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Genetic associations between stress-related disorders and autoimmune disease

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Supplementary methods

Data sources

The Swedish population and health registers are linked by the national identification numbers which are unique for all Swedish residents.(1) The National Patient Register contains nationwide data on inpatient care from 1987 and specialist outpatient care from 2001.(2) The Multi-Generation Register provides complete information on familial links for almost all individuals born in Sweden since 1932,(3) and the Causes of Death Register has death records for all deaths of Swedish residents since 1961.

UK Biobank is a cohort study where 502,507 participants, aged 40-69 years, were recruited across the UK between 2006 and 2010. At recruitment, information about socio-demographic characteristics and lifestyles was collected, and the participants also agreed to have their future health monitored, through data linkage with multiple national health registers. UK Biobank inpatient hospital data include data extracted from Hospital Episode Statistics from England, Patient Episode Database for Wales from Wales, and the Scottish Morbidity Record from Scotland, covering all the UK Biobank participants from 1997 onward.(4) As of 2017, the UK Biobank primary care data were obtained from multiple general practice databases, covering around 45% of the UK Biobank participants.(5) The individual-level genotyping data of UK Biobank were obtained from blood samples collected at baseline, using two genotyping arrays specifically designed for UK Biobank with 95% shared marker content.(4) Genotyping, quality control, and genotype imputation were performed by the UK Biobank team.(4) Kinship coefficients for checking family relationship, calculated using KING tool, and principal components (PCs), were also provided by the UK Biobank team.(4)

Summary statistics of genome-wide association studies (GWAS) for stress-related disorders was generated based on 9,831 cases and 19,225 controls in Danish population, available at website of iPSYCH, (6) while posttraumatic stress disorder was available at Psychiatric Genomics Consortium (23,212 cases and 151,447 controls).(7) In addition, we performed GWAS for autoimmune disease and specific autoimmune diseases (i.e., autoimmune thyroid disease, rheumatoid arthritis, ulcerative colitis, psoriasis, diabetes mellitus - insulin dependent and giant cell arteritis, see

Supplementary Methods Figure 1) using individual-level genotyping data from White British UK Biobank population. For PRS analysis, the base data was a subsample (half) of UK Biobank participants, whilst for the genetic analyses to identify common genes and pathways, the GWAS was performed using all individuals with available genotyping data. Detailed information of publicly available GWAS summary data is presented in Supplementary Table 1.

The requirement for informed consent is not needed in national register-based studies in Sweden, while the Swedish Twin Registry and the UK Biobank collected all data after written informed consent was obtained from each participant. Data from international consortia (summary statistics) are publicly available.

Quality control on UK Biobank genotyping data

Among 408,885 White British participants, we removed 1,540 individuals who were outliers based on a variant call <98%, and 30,474 related individuals with a kinship coefficient >0.0884. We also constrained the genetic analyses to autosomal biallelic SNPs and removed SNPs with a call rate <98%, minor allele frequency (MAF) <0.01, imputation quality score <0.8, or deviations from Hardy-Weinberg equilibrium ($P <1\times10^{-6}$). Considering the long-range linkage disequilibrium (LD) and special genetic architecture in the extended major histocompatibility complex (MHC) region (chr6: 25–34 Mb), we removed SNPs in this region. The final data contained 6,052,596 variants for 376,871 participants.

LD score genetic correlation analysis

In brief, LD score regression was implemented by regressing the test statistics of SNPs from GWAS summary against the LD scores for genetic variants across the whole genome to quantify the contributions of polygenic effects. GWAS summary statistics used for such analyses were described in Data Sources. With reference SNP panel of European ancestry LD scores from 1000 genomes,(8) we estimated the genetic correlation using unconstrained-intercept LD score regression, to control for the potential bias of population stratification.

Protein-protein interaction enrichment analysis

Specifically, for a given gene list of each trait, protein-protein interaction (PPI) enrichment analysis was applied based

on the following genomic interaction databases: STRING,(9) BioGrid,(10) OmniPath,(11) and InWeb_IM.(12) The

protein interaction network was formed by subset of proteins having physical interactions with at least one of the other

proteins in the list. By means of Molecular Complex Detection (MCODE) algorithm, network components with dense

connection were identified. Finally, based on pathway and process enrichment analysis applied to each MCODE

component independently, the significant pathways, according to q-values calculated using the Banjamini-Hochberg

procedure,(13) were retained as the functional description of the corresponding components.

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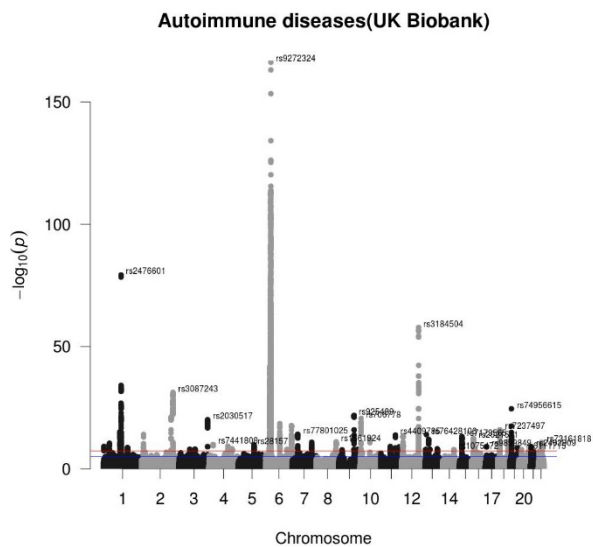
A. Autoimmune disease
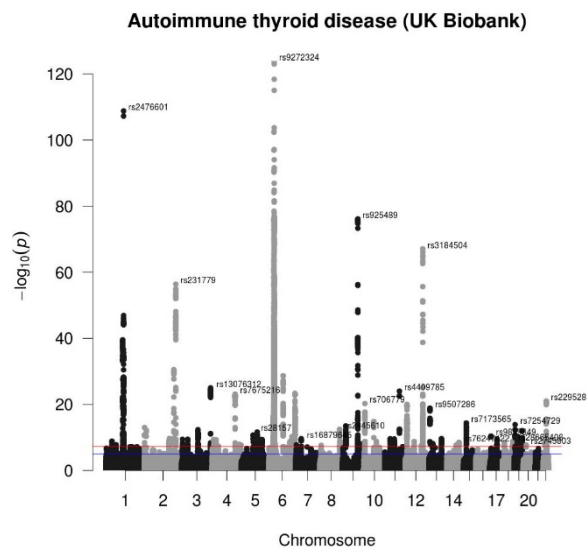
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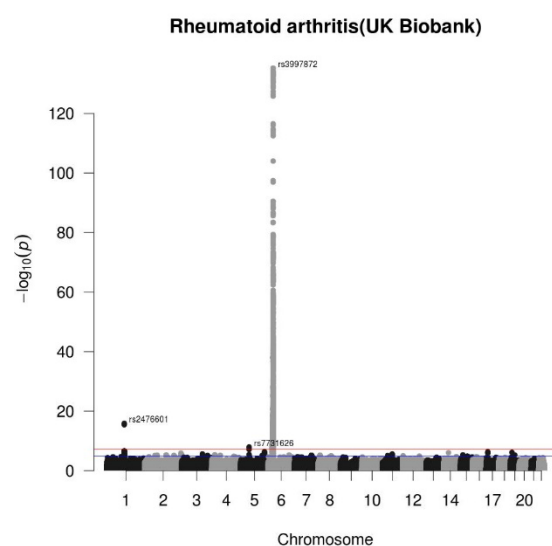
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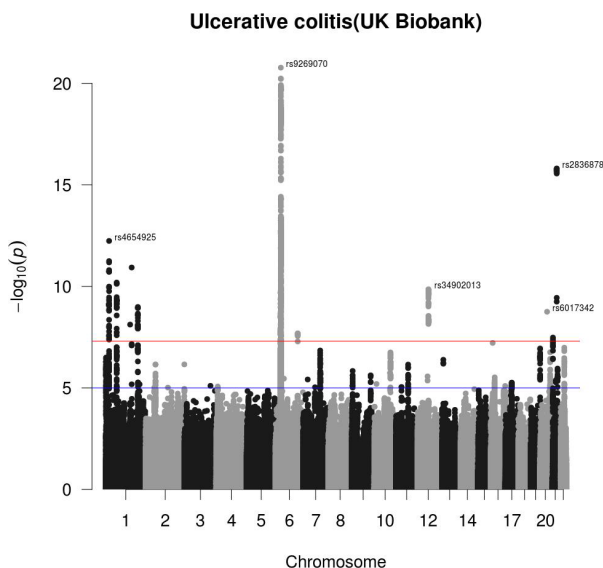
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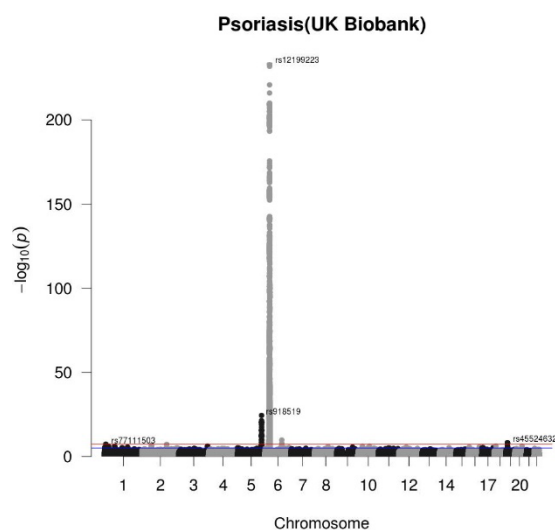
E. Psoriasis
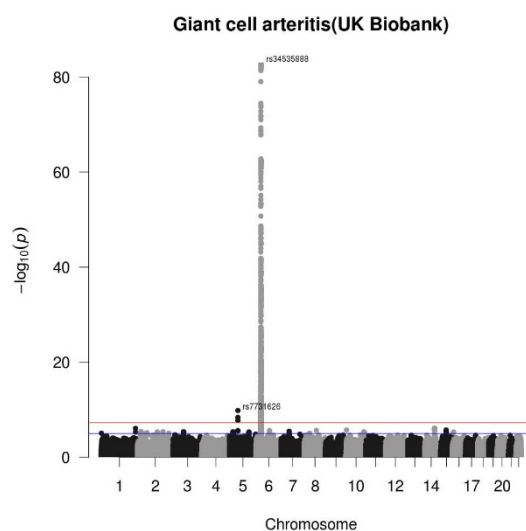
F. Giant cell arteritis/ Polymyalgia

Supplementary Method Figure 1 Manhattan of the SNP-Based GWAS of corresponding autoimmune disease using UK Biobank. SNP= single-nucleotide polymorphism. GWAS= genome-wide association studies.

Supplementary Tables

Table S1 Genome-wide Association Study summary statistics in this study

| Trait | UK Biobank GWAS data | | Publicly available GWAS data | | | |
	Cases	Controls	Publish year	Ancestry	Cases	Controls
Autoimmune disease	48,730	328,141	-	-	-	-
Autoimmune thyroid disease*	22,224	354,647	2020	European ancestry	30,234	725,172
Rheumatoid arthritis	6,729	370,142	2014	European ancestry	14,361	43,923
Ulcerative colitis	3,788	373,083	2017	European ancestry	12,366	33,609
Psoriasis	3,781	373,090	-	-	-	-
Diabetes mellitus - insulin dependent	3,329	373,542	2017	European ancestry	5,913	8,828
Giant cell arteritis/ Polymyalgia rheumatica	3,391	373,480	-	-	-	-
Stress-related disorders	-	-	2019	European ancestry	9,831	19,225
Posttraumatic stress disorder*	-	-	2019	European ancestry	23,212	151,447

* Publicly available GWAS data for autoimmune thyroid disease and posttraumatic stress disorder include UK Biobank samples, therefore it was not used for PRS calculation. -: No available data

Table S2 International Classification of Disease (ICD) codes, ninth (ICD-9) and tenth (ICD-10) revisions for diagnoses used in this study

Diseases	Diseases	ICD-9	ICD-10
All stress-related disorders		309, 308	F43
PTSD		309B	F43.1
Acute stress reaction		309A, 308	F43.0
Adjustment disorder		309X	F43.2
Other stress reaction		309X	F43.8, F43.9
Autoimmune diseases			
Disease of endocrine system	Diabetes mellitus, insulin dependent	250	E10
	Autoimmune thyroid disease	242A, 242X, 244W, 244X, 245C, 245W	E03.5, E03.9, E05.0, E05.5, E05.9, E06.3, E06.5
	Addison's disease	255E	E27.1, E27.2
	Autoimmune polyglandular syndrome	258B	E31.0
Inflammatory arthritis	Reactive arthritis (Reiter's syndrome)	099D, 711A	M02.3, M02.8, M02.9
	Rheumatoid arthritis	714A-D, 719D	M05, M06, M08.0, M08.1, M08.2, M08.3, M08.4
	Ankylosing spondylitis	720A	M45
Vasculitis	Polyarteritis nodosa and related condition (Incl. Kawasaki, Churg-Strauss syndrome,etc.)	446A, 446B	M30
	Thrombotic microangiopathy	446G	M31.1
	Granulomatosis with polyangiitis (Wegeners's granulomatosis)	446E	M31.3
	Microscopic polyangiitis		M31.7
	Giant cell arteritis/ Polymyalgia rheumatica	446F, 725	M35.3, M31.5, M31.6
Connective tissue disorders	Systemic lupus erythematosus	710A	M32
	Polymyositis/dermatomyositis	710E, 710D	M33.0, M33.1, M33.2, M33.9
	Systematic sclerosis (scleroderma)	710B	M34
	Sjögren's syndrome	710C	M35.0
	Mixed connective tissue disease	710X, 710W	M35.1
	Behcet's syndrome	136B	M35.2
Disease of skin system	Pemphigus vulgaris	694E	L10.0
	Bullous pemphigoid	694F	L12
	Dermatitis herpetiformis	694A	L13.0
	Psoriasis	696A, 696B	L40
	Alopecia areata	704A	L64
Disease of nervous system	Acute disseminated encephalomyelitis	-	G04
	Anti-NMDA receptor encephalitis	-	G13.1
	Multiple sclerosis	340	G35
	Neuromyelitis optica and ADEM	341A	G36

