Genetic analysis of over half a million people characterises C-reactive protein loci

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Supplementary Methods

FUMA reference panel

To define independent significant SNPs and genomic risk loci, FUMA uses the 1000G reference panel (including five population groups) and the UK Biobank release 2b reference panel (includes SNPs imputed with UK10K/1000G, included two population groups). Variants which do not exist in the selected reference panel are not included in any analyses[1]. More detail can be found elsewhere https://fuma.ctglab.nl/tutorial#refpanel .

Gene mapping in FUMA

Functionally annotated SNPs were subsequently mapped to protein coding genes using three strategies to obtain prioritised genes associated to CRP in FUMA[1]:

1) positional mapping based on annotations obtained from ANNOVAR[2]. Physical distance of SNP from known protein coding genes was set to the default window of 10kb, in the human reference assembly (hg19/GRCH37).

2) eQTL mapping was used to map independent significant SNP and SNPs in LD of them to genes that show a significant association to cis-eQTLs (i.e. the allelic variation of the SNP association to with expression levels of the gene). This maps SNPs to genes up to 1MB apart. eQTL mapping used data repositories on all tissue types available in FUMA at the time, consisting of GTEx[3] v6-8, BRAINEAC[4], CommInMind Consortium[5], xQTL server[6], MuTHER[7], Blood eQTLs[8], eQTL Gen[9] , DICE[10], van der Wijst et al. scRNA eQTLs[11], PsychENCODE[12]. We used significant eQTL associations were FDR < 0.05 recommended in FUMA[1].

3) Chromatin interaction mapping is performed by overlapping independent significant SNPs and SNPs in LD of them with one end of significantly interacting regions in tissue/cell types. These SNPs are subsequently mapped to genes which promoter regions (by default 250 bp up-stream and 500 bp down-stream of transcription start site) overlap with another end of the significant interactions[1]. This mapping can involve long range interaction as there is no distance boundary. FUMA uses data on the

3D structure of chromatin interactions of 23 tissues and cell types in Hi-C[13] data, tissue and cell type from FANTOM[14–16] and PsychENCODE[12] The significance threshold was defined as FDR < 1 x 10^{-6} in FUMA[1] based on prior recommendations[13].

Gene based analysis

MAGMA[17] using 1000 genomes phase 3 reference panels. For genome wide gene-based association analysis (GWGA) in MAGMA, input SNPs were mapped to protein coding genes obtained from Ensemble build 92, using a SNP-wise mode which analyses individual SNPs in a gene and aggregates the resulting SNP p-values into a gene test-statistic[17]. Genome-wide significance was determined by Bonferroni correction applied to 19,144 genes tested (p < 2.61 x 10^{-6}).

Gene-set analysis

MAGMA gene-set analysis is performed for curated gene sets and gene ontology (GO) terms obtained from molecular signature database (MsigDB) v5.2. This is to test whether the prioritised genes of the CRP GWAS meta-analysis clustered in specific biological pathways, cellular components or molecular functions. Competitive gene-set analysis examines if genes within the gene set are more strongly associated with each of the phenotypes than other genes. We performed the analysis with default parameters [1] using the results of the gene-based analysis. A total of 15,478 gene sets were tested, significance was determined by Bonferroni threshold (p < 3.23 x 10^{-6}) to account for multiple testing burden[18].

