1.010	0.981	1.039	0.152	1.015	0.994	1.036	0.001	0.899	0.569	48.708	50	0.525	48.725	51	0.565
	cathepsin L2	52	0.970	0.999	0.973	1.027	0.202	1.021	0.989	1.053	0.738	0.996	0.976	1.018	-0.002	0.721	0.328	52.832	50	0.365	52.969	51	0.398
	cathepsin O	52	0.534	1.009	0.982	1.036	0.436	1.012	0.982	1.042	0.543	1.007	0.986	1.028	-0.002	0.804	0.399	53.073	50	0.357	53.139	51	0.392
	cathepsin S	52	0.147	1.020	0.993	1.047	0.203	1.020	0.989	1.052	0.405	1.009	0.988	1.030	-0.008	0.192	0.695	41.416	50	0.801	43.164	51	0.774
	cathepsin Z	52	0.369	1.012	0.986	1.040	0.769	1.004	0.976	1.033	0.169	1.015	0.994	1.036	0.002	0.792	0.502	50.568	50	0.451	50.639	51	0.488

Table S3. (Continued).

exposure	outcome	nsnp	MR-Egger				Weighted median				Inverse variance weighted				MR-Egger intercept	MR-PRESSO global		MR-IVW			MR-Egeer		
			p_value	OR	OR_LC I95	OR_UC I95	p_value	OR	OR_LC I95	OR_UC I95	p_value	OR	OR_LC I95	OR_UC I95	egger intercept	p_value	p_value	Q	Q_df	Q_p val	Q	Q_df	Q_p val
diverticulosis	cathepsin B	169	0.388	0.903	0.718	1.137	0.590	0.965	0.846	1.100	0.447	0.969	0.892	1.052	0.004	0.526	0.934	139.480	167	0.941	139.884	168	0.944
	cathepsin E	169	0.258	0.875	0.695	1.102	0.692	0.976	0.866	1.100	0.935	1.003	0.924	1.090	0.008	0.215	0.933	139.275	167	0.942	140.825	168	0.937
	cathepsin F	169	0.056	0.795	0.629	1.004	0.753	0.979	0.856	1.119	0.538	0.974	0.895	1.059	0.013	0.070	0.313	172.284	167	0.374	175.721	168	0.326
	cathepsin G	169	0.396	0.905	0.719	1.139	0.094	1.123	0.980	1.287	0.320	1.043	0.960	1.132	0.009	0.198	0.602	161.266	167	0.611	162.934	168	0.596
	cathepsin H	169	0.531	0.929	0.738	1.169	0.146	0.911	0.803	1.033	0.031	0.914	0.841	0.992	−0.001	0.880	0.986	131.824	167	0.979	131.847	168	0.982
	cathepsin L2	169	0.465	0.913	0.715	1.165	0.257	0.928	0.815	1.056	0.094	0.928	0.851	1.013	0.001	0.885	0.151	187.208	167	0.136	187.231	168	0.147
	cathepsin O	169	0.450	0.915	0.727	1.152	0.968	0.997	0.876	1.136	0.247	0.953	0.877	1.034	0.002	0.713	0.600	163.048	167	0.572	163.184	168	0.591
	cathepsin S	169	0.315	1.129	0.892	1.428	0.484	1.049	0.918	1.199	0.767	1.013	0.931	1.102	−0.007	0.335	0.360	174.536	167	0.329	175.512	168	0.330
	cathepsin Z	169	0.587	0.936	0.736	1.189	0.557	1.044	0.905	1.204	0.795	0.989	0.908	1.077	0.003	0.629	0.218	180.704	167	0.222	180.957	168	0.234

Table S3. (Continued).

exposure	outcome	nsnp	MR-Egger				Weighted median				Inverse variance weighted				MR-Egger intercept	MR-PRESSO global		MR-IVW			MR-Egeer		
			p_value	OR	OR_LC I95	OR_UC I95	p_value	OR	OR_LC I95	OR_UC I95	p_value	OR	OR_LC I95	OR_UC I95	egger intercept	p_value	p_value	Q	Q_df	Q_p val	Q	Q_df	Q_p val
Crohn's disease of small intestine (CDSI)	cathepsin B	31	0.684	0.970	0.837	1.123	0.311	0.960	0.887	1.039	0.593	0.985	0.932	1.041	0.004	0.823	0.881	21.506	29	0.840	21.557	30	0.870
	cathepsin E	31	0.955	1.004	0.867	1.163	0.438	0.971	0.903	1.045	0.721	0.990	0.937	1.046	-0.003	0.837	0.829	23.065	29	0.774	23.109	30	0.811
	cathepsin F	31	0.939	1.006	0.856	1.184	0.587	0.976	0.894	1.065	0.589	0.983	0.926	1.045	-0.005	0.766	0.211	35.596	29	0.186	35.706	30	0.218
	cathepsin G	31	0.964	1.004	0.859	1.173	0.912	1.005	0.925	1.091	0.802	0.993	0.937	1.052	-0.002	0.882	0.306	32.871	29	0.283	32.896	30	0.327
	cathepsin H	31	0.161	0.898	0.776	1.040	0.158	1.062	0.977	1.155	0.263	1.033	0.976	1.093	0.032	0.053	0.401	27.263	29	0.558	31.340	30	0.399
	cathepsin L2	31	0.499	0.950	0.821	1.100	0.389	1.036	0.956	1.121	0.291	1.030	0.975	1.089	0.018	0.252	0.830	21.289	29	0.848	22.655	30	0.829
	cathepsin O	30	0.914	0.990	0.823	1.190	0.157	1.066	0.976	1.165	0.691	1.013	0.949	1.082	0.005	0.790	0.098	39.185	28	0.078	39.286	29	0.096
	cathepsin S	31	0.892	0.989	0.842	1.162	0.178	0.947	0.874	1.025	0.720	0.989	0.932	1.050	0.000	0.997	0.288	34.956	29	0.206	34.956	30	0.244
	cathepsin Z	31	0.490	1.059	0.902	1.243	0.974	0.999	0.916	1.089	0.322	0.970	0.913	1.031	-0.020	0.255	0.214	34.614	29	0.217	36.224	30	0.201