	Guillain-Barré syndrome	357A	G61.0, G61.1, G61.8, G61.9
	Myasthenia gravis	358A	G70.0
	Primary biliary cirrhosis	571G	K74.3
Disease of the digestive system	Crohn's disease	555	K50
	Ulcerative colitis	556	K51
	Coeliac disease	579A	K90.0
Others	Acute rheumatic fever and chorea	390-392	I00, I01.0, I01.1, I01.2, I01.8, I01.9, I02.0, I02.9
	Sarcoidosis	135	D86
	IgA nephropaty	580,582	N00, N01, N03, N05

Table S3 Primary care data READ v2/v3 codes for diagnoses used in this study

	Primary care V2 code	Primary care V3 code
Stress related disorders	E280., E281., E282., E283., E2830, E2831, E283z, E284., E28z., E2900, E2925, E292y, E292z, E293., E2930, E2931, E2932, E293z, E294., E29y., E29y1, E29y2, E29y4, E29yz, E29z., Eu43., Eu430, Eu431, Eu432, Eu433, Eu434, Eu435, Eu43y, Eu43z	1B1L., 1BE.., E280., E281., E282., E283., E2830, E2831, E283z, E284., E29.., E290., E290z, E291., E292., E2920, E2921, E2922, E2924, E2925, E292y, E292z, E293., E2930, E2931, E2932, E293z, E294., E29y., E29y0, E29y1, E29y2, E29y3, E29y4, E29y5, E29yz, E29z., Eu430, Eu432, Eu43y, Eu43z, Eu930, Ry15., Ua18k, Ua18L, Ub1T9, X00Sf, X00TT, X40Js, Xa028, Xa18j, Xa18v, XaC2u, XaX55, XaX56, XaX58, XE1Ym, XE1Yn, XE1Yo, XE1Yp, XE2uz, XM0As, XM1Q3

Table S4 Associations between **stress-related disorder PRSs** and the risk of **stress-related disorders** at different p value thresholds*

Pt	Inpatient stress-related disorders				Any stress-related disorders		
	N_SNP	OR (95% CI)	R^2	p value	OR (95% CI)	R^2	p value
Pt5e-08	1	1.06 (0.99-1.13)	1.48%	0.123	1.00 (0.98-1.03)	2.107%	0.689
Pt1e-06	5	1.01 (0.94-1.08)	1.458%	0.792	1.02 (1.00-1.04)	2.11%	0.085
Pt1e-04	170	1.02 (0.95-1.09)	1.461%	0.559	1.03 (1.01-1.05)	2.117%	3.3×10^{-3}
Pt0.001	1059	1.05 (0.98-1.12)	1.472%	0.200	1.05 (1.03-1.07)	2.131%	6.04×10^{-6}
Pt0.01	6627	1.16 (1.08-1.24)	1.613%	1.77×10^{-5}	1.08 (1.05-1.10)	2.16%	2.12×10^{-11}
Pt0.05	22802	1.18 (1.10-1.26)	1.643%	2.82×10^{-6}	1.10 (1.07-1.12)	2.196%	6.39×10^{-18}
Pt0.1	38527	1.17 (1.09-1.25)	1.634%	5.03×10^{-6}	1.10 (1.07-1.12)	2.194%	1.17×10^{-17}
Pt0.2	63805	1.17 (1.09-1.25)	1.625%	8.9×10^{-6}	1.09 (1.07-1.12)	2.191%	5.02×10^{-17}
Pt0.3	84551	1.17 (1.09-1.25)	1.628%	7.31×10^{-6}	1.09 (1.07-1.12)	2.188%	1.68×10^{-16}
Pt0.4	102255	1.17 (1.09-1.25)	1.634%	4.93×10^{-6}	1.09 (1.07-1.12)	2.188%	1.58×10^{-16}
Pt0.5	117262	1.17 (1.10-1.25)	1.634%	4.9×10^{-6}	1.09 (1.07-1.12)	2.187%	2.27×10^{-16}

*PRS for stress-related disorders was calculated based on **GWAS summary statistics from iPSYCH.**

ORs were adjusted for age, sex, genotyping array, and ancestry principal components.

Pt = p value threshold. N_SNP = the average number of SNP per individual used in predictive model. R^2 = Nagelkerke's squared (R square).

PRS = polygenic risk score.

Table S5 Associations between **autoimmune disease PRSs** and the risk of **autoimmune disease** at different p value thresholds*

Pt	N_SNP	OR (95% CI)	R^2	p value
Pt5e-08	13	1.16 (1.15-1.18)	2.843%	3.57×10^{-110}
Pt1e-06	24	1.19 (1.17-1.20)	2.93%	1.93×10^{-137}
Pt1e-04	97	1.20 (1.19-1.22)	3.002%	1.35×10^{-160}
Pt0.001	435	1.19 (1.18-1.21)	2.96%	4.89×10^{-147}
Pt0.01	2350	1.19 (1.17-1.20)	2.928%	6.41×10^{-137}
Pt0.05	7606	1.18 (1.16-1.19)	2.887%	8.99×10^{-124}
Pt0.1	12382	1.18 (1.16-1.20)	2.895%	1.93×10^{-126}
Pt0.2	19740	1.18 (1.16-1.19)	2.891%	4.48×10^{-125}
Pt0.3	25427	1.17 (1.16-1.19)	2.875%	7.87×10^{-120}
Pt0.4	30071	1.17 (1.16-1.19)	2.868%	1.14×10^{-117}
Pt0.5	33856	1.17 (1.16-1.19)	2.865%	8.38×10^{-117}

* PRSs for **autoimmune diseases** were calculated based **on UK Biobank GWAS data.**

ORs were adjusted for age, sex, genotyping array, and ancestry principal components.

Pt = p value threshold. N_SNP = the average number of SNP per individual used in predictive model. R^2 = Nagelkerke's squared (R square).

PRS = polygenic risk score.

Table S6 Associations between **autoimmune thyroid disease** PRSs and the risk of autoimmune thyroid disease at different p value thresholds*

Pt	N_SNP	OR (95% CI)	R^2	p value
Pt5e-08	17	1.34 (1.32-1.37)	6.419%	3.53×10^{-202}
Pt1e-06	34	1.38 (1.35-1.40)	6.608%	1.58×10^{-236}
Pt1e-04	132	1.38 (1.36-1.41)	6.635%	3.28×10^{-241}
Pt0.001	485	1.35 (1.33-1.38)	6.466%	4.93×10^{-209}
Pt0.01	2477	1.33 (1.31-1.36)	6.360%	2.82×10^{-189}
Pt0.05	7729	1.30 (1.28-1.33)	6.206%	1.84×10^{-160}
Pt0.1	12519	1.30 (1.27-1.32)	6.184%	1.9×10^{-156}
Pt0.2	19781	1.29 (1.27-1.32)	6.160%	4.77×10^{-152}
Pt0.3	25545	1.29 (1.27-1.32)	6.150%	4.93×10^{-150}
Pt0.4	30233	1.29 (1.26-1.31)	6.122%	6.2×10^{-145}
Pt0.5	33997	1.29 (1.26-1.31)	6.125%	2×10^{-145}

* PRSs for **autoimmune thyroid diseases** were calculated based **on UK Biobank GWAS data.**

ORs were adjusted for age, sex, genotyping array, and ancestry principal components.

Pt = p value threshold. N_SNP = the average number of SNP per individual used in predictive model. R^2 = Nagelkerke's squared (R square).

PRS = polygenic risk score.

Table S7 Associations between **rheumatoid arthritis** PRSs and the risk of **rheumatoid arthritis** disease at different p value thresholds

Pt	GWAS summary statistics from UK Biobank base data				Publicly available GWAS summary statistics			
	N_SNP	OR (95% CI)	R^2	p value	N_SNP	OR (95% CI)	R^2	p value
Pt5e-08	0	1.09 (1.06-1.13)	2.434%	6.53×10^{-8}	48	1.19 (1.16-1.21)	2.724%	7.29×10^{-49}
Pt1e-06	2	1.04 (1.01-1.08)	2.370%	0.017	83	1.22 (1.19-1.24)	2.813%	2.77×10^{-62}
Pt1e-04	40	1.04 (1.00-1.07)	2.365%	0.044	268	1.24 (1.21-1.27)	2.895%	1.19×10^{-73}
Pt0.001	262	1.02 (0.99-1.06)	2.358%	0.233	970	1.25 (1.22-1.28)	2.905%	4.57×10^{-74}
Pt0.01	1967	1.03 (1.00-1.06)	2.362%	0.095	5967	1.20 (1.17-1.23)	2.745%	3.81×10^{-50}
Pt0.05	7027	1.06 (1.02-1.10)	2.387%	7.39×10^{-4}	22071	1.19 (1.16-1.22)	2.703%	6.36×10^{-44}
Pt0.1	11845	1.06 (1.03-1.10)	2.391%	3.49×10^{-4}	40426	1.19 (1.16-1.22)	2.706%	2.19×10^{-44}
Pt0.2	19224	1.08 (1.05-1.12)	2.418%	2.39×10^{-6}	68939	1.18 (1.15-1.21)	2.679%	2.21×10^{-40}
Pt0.3	25050	1.09 (1.05-1.12)	2.421%	1.37×10^{-6}	93099	1.18 (1.15-1.21)	2.683%	4.81×10^{-41}
Pt0.4	29774	1.09 (1.05-1.13)	2.426%	5.97×10^{-7}	114531	1.18 (1.15-1.21)	2.687%	1.52×10^{-41}
Pt0.5	33667	1.09 (1.05-1.13)	2.428%	4.24×10^{-7}	132946	1.17 (1.15-1.20)	2.668%	8.52×10^{-39}

ORs were adjusted for age, sex, genotyping array, and ancestry principal components.

Pt = p value threshold. N_SNP = the average number of SNP per individual used in predictive model. R^2 = Nagelkerke's squared (R square).

PRS = polygenic risk score.

Table S8 Associations between **ulcerative colitis** PRSs and the risk of **ulcerative colitis** at different p value thresholds

Pt	GWAS summary statistics from UK Biobank base data				Publicly available GWAS summary statistics			
	N_SNP	OR (95% CI)	R^2	p value	N_SNP	OR (95% CI)	R^2	p value
Pt5e-08	1	1.18 (1.12-1.23)	0.562%	6.77×10^{-12}	92	1.57 (1.52-1.62)	2.081%	2.42×10^{-165}
Pt1e-06	3	1.13 (1.09-1.19)	0.485%	1.51×10^{-8}	167	1.61 (1.56-1.67)	2.334%	6.55×10^{-189}
Pt1e-04	42	1.09 (1.04-1.14)	0.404%	1.83×10^{-4}	735	1.60 (1.55-1.66)	2.278%	9.75×10^{-184}
Pt0.001	303	1.10 (1.06-1.15)	0.426%	1.52×10^{-5}	2892	1.56 (1.51-1.61)	2.042%	5.11×10^{-162}
Pt0.01	1979	1.12 (1.07-1.17)	0.446%	1.65×10^{-6}	15290	1.50 (1.46-1.55)	1.778%	7.81×10^{-138}
Pt0.05	6985	1.15 (1.10-1.20)	0.508%	1.66×10^{-9}	49750	1.48 (1.44-1.53)	1.671%	5.31×10^{-128}
Pt0.1	11689	1.14 (1.09-1.19)	0.492%	9.69×10^{-9}	81953	1.49 (1.44-1.54)	1.686%	1.9×10^{-129}
Pt0.2	19062	1.16 (1.11-1.21)	0.531%	1.26×10^{-10}	133502	1.48 (1.44-1.53)	1.673%	2.11×10^{-128}
Pt0.3	24921	1.15 (1.10-1.21)	0.520%	4.09×10^{-10}	175261	1.48 (1.43-1.53)	1.638%	3.27×10^{-125}
Pt0.4	29659	1.15 (1.10-1.20)	0.509%	1.37×10^{-9}	210201	1.47 (1.43-1.52)	1.620%	1.61×10^{-123}
Pt0.5	33520	1.15 (1.10-1.20)	0.510%	1.29×10^{-9}	240047	1.47 (1.43-1.52)	1.617%	3.12×10^{-123}

ORs were adjusted for age, sex, genotyping array, and ancestry principal components.

Pt = p value threshold. N_SNP = the average number of SNP per individual used in predictive model. R^2 = Nagelkerke's squared (R square).

PRS = polygenic risk score.

Table S9 Associations between **psoriasis** PRSs and the risk of **psoriasis** at different p value thresholds*

Pt	N_SNP	OR (95% CI)	R^2	p value
Pt5e-08	1	1.19 (1.14-1.24)	0.704%	3.65×10^{-16}
Pt1e-06	3	1.21 (1.16-1.26)	0.750%	2.8×10^{-18}
Pt1e-04	41	1.18 (1.13-1.23)	0.659%	2.24×10^{-13}
Pt0.001	282	1.12 (1.07-1.17)	0.527%	6.05×10^{-7}
Pt0.01	1895	1.10 (1.05-1.15)	0.497%	1.77×10^{-5}
Pt0.05	6846	1.09 (1.05-1.14)	0.484%	8.46×10^{-5}
Pt0.1	11542	1.11 (1.06-1.16)	0.504%	7.9×10^{-6}
Pt0.2	19027	1.10 (1.05-1.15)	0.492%	3.29×10^{-5}
Pt0.3	24841	1.11 (1.06-1.16)	0.505%	7.66×10^{-6}
Pt0.4	29561	1.10 (1.06-1.16)	0.501%	1.23×10^{-5}
Pt0.5	33431	1.10 (1.05-1.15)	0.498%	1.64×10^{-5}

* PRSs for **psoriasis** were calculated based **on UK Biobank GWAS data.**

ORs were adjusted for age, sex, genotyping array, and ancestry principal components.