Gene-property analysis

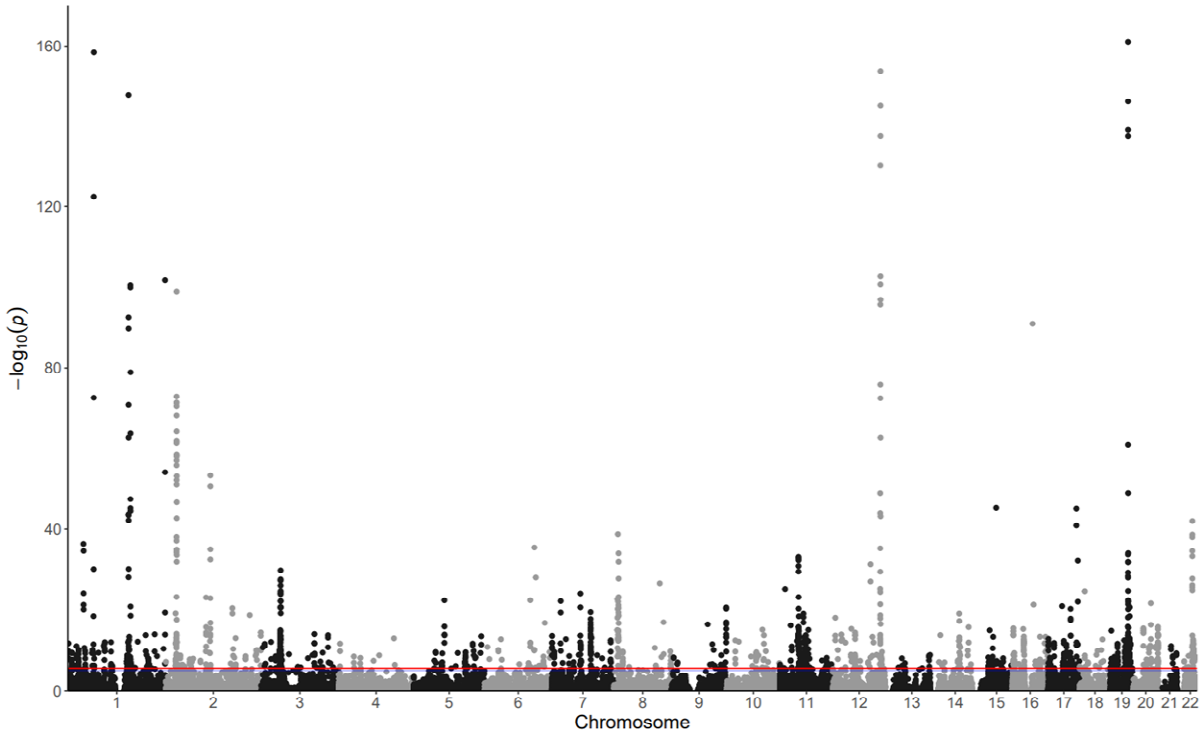
To identify tissue specificity of CRP, the relationship between tissue specific gene expression profiles and CRP-gene associations was tested using MAGMA gene-property analysis[17] in FUMA[1]. This tested relationships between tissue specific gene expression profiles and CRP-gene associations based on the earlier computed gene-based p values. The tissue enrichment tested 30 broad tissue types and 53 specific tissues. Tissue types were obtained from GTEx[3] v7 RNA-sequence data, expression values were

log2 transformed average RPKM per tissue type. Multiple testing for 53 specific and 30 general tissue type was accounted by Bonferroni correction ($p < 9.43 \times 10^{-4}$, $p < 1.67 \times 10^{-3}$).

