Supplementary

Table S1 Detailed information for data sources of CVDs outcomes

Data sources	Phenotypes	Sample size	Cases	Ethnicity	Cases definition	Adjustment
CARDIoGRAMplusC4D	Coronary artery disease	184,305	60,801	77% European	Myocardial infarction, acute coronary syndrome, chronic stable angina, or coronary stenosis of > 50%	Age, sex, principal components
	Myocardial infarction	184,305	43,676		Not reported	
Nielsen et al. GWAS	Atrial fibrillation	1,030,836	60,620	European	Paroxysmal or permanent atrial fibrillation and atrial flutter	Birth year, sex, genotype batch, and 1–4 principal components
HERMES	Heart failure	977,323	47,309	European	Clinical diagnosis of HF of any aetiology with no inclusion criteria based on LV ejection fraction	Age and sex, and principal components in individual studies where applicable
FinnGen	Coronary artery disease	260,405	25,707	European	ICD-8, code 410 or 4110; ICD-9, code 410 or 4110; ICD-10, code I20.0, I21, or I22	Age, sex, the first 10 genetic principal components, and genotyping batch
	Myocardial infarction	238,338	15,787	European	ICD-8, code 410; ICD-9, code 410; ICD-10, code I21, or I22	
	Atrial fibrillation	164,491	28,670	European	ICD-8, code 42792; ICD-9, code 4273; ICD-10, code I48	
	Heart failure	260,405	30,459	European	ICD-8, code 42700, 42710, 428, or 7824; ICD-9, code 4029B or 428; ICD-10, code I11.0, I13.0, I13.2, or I50	

CARDIoGRAMplusC4D, Coronary ARtery DIsease Genome-wide Replication and Meta-analysis plus The Coronary Artery Disease Genetics; HERMES, Heart Failure Molecular Epidemiology for Therapeutic Targets; CVDs, cardiovascular diseases; ICD, International Classification of Diseases.

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Table S2 Characteristics of the genetic variants associated with FI

SNP	EA	OA	EAF	R^2 (%)	F	SNP-Frailty index			SNP-Coronary artery disease (CARDIoGRAMplusC4D)			SNP-Coronary artery disease (FinnGen)			SNP-Myocardial infarction (CARDIoGRAMplusC4D)			SNP-Myocardial infarction (FinnGen)			SNP-Atrial fibrillation (Nielsen *et al.*)			SNP-Atrial fibrillation (FinnGen)			SNP-Heart failure (HERMES)			SNP-Heart failure (FinnGen)		
						Beta	SE	P-value	Beta	SE	P-value	Beta	SE	P-value	Beta	SE	P-value	Beta	SE	P-value	Beta	SE	P-value	Beta	SE	P-value	Beta	SE	P-value	Beta	SE	P-value
rs10891490	T	C	0.41	0.017	30.6	0.019	0.003	2.00E-08	-0.007	0.010	0.454	0.016	0.014	0.225	-0.004	0.011	0.676	0.008	0.016	0.624	0.003	0.007	0.660	0.020	0.016	0.189	0.011	0.008	0.173	0.025	0.012	0.031
rs12739243	T	C	0.78	0.020	34.6	0.024	0.004	1.30E-09	0.029	0.011	0.009	-0.018	0.014	0.206	0.019	0.013	0.138	-0.030	0.017	0.075	0.006	0.009	0.455	0.022	0.016	0.180	0.009	0.009	0.354	0.007	0.012	0.592
rs1363103	T	C	0.62	0.017	29.8	0.019	0.003	2.20E-08	0.008	0.010	0.420	0.030	0.013	0.025	0.020	0.011	0.067	0.033	0.016	0.037	0.001	0.007	0.919	0.016	0.015	0.306	-0.003	0.008	0.756	0.009	0.012	0.456
rs17612102	T	C	0.41	0.017	30.6	-0.019	0.003	2.80E-08	-0.002	0.010	0.805	-0.013	0.013	0.317	-0.013	0.011	0.240	-0.015	0.016	0.347	-0.008	0.007	0.296	-0.002	0.015	0.905	0.002	0.008	0.785	0.013	0.011	0.269
rs2071207	T	C	0.52	0.018	31.6	0.019	0.003	1.50E-08	0.024	0.010	0.013	-0.010	0.013	0.454	0.021	0.011	0.052	-0.006	0.016	0.693	0.003	0.007	0.671	0.004	0.015	0.774	0.014	0.008	0.079	-0.005	0.011	0.681
rs2396766	A	G	0.47	0.020	34.9	0.02	0.033	1.20E-09	0.005	0.010	0.637	0.021	0.013	0.106	0.011	0.011	0.293	0.025	0.016	0.108	0.011	0.007	0.133	0.026	0.015	0.083	0.015	0.008	0.050	0.037	0.011	0.001
rs3959554	A	G	0.58	0.018	30.8	-0.019	0.003	1.70E-08	-0.012	0.010	0.232	-0.025	0.014	0.067	-0.013	0.011	0.230	-0.034	0.017	0.044	-0.005	0.008	0.514	0.004	0.016	0.807	-0.004	0.008	0.622	0.005	0.012	0.663
rs4146140	T	C	0.38	0.019	33.0	-0.02	0.003	6.80E-09	0.007	0.010	0.499	0.031	0.014	0.022	0.008	0.011	0.468	0.029	0.017	0.079	0.005	0.008	0.510	-0.026	0.016	0.098	0.002	0.008	0.802	0.000	0.012	0.993
rs4952693	T	C	0.37	0.017	29.5	-0.019	0.003	1.50E-08	0.000	0.010	0.973	0.012	0.013	0.362	0.004	0.011	0.707	0.021	0.016	0.188	0.003	0.008	0.727	0.000	0.015	0.978	-0.003	0.008	0.710	0.012	0.011	0.277
rs56299474	A	C	0.17	0.016	28.5	0.024	0.004	3.90E-08	-0.003	0.016	0.854	-0.014	0.018	0.424	-0.017	0.018	0.342	0.009	0.021	0.669	0.029	0.010	0.004	0.025	0.020	0.221	0.022	0.011	0.048	0.004	0.015	0.786
rs583514	T	C	0.49	0.020	35.0	-0.02	0.003	1.70E-09	-0.017	0.009	0.074	-0.021	0.013	0.106	-0.027	0.010	0.010	-0.015	0.016	0.336	-0.014	0.007	0.050	-0.019	0.015	0.205	-0.015	0.008	0.061	-0.020	0.011	0.074
rs8089807	T	C	0.19	0.019	33.7	-0.025	0.004	6.50E-09	-0.003	0.012	0.782	0.015	0.018	0.428	0.000	0.014	0.996	-0.005	0.022	0.833	-0.001	0.010	0.933	-0.002	0.021	0.939	-0.018	0.010	0.086	-0.027	0.016	0.095
rs82334	A	C	0.68	0.021	36.9	0.022	0.004	3.10E-10	0.013	0.010	0.185	0.013	0.013	0.314	0.022	0.011	0.053	0.008	0.016	0.619	-0.014	0.008	0.065	0.005	0.015	0.718	-0.001	0.008	0.954	0.012	0.011	0.290
rs9275160	A	G	0.34	0.065	113.6	0.038	0.004	7.20E-28	NA	NA	NA	0.036	0.014	0.011	NA	NA	NA	0.055	0.017	0.001	-0.004	0.008	0.650	0.018	0.016	0.270	0.012	0.009	0.194	0.030	0.012	0.014