Table S3. (Continued).

exposure	outcome	nsnp	MR-Egger				Weighted median				Inverse variance weighted				MR-Egger intercept	MR-PRESSO global		MR-IVW			MR-Egeer		
			p_value	OR	OR_LC I95	OR_UC I95	p_value	OR	OR_LC I95	OR_UC I95	p_value	OR	OR_LC I95	OR_UC I95	egger intercept	p_value	p_value	Q	Q_df	Q_p val	Q	Q_df	Q_p val
Crohn's disease of large intestine (CDLI)	cathepsin B	26	0.933	0.994	0.855	1.155	0.145	1.055	0.982	1.133	0.075	1.051	0.995	1.110	0.013	0.441	0.978	12.492	24	0.974	13.107	25	0.975
	cathepsin E	26	0.633	1.046	0.871	1.256	0.896	1.006	0.924	1.094	0.712	0.988	0.925	1.055	-0.013	0.515	0.071	35.375	24	0.063	36.019	25	0.071
	cathepsin F	26	0.234	1.098	0.945	1.276	0.976	1.001	0.928	1.081	0.455	0.979	0.927	1.034	-0.026	0.123	0.649	19.578	24	0.720	22.139	25	0.628
	cathepsin G	26	0.993	0.999	0.849	1.177	0.512	0.974	0.899	1.055	0.753	0.991	0.935	1.050	-0.002	0.913	0.309	28.288	24	0.248	28.303	25	0.294
	cathepsin H	26	0.969	1.003	0.863	1.166	0.762	1.012	0.935	1.096	0.191	1.037	0.982	1.095	0.008	0.645	0.652	22.063	24	0.576	22.280	25	0.620
	cathepsin L2	26	0.365	1.073	0.923	1.248	0.476	1.030	0.950	1.116	0.900	0.996	0.944	1.052	-0.017	0.309	0.562	22.124	24	0.572	23.204	25	0.566
	cathepsin O	26	0.363	1.074	0.924	1.248	0.445	1.030	0.954	1.112	0.355	1.026	0.972	1.084	-0.010	0.531	0.671	21.311	24	0.620	21.715	25	0.652
	cathepsin S	26	0.774	1.027	0.859	1.228	0.448	1.031	0.952	1.117	0.572	1.018	0.956	1.085	-0.002	0.924	0.105	33.790	24	0.088	33.803	25	0.112
cathepsin Z	26	0.409	1.067	0.918	1.240	0.951	0.998	0.925	1.076	0.812	1.007	0.953	1.063	-0.013	0.427	0.741	19.535	24	0.723	20.188	25	0.737	

Table S3. (Continued).

exposure	outcome	nsnp	MR-Egger				Weighted median				Inverse variance weighted				MR-Egger intercept	MR-PRESSO global		MR-IVW			MR-Egeer		
			p_value	OR	OR_LC I95	OR_UC I95	p_value	OR	OR_LC I95	OR_UC I95	p_value	OR	OR_LC I95	OR_UC I95	egger intercept	p_value	p_value	Q	Q_df	Q_p_val	Q	Q_df	Q_p_val
ulcerative colitis (UC)	cathepsin B	63	0.219	0.884	0.728	1.074	0.389	1.037	0.955	1.126	0.848	1.006	0.945	1.072	0.019	0.173	0.050	78.482	61	0.065	80.924	62	0.054
	cathepsin E	63	0.420	1.077	0.900	1.289	0.069	1.083	0.994	1.181	0.322	1.030	0.972	1.091	−0.007	0.603	0.309	67.076	61	0.277	67.376	62	0.298
	cathepsin F	63	0.477	1.064	0.897	1.263	0.164	0.946	0.874	1.023	0.588	0.985	0.932	1.041	−0.011	0.351	0.717	54.657	61	0.704	55.542	62	0.706
	cathepsin G	63	0.729	1.032	0.865	1.232	0.921	1.004	0.924	1.092	0.816	1.007	0.951	1.065	−0.004	0.773	0.370	65.079	61	0.337	65.169	62	0.367
	cathepsin H	63	0.702	1.035	0.867	1.236	0.173	1.058	0.976	1.148	0.712	1.011	0.955	1.070	−0.003	0.780	0.370	65.538	61	0.322	65.623	62	0.352
	cathepsin L2	63	0.471	0.939	0.791	1.114	0.741	0.987	0.911	1.068	0.603	0.985	0.932	1.041	0.007	0.559	0.905	47.440	61	0.898	47.786	62	0.908
	cathepsin O	63	0.683	0.965	0.813	1.145	0.779	1.012	0.933	1.098	0.602	1.015	0.960	1.073	0.007	0.543	0.670	56.563	61	0.637	56.938	62	0.658
	cathepsin S	63	0.872	1.016	0.835	1.237	0.212	0.946	0.868	1.032	0.743	0.990	0.929	1.054	−0.004	0.779	0.060	80.091	61	0.051	80.195	62	0.060
cathepsin Z	63	0.326	0.912	0.761	1.094	0.936	1.003	0.922	1.092	0.844	1.006	0.948	1.067	0.014	0.270	0.236	68.666	61	0.234	70.064	62	0.225	