DEPICT

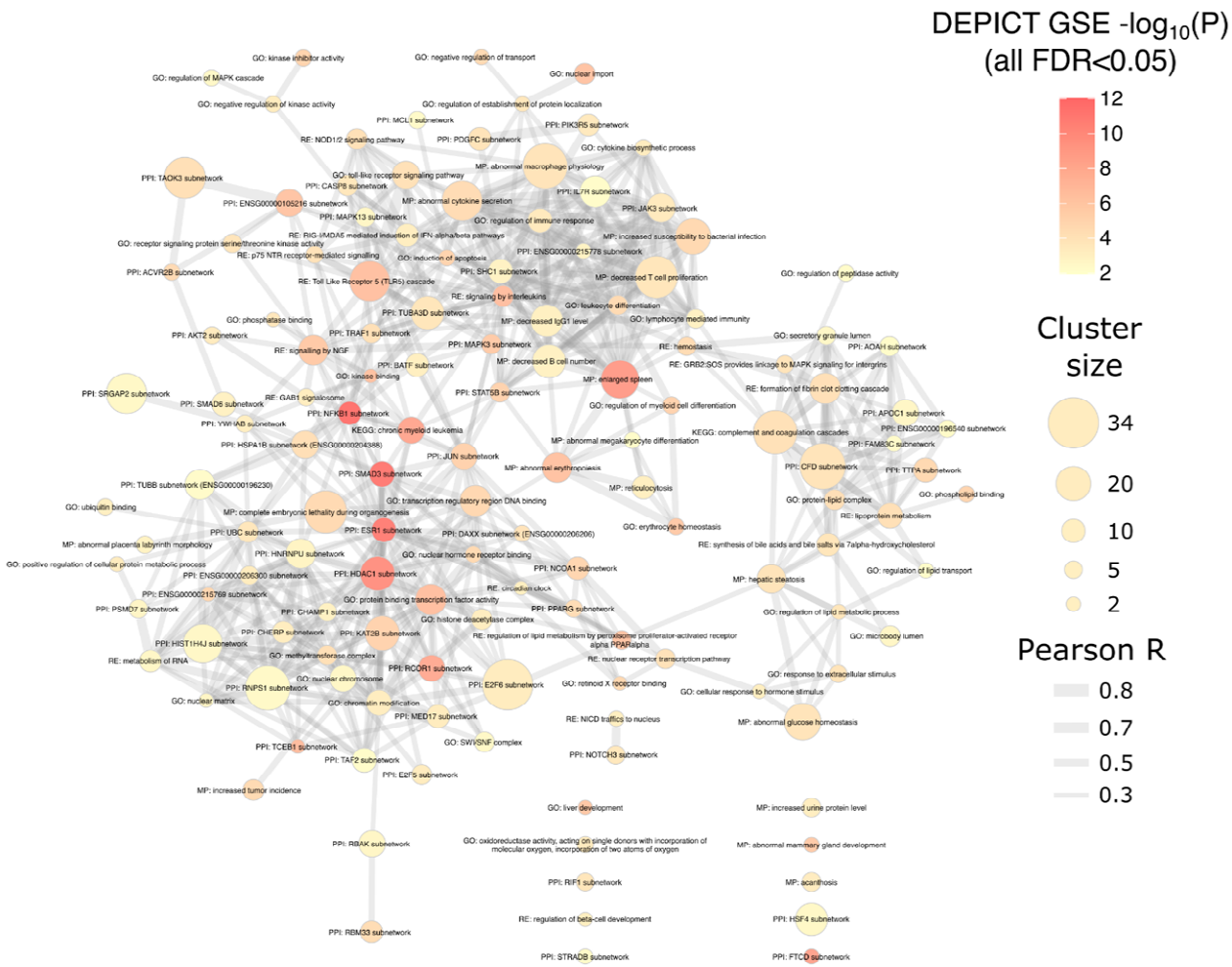
DEPICT[19] *v1rel194* beta version for 1000G imputed data was used to identify enriched pathways, processed, tissue types and prioritised genes from each GWAS locus. This method uses the assumption that trait-relevant genes from independent GWAS loci from the same GWAS should often be functionally similar and therefore share functional annotations. Briefly, DEPICT uses 1000G p1v3 reference panel (CEU, GBR and TSI subpopulations, release date 2010-11-23 [20]) to perform LD-clumping for all input SNPs using plink v1.9[21] using r2 <0.1 and 1Mb window. Positions in the genome were defined according to genome build GRCh37/hg19. Precomputed DEPICT loci were defined as LD-blocks of r^2>0.5 (1000G pilot phase) from each independent SNP, HLA region (chr6: 25Mb-35Mb, genome build GRCh37/hg19) was omitted from analyses. This method uses reconstituted gene sets (are a consequence of the gene function prediction, which is quantified using co-regulation between gene pairs based o,, n gene expression data) derived from gene expression array data from ~80,000 samples and correlates their reconstituted gene set membership scores to obtain enrichment score. Empirical enrichment p-values were calculated by using the permutations over 500 randomly selected sets of gene-density-matched loci and subsequently FDR was calculated by performing 50 repetitions of scoring and adjustment steps. Further details of DEPICT analyses can be found elsewhere[19].

