

SHORT COMMUNICATION

Causal relationship between cathepsin H and type 1 diabetes: A Mendelian randomization study

Supplementary Files

**Table S1. Additional information about genome-wide association study in the exposure groups**

Exposure	GWAS ID	Sample size	Number of SNPs	PubMed ID
Cathepsin B	prot-a-718	3,301	10,534,735	29875488
Cathepsin E	prot-a-720			
Cathepsin F	prot-a-722			
Cathepsin G	prot-a-723			
Cathepsin H	prot-a-725			
Cathepsin O	prot-a-726			
Cathepsin S	prot-a-727			
Cathepsin L2	prot-a-728			
Cathepsin Z	prot-a-729			

Abbreviations: GWAS: Genome-wide association study; SNP: Single nucleotide polymorphism.

**Table S2. Additional information about FinnGen in the outcome groups**

Outcome	Case	Control	Web source
Type 1 diabetes mellitus	4,96	308,252	<a href="https://storage.googleapis.com/finngen-public-data-r9/summary_stats/finngen_R9_T1D.gz">https://storage.googleapis.com/finngen-public-data-r9/summary_stats/finngen_R9_T1D.gz</a>
Type 2 diabetes mellitus	57,698	308,252	<a href="https://storage.googleapis.com/finngen-public-data-r9/summary_stats/finngen_R9_T2D.gz">https://storage.googleapis.com/finngen-public-data-r9/summary_stats/finngen_R9_T2D.gz</a>
Gestational diabetes mellitus	13,039	197,831	<a href="https://storage.googleapis.com/finngen-public-data-r9/summary_stats/finngen_R9_GEST_DIABETES.gz">https://storage.googleapis.com/finngen-public-data-r9/summary_stats/finngen_R9_GEST_DIABETES.gz</a>

Table S3. Cochran's Q test and Mendelian randomization-Egger intercept results in univariable Mendelian randomization analysis

Outcome	Exposure	IVW-Q test		Mendelian randomization-Egger intercept analysis		
		Q-statistic	Q-p-value	Intercept	SE	p-value
Type 1 diabetes mellitus	Cathepsin B	22.998	0.149	-0.023	0.019	0.242
	Cathepsin E	7.770	0.456	-0.003	0.013	0.838
	Cathepsin F	7.994	0.534	-0.022	0.197	0.293
	Cathepsin G	5.805	0.831	0.028	0.021	0.217
	Cathepsin H	9.026	0.435	-0.018	0.011	0.119
	Cathepsin O	15.457	0.417	0.001	0.026	0.958
	Cathepsin S	23.252	0.387	0.015	0.009	0.107
	Cathepsin L2	11.634	0.310	-0.037	0.219	0.126
	Cathepsin Z	10.630	0.561	-0.001	0.010	0.886
Type 2 diabetes mellitus	Cathepsin B	14.514	0.630	0.007	0.007	0.347
	Cathepsin E	13.311	0.102	0.002	0.007	0.802
	Cathepsin F	18.972	0.083	-0.029	0.025	0.266
	Cathepsin G	6.401	0.780	0.003	0.009	0.765
	Cathepsin H	16.381	0.059	-0.001	0.007	0.964
	Cathepsin O	28.488	0.003*	-0.003	0.012	0.806
	Cathepsin S	35.950	0.031*	-0.009	0.005	0.061
	Cathepsin L2	11.526	0.218	0.004	0.015	0.817
	Cathepsin Z	9.208	0.685	0.001	0.004	0.954
Gestational diabetes mellitus	Cathepsin B	14.160	0.656	0.010	0.014	0.486
	Cathepsin E	16.535	0.235	-0.028	0.012	0.149
	Cathepsin F	18.711	0.186	-0.056	0.045	0.243
	Cathepsin G	3.971	0.949	0.010	0.018	0.572
	Cathepsin H	11.198	0.262	-0.021	0.009	0.242
	Cathepsin O	13.706	0.250	-0.025	0.014	0.101
	Cathepsin S	41.968	0.006*	-0.005	0.011	0.624
	Cathepsin L2	15.761	0.107	-0.007	0.024	0.783
	Cathepsin Z	18.025	0.115	-0.016	0.009	0.119

Note: Asterisk (\*) represents  $p < 0.001$ .