Table S3. (Continued).

exposu re	outco me	nsn p	MR-Egger				Weighted median				Inverse variance weighted				MR-Egger intercept	MR-PRESSO global		MR-IVW			MR-Egeer		
			p_val ue	OR	OR_LC I95	OR_UC I95	p_val ue	OR	OR_LC I95	OR_UC I95	p_val ue	OR	OR_LC I95	OR_UC I95	egger intercept	p_val ue	p_value	Q	Q_ df	Q_p val	Q	Q_ df	Q_p val
non- alcohol ic fatty liver disease (NAFL D)	cathep isn B	23	0.457	0.9 44	0.813	1.096	0.210	1.0 63	0.966	1.169	0.502	1.0 23	0.956	1.095	0.020	0.247	0.361	21.8 64	21	0.407	23.3 41	22	0.383
	cathep isn E	23	0.341	0.9 17	0.771	1.091	0.015	0.8 84	0.800	0.976	0.517	0.9 75	0.902	1.053	0.015	0.452	0.087	29.5 38	21	0.102	30.3 63	22	0.110
	cathep isn F	23	0.324	1.0 78	0.931	1.248	0.602	1.0 26	0.932	1.130	0.248	1.0 40	0.973	1.111	−0.009	0.589	0.957	11.9 31	21	0.941	12.2 32	22	0.952
	cathep isn G	23	0.431	1.0 62	0.917	1.229	0.711	1.0 19	0.923	1.125	0.725	0.9 88	0.925	1.056	−0.018	0.294	0.597	17.6 69	21	0.670	18.8 28	22	0.656
	cathep isn H	23	0.872	0.9 88	0.853	1.144	0.558	1.0 30	0.933	1.138	0.962	0.9 98	0.935	1.066	0.003	0.875	0.798	16.5 62	21	0.737	16.5 87	22	0.786
	cathep isn L2	23	0.853	1.0 17	0.851	1.216	0.549	1.0 31	0.932	1.141	0.402	1.0 34	0.956	1.119	0.004	0.842	0.127	31.2 80	21	0.069	31.3 41	22	0.089
	cathep isn O	23	0.784	0.9 77	0.827	1.153	0.290	1.0 55	0.956	1.164	0.700	1.0 15	0.943	1.092	0.010	0.621	0.205	27.1 56	21	0.166	27.4 82	22	0.193
	cathep isn S	23	0.230	1.0 97	0.948	1.269	0.175	1.0 73	0.969	1.189	0.429	1.0 27	0.961	1.097	−0.017	0.335	0.742	16.4 14	21	0.746	17.3 88	22	0.742
cathep isn Z	23	0.008	1.2 48	1.078	1.446	0.007	1.1 47	1.039	1.267	0.001	1.1 19	1.044	1.198	−0.028	0.116	0.317	21.2 49	21	0.444	23.9 69	22	0.349	

Table S3. (Continued).