Supplementary Figures

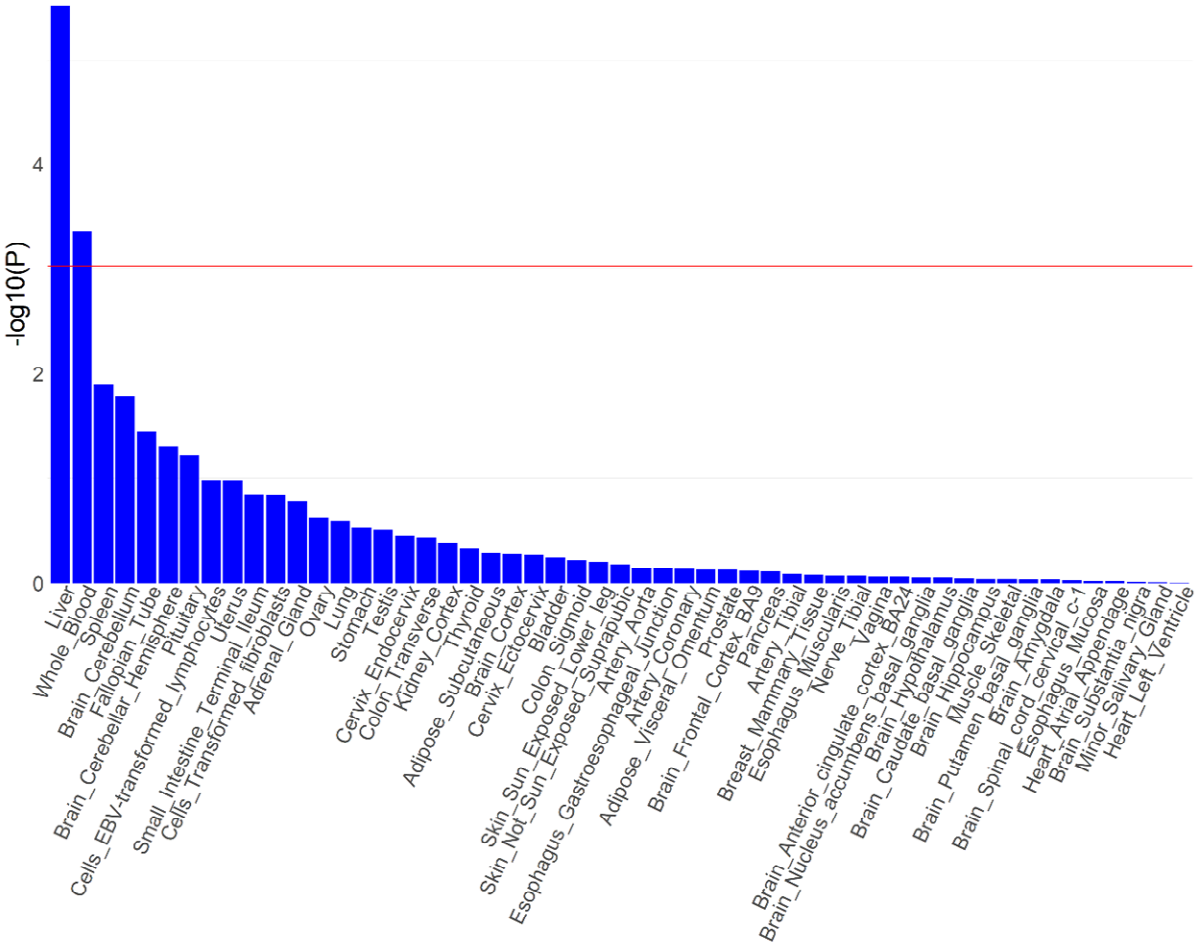


Supplementary Figure 1. Manhattan plot of genes association results for gene-based analysis of CRP.

