

Supplementary Materials

Genetically Determined Rheumatoid Arthritis may not Affect Heart Failure: Insights from Mendelian Randomization Study

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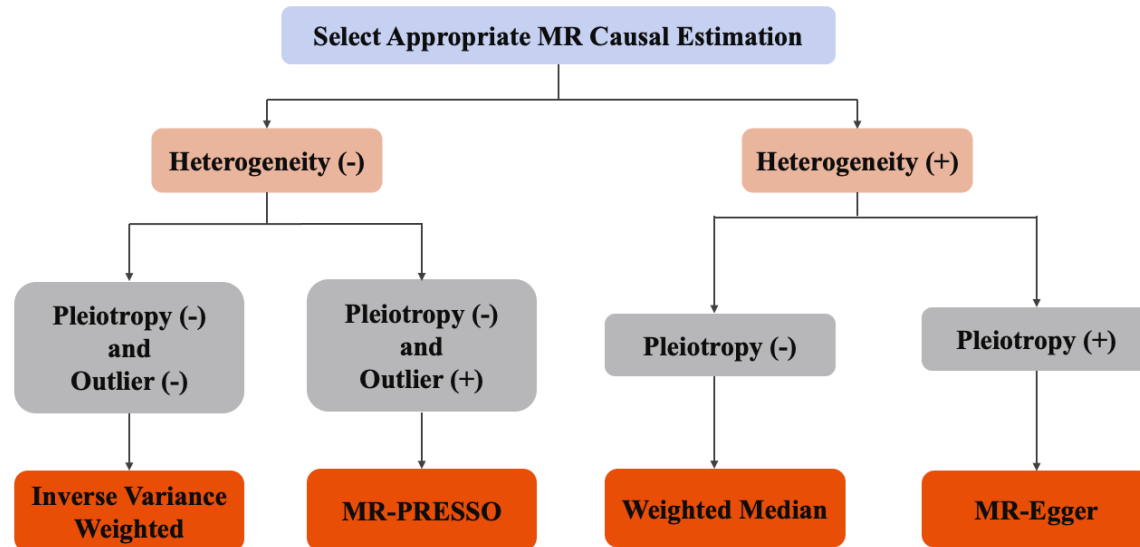
Figure: S4: Forest plots of variants specific inverse variance estimates for the casual association between rheumatoid arthritis and heart failure

Table S1 Contributing studies and more information on the datasets used for analyses

Use in MR	Phenotype	Data source	nCases	Sample size	Contributing studies	Sample overlap
Exposure	RA	Okada et al.	14,361	58,284	BRASS, CANADA, EIRA, NARAC1, NARAC2, WTCCC, Rheumatoid Arthritis Consortium International for Immunochip (RACI)-UK, RACI-US, RACI-SE-E, RACI-SE-U, RACI-NL, RACI-ES, RACI-i2b2, ReAct, Dutch (including AMC, BeSt, LUMC, and DREAM), anti-TNF response to therapy collection (ACR-REF: BRAGGSS, BRAGGSS2, ERA, KI, and TEAR), CORRONA, Vanderbilt,	0
Outcome	HF	Levin et al	95,524	1,366,492	HERMES, DISCOVERHR, EMERGE, FINNGEN, BIOME, PMBB	0

Abbreviation: MR, Mendelian randomization; RA, rheumatoid arthritis; HF, heart failure

Figure S2: Predefined decision tree of the selection of methods to evaluate associations using two-sample Mendelian randomization



Abbreviation: MR, Mendelian randomization; MR-PRESSO, Mendelian Randomization Pleiotropy RESidual Sum and Outlier

Table S2 Related traits of Rheumatic arthritis-associated SNPs

SNP	Chr	Pos	EA	NEA	Trait	Excluded from complementary analysis
rs61828284	1	173299743	T	C	Rheumatoid arthritis	No
rs60733400	1	2516781	A	G	Rheumatoid arthritis	No
rs2240336	1	17674402	T	C	Rheumatoid arthritis	No
rs28411352	1	38278579	T	C	Rheumatoid arthritis	No
rs6679677	1	114303808	A	C	Rheumatoid arthritis ; Basophil percentage of white cells; Crohns disease; Hypothyroidism; Juvenile idiopathic arthritis including oligoarticular and rheumatoid factor negative polyarticular JIA; Type 1 diabetes; Antineutrophil cytoplasmic antibody associated vasculitis; Pediatric autoimmune diseases; Systemic lupus erythematosus; Self-reported hyperthyroidism or thyrotoxicosis; Self-reported hypothyroidism or myxoedema	Yes (Systemic lupus erythematosus and hyperthyroidism or thyrotoxicosis)
rs13426947	2	191933254	A	G	Rheumatoid arthritis; Self-reported hypothyroidism or myxoedema	No
rs3087243	2	204738919	A	G	Alopecia areata; Graves disease; Rheumatoid arthritis; Selective immunoglobulin A deficiency IgAD; Type 1 diabetes; Self-reported hyperthyroidism or thyrotoxicosis; Self-reported hypothyroidism or myxoedema	Yes (hyperthyroidism or thyrotoxicosis)
rs9653442	2	100825367	T	C	Rheumatoid arthritis; Intelligence multi trait analysis; Years of educational attainment	No
rs34695944	2	61124850	C	T	Rheumatoid arthritis	No