exposure	outcome	nsnp	MR-Egger				Weighted median				Inverse variance weighted				MR-Egger intercept	MR-PRESSO global		MR-IVW			MR-Egeer		
			p_value	OR	OR_LC I95	OR_UC I95	p_value	OR	OR_LC I95	OR_UC I95	p_value	OR	OR_LC I95	OR_UC I95	egger intercept	p_value	p_value	Q	Q_df	Q_p_val	Q	Q_df	Q_p_val
Nonalcoholic Steatohepatitis (NASH)	cathepsin B	4	0.829	0.859	0.257	2.877	0.162	1.056	0.978	1.141	0.047	1.084	1.001	1.175	0.141	0.742	0.324	4.650	2	0.098	4.983	3	0.173
	cathepsin E	4	0.988	0.990	0.319	3.072	0.788	0.988	0.904	1.080	0.380	0.968	0.901	1.041	−0.014	0.972	0.303	4.083	2	0.130	4.086	3	0.252
	cathepsin F	4	0.340	2.165	0.641	7.313	0.871	1.007	0.929	1.090	0.942	0.996	0.898	1.105	−0.471	0.337	0.108	4.722	2	0.094	8.430	3	0.038
	cathepsin G	4	0.604	0.782	0.354	1.726	0.449	1.029	0.956	1.108	0.446	1.024	0.963	1.090	0.164	0.571	0.921	0.131	2	0.937	0.581	3	0.901
	cathepsin H	4	0.934	0.962	0.423	2.184	0.056	1.079	0.998	1.167	0.017	1.078	1.013	1.147	0.069	0.810	0.535	2.147	2	0.342	2.228	3	0.527
	cathepsin L2	4	0.394	1.546	0.700	3.414	0.677	1.016	0.944	1.092	0.947	1.002	0.942	1.066	−0.263	0.395	0.768	0.088	2	0.957	1.244	3	0.742
	cathepsin O	4	0.734	0.854	0.387	1.886	0.162	1.054	0.979	1.135	0.069	1.059	0.995	1.127	0.131	0.646	0.939	0.114	2	0.945	0.400	3	0.940
	cathepsin S	4	0.323	1.692	0.766	3.738	0.233	1.047	0.971	1.130	0.284	1.034	0.972	1.101	−0.299	0.346	0.626	0.600	2	0.741	2.091	3	0.554
	cathepsin Z	4	0.344	1.929	0.677	5.501	0.561	1.028	0.937	1.128	0.374	1.040	0.954	1.134	−0.375	0.366	0.195	3.500	2	0.174	5.853	3	0.119

Table S3. (Continued).

expos ure	outco me	nsn p	MR-Egger				Weighted median				Inverse variance weighted				MR-Egger intercept	MR-PRESSO global		MR-IVW			MR-Egeer		
			p_val ue	OR	OR_LC I95	OR_UC I95	p_val ue	OR	OR_LC I95	OR_UC I95	p_val ue	OR	OR_LC I95	OR_UC I95	egger intercept	p_val ue	p_value	Q	Q_ df	Q_p val	Q	Q_ df	Q_p val
Alcohol liver disease (ALD)	cathep isn B	12	0.008	1.3 87	1.143	1.683	0.103	1.1 16	0.978	1.273	0.249	1.0 74	0.951	1.213	-0.063	0.014	0.121	9.05 6	10	0.527	17.8 71	11	0.085
	cathep isn E	13	0.284	0.8 83	0.712	1.096	0.020	0.8 57	0.753	0.976	0.069	0.9 10	0.822	1.007	0.007	0.765	0.288	14.2 45	11	0.220	14.3 67	12	0.278
	cathep isn F	13	0.452	0.9 16	0.735	1.142	0.746	1.0 22	0.895	1.168	0.803	1.0 14	0.910	1.130	0.024	0.322	0.197	14.8 85	11	0.188	16.3 37	12	0.176
	cathep isn G	13	0.472	1.0 75	0.889	1.299	0.454	1.0 46	0.930	1.178	0.499	1.0 33	0.941	1.133	-0.009	0.646	0.966	4.60 0	11	0.949	4.82 4	12	0.964
	cathep isn H	13	0.945	1.0 07	0.833	1.217	0.636	1.0 31	0.908	1.172	0.614	0.9 76	0.890	1.072	-0.007	0.721	0.605	9.43 6	11	0.582	9.57 0	12	0.654
	cathep isn L2	13	0.893	1.0 13	0.839	1.225	0.688	1.0 26	0.904	1.165	0.622	1.0 24	0.933	1.124	0.002	0.907	0.956	5.51 0	11	0.904	5.52 4	12	0.938
	cathep isn O	13	0.438	1.0 81	0.894	1.306	0.667	1.0 29	0.904	1.171	0.498	1.0 33	0.941	1.133	-0.011	0.599	0.753	8.05 8	11	0.708	8.35 1	12	0.757
	cathep isn S	13	0.116	1.1 79	0.976	1.425	0.257	1.0 73	0.950	1.213	0.385	1.0 42	0.949	1.144	-0.029	0.169	0.869	4.57 5	11	0.950	6.74 1	12	0.874
	cathep isn Z	13	0.492	1.1 00	0.846	1.431	0.006	1.2 09	1.056	1.383	0.216	1.0 81	0.955	1.224	-0.004	0.885	0.054	21.2 25	11	0.031	21.2 67	12	0.047

Table S3. (Continued).