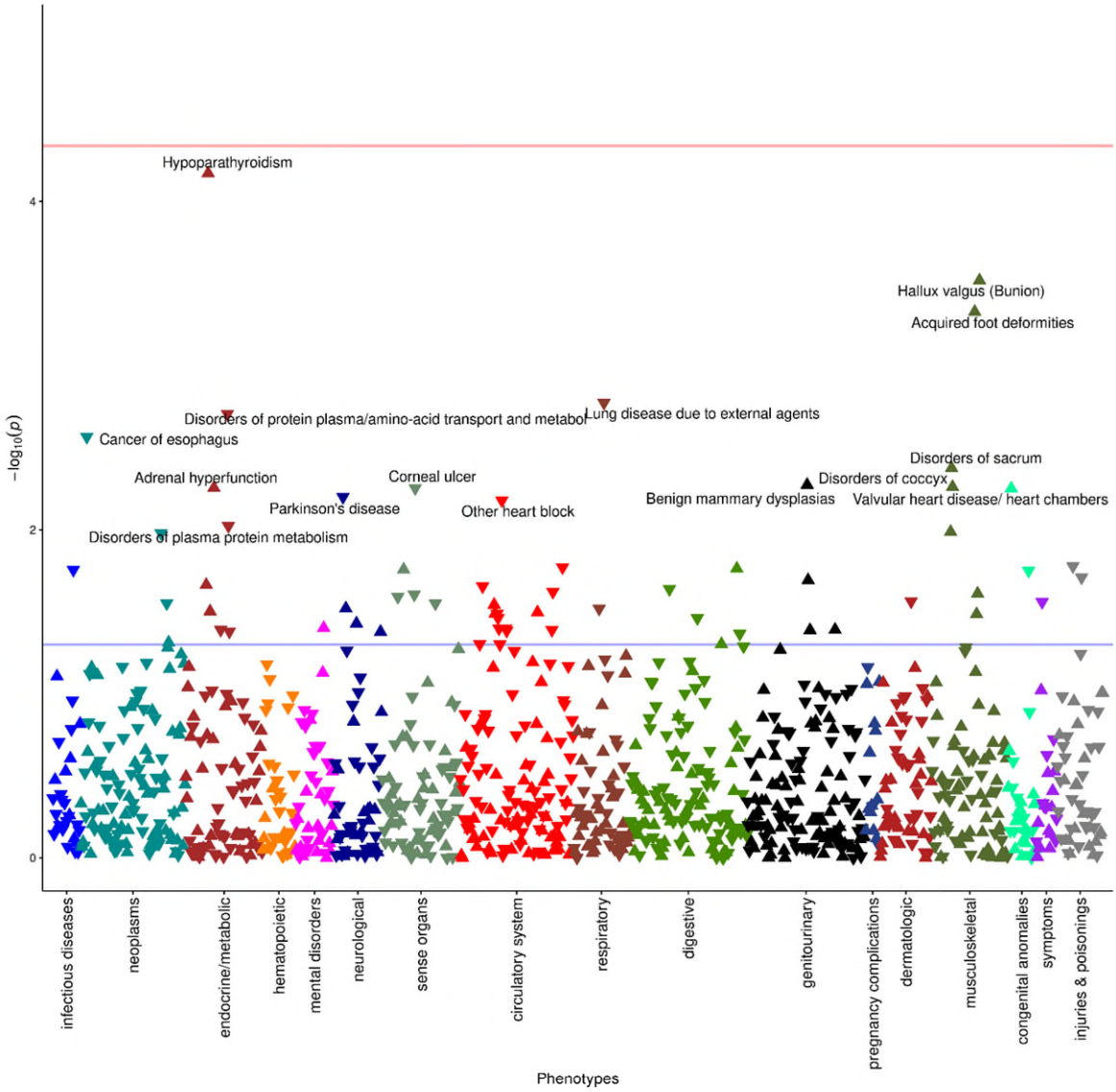
The red line indicates genome wide significance (p= 2.62 x 10^{-6}).