rs2661798	2	65635688	T	A	Rheumatoid arthritis; White blood cell count	No
rs9310852	3	27784997	G	A	Rheumatoid arthritis; Lymphocyte count	No
rs4452313	3	17047032	T	A	Rheumatoid arthritis	No
rs73081554	3	58302935	T	C	Rheumatoid arthritis	No
rs34046593	4	26111593	A	G	Rheumatoid arthritis; Self-reported hypothyroidism or myxoedema	No
rs7731626	5	55444683	A	G	Pediatric autoimmune diseases; Rheumatoid arthritis	No
rs2561477	5	102608924	A	G	Rheumatoid arthritis; Self-reported hypothyroidism or myxoedema	No
rs62395855	6	31884909	T	C	Lymphocyte count; Body fat percentage; Rheumatoid arthritis; Trunk fat percentage	No
rs56339890	6	29782742	T	C	Eosinophil percentage of white cells; Rheumatoid arthritis; Hemoglobin concentration; Reticulocyte count	No
rs2844456	6	31864674	C	T	Granulocyte count; Asthma; Self-reported hypothyroidism or myxoedema; Self-reported malabsorption or coeliac disease; Hemoglobin concentration; Rheumatoid arthritis; Intestinal malabsorption; Hemoglobin concentration; Lymphocyte count; Neutrophil count; Myeloid white cell count; Peak expiratory flow	No
rs6936656	6	32393281	T	C	Height; Psoriasis; Self-reported hyperthyroidism or thyrotoxicosis; Self-reported malabsorption or coeliac disease; Self-reported psoriasis; Self-reported psoriatic arthropathy; Rheumatoid arthritis	Yes (hyperthyroidism or thyrotoxicosis)
rs17264332	6	138005515	G	A	Celiac disease; Inflammatory bowel disease; Rheumatoid arthritis; Self-reported malabsorption or coeliac disease;	No

					Neutrophil percentage of white cells; Lymphocyte percentage of white cells	
rs62401699	6	31022928	T	C	Granulocyte count; IgA deficiency; Height; Rheumatoid arthritis	No
rs71565347	6	32722961	A	G	Rheumatoid arthritis; Self-reported psoriasis	No
rs1571878	6	167540842	T	C	Rheumatoid arthritis; Self-reported hypothyroidism or myxoedema	No
rs9275183	6	32654502	G	A	Body mass index males; Sum eosinophil basophil counts; IgA deficiency; Inflammatory bowel disease; Ulcerative colitis; Primary sclerosing cholangitis; Asthma; Nasal polyp; Long-standing illness, disability or infirmity; Intestinal malabsorption; Self-reported ulcerative colitis; Self-reported malabsorption or coeliac disease; Self-reported polymyalgia rheumatica	No
rs1042169	6	33048686	A	G	NA	No
rs212389	6	159489791	A	G	Granulocyte count; Rheumatoid arthritis; Myeloid white cell count; Neutrophil count	No
rs12539741	7	128596805	T	C	Rheumatoid arthritis; Systemic lupus erythematosus	Yes (Systemic lupus erythematosus)
rs11574914	9	34710338	A	G	NA	No
rs3799963	6	44231479	C	G	NA	No
rs10985070	9	123636121	A	C	Hayfever, allergic rhinitis or eczema; Rheumatoid arthritis; Lymphocyte count	No
rs12764378	10	63800004	A	G	Rheumatoid arthritis; Self-reported hypothyroidism or myxoedema; Trunk fat-free mass; Trunk predicted mass	No

