Table SI. Data sources of the Mendelian randomization study.

Trait	SNPs	Sample size	Ancestry	Access link
Cathepsin S	23	3,301	European	https://gwas.mrcieu.ac.uk/datasets/prot-a-727/
Cathepsin B	17	3,301	European	https://gwas.mrcieu.ac.uk/datasets/prot-a-718/
Cathepsin O	10	3,301	European	https://gwas.mrcieu.ac.uk/datasets/prot-a-726/
Cathepsin E	11	3,301	European	https://gwas.mrcieu.ac.uk/datasets/prot-a-720/
CathepsinL2	11	3,301	European	https://gwas.mrcieu.ac.uk/datasets/prot-a-728/
Cutaneous melanoma	113,960,19	375,767	European	https://gwas.mrcieu.ac.uk/datasets/ieu-b-4969/

Table SII. Summary statistics utilized in the Mendelian randomization study of cathepsin S in melanoma.

SNP	Effect allele	Other allele	F-statistic	Association with cathepsin S			Association with melanoma		
				Beta	SE	P-value	Beta	SE	P-value
rs1022239	T	A	21.40540709	0.1157	0.025	3.72E-06	-0.000256506	0.000233882	0.27
rs10516855	C	T	21.86069836	-0.1969	0.0421	2.95E-06	-8.42E-05	0.000390925	0.83
rs1060435	G	A	26.43880567	-0.1291	0.0251	2.75E-07	0.000349486	0.000233695	0.13
rs113108135	C	G	22.87388011	0.2349	0.0491	1.70E-06	-0.000293375	0.000458668	0.52
rs116623438	C	T	24.08049943	-0.43	0.0876	9.12E-07	0.000221798	0.000815015	0.79
rs118010753	C	T	21.5350913	0.5018	0.1081	3.47E-06	-0.000840262	0.00104254	0.42
rs12804405	A	G	22.49366459	0.612	0.129	2.09E-06	0.00329003	0.00123765	0.00790005
rs13150189	A	G	25.84122655	0.1556	0.0306	3.47E-07	6.64E-05	0.000283258	0.81
rs13196989	T	C	22.08164016	-0.1758	0.0374	2.57E-06	-0.00045318	0.000343742	0.19
rs13212873	C	T	21.4626871	0.5422	0.117	3.55E-06	-0.00225784	0.00110099	0.04
rs13411643	C	T	25.28778046	0.1831	0.0364	5.01E-07	-0.00021692	0.000334825	0.52
rs2470994	C	T	21.52183682	0.1304	0.0281	3.39E-06	0.000222866	0.000256553	0.39
rs41271951	G	A	421.5125353	-0.8605	0.0419	7.08E-94	-9.49E-05	0.000413968	0.82
rs4313886	C	T	21.34918141	0.1687	0.0365	3.89E-06	0.000444818	0.000340826	0.19
rs4581957	A	G	23.63457391	-0.1775	0.0365	1.15E-06	-0.000515589	0.000340896	0.13
rs529565	C	T	24.42446298	-0.1315	0.0266	7.76E-07	-0.000162778	0.000246153	0.51
rs6657328	C	G	20.79775245	-0.1291	0.0283	4.90E-06	0.000282287	0.000259216	0.28
rs73099998	T	C	22.45644831	-0.146	0.0308	2.19E-06	4.90E-05	0.000284611	0.86
rs74804137	C	T	27.5059455	-0.5178	0.0987	1.58E-07	0.000881532	0.000981908	0.37
rs7614425	A	G	22.78899972	-0.2082	0.0436	1.82E-06	-9.59E-05	0.00040612	0.81
rs77792819	G	A	22.65308518	0.3147	0.0661	1.95E-06	0.000157752	0.00059915	0.79
rs78767885	C	T	21.9998742	0.2238	0.0477	2.69E-06	-0.000537577	0.000447208	0.23
rs989576	T	C	22.09013523	0.1307	0.0278	2.57E-06	0.00017906	0.000253884	0.48

SNP, single nucleotide polymorphism; Beta, effect size of SNP exposure; SE, standard error of SNP exposure.

Table SIII. Summary statistics utilized in the Mendelian randomization study of cathepsin B in melanoma.