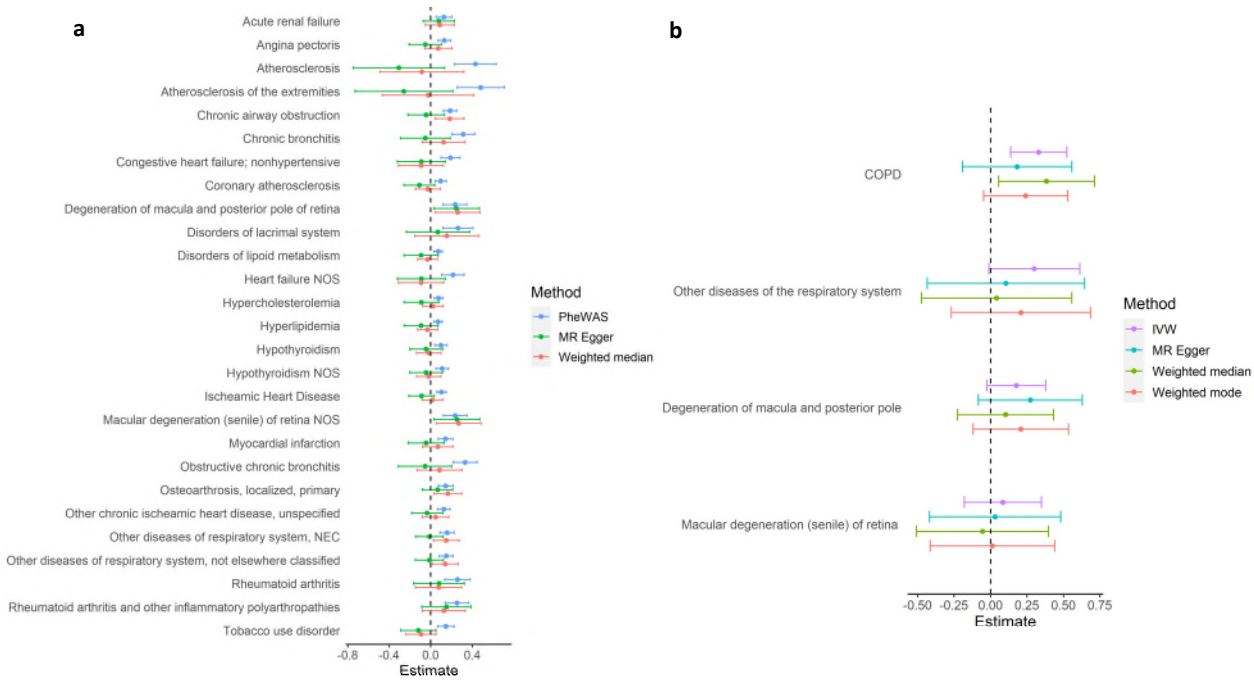
Supplementary Figure 2. Result of DEPICT gene set enrichment analysis. Each node represents an exemplar gene set from affinity-propagation clustering. There are 138 FDR <0.05 clusters of gene sets. Gene sets are represented by nodes coloured according to statistical significance, and links between them are indicated by their correlation (only correlations with $r > 0.3$ are shown). The size of the cluster is indicated by the size of the node. DEPICT GSE -$\log_{10}$ (P) refers to the gene-set enrichment two-sided p-value for that DEPICT gene-set generated by DEPICT.



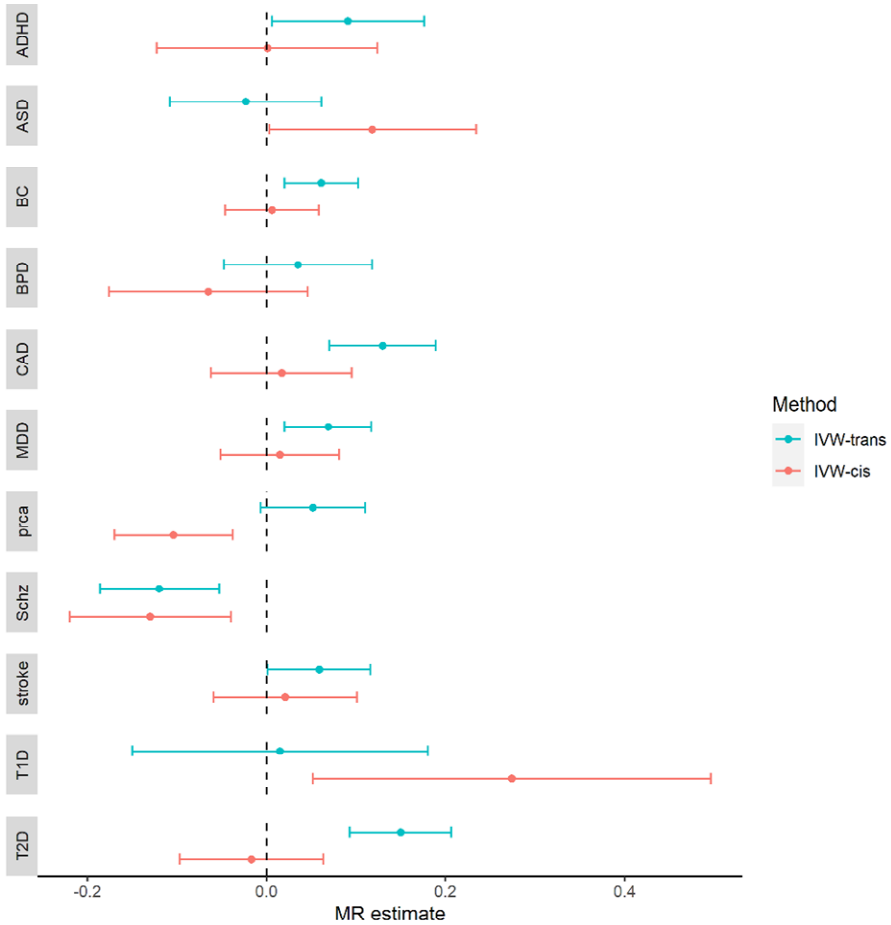
Supplementary Figure 3. MAGMA gene-property analysis results for 53 specific tissue types. The red line indicates the Bonferroni cut off (p=9.43 x 10^{-4}).