Pt = p value threshold. N_SNP = the average number of SNP per individual used in predictive model. R^2 = Nagelkerke's squared (R square).

PRS = polygenic risk score.

Table S10 Associations between **diabetes mellitus - insulin dependent** PRSs and the risk of **diabetes mellitus - insulin dependent** at different p value thresholds

Pt	GWAS summary statistics from UK Biobank base data				Publicly available GWAS summary statistics			
	N_SNP	OR (95% CI)	R^2	p value	N_SNP	OR (95% CI)	R^2	p value
Pt5e-08	1	1.20 (1.14-1.26)	1.383%	1.86×10^{-13}	24	1.21 (1.17-1.25)	1.523%	1.39×10^{-29}
Pt1e-06	2	1.10 (1.05-1.15)	1.177%	1.29×10^{-4}	34	1.22 (1.18-1.26)	1.539%	6.16×10^{-31}
Pt1e-04	39	1.10 (1.05-1.16)	1.187%	4.78×10^{-5}	165	1.22 (1.18-1.26)	1.540%	8.99×10^{-31}
Pt0.001	270	1.07 (1.02-1.12)	1.142%	5.63×10^{-3}	634	1.18 (1.14-1.22)	1.422%	7.9×10^{-21}
Pt0.01	1845	1.17 (1.11-1.23)	1.313%	1.45×10^{-10}	2950	1.16 (1.12-1.20)	1.379%	3.2×10^{-17}
Pt0.05	6841	1.16 (1.11-1.22)	1.298%	6.56×10^{-10}	9009	1.16 (1.12-1.20)	1.387%	7.13×10^{-18}
Pt0.1	11576	1.16 (1.11-1.22)	1.291%	1.28×10^{-9}	14284	1.16 (1.12-1.20)	1.383%	1.48×10^{-17}
Pt0.2	19099	1.16 (1.10-1.21)	1.282%	3.13×10^{-9}	22203	1.16 (1.12-1.20)	1.372%	1.32×10^{-16}
Pt0.3	24929	1.15 (1.10-1.21)	1.270%	1.07×10^{-8}	28620	1.15 (1.11-1.19)	1.363%	7.49×10^{-16}
Pt0.4	29670	1.15 (1.09-1.20)	1.264%	2.04×10^{-8}	33716	1.15 (1.11-1.19)	1.362%	8.64×10^{-16}
Pt0.5	33598	1.14 (1.09-1.20)	1.259%	3.19×10^{-8}	37907	1.15 (1.11-1.19)	1.355%	3.27×10^{-15}

ORs were adjusted for age, sex, genotyping array, and ancestry principal components.

Pt = p value threshold. N_SNP = the average number of SNP per individual used in predictive model. R^2 = Nagelkerke's squared (R square).

PRS = polygenic risk score.

Table S11 Associations between **giant cell arteritis** PRSs and the risk of **giant cell arteritis** at different p value thresholds*

Pt	N_SNP	OR (95% CI)	R^2	p value
Pt5e-08	0	0.99 (0.95-1.04)	6.821%	0.79
Pt1e-06	1	1.03 (0.99-1.08)	6.831%	0.17
Pt1e-04	29	1.03 (0.98-1.08)	6.829%	0.205
Pt0.001	254	1.04 (0.99-1.09)	6.833%	0.132
Pt0.01	1824	1.05 (1.00-1.10)	6.842%	0.045
Pt0.05	6791	1.07 (1.02-1.12)	6.857%	8.38×10^{-3}
Pt0.1	11585	1.08 (1.03-1.13)	6.870%	1.96×10^{-3}
Pt0.2	19061	1.06 (1.01-1.12)	6.853%	0.012
Pt0.3	24888	1.06 (1.01-1.12)	6.853%	0.012
Pt0.4	29704	1.06 (1.01-1.11)	6.848%	0.022
Pt0.5	33647	1.06 (1.01-1.11)	6.850%	0.017

* PRSs for **giant cell arteritis** were calculated based **on UK Biobank GWAS data.**

ORs were adjusted for age, sex, genotyping array, and ancestry principal components.

Pt = p value threshold. N_SNP = the average number of SNP per individual used in predictive model. R^2 = Nagelkerke's squared (R square).

PRS = polygenic risk score.

Table S12 Consistency of variants[a] associated with autoimmune thyroid disease between UK Biobank GWAS data and publicly available GWAS data

SNP	CHR	BP	A1	A2	Public GWAS*		UK Biobank GWAS	
					OR	P	OR	P[b]
rs2476601	1	114377568	A	G	1.44	2.20E-160	1.39	**1.55E-109**
rs3184504	12	111884608	T	C	1.23	9.40E-116	1.19	**8.25E-68**
rs925489	9	100546600	C	T	0.81	8.50E-110	0.82	**7.26E-77**
rs231775	2	204732714	G	A	1.18	1.60E-74	1.17	**6.22E-55**
rs654537	6	90990050	G	A	0.88	6.10E-42	0.89	**7.18E-28**
rs7568275	2	191966452	G	C	1.15	4.50E-39	1.14	**6.55E-31**
rs2757041	6	167370532	G	C	0.88	1.70E-37	0.90	**4.36E-24**
rs4409785	11	95311422	C	T	1.15	5.30E-31	1.14	**9.95E-25**
rs229527	22	37581485	A	C	1.11	2.90E-30	1.10	**2.76E-21**
rs6535628	4	149634038	G	A	0.88	6.40E-30	0.88	**1.80E-23**
rs7090530	10	6110875	C	A	0.91	2.00E-26	0.91	**2.61E-18**
rs3764022	12	9833524	G	C	0.91	2.20E-24	0.92	**1.49E-13**
rs76428106	13	28604007	C	T	1.46	2.40E-24	1.41	**8.76E-16**
rs17364832	13	24786915	G	T	1.10	2.10E-23	1.09	**1.41E-15**
rs11675342	2	1407628	T	C	1.09	1.40E-21	1.08	**9.86E-14**
rs1534430	2	12644736	T	C	0.92	3.10E-20	0.93	**6.35E-13**
rs4293777	4	10716939	C	G	1.08	2.30E-19	1.06	**4.80E-10**
rs7173565	15	38850330	C	T	1.09	9.40E-18	1.09	**4.03E-15**
rs2445610	8	128197088	G	A	0.93	1.30E-15	0.93	**3.37E-13**
rs11079788	17	45820723	T	C	1.09	2.70E-15	1.08	**9.26E-10**
rs12582330	12	103892941	G	T	1.08	7.70E-15	1.06	**2.50E-08**
rs7441808	4	26090375	G	A	1.08	9.80E-15	1.07	**3.97E-09**
rs9533118	13	43047260	G	A	0.93	9.90E-15	0.94	**1.10E-08**
rs1990760	2	163124051	C	T	0.93	1.10E-14	0.94	**6.58E-09**
rs244688	5	133423495	T	C	1.11	1.10E-13	1.09	**9.37E-10**
rs6457834	6	35536195	C	A	0.93	6.00E-13	0.95	2.13E-07
rs35667974	2	163124637	C	T	0.79	8.80E-13	0.85	4.02E-06
rs2069556	8	133920518	A	G	1.07	1.40E-12	1.06	**2.35E-09**
rs2745803	20	17859706	G	A	0.92	1.60E-12	0.93	**1.80E-08**
rs6867654	5	76543768	A	G	1.07	2.90E-12	1.07	**2.47E-11**
rs9494389	6	136115507	C	T	1.07	9.50E-12	1.05	1.35E-06
rs9878908	3	12302462	C	T	1.08	9.90E-12	1.05	3.61E-05
rs6505765	18	12782849	G	C	1.07	1.90E-11	1.06	**3.65E-09**
rs2271194	12	56477694	A	T	1.06	2.00E-11	1.05	3.45E-07
rs2234167	1	2494330	A	G	1.09	2.10E-11	1.08	2.01E-07
rs7251	19	50162909	G	C	0.94	3.70E-11	0.93	**1.30E-10**
rs12697352	5	35837234	A	G	0.94	3.90E-11	0.95	2.07E-07
rs3784099	14	68749927	A	G	0.94	3.90E-11	0.95	1.37E-05
rs1991797	5	102622453	T	G	0.94	4.60E-11	0.93	**6.04E-11**
rs763361	18	67531642	T	C	1.06	5.10E-11	1.05	1.73E-07
rs2823272	21	16798586	A	T	0.94	5.70E-11	0.95	2.45E-06
rs11720041	3	39320000	T	C	1.08	9.70E-11	1.07	1.73E-06

SNP	CHR	BP	A1	A2	OR	P	OR	P
rs11898293	2	160552593	C	T	0.94	1.30E-10	0.94	**8.94E-09**
rs61776678	1	38377021	A	G	0.94	1.50E-10	0.94	**1.60E-09**
rs7218886	17	8841140	G	T	0.92	4.40E-10	0.93	2.04E-07
rs12114596	8	61518399	T	C	1.06	4.90E-10	1.05	6.56E-06
rs7428218	3	5015894	C	T	1.08	6.30E-10	1.08	**1.70E-08**
rs221796	7	100284913	C	G	0.92	7.40E-10	0.92	3.92E-07
rs7758816	6	112098896	C	T	0.95	7.90E-10	0.95	6.70E-07
rs1045216	10	124189197	A	G	0.95	8.30E-10	0.96	2.33E-05
rs1561924	8	129569371	A	G	0.92	9.20E-10	0.92	**2.07E-08**
rs607404	18	23598160	T	A	0.94	1.00E-09	0.95	8.42E-07
rs12756886	1	200840467	C	T	1.08	3.10E-09	1.07	2.65E-06
rs1079418	6	166047034	G	A	0.94	3.60E-09	0.94	8.58E-08
rs7594497	2	55872538	C	T	1.12	4.10E-09	1.11	7.96E-07
rs12793348	11	93913036	G	A	0.90	5.30E-09	0.92	2.68E-05
rs35677470	3	58183636	A	G	1.10	8.90E-09	1.08	1.22E-05
rs2681417	3	121825197	G	A	1.10	3.30E-08	1.08	3.25E-05

[a] Variants in both public GWAS and UK Biobank GWAS. We confirmed 38 variants in 58 significant SNPs of previously published autoimmune thyroid disease GWAS (overlaps of top SNPs=60.34%).

[b] P value in UK Biobank GWAS reached significant threshold (i.e. P<5E-8) was set **bold.**

*Publicly available GWAS data for autoimmune thyroid disease include UK Biobank samples

GWAS= genome-wide association studies. SNP = single-nucleotide polymorphism. CHR = chromosome. BP = base position. A1 = risk allele. A2 = reference allele. OR = odds ratio.

Table S13 Consistency of variants[a] associated with rheumatoid arthritis between UK Biobank GWAS data and publicly available GWAS data

SNP	CHR	BP	A1	A2	Public GWAS OR	Public GWAS P	UK Biobank GWAS OR	UK Biobank GWAS P[b]
rs9268839	6	32428772	G	A	2.50	1.00E-250	1.35	**4.86E-66**
rs2476601	1	114377568	A	G	1.81	1.60E-149	1.25	**1.17E-16**
rs7731626	5	55444683	A	G	0.82	7.90E-23	0.90	**1.09E-08**
rs3087243	2	204738919	A	G	0.87	9.20E-20	0.97	6.46E-02
rs17264332	6	138005515	G	A	1.18	7.10E-19	1.07	5.60E-04
rs7752903	6	138227364	G	T	1.41	1.40E-17	1.06	2.27E-01
rs8026898	15	69991417	A	G	1.16	2.40E-17	1.08	8.15E-05
rs11933540	4	26120001	C	T	1.15	9.20E-17	1.05	1.58E-02
rs10790268	11	118729391	A	G	0.85	3.30E-15	0.96	1.03E-01
rs1571878	6	167540842	C	T	1.12	4.90E-15	1.03	7.58E-02
rs34695944	2	61124850	C	T	1.12	4.40E-14	1.02	3.93E-01
rs11574914	9	34710338	A	G	1.13	1.50E-13	1.00	9.26E-01
rs8032939	15	38834033	C	T	1.12	2.40E-12	1.06	5.98E-03
rs9653442	2	100825367	C	T	1.11	3.60E-12	1.05	7.91E-03
rs11889341	2	191943742	T	C	1.13	6.50E-12	1.09	1.68E-05
rs706778	10	6098949	T	C	1.11	7.10E-12	1.04	2.02E-02
rs1980422	2	204610396	C	T	1.12	6.00E-11	1.06	7.88E-03
rs9603616	13	40368069	T	C	0.90	8.40E-11	0.95	8.64E-03
rs4452313	3	17047032	T	A	1.11	2.70E-10	1.03	1.79E-01
rs909685	22	39747671	A	T	1.11	3.10E-10	1.05	6.44E-03
rs2561477	5	102608924	A	G	0.90	5.20E-10	0.96	4.43E-02
rs1858037	2	65598300	A	T	0.90	5.90E-10	0.96	2.39E-02
rs2451258	6	159506600	C	T	0.90	6.60E-10	1.00	9.04E-01
rs947474	10	6390450	G	A	0.88	2.80E-09	0.94	9.19E-03
rs28411352	1	38278579	T	C	1.11	5.20E-09	1.02	3.47E-01
rs2301888	1	17672730	A	G	0.90	5.50E-09	0.97	7.95E-02
rs2105325	1	173349725	A	C	0.90	1.00E-08	0.97	8.95E-02
rs2233424	6	44233921	T	C	1.33	3.30E-08	1.07	9.20E-02
rs2234067	6	36355654	A	C	0.88	4.10E-08	0.97	1.83E-01
rs624988	1	117263790	T	C	1.09	4.60E-08	1.04	1.55E-02

[a] Variants in both public GWAS and UK Biobank GWAS. We confirmed 3 variants in 30 significant SNPs of previously published rheumatoid arthritis GWAS (overlaps of top SNPs=10%).