exposure	outcome	nsnp	MR-Egger				Weighted median				Inverse variance weighted				MR-Egger intercept	MR-PRESSO global		MR-IVW			MR-Egeer		
			p_value	OR	OR_LC I95	OR_UC I95	p_value	OR	OR_LC I95	OR_UC I95	p_value	OR	OR_LC I95	OR_UC I95	egger intercept	p_value	p_value	Q	Q_df	Q_p_val	Q	Q_df	Q_p_val
liver cirrhosis	cathepsin B	15	0.771	0.983	0.877	1.101	0.132	1.063	0.982	1.150	0.014	1.070	1.014	1.129	0.035	0.120	0.538	10.667	13	0.639	13.443	14	0.492
	cathepsin E	15	0.068	0.885	0.785	0.998	0.066	0.929	0.860	1.005	0.422	0.975	0.917	1.037	0.040	0.096	0.169	14.616	13	0.332	18.230	14	0.197
	cathepsin F	15	0.291	1.084	0.939	1.250	0.672	1.017	0.941	1.100	0.288	1.037	0.970	1.109	-0.018	0.504	0.147	20.603	13	0.081	21.350	14	0.093
	cathepsin G	15	0.389	0.950	0.848	1.064	0.518	1.026	0.949	1.109	0.653	0.988	0.936	1.043	0.016	0.455	0.502	12.679	13	0.473	13.272	14	0.505
	cathepsin H	15	0.125	1.100	0.982	1.232	0.603	1.022	0.942	1.108	0.709	1.010	0.957	1.067	-0.035	0.121	0.427	11.567	13	0.563	14.319	14	0.426
	cathepsin L2	15	0.728	1.021	0.909	1.147	0.811	1.009	0.936	1.088	0.850	0.995	0.942	1.050	-0.011	0.622	0.500	13.646	13	0.399	13.913	14	0.456
	cathepsin O	15	0.247	1.073	0.958	1.202	0.311	1.039	0.965	1.120	0.286	1.030	0.976	1.087	-0.017	0.437	0.923	7.321	13	0.885	7.963	14	0.891
	cathepsin S	15	0.082	1.115	0.996	1.249	0.031	1.086	1.008	1.171	0.013	1.071	1.014	1.130	-0.017	0.437	0.820	8.681	13	0.797	9.325	14	0.810
	cathepsin Z	15	0.030	1.191	1.034	1.372	0.012	1.102	1.021	1.188	0.006	1.101	1.028	1.179	-0.032	0.236	0.088	20.199	13	0.090	22.596	14	0.067

Table S3. (Continued).

exposure	outcome	nsn	MR-Egger			Weighted median				Inverse variance weighted				MR-Egger intercept		MR-PRESSO global		MR-IVW			MR-Egger		
			p_value	OR	OR_LC I95	OR_UC I95	p_value	OR	OR_LC I95	OR_UC I95	p_value	OR	OR_LC I95	OR_UC I95	egger intercept	p_value	p_value	Q	Q_df	Q_p_val	Q	Q_df	Q_p_val
Cholangitis	cathepsin B	4	0.678	0.813	0.350	1.890	0.451	0.942	0.808	1.100	0.292	0.930	0.813	1.064	0.048	0.781	0.684	1.822	2	0.402	1.922	3	0.589
	cathepsin E	4	0.314	0.563	0.242	1.309	0.171	0.893	0.759	1.050	0.081	0.887	0.776	1.015	0.161	0.397	0.742	0.351	2	0.839	1.495	3	0.683
	cathepsin F	4	0.632	1.381	0.446	4.274	0.013	0.798	0.667	0.954	0.137	0.880	0.744	1.041	-0.159	0.512	0.286	3.592	2	0.166	4.717	3	0.194
	cathepsin G	4	0.297	0.548	0.236	1.274	0.280	0.914	0.778	1.075	0.085	0.889	0.777	1.017	0.171	0.373	0.625	0.769	2	0.681	2.063	3	0.559
	cathepsin H	4	0.673	0.810	0.349	1.883	0.720	0.971	0.828	1.140	0.766	0.980	0.857	1.121	0.067	0.699	0.712	1.357	2	0.507	1.556	3	0.669
	cathepsin L2	4	0.157	2.593	1.115	6.027	0.086	0.858	0.720	1.022	0.516	0.940	0.781	1.132	-0.359	0.140	0.232	0.009	2	0.996	5.707	3	0.127
	cathepsin O	4	0.861	1.089	0.469	2.532	0.388	0.933	0.798	1.092	0.351	0.938	0.820	1.073	-0.053	0.758	0.984	0.048	2	0.976	0.172	3	0.982
	cathepsin S	4	0.323	1.749	0.753	4.067	0.463	1.060	0.907	1.239	0.240	1.084	0.948	1.240	-0.169	0.377	0.736	0.089	2	0.956	1.360	3	0.715
	cathepsin Z	4	0.933	0.926	0.186	4.609	0.307	1.088	0.926	1.279	0.497	1.076	0.872	1.328	0.053	0.870	0.148	7.244	2	0.027	7.369	3	0.061

Table S3. (Continued).