rs706778	10	6098949	T	C	Alopecia areata; Rheumatoid arthritis; Primary sclerosing cholangitis; Pediatric autoimmune diseases; Self-reported hypothyroidism or myxoedema	No
rs537544	10	8108382	T	C	Rheumatoid arthritis; Asthma	No
rs10790268	11	118729391	G	A	Allergic disease; Rheumatoid arthritis	No
rs9603608	13	40318819	C	A	Eosinophil count; Rheumatoid arthritis; Neutrophil percentage of granulocytes	No
rs8032939	15	38834033	C	T	Rheumatoid arthritis; Self-reported hypothyroidism or myxoedema; Eosinophil percentage of white cells	No
rs8026898	15	69991417	A	G	Rheumatoid arthritis; Height	No
rs13330176	16	86019087	A	T	Rheumatoid arthritis; Monocyte count	No
rs12232497	17	38040119	C	T	Allergic disease; High density lipoprotein; Asthma; Primary biliary cirrhosis; Crohns disease; Ulcerative colitis; Inflammatory bowel disease; Rheumatoid arthritis	No
rs592390	18	12822314	C	T	Rheumatoid arthritis	No
rs34536443	19	10463118	C	G	Juvenile idiopathic arthritis including oligoarticular and rheumatoid factor negative polyarticular JIA; Psoriasis; Self-reported hypothyroidism or myxoedema; Rheumatoid arthritis	No
rs4239702	20	44749251	C	T	Rheumatoid arthritis	No
rs8133843	21	36738242	A	G	Rheumatoid arthritis, Eosinophil percentage of white cells	No
rs225433	21	43809418	G	C	Rheumatoid arthritis	No
rs2069235	22	39747780	A	G	Primary biliary cirrhosis; Weight; Rheumatoid arthritis	No

Abbreviation: SNP, single nucleotide polymorphis; Chr, chromosome; Pos, Position; EA, Effect allele; NEA, non Effect allele

Evidence of association ($p < 5 \times 10^{-8}$) of the SNPs used as genetic variants for Mendelian randomization analyses of rheumatoid arthritis with confounders or heart failure s in the PhenoScanner and the GWAS catalog.

Table S3 Harmonized dataset of two-sample Mendelian randomization for the effect of rheumatoid arthritis on heart failure

SNP	Chr	Pos (GRCh38)	EA	NEA	EAF	RA			HF			+R ² (%)	ϕF- statistic
						β	SE	p-value	β	SE	p-value		
rs10790268	11	118729391	G	A	0.81	0.16	0.021	3.30E-15	-0.010	0.0065	0.12	0.80	475.56
rs10985070	9	123636121	A	C	0.57	-0.083	0.015	1.70E-08	-0.0091	0.005	0.071	0.30	199.80
rs11574914	9	34710338	A	G	0.32	0.12	0.017	1.50E-13	-0.0051	0.0058	0.38	0.60	378.20
rs12232497	17	38040119	C	T	0.47	0.094	0.016	3.60E-09	-0.017	0.0051	0.00099	0.40	257.70
rs12764378	10	63800004	A	G	0.25	0.13	0.018	1.90E-13	-0.0044	0.0061	0.48	0.60	372.54
rs13330176	16	86019087	A	T	0.24	0.11	0.020	9.00E-09	-0.0022	0.0060	0.72	0.50	274.04
rs13426947	2	191933254	A	G	0.19	0.13	0.019	2.40E-12	0.0028	0.0061	0.64	0.50	310.75
rs1571878	6	167540842	T	C	0.58	-0.12	0.015	4.90E-15	-0.0066	0.005	0.19	0.70	388.43
rs17264332	6	138005515	G	A	0.17	0.16	0.018	7.10E-19	-0.0019	0.0067	0.77	0.70	435.61
rs2069235	22	39747780	A	G	0.30	0.10	0.017	3.00E-10	0.0068	0.0056	0.22	0.50	267.41
rs212389	6	159489791	A	G	0.63	0.095	0.016	1.10E-09	0.0010	0.0055	0.86	0.40	247.87
rs2240336	1	17674402	T	C	0.42	-0.11	0.017	1.40E-09	0.0066	0.0051	0.19	0.50	315.73
rs225433	21	43809418	G	C	0.19	-0.13	0.023	1.80E-08	0.0012	0.0060	0.84	0.50	293.44

