Supplemental information
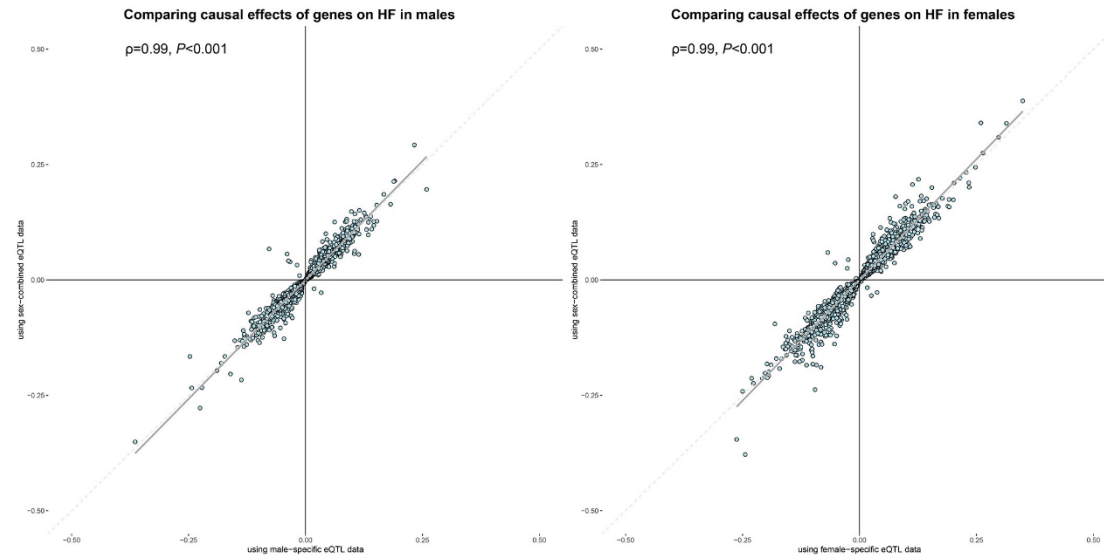
Sex-stratified genome-wide association

and transcriptome-wide Mendelian randomization

studies reveal drug targets of heart failure

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Figure S1. Comparison of causal effects estimated for heart failure using sex-stratified and sex-combined eQTLs data, related to Figure 2.

HF, heart failure. The x-axis represents estimates using sex-stratified eQTLs data and the y-axis represents estimates using sex-combined eQTLs data. The grey smoothing lines and shaded regions around them represent the overall trend and 95% confidence intervals (CI) of the estimates. ρ calculated by Spearman correlation methods were used to quantify the correlations.

Table S1. Summary of data processing for the eQTLs, related to STAR Methods.

	Male	Female	Both sex
cis-eQTL with P<1e-4	18235 eQTLs of 7872 genes	18248 eQTLs of 7914 genes	24145 eQTLs of 9680 genes
cis-eQTL with P<1e-5	18235 (100%) eQTLs of 7872 genes	18248 (100%) eQTLs of 7914 genes	23689 (98%) eQTLs of 9558 genes
Removing weak instruments (F-statistics<10)	15292 (84%) eQTLs of 6565 genes	15453 (85%) eQTLs of 6644 genes	15928 (66%) eQTLs of 6600 genes
shared eQTLs available in both males and females	10592 (58%) eQTLs of 4589 genes		
match with HF	6555 eQTLs of 3335 genes		12437 eQTLs of 5656 genes
after steiger filtering	6555 eQTLs of 3335 genes		12437 eQTLs of 5656 genes
match with LVEF	7931 eQTLs of 3771 genes		/
after steiger filtering	7931 eQTLs of 3771 genes		/
match with HFrEF	6254 eQTLs of 3304 genes	/	/
after steiger filtering	6254 eQTLs of 3304 genes	/	/
match with HFpEF	6254 eQTLs of 3304 genes	/	/
after steiger filtering	6254 eQTLs of 3304 genes	/	/

Table S2. Data sources, related to STAR Methods

Phenotype	Sex	Case	Control	Total Participants	Reference
eQTLs	Both sex, male, and female	/	/	838 (557 males, 281 females)	GTEx
LVEF	Male	/	/	17,899	This study
LVEF	Female	/	/	19,467	This study
HF	Both sex	47,309 (59.1% males)	930,014 (47.2% males)	977,323	HERMES
HF	Both sex	28,795	772,854	801,649	GBMI
HF	Male	10,288	10,006	20,294	GBMI
HF	Female	6,414	12,211	18,625	GBMI
HFrEF	Male-dominate	19,495	258,943	278,438	MVP
HFpEF	Male-dominate	19,589	258,943	278,532	MVP

GTEx, Genotype-Tissue Expression project; HERMES, Heart Failure Molecular Epidemiology for Therapeutic Targets Consortium; GBMI, Global Biobank Meta-analysis Initiative; MVP, Million Veteran Program.