Abbreviations: IVW: Inverse-variance weighted; SE: Standard error.

**Table S4. Results of inverse-variance weighted method in univariable Mendelian randomization analysis**

Outcome	Exposure	SNPs	OR	95% CI	p-value
Type 1 diabetes mellitus	Cathepsin B	18	1.024	0.964 – 1.087	0.442
	Cathepsin E	9	1.016	0.957 – 1.079	0.602
	Cathepsin F	10	0.996	0.940 – 1.056	0.904
	Cathepsin G	11	0.996	0.932 – 1.065	0.918
	Cathepsin H	10	1.104	1.065 – 1.145	< 0.001*
	Cathepsin O	12	0.978	0.878 – 1.090	0.687
	Cathepsin S	23	0.988	0.943 – 1.034	0.597
	Cathepsin L2	11	0.981	0.898 – 1.073	0.681
	Cathepsin Z	13	1.033	0.982 – 1.086	0.206
Type 2 diabetes mellitus	Cathepsin B	18	1.003	0.980 – 1.025	0.825
	Cathepsin E	9	0.999	0.965 – 1.034	0.953
	Cathepsin F	10	0.942	0.874 – 1.016	0.124
	Cathepsin G	11	0.988	0.960 – 1.017	0.419
	Cathepsin H	10	0.994	0.973 – 1.015	0.556
	Cathepsin O	12	1.001	0.953 – 1.053	0.954
	Cathepsin S	23	1.006	0.981 – 1.032	0.642
	Cathepsin L2	11	0.993	0.942 – 1.048	0.807
	Cathepsin Z	13	1.005	0.983 – 1.027	0.661
Gestational diabetes mellitus	Cathepsin B	18	1.041	0.997 – 1.087	0.072
	Cathepsin E	9	1.006	0.935 – 1.082	0.868
	Cathepsin F	10	0.969	0.846 – 1.110	0.647
	Cathepsin G	11	0.993	0.939 – 1.050	0.794
	Cathepsin H	10	1.008	0.975 – 1.042	0.635
	Cathepsin O	12	1.008	0.943 – 1.077	0.823
	Cathepsin S	23	1.005	0.954 – 1.059	0.859
	Cathepsin L2	11	0.992	0.909 – 1.083	0.855
	Cathepsin Z	13	1.021	0.970 – 1.075	0.433

Note: Asterisk (\*) represents  $p < 0.001$ .

Abbreviations: CI: Confidence interval; OR: Odds ratio; SNPs: Single nucleotide polymorphisms.

**Table S5. Results of inverse-variance weighted method in reverse Mendelian randomization analysis**

Outcome	Exposure	SNPs	OR	95% CI	p-value
Cathepsin B	Type 1 diabetes mellitus	101	1.002	0.967 – 1.038	0.927
Cathepsin E		101	1.003	0.971 – 1.037	0.838
Cathepsin F		101	1.003	0.967 – 1.035	0.982
Cathepsin G		101	0.988	0.953 – 1.025	0.522
Cathepsin H		101	1.044	0.932 – 1.170	0.454
Cathepsin O		101	1.031	0.996 – 1.068	0.083
Cathepsin S		101	1.032	0.997 – 1.068	0.077
Cathepsin L2		101	1.023	0.987 – 1.060	0.215
Cathepsin Z		101	1.030	0.996 – 1.065	0.084
Cathepsin B		Type 2 diabetes mellitus	151	1.025	0.955 – 1.101
Cathepsin E	151		0.970	0.903 – 1.043	0.412
Cathepsin F	151		1.021	0.934 – 1.115	0.650
Cathepsin G	151		1.000	0.926 – 1.080	0.992
Cathepsin H	151		1.023	0.953 – 1.098	0.522
Cathepsin O	151		1.005	0.937 – 1.079	0.885
Cathepsin S	151		0.995	0.921 – 1.075	0.906
Cathepsin L2	151		1.008	0.939 – 1.082	0.820
Cathepsin Z	151		1.043	0.966 – 1.127	0.283
Cathepsin B	Gestational diabetes mellitus		43	1.030	0.945 – 1.122
Cathepsin E		43	1.019	0.923 – 1.124	0.710
Cathepsin F		43	0.979	0.872 – 1.100	0.724
Cathepsin G		43	1.009	0.914 – 1.115	0.854
Cathepsin H		43	0.964	0.885 – 1.049	0.392
Cathepsin O		43	0.932	0.856 – 1.014	0.103
Cathepsin S		43	1.045	0.953 – 1.146	0.344
Cathepsin L2		43	0.981	0.894 – 1.077	0.691
Cathepsin Z		43	1.066	0.968 – 1.173	0.195