rs2561477	5	102608924	A	G	0.30	-0.11	0.017	5.20E-10	-0.018	0.0055	0.0012	0.50	274.05
rs2661798	2	65635688	T	A	0.45	0.094	0.015	1.10E-09	0.015	0.0052	0.0050	0.40	257.56
rs28411352	1	38278579	T	C	0.25	0.10	0.018	5.20E-09	-0.0043	0.0057	0.45	0.40	239.33
rs2844456	6	31864674	C	T	0.04	0.89	0.029	1.00E-200	0.012	0.014	0.39	6.10	3789.59
rs34046593	4	26111593	A	G	0.32	0.14	0.017	9.20E-17	-0.0074	0.0059	0.21	0.90	500.61
rs34536443	19	10463118	C	G	0.028	-0.38	0.047	4.60E-16	-0.0074	0.015	0.62	0.80	457.90
rs34695944	2	61124850	C	T	0.36	0.12	0.015	4.40E-14	-0.0095	0.0056	0.090	0.60	367.37
rs4239702	20	44749251	C	T	0.71	0.14	0.018	4.20E-14	-0.0095	0.0056	0.089	0.80	466.59
rs4452313	3	17047032	T	A	0.31	0.11	0.017	2.70E-10	0.013	0.0053	0.017	0.50	277.20
rs537544	10	8108382	T	C	0.62	-0.12	0.018	8.00E-11	0.0057	0.0052	0.27	0.60	375.23
rs56339890	6	29782742	T	C	0.020	-0.40	0.065	7.10E-10	-0.023	0.023	0.32	0.60	368.74
rs592390	18	12822314	C	T	0.48	-0.095	0.016	3.80E-09	-0.0047	0.0052	0.37	0.50	265.37
rs60733400	1	2516781	A	G	0.31	-0.12	0.017	1.30E-09	-0.0012	0.0056	0.82	0.50	280.11
rs61828284	1	173299743	T	C	0.080	-0.20	0.034	8.70E-09	0.016	0.011	0.14	0.60	337.89
rs62395855	6	31884909	T	C	0.020	-0.62	0.065	4.40E-21	-0.036	0.018	0.040	1.50	880.56

rs62401699	6	31022928	T	C	0.04 0	-0.24	0.041	1.30E-08	0.0088	0.013	0.48	0.40	249.78
rs706778	10	6098949	T	C	0.41	0.10	0.015	7.10E-12	-0.0025	0.005	0.62	0.50	309.51
rs71565347	6	32722961	A	G	0.02 0	-0.46	0.071	9.80E-11	0.012	0.019	0.52	0.80	491.84
rs73081554	3	58302935	T	C	0.05 2	0.17	0.030	4.70E-08	-0.0066	0.011	0.55	0.30	156.98
rs7731626	5	55444683	A	G	0.38	-0.20	0.020	7.90E-23	0.0020	0.0057	0.73	1.90	1099.34
rs8026898	15	69991417	A	G	0.29	0.15	0.018	2.40E-17	0.0022	0.0058	0.71	0.90	528.32
rs8032939	15	38834033	C	T	0.02 4	0.12	0.017	2.40E-12	0.0078	0.0056	0.16	0.10	37.25
rs8133843	21	36738242	A	G	0.63	0.095	0.016	6.00E-09	-5.00E- 04	0.0051	0.92	0.40	249.18
rs9275183	6	32654502	G	A	0.16	0.78	0.023	1.00E- 200	0.0054	0.0068	0.43	16.2	11274.04
rs9310852	3	27784997	G	A	0.46	0.083	0.015	3.20E-08	-0.0044	0.0052	0.40	0.30	202.14
rs9603608	13	40318819	C	A	0.34	- 0.104	0.016	7.60E-11	-0.0033	0.0053	0.53	0.50	287.86
rs9653442	2	100825367	T	C	0.55	-0.11	0.015	3.60E-12	-8.00E- 04	0.0050	0.87	0.60	322.44

Abbreviation: SNP, single nucleotide polymorphism; Chr, chromosome; Pos, Position; EA, Effect allele; NEA, non Effect allele; EAF, effect allele frequency; SE, standard error; RA, rheumatoid arthritis; HF, heart failure; $+R^2$, explained variation by SNPs; $^{\circ}F$ -statistic, the strength of the IV-exposure correlation

Table S4 Heterogeneity and horizontal pleiotropy analyses between rheumatoid arthritis and heart failure

SNP	Heterogeneity			Horizontal pleiotropy			MR-PRESSO	Power estimation (power= 80%)
	IVW Q	IVW Q df	<i>p</i> -value	Egger intercept	SE	<i>p</i> -value		
ALL	62.91	38	0.0067	-0.0016	0.0020	0.41	0.99	1.04 (0.96)
Removed	41.70	36	0.24	-0.0016	0.0017	0.36	NA	

Abbreviation: IVW Q, Inverse variance weighted Q Cochran's Q test estimate; IVW Q df, Inverse variance weighted Q Cochran's Q test degrees of freedom; SE, standard error; MR-PRESSO, Mendelian Randomization Pleiotropy RESidual Sum and Outlier

Table S5 SNP excluded from the outlier corrected MR-MRPRESSO analyses between rheumatoid arthritis and heart failure