Supplementary Figure 4. CRP gene locus weighted GRS PheWAS Manhattan plot. The red line indicates FDR threshold (q<0.05) and the blue line indicates the nominal threshold (*p*<0.05). The triangle pointing up represents positive association and down a negative association. Phenotypes with *p* <0.01 have been annotated.



Supplementary Figure 5 a- Forest plot of PheWAS and MR_UKB estimates. PheWAS beta estimates (non-standardised) of 27 disease outcomes are shown with two-sample MR Egger and weighted median estimates. b- Forest plot of replicated MR estimates. Outcomes that were Bonferroni significant for MR_UKB IVW estimate and nominally for weighted median or Egger are presented with MR IVW and sensitivity tests. The points are the beta estimates from the MR analyses and error bars are the 95% confidence intervals.



Supplementary Figure 6. Forest plot of cis and trans-acting CRP IVs IVW MR result. The points are the beta estimates from the MR analyses and error bars are the 95% confidence intervals. ADHD = Attention-Deficit/Hyperactivity Disorder, ASD = Autism Spectrum Disorder, BC = Breast Cancer, BPD = Bipolar Disorder, CAD = Coronary Artery Disease, MDD = Major Depressive Disorder, PrC = Prostate Cancer, Schz = Schizophrenia. T1D = Type 1 Diabetes, T2D = Type 2 Diabetes.

Supplementary Tables

Supplementary Table 1. UKB study characteristics.

Attribute	Value (mean, SD)
Age (years)	56.53 (± 8.10)
Female (%)	54.41%
BMI (kg/m^2)[1]	27.39 (± 4.79)
CRP (mg/l)[2]	1.33(IQR 2.1)*

[1] BMI Body mass index, [2] C reactive protein ,*median and IQR= interquartile range

Supplementary Table 2. List of immune modulating drugs and immune related diseases and conditions excluded from UKB data.

Code	Immunomodulating drug	Use
1141172616	glatiramer	multiple sclerosis
1141172486	interferon beta	multiple sclerosis
1140923792	interferon beta- 1b	multiple sclerosis
1141150594	interferon beta- 1a	multiple sclerosis
1141157420	interferon beta- 1b product	multiple sclerosis
1140869848	methotrexate	rheumatoid arthritis /cancers
1141166294	leflunomide	rheumatoid arthritis / and other autoimmune diseases
1140884308	hydroxychloroquine	rheumatoid arthritis /malaria/lupus
1140909702	sulfasalazine	rheumatoid arthritis /chrons disease/ulcerative colitis/ankylosing spondylitis
1140909844	Ciclosporin	transplant/ rheumatoid arthritis /psoriasis/chrons disease/nephrotic syndrome/ulcerative colitis
1141172620	Copaxone	multiple sclerosis
1140869930	azathioprine	chrons/ rheumatoid arthritis /ulcerative cholitis/transplants/ myasthenia gravis/polyarteritis nodosa
1140925978	mycophenolate	transplant/ myasthenia gravis

code	phenotypes to exclude
1234	adrenocortical insufficiency/Addison's disease
1261	multiple sclerosis
1311	spine arthritis/spondylitis
1313	ankylosing spondylitis
1322	myositis/myopathy
1345	pemphigoid/pemphigus
1372	vasculitis
1373	connective tissue disorder
1380	polyartertis nodosa
1381	systemic lupus erythematosis
1382	Sjogrens syndrome/sicca syndrome
1384	scleroderma/systemic sclerosis

1437	myasthenia gravis
1453	psoriasis
1456	coeliac disease
1463	ulcerative colitis
1464	rheumatoid arthritis
1477	psoriatic arthropathy
1522	graves disease
1564	antiphospholipid syndrome

Supplementary Table 3. Information on PheWAS outcomes tested in two-sample MR.