[b] P value in UK Biobank GWAS reached significant threshold (i.e. P<5E-8) was set **bold.**

GWAS= genome-wide association studies. SNP = single-nucleotide polymorphism. CHR = chromosome. BP = base position. A1 = risk allele.

A2 = reference allele. OR = odds ratio.

.

Table S14 Consistency of variants[a] associated with ulcerative colitis between UK Biobank GWAS data and publicly available GWAS data

SNP	CHR	BP	A1	A2	Public GWAS OR	Public GWAS P	UK Biobank GWAS OR	UK Biobank GWAS P[b]
rs6426833	1	20171860	G	A	0.80	3.035E-42	0.85	**6.57E-12**
rs11581607	1	67707690	A	G	0.62	3.539E-41	0.70	**7.39E-11**
rs2836878	21	40465534	A	G	0.80	1.834E-32	0.80	**1.55E-16**
rs6017342	20	43065028	A	C	0.82	3.952E-30	0.87	**1.77E-09**
rs3024505	1	206939904	A	G	1.23	1.525E-23	1.14	2.60E-05
rs7608910	2	61204856	G	A	1.17	4.345E-23	1.08	6.03E-04
rs4409764	10	101284237	T	G	1.16	2.485E-21	1.12	6.42E-07
rs3197999	3	49721532	A	G	1.17	8.398E-20	1.08	3.71E-03
rs1801274	1	161479745	A	G	1.15	1.515E-18	1.17	**1.17E-11**
rs6062496	20	62329099	G	A	0.87	8.966E-17	0.91	6.90E-05
rs12946510	17	37912377	T	C	1.14	1.523E-16	1.08	1.03E-03
rs10781499	9	139266405	A	G	1.14	2.071E-16	1.08	4.99E-04
rs7554511	1	200877562	A	C	0.87	4.267E-16	0.90	2.17E-05
rs10761659	10	64445564	A	G	0.88	1.327E-15	0.91	7.72E-05
rs12568930	1	22702231	C	T	0.84	1.602E-15	0.90	1.31E-03
rs6920220	6	138006504	A	G	1.16	2.891E-15	1.16	5.15E-08
rs11236797	11	76299649	A	C	1.13	5.268E-15	1.10	1.90E-05
rs17085007	13	27531267	C	T	1.17	1.21E-14	1.16	4.11E-07
rs2823286	21	16817938	A	G	0.88	1.591E-13	0.91	4.16E-04
rs2816958	1	200101920	A	G	0.83	2E-13	0.78	**1.15E-09**
rs7282490	21	45615741	G	A	1.12	5.331E-13	1.11	1.76E-05
rs798502	7	2789880	C	A	0.89	3.895E-11	0.94	2.49E-02
rs12942547	17	40527544	G	A	0.90	1.203E-10	0.93	1.71E-03
rs10797432	1	2501338	T	C	0.90	1.203E-10	0.95	1.62E-02
rs5771069	22	50435480	G	A	1.10	2.472E-10	1.06	7.25E-03
rs16940202	16	86014241	C	T	1.14	3.073E-10	1.07	3.08E-02
rs2413583	22	39659773	T	C	1.15	3.149E-10	0.90	8.83E-04
rs4728142	7	128573967	A	G	1.10	3.232E-10	1.08	1.14E-03
rs3851228	6	111848191	T	A	1.21	5.927E-10	1.11	2.56E-02
rs3766606	1	8022197	T	G	0.88	3.941E-09	0.99	7.75E-01
rs1811711	2	228670476	G	C	0.88	6.086E-09	0.89	6.89E-05
rs113986290	6	19781009	T	C	0.74	7.593E-09	0.74	6.18E-04
rs17656349	5	149605994	C	T	0.91	1.54E-08	0.97	1.74E-01
rs7911117	10	27179596	G	T	0.87	1.838E-08	1.01	7.97E-01
rs17293632	15	67442596	T	C	1.11	2.107E-08	1.07	1.03E-02
rs254560	5	134443606	A	G	1.09	2.624E-08	1.08	1.33E-03
rs138788	22	35729721	G	A	0.91	2.949E-08	0.95	4.85E-02
rs1728785	16	68591230	A	C	0.90	3.762E-08	0.97	2.73E-01
rs4976646	5	176788570	C	T	1.10	4.483E-08	1.04	1.51E-01

[a] Variants in both public GWAS and UK Biobank GWAS. We confirmed 6 variants in 39 significant SNPs of previously published ulcerative colitis GWAS (overlaps of top SNPs=15.35%).

[b] P value in UK Biobank GWAS reached significant threshold (i.e. P<5E-8) was set **bold.**

GWAS= genome-wide association studies. SNP = single-nucleotide polymorphism. CHR = chromosome. BP = base position. A1 = risk allele. A2 = reference allele. OR = odds ratio.

Table S15 Consistency of variants[a] associated with diabetes mellitus - insulin dependent between UK Biobank GWAS data and publicly available GWAS data

					Public GWAS		UK Biobank GWAS	
SNP	CHR	BP	A1	A2	OR	P	OR	P[b]
rs6679677	1	114303808	A	C	2.00	1.00E-74	1.38	**7.98E-19**
rs12722496	10	6096667	G	A	0.65	2.41E-23	0.81	8.94E-07
rs7297175	12	56473808	T	C	1.28	7.57E-23	1.07	5.62E-03
rs3087243	2	204738919	A	G	0.84	1.08E-12	0.93	5.70E-03
rs7020673	9	4291747	C	G	0.86	3.22E-09	0.98	4.19E-01
rs10230978	7	50477144	A	G	0.86	3.80E-08	1.02	3.87E-01
rs2269246	1	64107491	C	T	1.18	4.99E-08	0.98	5.31E-01

[a] Variants in both public GWAS and UK Biobank GWAS. We confirmed 1 variant in 5 significant SNPs of previously published diabetes mellitus - insulin dependent GWAS (overlaps of top SNPs=20%)

[b] P value in UK Biobank GWAS reached significant threshold (i.e. P<5E-8) was set **bold.**

GWAS= genome-wide association studies. SNP = single-nucleotide polymorphism. CHR = chromosome. BP = base position. A1 = risk allele. A2 = reference allele. OR = odds ratio.

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Table S16 The proportions of specific subtypes of stress-related disorders in database

Subtype of stress-related disorders	Based on diagnoses in **the Swedish Patient Register**	Based on diagnoses in **UK Biobank inpatient hospital and primary care data**	Based on diagnoses in the UK Biobank **inpatient hospital data**
Posttraumatic stress disorder	6.20%	7.50%	41.66%
Acute stress reaction	43.90%	12.03%	15.36%
Adjustment disorder and other stress reaction	49.90%	80.48%	42.98%

Table S17 Genetic associations between stress-related disorders and autoimmune disease (PRS based on publicly available GWAS data)

Disease	PRS for stress-related disorder [a] and risk of autoimmune disease			PRS for autoimmune disease [b] and risk of any stress-related disorder			PRS for autoimmune disease [b] and risk of inpatient stress-related disorder		
	OR[c]	95% CI	P	OR[c]	95% CI	P	OR[c]	95% CI	P
Autoimmune disease	1.05	1.04-1.06	3.23×10^{-24}	-	-	-	-	-	-
Specific disease types				-	-	-	-	-	-
Autoimmune thyroid disease*	1.05	1.03-1.06	1.37×10^{-11}	-	-	-	-	-	-
Rheumatoid arthritis	1.06	1.03-1.09	2.07×10^{-6}	1.02	1.00-1.04	0.047	0.98	0.91-1.04	0.989
Ulcerative colitis	1.03	1.00-1.07	0.051	1.07	1.04-1.09	3.11×10^{-9}	0.94	0.88-1.01	0.7
Psoriasis	1.06	1.02-1.09	1.07×10^{-3}	-	-	-	-	-	-
Diabetes mellitus - insulin dependent	1.08	1.04-1.12	1.52×10^{-5}	1.03	1.00-1.05	0.018	0.97	0.90-1.04	0.327
Giant cell arteritis	1.05	1.02-1.09	2.75×10^{-3}	-	-	-	-	-	-

[a] PRS for stress-related disorders was calculated based on **GWAS summary statistics from iPSYCH.**

[b] PRS for specific autoimmune disease was calculated based **on publicly available GWAS summary statistics**

[c] ORs and 95% CIs (per standard deviation increase in the corresponding PRS) were estimated by logistic regression models, adjusted for age, sex, genotyping array, and ancestry principal components.

*Publicly available GWAS data for autoimmune thyroid disease include UK Biobank samples, therefore it was not used for PRS calculation.

OR = odds ratio. P = P value. PRS = polygenic risk score. -= no publicly available GWAS summary statistics

Table S18 Top three pathways of the corresponding shared MCODE components between **stress-related disorder** and **autoimmune diseases** based on protein-protein interaction enrichment analyses

Biological Functions	Enriched terms	Description	P value	q-value [a]
Signaling by G proteins/ GPCR	R-HSA-418594	G alpha (i) signalling events	2.51E-33	1.00E-29
	R-HSA-500792	GPCR ligand binding	2.00E-30	1.00E-27
	R-HSA-388396	GPCR downstream signalling	3.98E-28	1.00E-25
Cilium Assembly	R-HSA-5620924	Intraflagellar transport	2.00E-11	1.00E-12
	R-HSA-1852241	Organelle biogenesis and maintenance	1.26E-09	1.00E-12
	R-HSA-5617833	Cilium Assembly	1.58E-08	1.00E-12
Membrane Trafficking	R-HSA-199991	Membrane Trafficking	1.00E-05	2.00E-04
	R-HSA-5653656	Vesicle-mediated transport	1.00E-05	2.51E-04
Eukaryotic Translation Initiation	R-HSA-156827	L13a-mediated translational silencing of Ceruloplasmin expression	2.51E-14	1.00E-12
	R-HSA-72706	GTP hydrolysis and joining of the 60S ribosomal subunit	2.51E-14	1.00E-12
	R-HSA-72737	Cap-dependent Translation Initiation	3.98E-14	1.00E-12
Cell cycle	R-HSA-380287	Centrosome maturation	1.00E-19	1.00E-17
	R-HSA-380270	Recruitment of mitotic centrosome proteins and complexes	1.00E-19	1.00E-17
	R-HSA-5620912	Anchoring of the basal body to the plasma membrane	3.98E-19	1.00E-16

[a] The q-value were calculated using the Benjamini-Hochberg procedure to account for multiple testing.

MCODE =Molecular Complex Detection algorithm.

Table S19 Top three pathways of the corresponding shared MCODE components between **stress-related disorders** and **autoimmune thyroid disease*** based on protein-protein interaction enrichment analyses

Biological Functions	Enriched terms	Description	P value	q-value [a]
Signaling by G proteins/ GPCR	R-HSA-418594	G alpha (i) signalling events	1.26E-08	3.98E-07
	R-HSA-373076	Class A/1 (Rhodopsin-like receptors)	1.58E-08	5.01E-07
	hsa04080	Neuroactive ligand-receptor interaction	2.00E-08	6.31E-07
Cilium Assembly	R-HSA-5620912	Anchoring of the basal body to the plasma membrane	1.00E-10	5.01E-09
	R-HSA-5617833	Cilium Assembly	2.00E-09	7.94E-08
	R-HSA-1852241	Organelle biogenesis and maintenance	1.00E-08	3.16E-07
Membrane Trafficking	R-HSA-8856825	Cargo recognition for clathrin-mediated endocytosis	3.98E-08	1.26E-06
	R-HSA-8856828	Clathrin-mediated endocytosis	1.00E-07	3.16E-06
	R-HSA-199991	Membrane Trafficking	1.00E-05	2.00E-04
Interferons Signaling in Immune System	R-HSA-912694	Regulation of IFNA signaling	1.00E-32	1.00E-29
	R-HSA-933541	TRAF6 mediated IRF7 activation	1.00E-31	1.00E-28
	WP4558	Overview of interferons-mediated signaling pathway	1.00E-30	1.00E-27
Antigen Processing	R-HSA-983168	Antigen processing: Ubiquitination & Proteasome degradation	5.01E-10	2.00E-08
	R-HSA-983169	Class I MHC mediated antigen processing & presentation	1.58E-09	6.31E-08
	R-HSA-174084	Autodegradation of Cdh1 by Cdh1:APC/C	6.31E-09	2.51E-07

*Publicly available GWAS data for autoimmune thyroid disease include UK Biobank samples

[a] The q-value were calculated using the Benjamini-Hochberg procedure to account for multiple testing.

MCODE = Molecular Complex Detection algorithm.