SNP	RSSobs	p-value	SNP	RSSobs	p-value
rs10790268	1.16E-04	1	rs4239702	1.02E-04	1
rs10985070	7.98E-05	1	rs4452313	1.57E-04	0.6786
rs11574914	3.05E-05	1	rs537544	3.75E-05	1
rs12232497	2.97E-04	0.0039	rs56339890	4.94E-04	1
rs12764378	2.35E-05	1	rs592390	2.00E-05	1
rs13330176	6.52E-06	1	rs60733400	8.19E-07	1
rs13426947	6.02E-06	1	rs61828284	2.80E-04	1
rs1571878	4.05E-05	1	rs62395855	1.26E-03	1
rs17264332	5.81E-06	1	rs62401699	9.18E-05	1
rs2069235	4.31E-05	1	rs706778	8.05E-06	1
rs212389	5.34E-07	1	rs71565347	1.92E-04	1
rs2240336	4.89E-05	1	rs73081554	5.07E-05	1
rs225433	2.53E-06	1	rs7731626	7.11E-06	1
rs2561477	3.09E-04	0.0429	rs8026898	3.26E-06	1
rs10790268	1.16E-04	1	rs8032939	5.71E-05	1
rs28411352	2.16E-05	1	rs8133843	6.14E-07	1
rs2844456	1.16E-04	1	rs9275183	2.58E-05	1
rs34046593	6.29E-05	1	rs9310852	2.19E-05	1
rs34536443	4.13E-05	1	rs9603608	9.20E-06	1
rs34695944	9.92E-05	1	rs9653442	2.52E-07	1

Abbreviation: SNP, single nucleotide polymorphism

Figure S3: Leave-one-out plot to assess if a single variant is driving the association between rheumatoid arthritis and heart failure

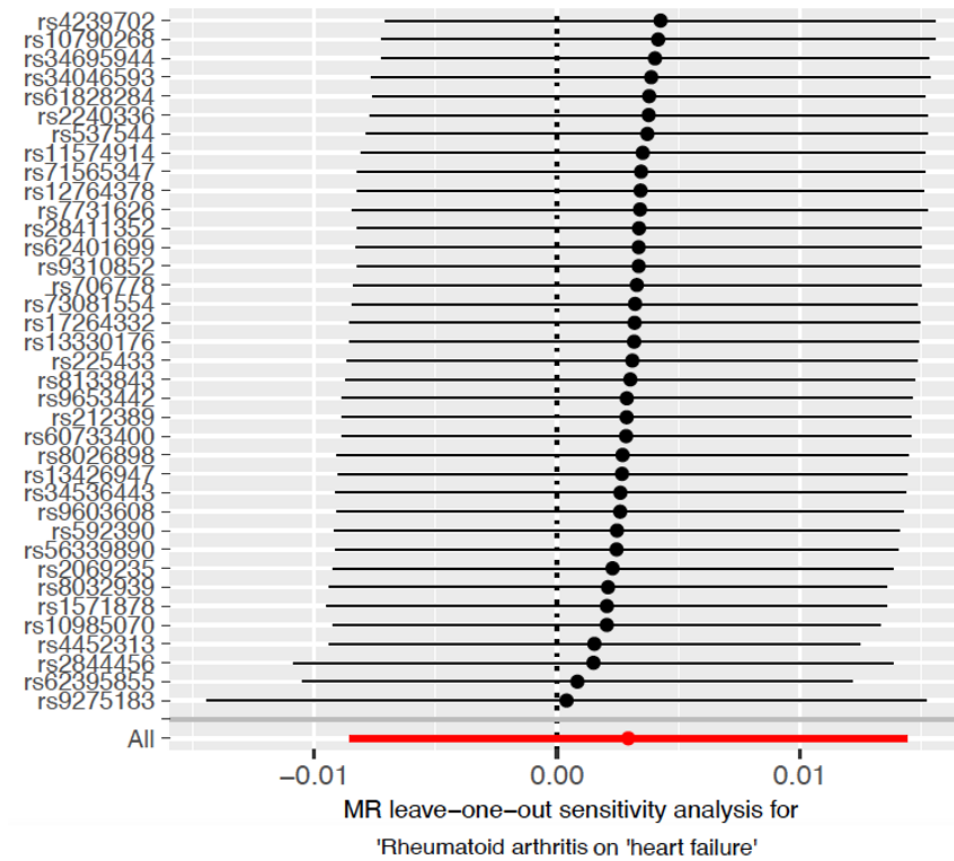


Figure S4: Forest plots of variants specific inverse variance estimates for the casual association between rheumatoid arthritis and heart failure