exposur e	outco me	nsn p	MR-Egger				Weighted median				Inverse variance weighted				MR-Egger intercept	MR-PRESSO global		MR-IVW			MR-Egeer		
			p_val ue	OR	OR_LC I95	OR_UC I95	p_val ue	OR	OR_LC I95	OR_UC I95	p_val ue	OR	OR_LC I95	OR_UC I95	egger intercept	p_val ue	p_value	Q	Q_ df	Q_p val	Q	Q_ df	Q_p val
Cholecys titis	cathep isn B	20	0.015	1.2 30	1.057	1.431	0.051	1.1 02	1.000	1.215	0.029	1.0 74	1.007	1.145	0.028	0.405	0.120	14.3 22	9	0.11 1	15.5 35	10	0.11 4
	cathep isn E	9	0.268	0.9 24	0.813	1.051	0.202	0.9 34	0.842	1.037	0.233	0.9 54	0.883	1.031	0.015	0.657	0.194	13.7 88	9	0.13 0	14.1 11	10	0.16 8
	cathep isn F	12	0.420	1.0 87	0.895	1.321	0.215	0.9 36	0.843	1.039	0.454	0.9 68	0.888	1.055	−0.003	0.896	0.863	5.66 0	9	0.77 3	5.67 8	10	0.84 2
	cathep isn G	12	0.840	0.9 78	0.797	1.202	0.307	0.9 37	0.827	1.062	0.232	0.9 46	0.864	1.036	−0.006	0.858	0.214	13.2 75	9	0.15 1	13.3 24	10	0.20 6
	cathep isn H	11	0.455	1.0 29	0.958	1.104	0.530	1.0 16	0.967	1.067	0.745	1.0 08	0.959	1.060	0.003	0.922	0.846	5.93 2	9	0.74 7	5.94 2	10	0.82 0
	cathep isn L2	9	0.982	1.0 05	0.637	1.586	0.159	1.1 59	0.944	1.425	0.137	1.1 64	0.953	1.422	0.031	0.502	0.128	13.5 25	7	0.06 0	14.4 92	8	0.07 0
	cathep isn O	12	0.866	1.0 19	0.825	1.258	0.666	1.0 27	0.910	1.159	0.867	1.0 08	0.920	1.103	−0.001	0.958	0.487	9.94 2	9	0.35 5	9.94 5	10	0.44 5
	cathep isn S	23	0.371	1.0 47	0.949	1.154	0.181	1.0 61	0.973	1.156	0.618	1.0 15	0.958	1.074	0.016	0.620	0.227	12.5 51	9	0.18 4	12.9 20	10	0.22 8
	cathep isn Z	13	0.656	1.0 27	0.916	1.152	0.862	1.0 08	0.925	1.098	0.830	1.0 08	0.939	1.081	0.017	0.538	0.417	10.0 27	9	0.34 8	10.4 84	10	0.39 9

Table S3. (Continued).

exposure	outcome	nsnp	MR-Egger				Weighted median				Inverse variance weighted				MR-Egger intercept	MR-PRESSO global		MR-IVW			MR-Egger		
			p_value	OR	OR_LC I95	OR_UC I95	p_value	OR	OR_LC I95	OR_UC I95	p_value	OR	OR_LC I95	OR_UC I95	egger intercept	p_value	p_value	Q	Q_df	Q_pval	Q	Q_df	Q_pval
Cholelithiasis	cathepsin B	144	0.797	0.982	0.855	1.128	0.655	1.032	0.898	1.187	0.807	0.990	0.916	1.071	0.001	0.885	0.084	169.698	142	0.056	169.723	143	0.063
	cathepsin E	145	0.238	1.085	0.948	1.241	0.025	1.152	1.018	1.303	0.447	1.030	0.955	1.111	−0.004	0.361	0.154	160.300	143	0.153	161.243	144	0.155
	cathepsin F	140	0.504	1.046	0.918	1.191	0.677	1.030	0.897	1.183	0.529	0.977	0.908	1.051	−0.006	0.216	0.739	126.426	138	0.751	127.970	139	0.739
	cathepsin G	145	0.556	1.039	0.914	1.181	0.272	1.073	0.946	1.218	0.828	0.992	0.923	1.066	−0.004	0.390	0.436	145.622	143	0.423	146.379	144	0.429
	cathepsin H	145	0.830	1.014	0.893	1.151	0.402	1.047	0.940	1.168	0.983	0.999	0.930	1.073	−0.001	0.784	0.840	125.991	143	0.843	126.066	144	0.856
	cathepsin L2	145	0.061	1.134	0.995	1.291	0.154	1.105	0.963	1.267	0.152	1.055	0.980	1.136	−0.006	0.193	0.316	150.427	143	0.319	152.230	144	0.303
	cathepsin O	145	0.042	1.142	1.006	1.297	0.063	1.132	0.993	1.291	0.210	1.047	0.975	1.124	−0.007	0.105	0.675	133.035	143	0.714	135.690	144	0.677
	cathepsin S	140	0.855	1.013	0.882	1.163	0.407	1.062	0.921	1.226	0.403	1.034	0.956	1.117	0.002	0.729	0.141	155.661	138	0.144	155.798	139	0.156
	cathepsin Z	139	0.641	0.967	0.841	1.112	0.757	1.022	0.892	1.170	0.127	0.941	0.870	1.018	−0.002	0.636	0.113	157.163	137	0.115	157.421	138	0.123

Table S3. (Continued).