Table S20 Risk genes shared by **posttraumatic stress disorder and autoimmune disease***

Gene ID	Gene Symbol	Description	Biological Process (GO)
10632	ATP5L	ATP synthase membrane subunit g	GO:0042776 proton motive force-driven mitochondrial ATP synthesis
8510	MMP23B	matrix metallopeptidase 23B	GO:0030574 collagen catabolic process
95681	CEP41	centrosomal protein 41	GO:0018095 protein polyglutamylation
100873782	RNU6-83P	RNA, U6 small nuclear 83, pseudogene	
100874080	FARP1-AS1	FARP1 antisense RNA 1	
100270909	RPL7P31	ribosomal protein L7 pseudogene 31	
6885	MAP3K7	mitogen-activated protein kinase kinase kinase 7	GO:0043276 anoikis
338657	CCDC84	centrosomal AT-AC splicing factor	GO:0010826 negative regulation of centrosome duplication
643	CXCR5	C-X-C motif chemokine receptor 5	GO:0048535 lymph node development
136259	KLF14	Kruppel like factor 14	GO:1902068 regulation of sphingolipid mediated signaling pathway
100302113	MIR1200	microRNA 1200	
56912	IFT46	intraflagellar transport 46	GO:0035720 intraciliary anterograde transport
106481545	RNU6-1157P	RNA, U6 small nuclear 1157, pseudogene	
100271539	RPL7AP61	ribosomal protein L7a pseudogene 61	
728642	CDK11A	cyclin dependent kinase 11A	GO:0050684 regulation of mRNA processing
677800	SNORA12	small nucleolar RNA, H/ACA box 12	GO:0006396 RNA processing
100420200	RPL7L1P12	ribosomal protein L7 like 1 pseudogene 12	
442668	NECAP1P1	NECAP endocytosis associated 1 pseudogene 1	
10846	PDE10A	phosphodiesterase 10A	GO:0046069 cGMP catabolic process
100874096	DOCK9-AS1	DOCK9 antisense RNA 1	
8511	MMP23A	matrix metallopeptidase 23A (pseudogene)	
1656	DDX6	DEAD-box helicase 6	GO:0019072 viral genome packaging
23187	PHLDB1	pleckstrin homology like domain family B member 1	GO:1904259 regulation of basement membrane assembly involved in embryonic body morphogenesismorphogenesis
11181	TREH	trehalase	GO:0005993 trehalose catabolic process
9844	ELMO1	engulfment and cell motility 1	GO:0016601 Rac protein signal transduction
372	ARCN1	archain 1	GO:0021691 cerebellar Purkinje cell layer maturation

*GWAS summary statistics for posttraumatic stress disorder were from Psychiatric Genomics Consortium (23,212 cases and 151,447 controls) including UK Biobank samples.

Table S21 Top three pathways of the corresponding shared MCODE components between **posttraumatic stress disorder** and **autoimmune diseases** based on protein-protein interaction enrichment analyses*

Biological Functions	Enriched terms	Description	P value	q-value [a]
Signaling by G proteins/ GPCR	R-HSA-418594	G alpha (i) signalling events	5.11E-12	1.03E-10
	R-HSA-500792	GPCR ligand binding	3.78E-11	7.58E-10
	R-HSA-388396	GPCR downstream signalling	2.79E-10	2.06E-09
Eukaryotic Translation Initiation	R-HSA-72649	Translation initiation complex formation	3.78E-11	7.58E-10
	R-HSA-72702	Ribosomal scanning and start codon recognition	3.78E-11	7.58E-10
	R-HSA-72662	Activation of the mRNA upon binding of the cap-binding complex and eIFs, and subsequent binding to 43S	3.78E-11	7.58E-10
Regulation of apoptotic process	GO:1902253	regulation of intrinsic apoptotic signaling pathway by p53 class mediator	9.12E-04	3.70E-03
	GO:0043408	regulation of MAPK cascade	2.03E-03	8.23E-03
	GO:2001233	regulation of apoptotic signaling pathway	3.70E-03	1.36E-02
MAPK1/MAPK3 signaling	R-HSA-5658442	Regulation of RAS by GAPs	3.35E-04	1.50E-03
	R-HSA-5673001	RAF/MAP kinase cascade	2.24E-03	8.23E-03
	R-HSA-5684996	MAPK1/MAPK3 signaling	2.24E-03	8.23E-03
RHO GTPase cycle	R-HSA-9013404	RAC2 GTPase cycle	3.04E-04	1.36E-03
	R-HSA-9013423	RAC3 GTPase cycle	3.70E-03	1.23E-02
	WP185	Integrin-mediated cell adhesion	4.09E-03	1.36E-02
Innate Immune System	R-HSA-2424491	DAP12 signaling	1.52E-08	1.13E-07
	R-HSA-2172127	DAP12 interactions	4.14E-08	3.06E-07
	GO:0002223	stimulatory C-type lectin receptor signaling pathway	1.67E-05	5.55E-05
TNF signaling	R-HSA-5357956	TNFR1-induced NFkappaB signaling pathway	4.10E-04	1.84E-03
	R-HSA-420092	Glucagon-type ligand receptors	5.00E-04	2.03E-03
	R-HSA-168638	NOD1/2 Signaling Pathway	5.53E-04	2.48E-03
Gene expression (Transcription)	GO:0006366	transcription by RNA polymerase II	6.14E-06	4.54E-05
	GO:0006351	transcription, DNA-templated	4.54E-05	1.84E-04
	GO:0097659	nucleic acid-templated transcription	4.54E-05	1.84E-04
Disease-related pathway	R-HSA-5663202	Diseases of signal transduction by growth factor receptors and second messengers	1.23E-03	4.99E-03
	hsa05226	Gastric cancer	2.74E-03	1.01E-02
	hsa04810	Regulation of actin cytoskeleton	4.52E-03	1.50E-02

*GWAS summary statistics for posttraumatic stress disorder were from Psychiatric Genomics Consortium (23,212 cases and 151,447 controls) including UK Biobank samples.

[a] The q-value were calculated using the Benjamini-Hochberg procedure to account for multiple testing.

MCODE = Molecular Complex Detection algorithm.

Table S22 Risk genes shared by **posttraumatic stress disorder** and **autoimmune thyroid disease***

Gene ID	Gene Symbol	Description	Biological Process (GO)
100526820	CAHM	colon adenocarcinoma hypermethylated	
106481023	RN7SL366P	RNA, 7SL, cytoplasmic 366, pseudogene	
106479000	RNA5SP226	RNA, 5S ribosomal pseudogene 226	
10846	PDE10A	phosphodiesterase 10A	GO:0046069 cGMP catabolic process
6885	MAP3K7	mitogen-activated protein kinase kinase kinase 7	GO:0043276 anoikis
5071	PARK2	parkin RBR E3 ubiquitin protein ligase	GO:1904049 negative regulation of spontaneous neurotransmitter secretion
9444	QKI	QKI, KH domain containing RNA binding	GO:0042759 long-chain fatty acid biosynthetic process
106479889	RNU6-730P	RNA, U6 small nuclear 730, pseudogene	
6068	U3	small nucleolar RNA, C/D box 3 pseudogene 1	
135138	PACRG	parkin coregulated	GO:0034620 cellular response to unfolded protein
100505705	SDIM1	stress responsive DNAJB4 interacting membrane protein 1	GO:0051402 neuron apoptotic process

* GWAS summary statistics for posttraumatic stress disorder were from Psychiatric Genomics Consortium (23,212 cases and 151,447 controls) including UK Biobank samples. Publicly available GWAS data for autoimmune thyroid disease include UK Biobank samples.

Table S23 Top three pathways of the corresponding shared MCODE components between **posttraumatic stress disorder** and **autoimmune thyroid diseases** based on protein-protein interaction enrichment analyses*

Biological Functions	Enriched terms	Description	P value	q-value [a]
Signaling by G proteins/ GPCR	R-HSA-420092	Glucagon-type ligand receptors	4.54E-05	1.84E-04
	R-HSA-9660821	ADORA2B mediated anti-inflammatory cytokines production	4.54E-05	1.84E-04
	R-HSA-418555	G alpha (s) signalling events	6.13E-05	2.75E-04
Regulation of apoptotic process	R-HSA-5683057	MAPK family signaling cascades	1.01E-02	2.73E-02
	hsa04151	PI3K-Akt signaling pathway	1.11E-02	3.02E-02
	GO:0006417	regulation of translation	1.66E-02	4.08E-02
MAPK1/MAPK3 signaling	M269	PID RAS PATHWAY	4.10E-04	1.66E-03
	R-HSA-5673001	RAF/MAP kinase cascade	9.12E-04	3.35E-03
	R-HSA-5684996	MAPK1/MAPK3 signaling	1.01E-03	3.35E-03
Cytokine Signaling	R-HSA-1280215	Cytokine Signaling in Immune system	2.79E-10	5.60E-09
	R-HSA-5658442	Regulation of RAS by GAPs	5.60E-09	4.14E-08
	R-HSA-8854050	FBXL7 down-regulates AURKA during mitotic entry and in early mitosis	1.52E-08	1.13E-07
VEGF Signaling	M279	PID RB 1PATHWAY	2.74E-03	8.23E-03
	WP3888	VEGFA-VEGFR2 signaling pathway	6.10E-03	1.83E-02
	GO:0002064	epithelial cell development	1.01E-02	2.73E-02
Cardiac conduction	R-HSA-5576892	Phase 0 - rapid depolarisation	8.25E-04	3.03E-03
	GO:2001257	regulation of cation channel activity	9.12E-04	3.35E-03
	GO:0043269	regulation of ion transport	1.50E-03	5.52E-03

* GWAS summary statistics for posttraumatic stress disorder were from Psychiatric Genomics Consortium (23,212 cases and 151,447 controls) including UK Biobank samples. Publicly available GWAS data for autoimmune thyroid disease include UK Biobank samples.

[a] The q-value were calculated using the Benjamini-Hochberg procedure to account for multiple testing.

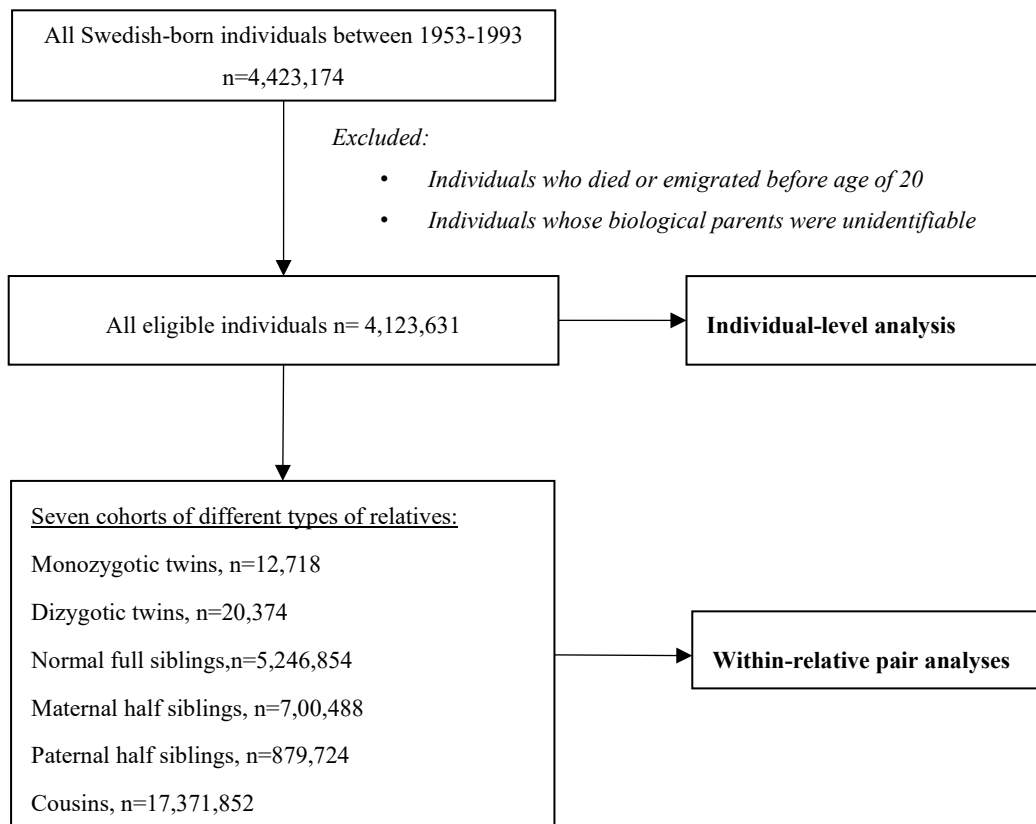MCODE = Molecular Complex Detection algorithm.

Supplementary Figures

All Swedish-born individuals between 1953-1993
n=4,423,174

Excluded:
- *Individuals who died or emigrated before age of 20*
- *Individuals whose biological parents were unidentifiable*

All eligible individuals n= 4,123,631 → **Individual-level analysis**

Seven cohorts of different types of relatives:

Monozygotic twins, n=12,718

Dizygotic twins, n=20,374

Normal full siblings,n=5,246,854

Maternal half siblings, n=7,00,488

Paternal half siblings, n=879,724

Cousins, n=17,371,852

→ **Within-relative pair analyses**

Figure S1 Study design for familial co-aggregation analyses

Figure S2 Study design for phenotypic association analyses in UK Biobank

UK Biobank individuals recruited between 2006-2010

n=502,507

Excluded:

- *19 withdrew from UK Biobank*
- *92,887 non-white British ancestry*
- *716 without genotyping data*
- *1,540 failed to pass GWAS QC steps*
- *30,474 shared relationships up to second degree*

All eligible individuals n= 376,871

The association of PRS for SRD and IMMU

Base data of SRD
GWAS summary statistics from **public database**, 9,831 cases and 19,225 controls from a Danish population*

Target data
UK Biobank participants
(n=376,871)
- 831 individuals with inpatient SRD
- 8815 individuals with any SRD
- 48,730 individuals with IMMU

The association of PRS for IMMU and SRD

No publicly available summary statistics for IMMU

All eligible individuals n= 376.871

Removed SRD patients(n=8,815)

Individuals without SRD n= 368,056

Randomly divided the subset into half

Participants n= 184,028

Participants n= 184,028

SRD n= 8,815

Base data
Generate GWAS summary statistics for IMMU
23,782 individuals with IMMU diagnosed in inpatient record

Target data n= 192843
- 24,948 individuals with IMMU
- 831 individuals with inpatient SRD
- 8,815 individuals with any SRD

Figure S3 Study design for polygenic risk scores (PRSs) analyses

*GWAS summary statistics for stress-related disorders were from iPSYCH.