SNP, single-nucleotide polymorphism; EA, effect allele; OA, other allele; EAF, effect allele frequency; R^2, percentage of the variation of frailty index explained by the SNPs; F, F statistic; HERMES, Heart Failure Molecular Epidemiology for Therapeutic Targets; Beta, the per-allele effect on frailty index; SE, standard error; P-value is for the genetic association. FI, frailty index.

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Table S3 Priori power calculations in Mendelian randomization study of frailty index and risk of cardiovascular diseases

Outcomes	Data sources	OR=1.20	OR=1.40	OR=1.60	OR=1.80
Coronary artery disease	CARDIoGRAMplusC4D	0.46	0.94	1.00	1.00
	FinnGen	0.38	0.90	1.00	1.00
Myocardial infarction	CARDIoGRAMplusC4D	0.39	0.90	1.00	1.00
	FinnGen	0.26	0.75	0.97	1.00
Atrial fibrillation	Nielsen et al.	0.74	1.00	1.00	1.00
	FinnGen	0.38	0.89	1.00	1.00
Heart failure	HERMES	0.64	1.00	1.00	1.00
	FinnGen	0.42	0.93	1.00	1.00

CARDIoGRAMplusC4D, Coronary ARtery DIsease Genome-wide Replication and Meta-analysis (CARDIoGRAM) plus The Coronary Artery Disease (C4D) Genetics; HERMES, Heart Failure Molecular Epidemiology for Therapeutic Targets; OR, odds ratio.

Table S4 Evaluation of heterogeneity and horizontal pleiotropy using different methods

Outcomes	Data sources	Heterogeneity			Horizontal pleiotropy test		
		Cochran's Q statistic	Cochran's P	I^2 (%)	MR-Egger intercept	MR-Egger intercept P	Outlier detected by MR-PRESSO
Coronary artery disease	CARDIoGRAMplusC4D	13.7	0.323	12.2	-0.0187	0.589	None
	FinnGen	28.8	0.007	54.9	-0.0126	0.637	rs4146140
Myocardial infarction	CARDIoGRAMplusC4D	15.5	0.213	22.8	0.0198	0.629	None
	FinnGen	26.4	0.015	50.8	-0.0327	0.280	None
Atrial fibrillation	Nielsen et al.	18.8	0.131	30.7	0.0093	0.456	None
	FinnGen	5.6	0.958	0.0	0.0028	0.887	None
Heart failure	HERMES	10.5	0.650	0.0	-0.0027	0.802	None
	FinnGen	22.2	0.052	41.4	-0.0224	0.255	None

CARDIoGRAMplusC4D, Coronary ARtery DIsease Genome-wide Replication and Meta-analysis (CARDIoGRAM) plus The Coronary Artery Disease (C4D) Genetics; HERMES, Heart Failure Molecular Epidemiology for Therapeutic Targets; MR-Egger, Mendelian randomization-Egger; MR-PRESSO, MR-pleiotropy residual sum and outlier.

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