exposure	outcome	nsnp	MR-Egger				Weighted median				Inverse variance weighted				MR-Egger intercept	MR-PRESSO global		MR-IVW			MR-Egger		
			p_value	OR	OR_LC I95	OR_UC I95	p_value	OR	OR_LC I95	OR_UC I95	p_value	OR	OR_LC I95	OR_UC I95	egger intercept	p_value	p_value	Q	Q_df	Q_p_val	Q	Q_df	Q_p_val
acute pancreatitis (AP)	cathepsin B	22	0.198	0.896	0.762	1.053	0.796	1.019	0.883	1.175	0.675	0.979	0.885	1.082	0.021	0.187	0.674	15.533	20	0.745	17.403	21	0.686
	cathepsin E	22	0.364	1.081	0.917	1.273	0.606	1.037	0.903	1.191	0.253	1.060	0.959	1.173	−0.005	0.775	0.509	20.460	20	0.430	20.546	21	0.487
	cathepsin F	22	0.886	0.985	0.806	1.204	0.697	1.031	0.886	1.199	0.412	1.053	0.930	1.192	0.016	0.416	0.070	30.704	20	0.059	31.765	21	0.062
	cathepsin G	22	0.718	1.031	0.876	1.213	0.991	1.001	0.867	1.156	0.327	1.052	0.951	1.163	0.005	0.761	0.465	20.113	20	0.451	20.208	21	0.508
	cathepsin H	22	0.433	1.068	0.909	1.256	0.267	1.081	0.942	1.240	0.184	1.071	0.968	1.184	0.001	0.973	0.984	10.008	20	0.968	10.009	21	0.979
	cathepsin L2	22	0.483	0.938	0.786	1.119	0.991	1.001	0.866	1.157	0.950	1.004	0.899	1.120	0.016	0.347	0.235	23.823	20	0.250	24.928	21	0.250
	cathepsin O	22	0.561	1.050	0.893	1.235	0.459	1.055	0.916	1.215	0.227	1.064	0.962	1.177	0.003	0.840	0.932	11.869	20	0.921	11.911	21	0.942
	cathepsin S	22	0.550	1.053	0.891	1.244	0.286	1.082	0.936	1.249	0.133	1.081	0.977	1.196	0.006	0.699	0.436	21.174	20	0.387	21.336	21	0.439
	cathepsin Z	22	0.936	0.993	0.829	1.188	0.577	1.045	0.895	1.219	0.436	1.045	0.935	1.167	0.012	0.483	0.217	24.742	20	0.211	25.375	21	0.231

Table S3. (Continued).

exposure	outcome	nsnp	MR-Egger				Weighted median				Inverse variance weighted				MR-Egger intercept	MR-PRESSO global		MR-IVW			MR-Egger		
			p_value	OR	OR_LC I95	OR_UC I95	p_value	OR	OR_LC I95	OR_UC I95	p_value	OR	OR_LC I95	OR_UC I95	egger intercept	p_value	p_value	Q	Q_df	Q_p_val	Q	Q_df	Q_p_val
chronic pancreatitis (CP)	cathepsin B	20	0.851	1.023	0.808	1.295	0.561	1.041	0.909	1.192	0.832	1.011	0.914	1.118	-0.002	0.913	0.862	12.603	18	0.815	12.615	19	0.858
	cathepsin E	20	0.523	1.081	0.855	1.369	0.010	0.838	0.732	0.958	0.024	0.891	0.806	0.985	-0.032	0.091	0.818	10.627	18	0.910	13.812	19	0.795
	cathepsin F	20	0.124	0.800	0.610	1.049	0.063	0.876	0.762	1.007	0.031	0.882	0.786	0.988	0.016	0.446	0.204	23.861	18	0.160	24.664	19	0.172
	cathepsin G	20	0.323	0.865	0.655	1.144	0.258	0.916	0.787	1.066	0.981	1.001	0.888	1.129	0.024	0.272	0.106	25.247	18	0.118	27.049	19	0.104
	cathepsin H	20	0.693	1.050	0.829	1.328	0.351	0.938	0.819	1.074	0.274	0.945	0.855	1.045	-0.017	0.350	0.997	5.747	18	0.997	6.668	19	0.996
	cathepsin L2	20	0.163	0.840	0.663	1.063	0.105	0.889	0.772	1.025	0.017	0.885	0.800	0.978	0.009	0.636	0.861	12.166	18	0.839	12.398	19	0.868
	cathepsin O	20	0.822	1.028	0.812	1.301	0.159	0.908	0.794	1.039	0.317	0.950	0.859	1.050	-0.013	0.478	0.772	13.844	18	0.739	14.368	19	0.762
	cathepsin S	20	0.671	1.062	0.809	1.392	0.236	0.910	0.779	1.064	0.385	0.950	0.847	1.066	-0.018	0.388	0.178	23.861	18	0.160	24.896	19	0.164
	cathepsin Z	20	0.626	0.931	0.701	1.235	0.934	0.994	0.859	1.150	0.328	0.943	0.839	1.061	0.002	0.922	0.142	25.994	18	0.100	26.008	19	0.130

Table S3. (Continued).