Abbreviations: CI: Confidence interval; OR: Odds ratio; SNPs: Single nucleotide polymorphisms.

**Table S6. Results of multivariable Mendelian randomization analysis**

Outcome	Exposure	SNPs	OR	95% CI	p-value
Type 1 diabetes mellitus	Cathepsin B	94	1.028	0.974 – 1.086	0.312
	Cathepsin E		1.025	0.966 – 1.089	0.413
	Cathepsin F		1.003	0.936 – 1.076	0.923
	Cathepsin G		1.015	0.950 – 1.086	0.656
	Cathepsin H		1.090	1.048 – 1.133	<0.001*
	Cathepsin O		1.017	0.926 – 1.116	0.725
	Cathepsin S		0.977	0.929 – 1.026	0.350
	Cathepsin L2		0.931	0.855 – 1.014	0.102
	Cathepsin Z		1.019	0.955 – 1.087	0.575
Type 2 diabetes mellitus	Cathepsin B	94	1.009	0.976 – 1.043	0.593
	Cathepsin E		0.994	0.959 – 1.031	0.766
	Cathepsin F		1.062	0.962 – 1.172	0.267
	Cathepsin G		1.010	0.970 – 1.052	0.631
	Cathepsin H		0.994	0.971 – 1.017	0.616
	Cathepsin O		1.032	0.976 – 1.092	0.267
	Cathepsin S		1.008	0.978 – 1.039	0.603
	Cathepsin L2		0.973	0.924 – 1.024	0.297
	Cathepsin Z		1.037	0.997 – 1.078	0.068
Gestational diabetes mellitus	Cathepsin B	94	1.016	0.954 – 1.081	0.626
	Cathepsin E		1.030	0.961 – 1.103	0.404
	Cathepsin F		0.938	0.866 – 1.016	0.117
	Cathepsin G		1.022	0.946 – 1.103	0.580
	Cathepsin H		0.998	0.955 – 1.042	0.918
	Cathepsin O		1.055	0.948 – 1.174	0.324
	Cathepsin S		0.990	0.936 – 1.048	0.737
	Cathepsin L2		0.965	0.875 – 1.065	0.479
	Cathepsin Z		1.060	0.984 – 1.142	0.126