SNP	Effect allele	Other allele	F-statistic	Association with cathepsin B			Association with melanoma		
				Beta	SE	P-value	Beta	SE	P-value
rs1065853	T	G	23.93837248	0.2266	0.0463	0.000001	0.000103516	0.000422768	0.81
rs113646963	T	C	21.83745963	0.1996	0.0427	2.95121E-06	-0.000160673	0.000396216	0.69
rs11563944	G	A	21.55260075	0.1291	0.0278	3.54813E-06	0.000191284	0.00025882	0.46
rs117345475	G	A	21.54519354	-0.4332	0.0933	3.46737E-06	0.00180225	0.000980079	0.0659994
rs117486267	C	T	23.02373989	-0.4003	0.0834	1.58489E-06	-0.000619459	0.000821561	0.450001
rs13152767	A	G	22.98622038	0.4158	0.0867	1.62181E-06	-0.000107863	0.00110034	0.92
rs143557119	A	G	20.9087615	0.4327	0.0946	4.7863E-06	0.00023359	0.00094662	0.81
rs148930853	C	T	21.80145662	0.5516	0.1181	3.01995E-06	0.00242802	0.00116304	0.0369999
rs150370599	T	C	22.80404359	0.2183	0.0457	1.77828E-06	0.000704354	0.000421517	0.0949992
rs150811995	C	A	21.00638473	0.4603	0.1004	4.57088E-06	-2.54067E-05	0.00104197	0.98
rs1692819	A	G	239.9913812	0.4246	0.0274	5.24807E-54	-0.000239388	0.000261217	0.36
rs36021960	A	G	21.80617016	0.1747	0.0374	3.01995E-06	-0.000422139	0.000351558	0.23
rs7249773	A	G	24.8143085	0.1749	0.0351	6.0256E-07	-7.61543E-05	0.000329166	0.82
rs72863882	A	G	29.23329576	-0.2569	0.0475	6.45654E-08	0.000345738	0.000428901	0.42
rs75773690	A	G	21.17723044	-0.3945	0.0857	4.16869E-06	-0.00136152	0.000785238	0.0830004
rs76089522	A	G	21.90513066	-0.1971	0.0421	2.88403E-06	0.000201875	0.000379787	0.6
rs9905973	A	G	25.89830109	-0.1405	0.0276	3.54813E-07	0.000245291	0.000257796	0.34

SNP, single nucleotide polymorphism; Beta, effect size of SNP exposure; SE, standard error of SNP exposure.

Table SIV. Summary statistics utilized in the Mendelian randomization study of cathepsin O in melanoma.

SNP	Effect allele	Other allele	F-statistic	Association with cathepsin O			Association with melanoma		
				Beta	SE	P-value	Beta	SE	P-value
rs10902420	G	A	23.54865779	-0.2097	0.0432	1.23E-06	-9.73935E-06	0.000396446	0.98
rs146963690	G	T	22.30888376	0.6246	0.1322	2.29E-06	-0.00201118	0.00114153	0.0779992
rs17288007	G	A	22.20844083	-0.2456	0.0521	2.45E-06	0.000154814	0.000479601	0.75
rs181844705	G	A	23.75257184	0.4412	0.0905	1.10E-06	-1.53446E-05	0.00097194	0.99
rs1870736	G	C	24.07024489	0.1222	0.0249	9.33E-07	-0.000562963	0.000233159	0.016
rs2439803	G	A	25.21315437	0.1763	0.0351	5.13E-07	0.000323345	0.000320375	0.31
rs4297371	C	A	21.53670923	0.1453	0.0313	3.55E-06	-2.55142E-05	0.000290639	0.93
rs4843804	A	G	21.53419856	-0.3124	0.0673	3.47E-06	0.000351982	0.000654834	0.59
rs7140599	C	T	23.57201775	-0.1219	0.0251	1.17E-06	-8.03161E-05	0.000232648	0.73
rs78943701	A	G	21.82529323	-0.479	0.1025	2.95E-06	-0.000478142	0.000901549	0.6
rs9932172	T	C	22.79216617	0.1915	0.0401	1.74E-06	-0.000254072	0.000378278	0.5

SNP, single nucleotide polymorphism; Beta, effect size of SNP exposure; SE, standard error of SNP exposure.

Table SV. Summary statistics utilized in the Mendelian randomization study of cathepsin E in melanoma.