GWAS=genome-wide association studies; QC=quality control; PRS=polygenic risk score; SRD=stress-related disorders; IMMU=autoimmune disease.
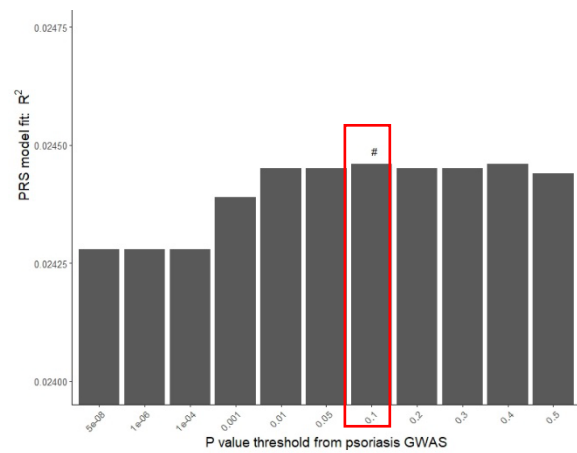
Autoimmune disease variance explained by **stress-related disorders** PRS
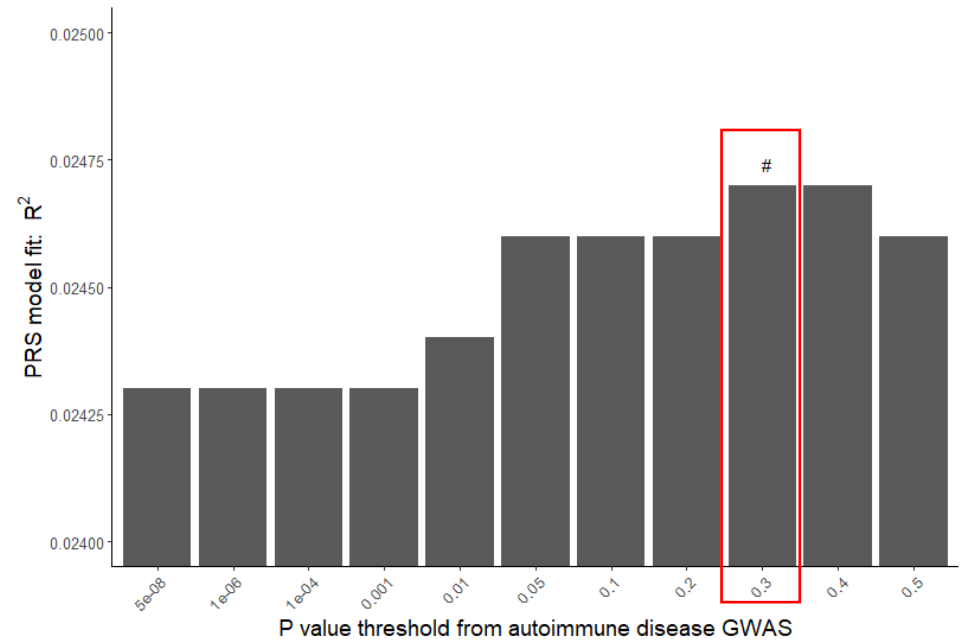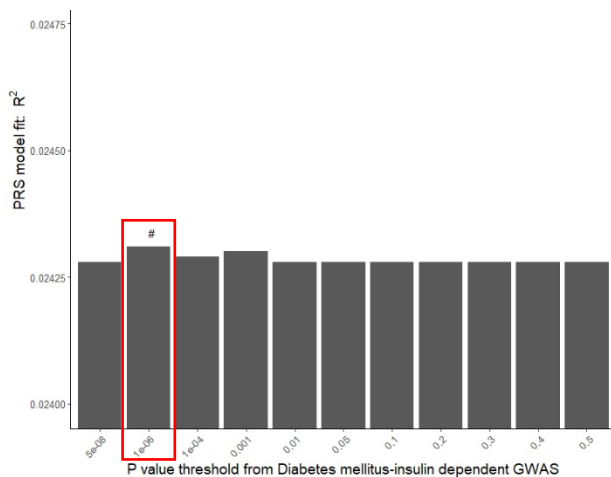

Stress-related disorders variance explained by **autoimmune disease** PRS

Figure S4 Variance explained for one trait by polygenic risk scores (PRSs) for another trait under 11 p value thresholds

The p value threshold with the highest variance explained was reported.
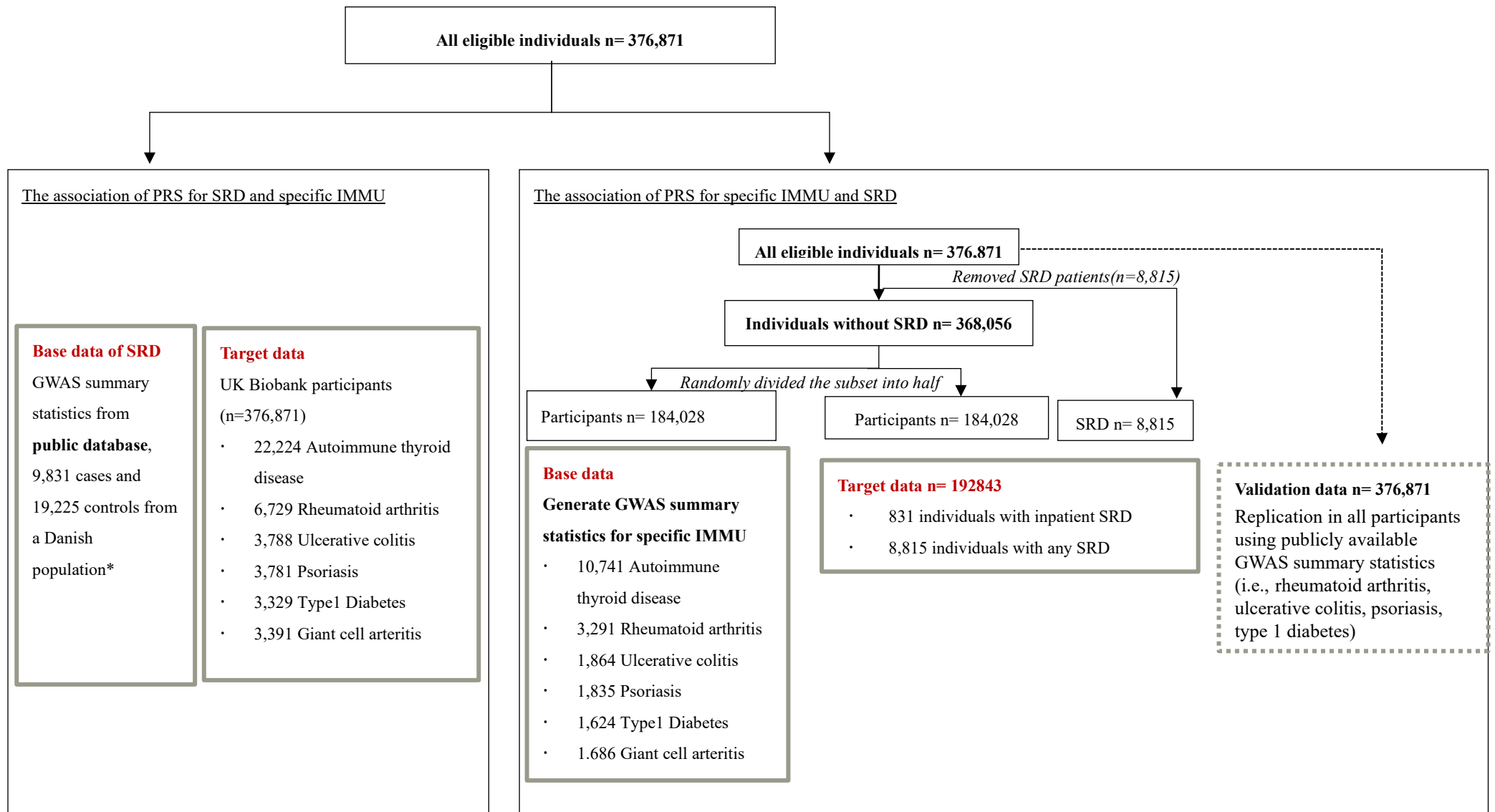
Figure S5 Study design for polygenic risk scores (PRSs) analyses of specific disease type

*GWAS summary statistics for stress-related disorders were from iPSYCH.

GWAS=genome-wide association studies; QC=quality control; PRS=polygenic risk score; SRD=stress-related disorders; IMMU=autoimmune disease.
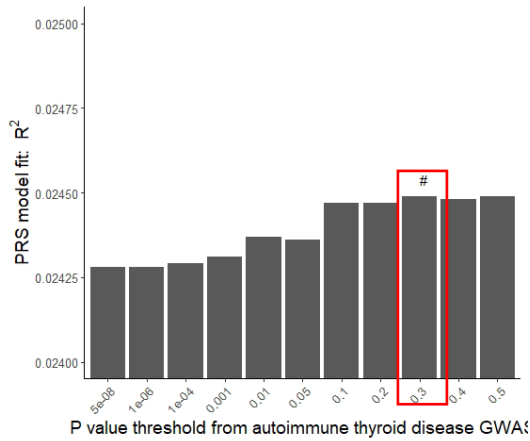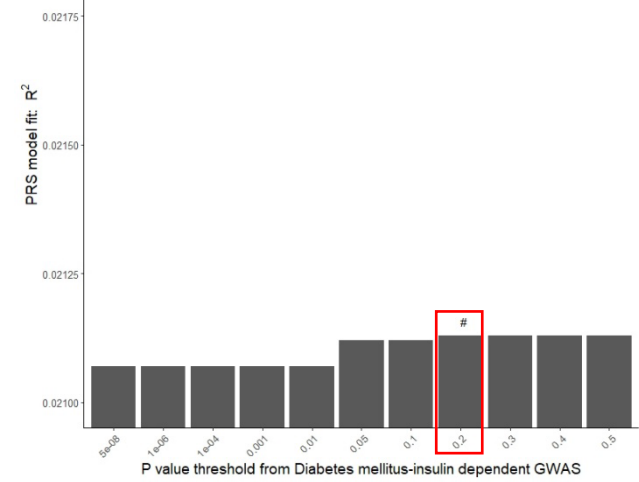
Variance explained by **autoimmune thyroid disease** PRS
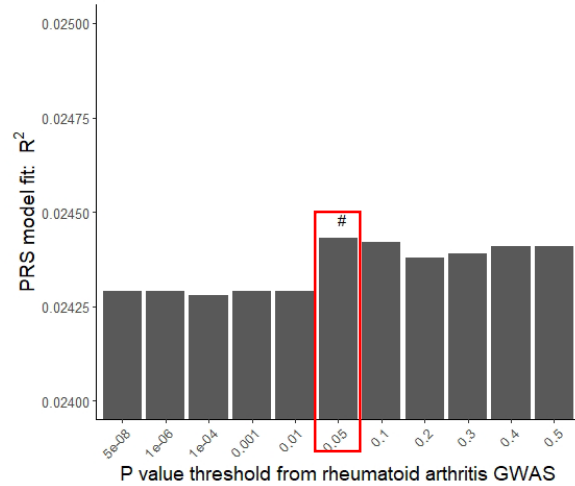
Variance explained by **rheumatoid arthritis** PRS
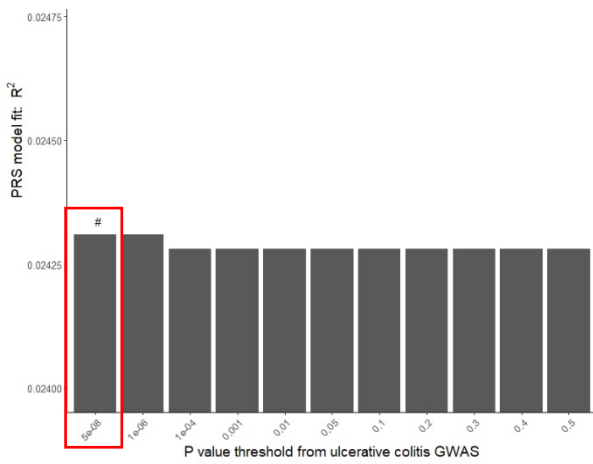
Variance explained by **ulcerative colitis** PRS

Variance explained by **psoriasis** PRS

Variance explained by **diabetes mellitus-insulin dependent** PRS
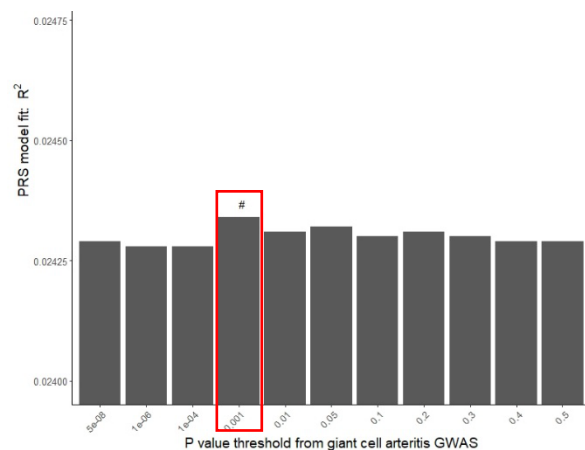
Variance explained by **giant cell arteritis** PRS

Figure S6 Variance explained for stress-related disorders by polygenic risk scores (PRSs) for corresponding autoimmune disease under 11 p value thresholds (GWAS summary statistics from **UK Biobank GWAS data)**