exposur e	outco me	nsn p	MR-Egger				Weighted median				Inverse variance weighted				MR-Egger intercept	MR-PRESSO global		MR-IVW			MR-Egeer		
			p_val ue	OR	OR_LC I95	OR_UC I95	p_val ue	OR	OR_LC I95	OR_UC I95	p_val ue	OR	OR_LC I95	OR_UC I95	egger intercept	p_val ue	p_value	Q	Q_ df	Q_p val	Q	Q_ df	Q_p val
acute appendi citis (AA)	cathep isn B	54	0.116	0.677	0.420	1.091	0.555	0.930	0.730	1.184	0.205	0.893	0.749	1.064	0.016	0.228	0.030	72.242	52	0.033	74.306	53	0.028
	cathep isn E	56	0.776	0.943	0.629	1.412	0.457	0.921	0.742	1.143	0.326	0.929	0.803	1.076	−0.001	0.941	0.829	44.668	54	0.813	44.673	55	0.839
	cathep isn F	56	0.903	1.026	0.685	1.536	0.544	0.934	0.750	1.164	0.745	0.976	0.843	1.130	−0.003	0.798	0.625	50.971	54	0.592	51.037	55	0.627
	cathep isn G	56	0.387	0.835	0.558	1.251	0.261	0.886	0.718	1.094	0.120	0.891	0.769	1.031	0.004	0.741	0.822	45.096	54	0.801	45.207	55	0.824
	cathep isn H	56	0.667	1.106	0.701	1.742	0.612	1.057	0.852	1.312	0.387	1.075	0.913	1.265	−0.002	0.896	0.106	68.486	54	0.089	68.508	55	0.104
	cathep isn L2	56	0.362	0.827	0.552	1.239	0.251	0.880	0.708	1.094	0.491	0.950	0.821	1.100	0.008	0.476	0.555	52.134	54	0.547	52.650	55	0.565
	cathep isn O	56	0.203	1.330	0.862	2.052	0.053	1.238	0.998	1.537	0.100	1.140	0.975	1.333	−0.009	0.459	0.231	62.271	54	0.206	62.912	55	0.217
	cathep isn S	56	0.895	0.973	0.649	1.459	0.414	1.094	0.882	1.355	0.667	1.033	0.892	1.195	0.004	0.758	0.464	54.345	54	0.461	54.441	55	0.496
	cathep isn Z	56	0.789	0.946	0.632	1.417	0.358	1.104	0.894	1.363	0.304	1.080	0.933	1.250	0.008	0.495	0.760	46.834	54	0.745	47.307	55	0.760

Table S3. (Continued).

exposur e	outco me	nsn p	MR-Egger				Weighted median				Inverse variance weighted				MR-Egger intercept	MR-PRESSO global		MR-IVW			MR-Egeer		
			p_val ue	OR	OR_LC I95	OR_UC I95	p_val ue	OR	OR_LC I95	OR_UC I95	p_val ue	OR	OR_LC I95	OR_UC I95	egger intercept	p_val ue	p_value	Q	Q_ df	Q_p val	Q	Q_ df	Q_p val
other appendi citis (OA)	cathep isn B	9	0.521	1.1 18	0.808	1.547	0.243	1.1 19	0.927	1.351	0.573	1.0 41	0.906	1.196	−0.015	0.642	0.402	8.52 5	7	0.289	8.81 3	8	0.358
	cathep isn E	9	0.638	0.9 09	0.620	1.332	0.611	1.0 51	0.868	1.271	0.625	1.0 43	0.882	1.233	0.029	0.455	0.119	11.8 29	7	0.106	12.8 85	8	0.116
	cathep isn F	9	0.229	1.2 44	0.899	1.723	0.983	0.9 98	0.838	1.189	0.650	1.0 36	0.890	1.205	−0.038	0.256	0.252	8.57 3	7	0.285	10.4 51	8	0.235
	cathep isn G	9	0.653	1.0 73	0.800	1.440	0.857	1.0 16	0.852	1.213	0.446	1.0 53	0.922	1.202	−0.004	0.891	0.656	6.01 0	7	0.539	6.03 0	8	0.644
	cathep isn H	9	0.724	1.0 57	0.787	1.418	0.794	1.0 22	0.867	1.206	0.818	1.0 16	0.890	1.159	−0.008	0.776	0.993	1.61 1	7	0.978	1.69 8	8	0.989
	cathep isn L2	9	0.996	0.9 99	0.744	1.341	0.403	1.0 75	0.908	1.271	0.092	1.1 20	0.981	1.279	0.024	0.421	0.958	1.81 7	7	0.969	2.54 7	8	0.960
	cathep isn O	9	0.459	0.8 89	0.662	1.193	0.197	1.1 24	0.941	1.343	0.223	1.0 90	0.949	1.253	0.042	0.172	0.392	6.51 1	7	0.482	8.82 9	8	0.357
	cathep isn S	8	0.799	0.9 45	0.622	1.434	0.850	1.0 19	0.841	1.235	0.844	0.9 83	0.827	1.168	0.008	0.843	0.162	10.7 39	6	0.097	10.8 16	7	0.147
	cathep isn Z	9	0.539	0.8 84	0.607	1.287	0.695	0.9 62	0.791	1.169	0.373	0.9 30	0.793	1.091	0.011	0.773	0.198	11.4 17	7	0.121	11.5 64	8	0.172