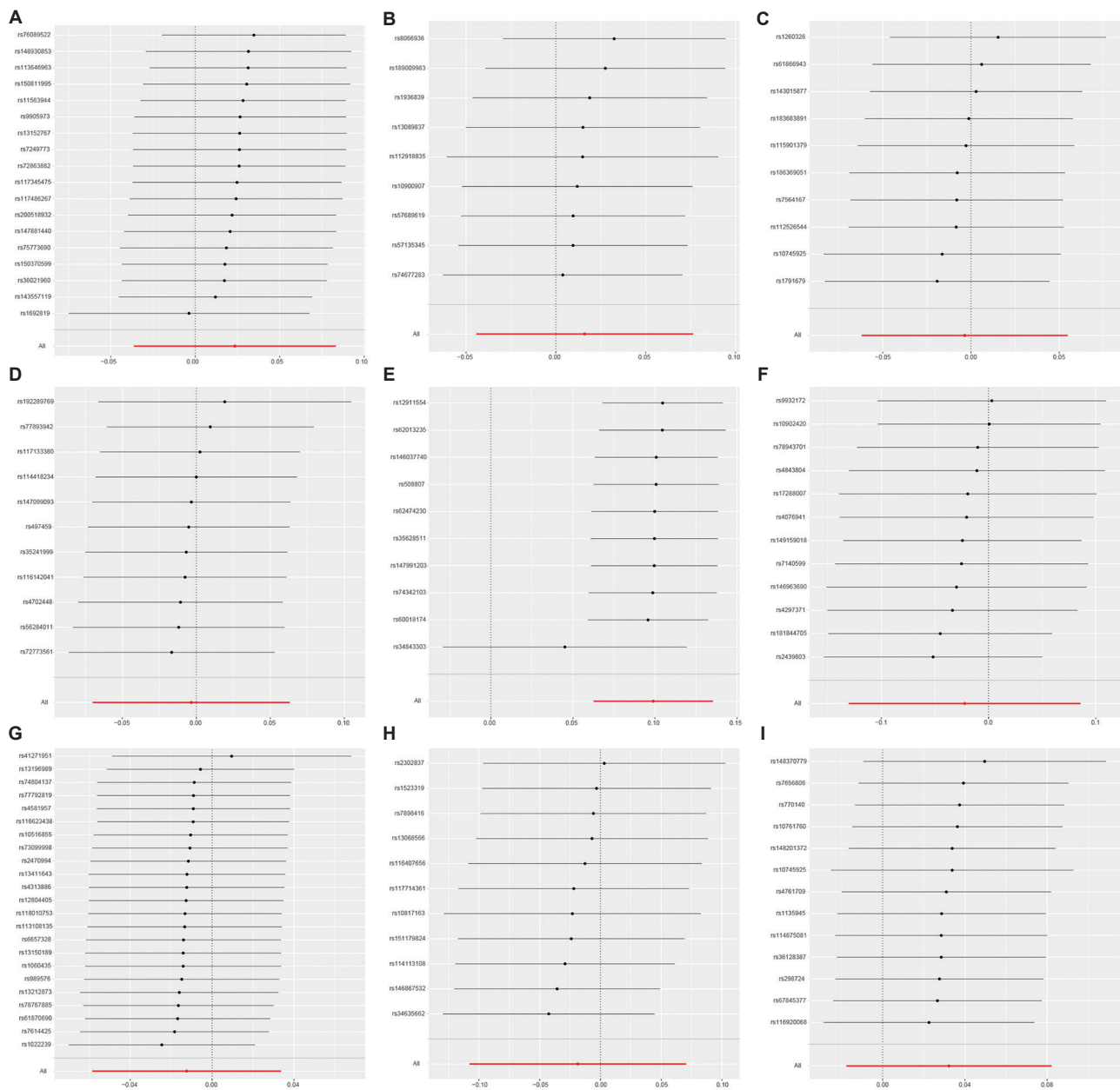
Note: Asterisk (\*) represents  $p < 0.001$ .

Abbreviations: CI: Confidence interval; OR: Odds ratio; SNPs: Single nucleotide polymorphisms.