The p value threshold with the highest variance explained was selected for subsequent analyses

a
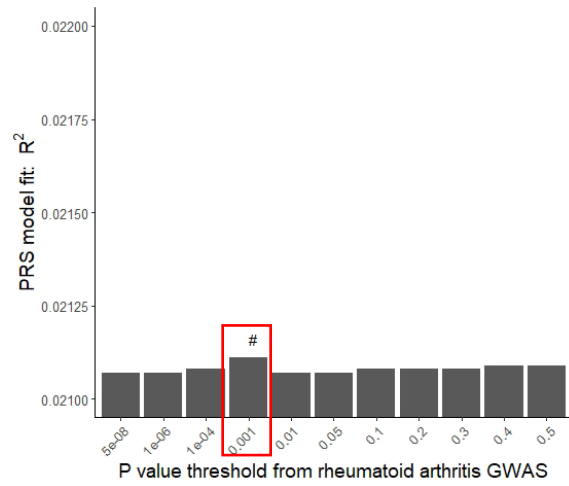
Variance explained by **rheumatoid arthritis** PRS
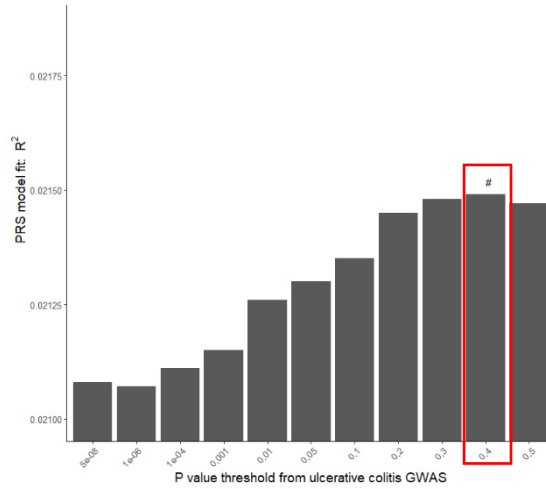
Variance explained by **ulcerative colitis** PRS

Variance explained by **diabetes mellitus-insulin dependent** PRS

Figure S7 Variance explained for stress-related disorders by polygenic risk scores (PRSs) for corresponding autoimmune disease under 11 p value thresholds (GWAS summary statistics from **publicly available GWAS data**)

The p value threshold with the highest variance explained was selected for subsequent analyses
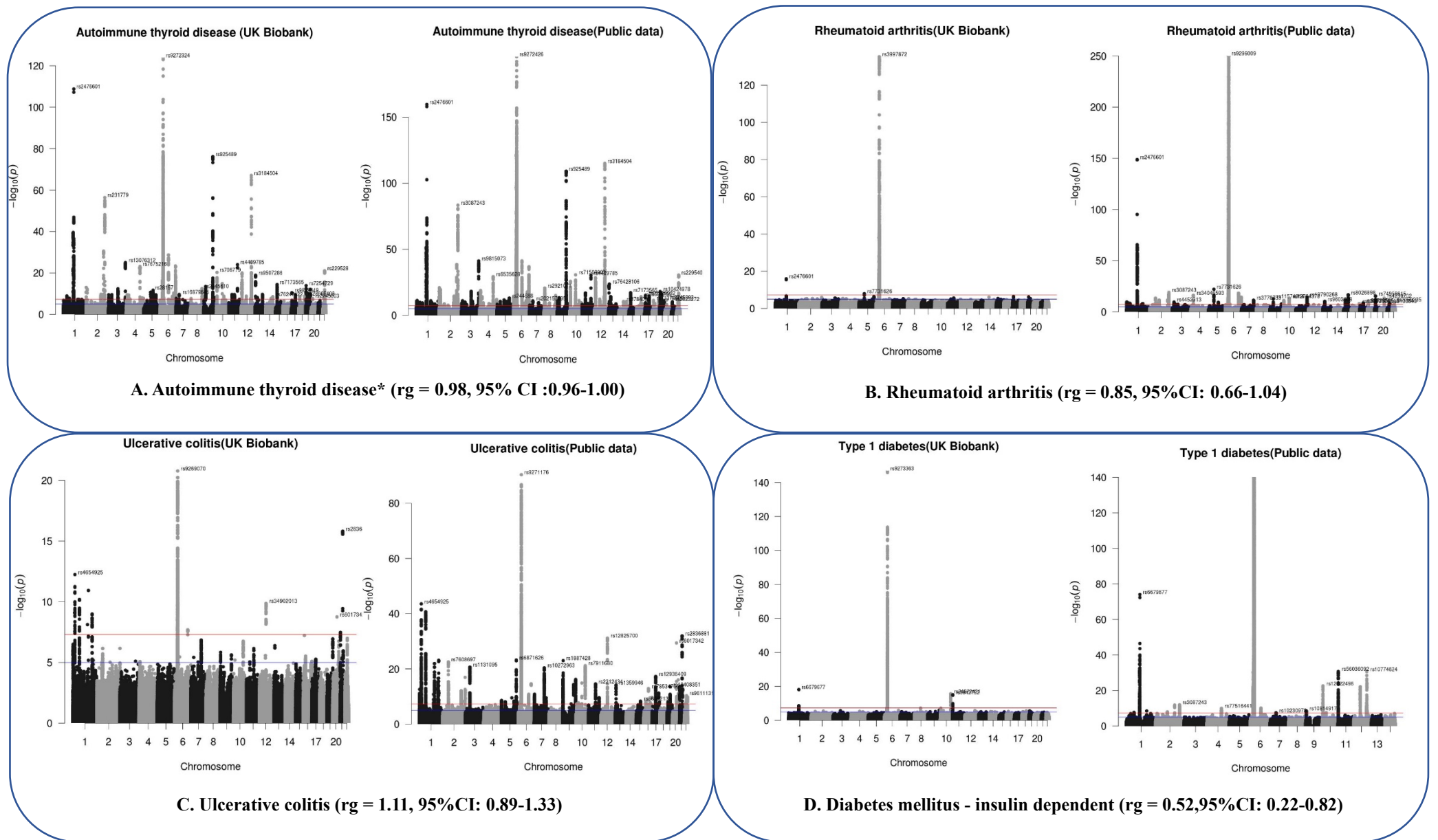
Figure S8 Manhattan of the SNP-Based GWAS of corresponding autoimmune disease using UK Biobank data comparing with publicly available GWAS data.
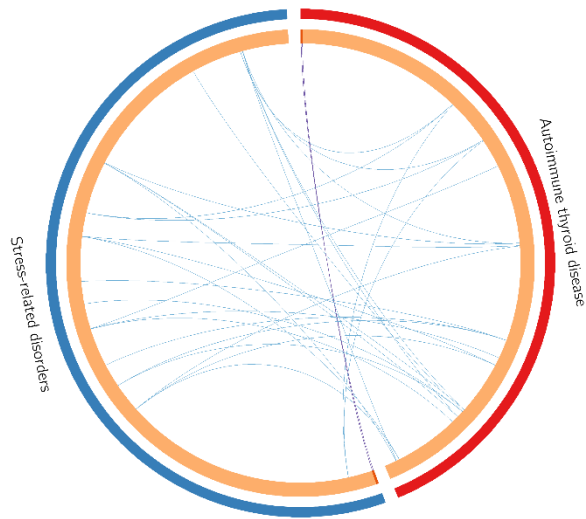
*Publicly available GWAS data for autoimmune thyroid disease include UK Biobank samples

SNP = single-nucleotide polymorphism. GWAS = genome-wide association studies. rg = genetic correlation assessed by LD score regression. CI = confidence interval.

	Inpatient Stress-related disorder		Inpatient posttraumatic stress disorder		
	N(%) in patients / individuals without inpatient stress-related disorder	OR(95% CI)	N(%) in patients / individuals without inpatient PTSD	OR(95% CI)	
The whole UK Biobank participants(n=502,488)					
Autoimmune diseases	267 (24.7%)/64,880 (12.94%)	2.13(1.85 - 2.45)	119 (25.7%)/65,028 (12.95%)	2.35 (1.90, 2.91)	
Autoimmune thyroid disease	125 (11.56%)/29,610 (5.91%)	2.15 (1.78 - 2.61)	54 (11.66%)/29,681 (5.91%)	2.39 (1.78, 3.20)	
Rheumatoid arthritis	35 (3.24%)/9,072 (1.81%)	1.64 (1.16 - 2.30)	18 (3.89%)/9,089 (1.81%)	2.08 (1.29, 3.35)	
Ulcerative colitis	19 (1.76%)/5,057 (1.01%)	1.66 (1.06 - 2.63)	8 (1.73%)/5,068 (1.01%)	1.62 (0.80, 3.26)	
Psoriasis	29 (2.68%)/5,025 (1.00%)	2.19 (1.51 - 3.18)	15 (3.24%)/5,039 (1.00%)	2.58 (1.54, 4.33)	
Diabetes mellitus - insulin dependent	29 (2.68%)/4,655 (0.93%)	2.06 (1.42 - 3.00)	14 (3.02%)/4,670 (0.93%)	2.22 (1.29, 3.80)	
Giant cell arteritis/ Polymyalgia rheumatica	13 (1.2%)/4,273 (0.85%)	1.99 (1.14 - 3.45)	3 (0.65%)/4,283 (0.85%)	1.23 (0.39, 3.84)	
The white British UK Biobank participants(n=409,601)					
Autoimmune diseases	201 (24.13%)/53,028 (12.97%)	2.04 (1.73 - 2.40)	86 (24.29%)/53,143 (12.99%)	2.18 (1.70, 2.80)	
Autoimmune thyroid disease	99 (11.88%)/24,204 (5.92%)	2.22 (1.79 - 2.76)	41 (11.58%)/24,262 (5.93%)	2.41 (1.72, 3.38)	
Rheumatoid arthritis	23 (2.76%)/7,378 (1.80%)	1.39 (0.91 - 2.11)	10 (2.82%)/7,391 (1.81%)	1.52 (0.80, 2.86)	
Ulcerative colitis	14 (1.68%)/4,089 (1.00%)	1.58 (0.93 - 2.68)	5 (1.41%)/4,098 (1.00%)	1.29 (0.53, 3.13)	
Psoriasis	23 (2.76%)/4,108 (1.00%)	2.16 (1.42 - 3.29)	12 (3.39%)/4,119 (1.01%)	2.58 (1.44, 4.61)	
Diabetes mellitus, insulin dependent	25 (3.00%)/3,575 (0.87%)	2.41 (1.61 - 3.61)	12 (3.39%)/3,588 (0.88%)	2.58 (1.44, 4.63)	
Giant cell arteritis/ Polymyalgia rheumatica	10 (1.20%)/3,680 (0.9%)	1.85 (0.99 - 3.47)	2 (0.56%)/3,688 (0.90%)	1.01 (0.25, 4.07)	

Legend:
■ Inpatient stress-related disorder
■ Inpatient posttraumatic stress disorder

(x-axis) OR(95%CI): 0 0.5 1 1.5 2 3 4 5

Figure S9 Association between inpatient stress-related disorders/ posttraumatic stress disorder and autoimmune disease

Odd ratio (OR) and 95% confidence interval (CI) were estimated by logistic regression models, adjusting for sex, birth year, sociodemographic factors (i.e., race/ethnicity, Townsend deprivation index, educational attainment, and annual household income), and life-style factors (i.e., body mass index, drinking status, and smoking status). N = number of cases of corresponding autoimmune disease. PTSD = posttraumatic stress disorder
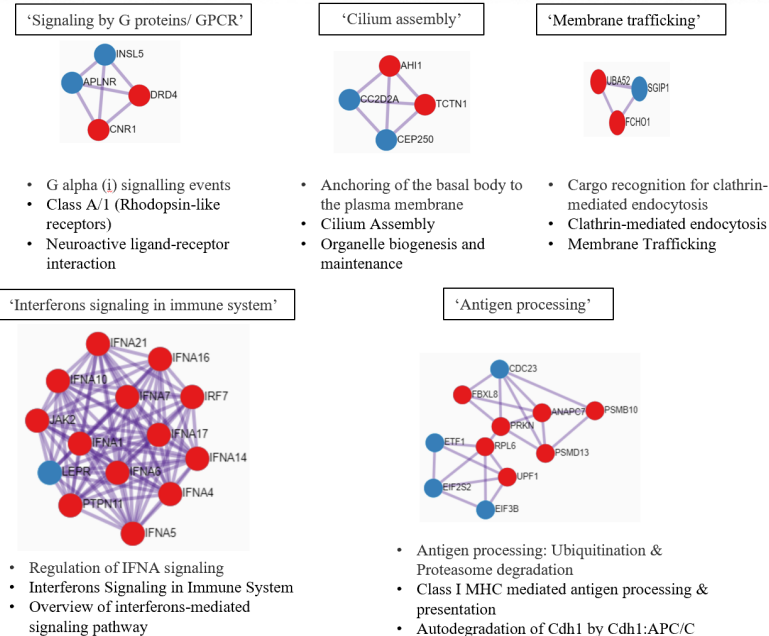
Gene ID	Gene Symbol	Description	Biological Process (GO)	Related disease
6068	SNORD3P1	small nucleolar RNA, C/D box 3 pseudogene 1		Alzheimer's disease or family history of Alzheimer's disease; Phosphatidylethanolamine levels; Body mass index; Parental longevity
692215	SNORD112	small nucleolar RNA, C/D box 112	GO:0006396 RNA processing	

B. Risk genes shared by stress-related disorders and autoimmune thyroid disease

'Signaling by G proteins/ GPCR'
- G alpha (i) signalling events
- Class A/1 (Rhodopsin-like receptors)
- Neuroactive ligand-receptor interaction

'Cilium assembly'
- Anchoring of the basal body to the plasma membrane
- Cilium Assembly
- Organelle biogenesis and maintenance

'Membrane trafficking'
- Cargo recognition for clathrin-mediated endocytosis
- Clathrin-mediated endocytosis
- Membrane Trafficking

'Interferons signaling in immune system'
- Regulation of IFNA signaling
- Interferons Signaling in Immune System
- Overview of interferons-mediated signaling pathway

'Antigen processing'
- Antigen processing: Ubiquitination & Proteasome degradation
- Class I MHC mediated antigen processing & presentation
- Autodegradation of Cdh1 by Cdh1:APC/C