SNP	Effect allele	Other allele	F-statistic	Association with cathepsin E			Association with melanoma		
				Beta	SE	P-value	Beta	SE	P-value
rs10401027	A	G	22.35678964	-0.1225	0.0259	2.24E-06	-4.91418E-05	0.000230607	0.83
rs10900907	A	G	21.69148634	0.1188	0.0255	3.24E-06	-0.000250713	0.000235379	0.29
rs112918835	T	C	21.40341885	0.7062	0.1526	3.72E-06	1.45731E-05	0.00138755	0.99
rs13089837	C	T	21.22079901	-0.1152	0.025	4.17E-06	-3.16658E-05	0.000231142	0.89
rs149553686	C	T	21.32267416	0.2425	0.0525	3.89E-06	0.000189147	0.000483935	0.7
rs189009983	T	C	20.94717929	0.7055	0.1541	4.68E-06	0.00108797	0.00164043	0.51
rs1936839	C	G	22.52719168	0.1562	0.0329	2.00E-06	-0.000240515	0.000315344	0.450001
rs57135345	T	C	21.86221422	0.2535	0.0542	2.95E-06	-0.000489678	0.000505801	0.33
rs57689619	G	A	21.89081534	-0.2078	0.0444	2.82E-06	6.95676E-05	0.000405742	0.86
rs74677283	T	C	24.63482669	0.4379	0.0882	6.76E-07	-5.97915E-05	0.000800042	0.94
rs8066936	A	G	21.06239317	-0.1492	0.0325	4.27E-06	0.000366887	0.000296816	0.22

SNP, single nucleotide polymorphism; Beta, effect size of SNP exposure; SE, standard error of SNP exposure.

Table SVI. Summary statistics utilized in the Mendelian randomization study of cathepsin L2 in melanoma.

SNP	Effect allele	Other allele	F-statistic	Association with cathepsin L2			Association with melanoma		
				Beta	SE	P-value	Beta	SE	P-value
rs10817163	A	T	42.52409233	0.1983	0.0304	7.08E-11	-0.000339776	0.000276827	0.22
rs114113108	C	G	25.51633962	-0.5922	0.1172	4.37E-07	-0.00104813	0.00106723	0.33
rs116407656	C	T	21.97576479	0.4014	0.0856	2.75E-06	0.00109891	0.000855807	0.2
rs117714361	G	A	20.83697997	-0.3452	0.0756	4.90E-06	-0.0010076	0.000738094	0.17
rs13068566	G	A	21.92853421	0.1157	0.0247	2.88E-06	-0.000300796	0.000230834	0.19
rs148608463	A	G	20.99718745	-0.1178	0.0257	4.57E-06	-7.15254E-06	0.000240528	0.98
rs151179824	A	G	22.24529745	0.4449	0.0943	2.34E-06	0.000160632	0.00091301	0.86
rs1523319	G	C	21.43154162	-0.1292	0.0279	3.55E-06	-0.000164091	0.000255026	0.52
rs2302837	G	A	26.01881036	-0.2541	0.0498	3.31E-07	0.000913752	0.000471098	0.0519996
rs7669728	C	T	26.21947256	-0.1301	0.0254	3.09E-07	-0.000167489	0.000233264	0.47
rs7898416	G	A	21.66931257	-0.2277	0.0489	3.24E-06	-0.00024718	0.000443439	0.58

SNP, single nucleotide polymorphism; Beta, effect size of SNP exposure; SE, standard error of SNP exposure.

Table SVII. Heterogeneity tests of cathepsins in melanoma.

Cathepsins	Method	Q	Q_df	Q_pval
Cathepsin S	MR-Egger	27.41523	21	0.157528
	Inverse variance weighted	27.42115	22	0.195666
Cathepsin B	MR-Egger	18.78225	15	0.223772
	Inverse variance weighted	19.01359	16	0.267959
Cathepsin O	MR-Egger	4.114091	8	0.846686
	Inverse variance weighted	5.165336	9	0.819664
Cathepsin E	MR-Egger	3.565834	9	0.937601
	Inverse variance weighted	4.08573	10	0.943397
Cathepsin L2	MR-Egger	11.64423	9	0.234117
	Inverse variance weighted	12.68277	10	0.241953

MR-Egger, Mendelian randomization-Egger; Q_df, the degrees of freedom of the sum of squared residuals ; Q-pval, P-value of the test statistic.

Table SVIII. Test for the directional horizontal pleiotropy of cathepsins in melanoma.

Cathepsins	egger_intercept	Standard error	P-value
Cathepsin S	-9.30E-06	0.000137	0.94694
Cathepsin B	-0.000112	0.00026	0.67343
Cathepsin O	0.0003042	0.000297	0.335221
Cathepsin E	-0.000167	0.000231	0.489191
Cathepsin L2	-0.000238	0.000265	0.393618