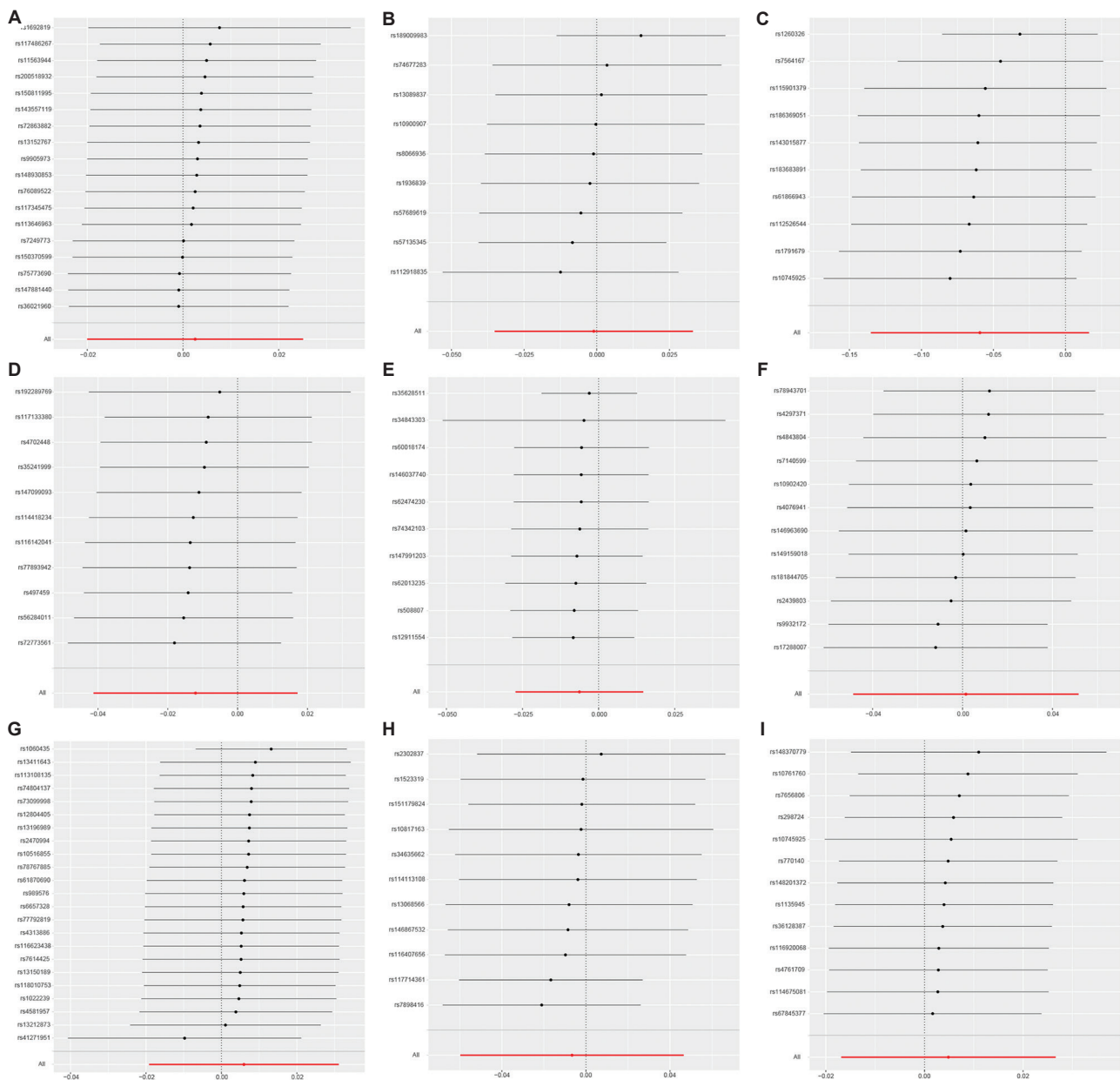
**Table S7. Cochran's Q test and Mendelian randomization-Egger intercept in multivariable Mendelian randomization analysis**

Outcome	IVW-Q test		Mendelian randomization-Egger		
	Q-statistic	Q-p-value	Intercept	SE	p-value
Type 1 diabetes mellitus	92.143	0.255	0.019	0.033	0.575
Type 2 diabetes mellitus	99.694	0.138	0.002	0.002	0.440
Gestational diabetes mellitus	93.425	0.217	0.002	0.004	0.594