Disease	GWAS data source	Genetic association assessed by LD score regression		Statistics of input gene lists in PPI enrichment analysis	
		rg (95% CI)	P	Number of Entrez gene ID	Color
Autoimmune thyroid disease	UK Biobank and Iceland	**0.14(0.03-0.25)**	0.01	509	
Stress-related disorders	iPSYCH			635	

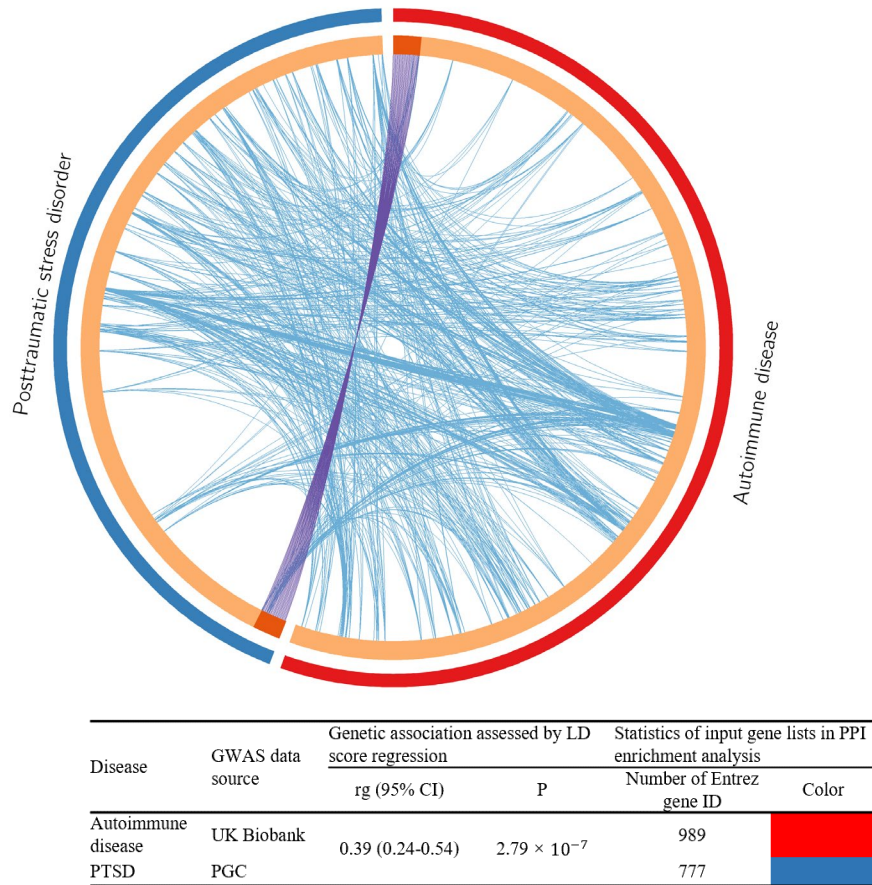**A. Genetic association and overlap between gene lists**

C. Shared MCODE components identified in protein-protein interaction network and the top pathways of the corresponding components

Figure S10 Identification of genes and pathways shared by stress-related disorders and autoimmune thyroid disease*
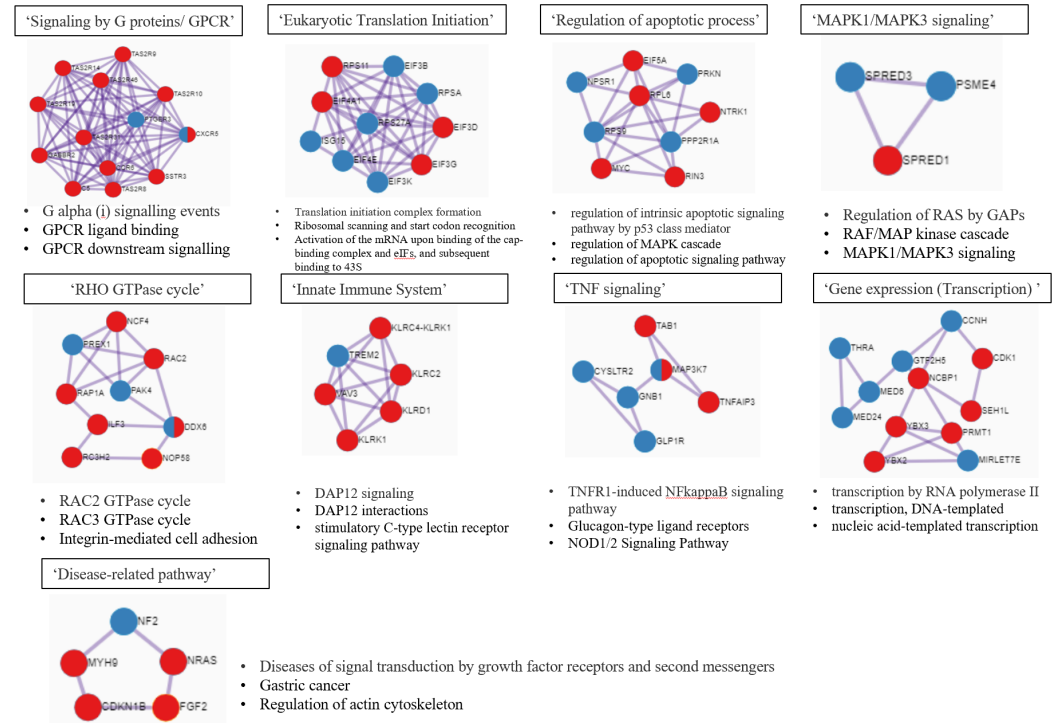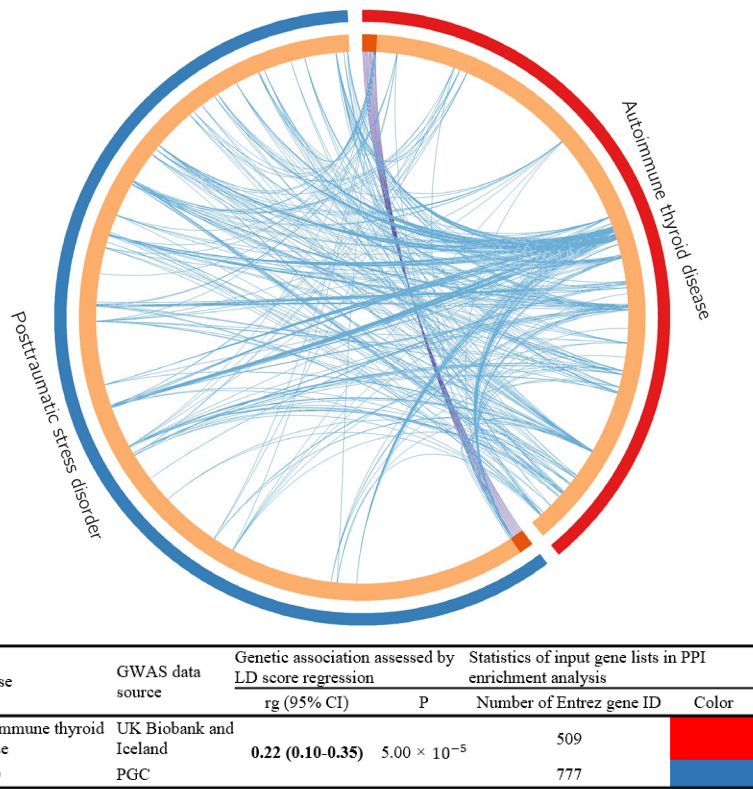
A. Genetic association and overlap between gene lists. Each candidate gene is assigned to one spot on the arc of the corresponding gene lists. Dark orange color represents the genes that appear in both lists and light orange color represents genes that are unique to that gene list. Purple curves link identical genes, and blue curves link genes that have different identities but share an enriched pathway/process (i.e., they represent the functional overlaps between gene lists). **B.** Risk genes shared by stress-related disorders and autoimmune thyroid disease. The short description for identical genes were annotated using the Metascape tool, and the related diseases were reported based on GWAS catalog. **C.** Shared MCODE component identified in protein-protein interaction network and the top pathways of the corresponding components, where each node represents a protein with a pie chart encoding its origin (i.e., blue for stress-related disorders and red for autoimmune thyroid disease).

GWAS=genome-wide association studies. rg = genetic correlation. P = P value. CI = confidence interval. GPCR=G Protein Coupled Receptors. MCODE =Molecular Complex Detection algorithm.

*Publicly available GWAS data for autoimmune thyroid disease include UK Biobank samples

Disease	GWAS data source	Genetic association assessed by LD score regression		Statistics of input gene lists in PPI enrichment analysis	
		rg (95% CI)	P	Number of Entrez gene ID	Color
Autoimmune disease	UK Biobank	0.39 (0.24-0.54)	2.79×10^{-7}	989	(red)
PTSD	PGC			777	(blue)

A. Genetic association and overlap between gene lists

B. Shared MCODE components identified in protein-protein interaction network and the top pathways of the corresponding components

Figure S11 Identification of genes and pathways shared by posttraumatic stress disorder and autoimmune disease*

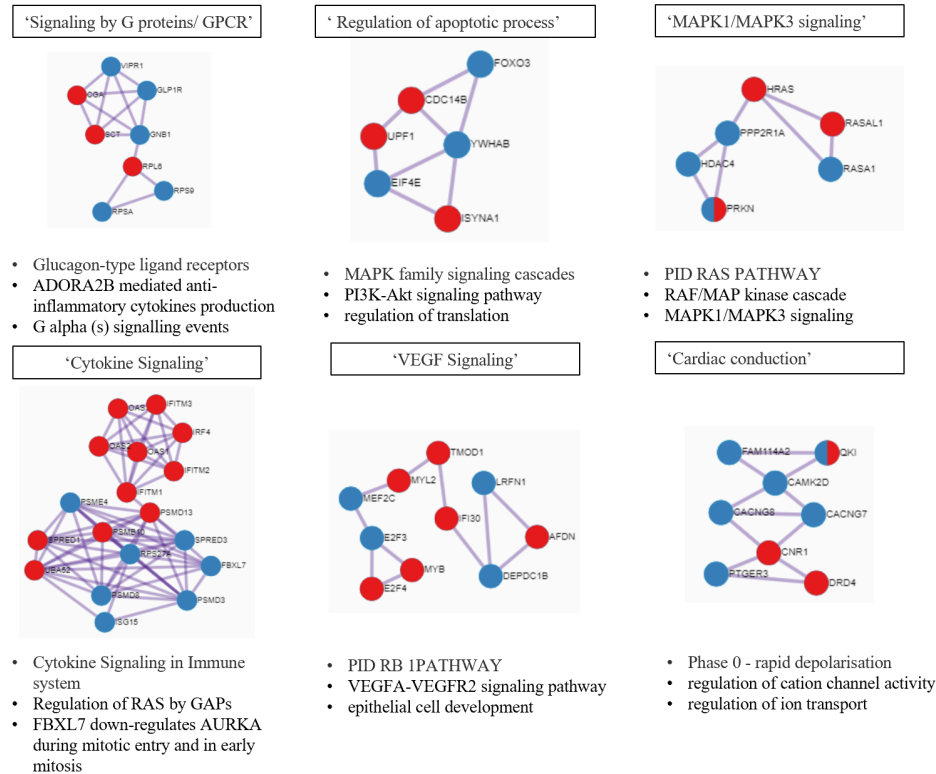**A.** Genetic association and overlap between gene lists. Each candidate gene is assigned to one spot on the arc of the corresponding gene lists. Dark orange color represents the genes that appear in both lists and light orange color represents genes that are unique to that gene list. Purple curves link identical genes, and blue curves link genes that have different identities but share an enriched pathway/process (i.e., they represent the functional overlaps between gene lists). **B.** Shared MCODE component identified in protein-protein interaction network and the top pathways of the corresponding components, where each node represents a protein with a pie chart encoding its origin (i.e., blue for posttraumatic stress disorder and red for autoimmune disease).

* GWAS summary statistics for posttraumatic stress disorder were from Psychiatric Genomics Consortium (23,212 cases and 151,447 controls) including UK Biobank samples.

PTSD = posttraumatic stress disorder. GWAS=genome-wide association studies. PGC = Psychiatric Genomics Consortium. GPCR=G Protein Coupled Receptors. rg = genetic correlation. P = P value. CI = confidence interval. GPCR=G Protein Coupled Receptors. MCODE =Molecular Complex Detection algorithm

A. Genetic association and overlap between gene lists

B. Shared MCODE components identified in protein-protein interaction network and the top pathways of the corresponding components

Figure S12 Identification of genes and pathways shared by posttraumatic stress disorder and autoimmune thyroid disease*

A. Genetic association and overlap between gene lists. Each candidate gene is assigned to one spot on the arc of the corresponding gene lists. Dark orange color represents the genes that appear in both lists and light orange color represents genes that are unique to that gene list. Purple curves link identical genes, and blue curves link genes that have different identities but share an enriched pathway/process (i.e., they represent the functional overlaps between gene lists). **B.** Shared MCODE component identified in protein-protein interaction network and the top pathways of the corresponding components, where each node represents a protein with a pie chart encoding its origin ((i.e., blue for posttraumatic stress disorder and red for autoimmune thyroid disease).

* GWAS summary statistics for posttraumatic stress disorder were from Psychiatric Genomics Consortium (23,212 cases and 151,447 controls) including UK Biobank samples. Publicly available GWAS data for autoimmune thyroid disease include UK Biobank samples.

PTSD = posttraumatic stress disorder. GWAS=genome-wide association studies. PGC = Psychiatric Genomics Consortium. GPCR=G Protein Coupled Receptors. rg = genetic correlation. P = P value. CI = confidence interval. GPCR=G Protein Coupled Receptors. MCODE =Molecular Complex Detection algorithm