Table S13. Sex-differential genes showed robust causal effects on LVEF in both males and females, related to STAR Methods

Exposure	Gene	SNP	Tissue	Outcome	Male		Female		P(Z)
					Effect size	P value	Effect size	P value	
ENSG00000172322.13	CLEC12A	rs199560361	Adipose_Visceral_Omentum	LVEF	-0.22 (-0.38, -0.06)	6.33E-03	0.17 (0.03, 0.31)	1.46E-02	2.50E-04
ENSG00000256660.5	CLEC12B	rs199560361	Adipose_Subcutaneous	LVEF	-0.17 (-0.29, -0.05)	6.33E-03	0.15 (0.03, 0.27)	1.46E-02	2.60E-04
ENSG00000172322.13	CLEC12A	rs199560361	Adipose_Subcutaneous	LVEF	-0.15 (-0.26, -0.04)	6.33E-03	0.14 (0.03, 0.25)	1.46E-02	2.82E-04
ENSG00000165682.14	CLEC1B	rs199560361	Adipose_Subcutaneous	LVEF	-0.16 (-0.28, -0.05)	6.33E-03	0.15 (0.03, 0.28)	1.46E-02	2.51E-04
ENSG00000172322.13	CLEC12A	rs199560361	Heart_Left_Ventricle	LVEF	-0.16 (-0.28, -0.05)	6.33E-03	0.17 (0.03, 0.30)	1.46E-02	2.55E-04
ENSG00000256660.5	CLEC12B	rs199560361	Adipose_Visceral_Omentum	LVEF	-0.23 (-0.39, -0.06)	6.33E-03	0.25 (0.05, 0.45)	1.46E-02	2.96E-04
ENSG00000172322.13	CLEC12A	rs199560361	Artery_Tibial	LVEF	-0.21 (-0.36, -0.06)	6.33E-03	0.16 (0.03, 0.29)	1.46E-02	2.62E-04
ENSG00000165682.14	CLEC1B	rs199560361	Whole_Blood	LVEF	-0.57 (-0.98, -0.16)	6.33E-03	0.37 (0.07, 0.66)	1.46E-02	2.71E-04
ENSG00000125510.15	OPRL1	rs8126001	Pancreas	LVEF	-0.19 (-0.31, -0.06)	3.51E-03	0.16 (0.05, 0.27)	6.07E-03	6.18E-05

Table S14. SNPs robustly and independently associated with LVEF in males and females, related to Figure 4

Sex	SNP	gene	eaf	beta	se	F statistics	pval
	rs848217	ZBTB17	0.499887	-0.458882	0.0664135	47.74075782	4.90E-12
	rs2128160	LOC105376958	0.440248	0.396163	0.0671817	34.77329501	3.70E-09
male	rs4151702	CDKN1A	0.801135	-0.584733	0.0835766	48.94922383	2.60E-12
	rs72840788	BAG3	0.781904	-0.585573	0.0814678	51.66424777	6.60E-13
female	rs730506	CDKN1A	0.802495	-0.451082	0.0709352	40.43778879	2.00E-10
	rs72840788	BAG3	0.783594	-0.531044	0.0686636	59.81469238	1.00E-14

Table S15. Effects of LVEF on HF/HF subtypes, related to Figure 4

Exposure	Outcome	Method	N_SNP	b	se	pval	OR (95% CI)
female_LVEF	female_GBMI	Inverse variance weighted	2	-0.175773872	0.034175602	2.70E-07	0.84 (0.78-0.90)
male_LVEF	male_GBMI	MR Egger	4	-0.370140541	0.105995004	0.073123555	0.69 (0.56-0.85)
		Weighted median	4	-0.108287229	0.024368229	8.84E-06	0.90 (0.86-0.94)
		Inverse variance weighted	4	-0.109444117	0.025561144	1.86E-05	0.90 (0.85-0.94)
		Simple mode	4	-0.124971553	0.041590649	0.057448914	0.88 (0.81-0.96)
		Weighted mode	4	-0.122956324	0.039265025	0.052007152	0.88 (0.82-0.96)
male_LVEF	MVP_HFrEF	MR Egger	3	-0.452341496	0.157675332	0.213525803	0.64 (0.47-0.87)
		Weighted median	3	-0.189090722	0.026841807	1.86E-12	0.83 (0.79-0.87)
		Inverse variance weighted	3	-0.199669018	0.025064276	1.64E-15	0.82 (0.78-0.86)
		Simple mode	3	-0.192349092	0.037073279	0.035198869	0.83 (0.77-0.89)
		Weighted mode	3	-0.179571667	0.035441937	0.036816817	0.84 (0.78-0.90)
male_LVEF	MVP_HFpEF	MR Egger	3	-0.009085125	0.264713768	0.978159424	0.99

						(0.59-1.66)
		Weighted median	3	0.028997452	0.018720109	0.121381684	1.03 (0.99-1.07)
		Inverse variance weighted	3	0.026729423	0.02218512	0.228266763	1.03 (0.98-1.07)
		Simple mode	3	0.041570141	0.027436769	0.268968003	1.04 (0.99-1.10)
		Weighted mode	3	0.038271035	0.030107438	0.331512881	1.04 (0.98-1.10)