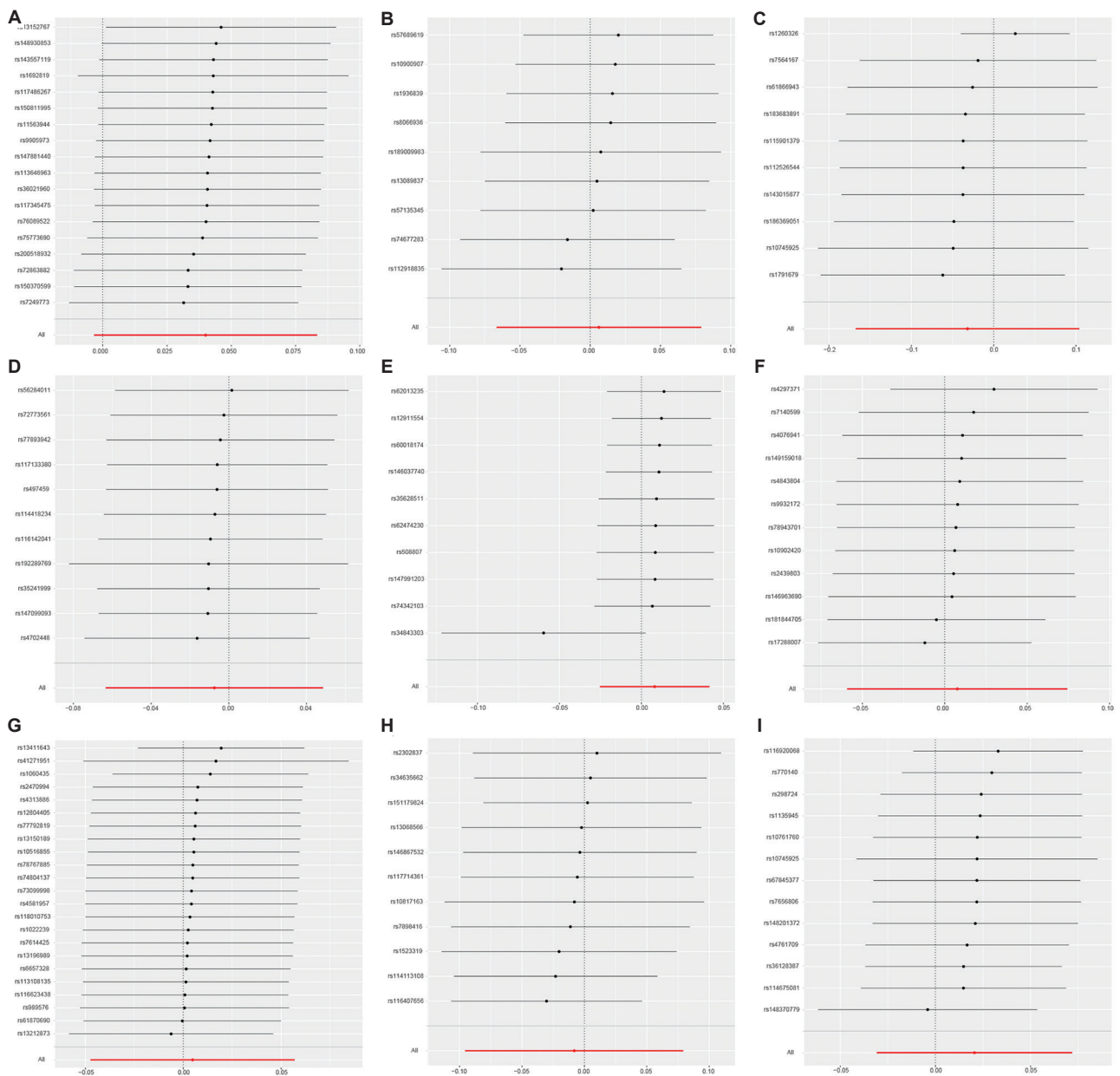
Abbreviations: IVW: Inverse-variance weighted; SE: Standard error.



**Figure S1.** Leave-one-out analysis of cathepsins on type 1 diabetes mellitus for (A) cathepsin B; (B) cathepsin E; (C) cathepsin F; (D) cathepsin G; (E) cathepsin H; (F) cathepsin O; (G) cathepsin S; (H) cathepsin L2; and (I) cathepsin Z. Each point shows the result of the Mendelian randomization analysis after removing one single nucleotide polymorphism at a time. This helps determine whether any single nucleotide polymorphism strongly influences the overall result.



**Figure S2.** Leave-one-out analysis of cathepsins on type 2 diabetes mellitus for (A) cathepsin B; (B) cathepsin E; (C) cathepsin F; (D) cathepsin G; (E) cathepsin H; (F) cathepsin O; (G) cathepsin S; (H) cathepsin L2; and (I) cathepsin Z. Each point shows the result of the Mendelian randomization analysis after removing one single nucleotide polymorphism at a time. This helps determine whether any single nucleotide polymorphism strongly influences the overall result.



**Figure S3.** Leave-one-out analysis of cathepsins on gestational diabetes mellitus for (A) cathepsin B; (B) cathepsin E; (C) cathepsin F; (D) cathepsin G; (E) cathepsin H; (F) cathepsin O; (G) cathepsin S; (H) cathepsin L2; and (I) cathepsin Z. Each point shows the result of the Mendelian randomization analysis after removing one single nucleotide polymorphism at a time. This helps determine whether any single nucleotide polymorphism strongly influences the overall result.