Description	Group	N cases	N control	N*	Two-sample MR ID	Trait	Study pmid/author	Population
Chronic airway obstruction/COPD	respiratory	2372	83986	4614	Finn-a-J10_COPD	Chronic obstructive pulmanary diease,COPD	FinnGen biobank analysis	European
Chronic bronchitis	respiratory	177	83986	353	finn-a-J10_BRONCHNAS	Unspecified chronic bronchitis	2020 FinnGen biobank analysis	European
Other diseases of respiratory system, NEC	respiratory	840	95659	1665	finn-a-J10_RESPOTHER	Other diseases of the respiratory system	2020 FinnGen biobank analysis	European
Rheumatoid arthritis	musculoskeletal	19234	61565	29311	ieu-a-833	Rheumatoid arthritis	24390342/Okada Y 2014	Mixed
Macular degeneration (senile) of retina NOS	sense organs	1266	47,560	2466	finn-a-CUSTOM_AMD	Wet or dry macular degeneration	FinnGen biobank analysis	European
Degeneration of macula and posterior pole of retina	sense organs	2215	90618	4324	finn-a-H7_MACULADEGEN	Degeneration of macula and posterior pole	FinnGen biobank analysis	European
Ischemic Heart Disease	circulatory system	63746	130681	85692	ieu-a-7	Coronary heart disease (Ischeamic heart disease)	26343387/Nikpay 2015	Mixed
Other chronic ischeamic heart disease, unspecified	circulatory system	21362	75137	33266	finn-a-I9_OTHHEART	Other heart disease (Ischeamic heart disease)	FinnGen biobank analysis	European
Angina pectoris	circulatory system	6382	85760	11880	finn-a-I9_ANGINA	Angina pectoris	FinnGen biobank analysis	European
Atherosclerosis	circulatory system	2196	92349	4290	finn-a-I9_ATHSCLE	Atherosclerosis, excluding cerebral, coronary and PAD	FinnGen biobank analysis	European

Atherosclerosis of the extremities	circulatory system	2181	75420	4239	finn-a-DM_PERIPHATHERO	Peripheral atherosclerosis	FinnGen biobank analysis	European
Coronary atherosclerosis	circulatory system	7661	85760	14066	finn-a-I9_CORATHER	Coronary atherosclerosis	FinnGen biobank analysis	European
Heart failure NOS	circulatory system	8016	75137	14487	finn-a-HEARTFAIL	Heart failure	FinnGen biobank analysis	European
Congestive heart failure; non-hypertensive	circulatory system	9413	203040	17992	bbj-a-109	Congestive heart failure	Ishigaki K 2019 (east Asian sample)	East Asian
Myocardial infarction	circulatory system	43676	128199	65155	ieu-a-798	Myocardial infarction	Nikpay 2015/26343387	Mixed
Hypothyroidism	endocrine/metabolic	10211	32736	15567	finn-a-HYPOTHYROIDISM	Hypothyroidism (congenital or acquired)	FinnGen biobank analysis	European
Hypothyroidism NOS	endocrine/metabolic	10192	84518	18190	finn-a-E4_HYTHYNAS	Hypothyroidism,other/unspecified	FinnGen biobank analysis	European
Disorders of lacrimal system	sense organs	2256	90757	4403	finn-a-H7_LACRIMALSYSTEM	Disorders of lacrimal system	FinnGen biobank analysis	European
Hypercholesterolemia	endocrine/metabolic	3262	91366	6299	finn-a-E4_HYPERCHOL	Pure hypercholesterolaemia	FinnGen biobank analysis	European
Disorders of lipoid metabolism	endocrine/metabolic	5133	88782	9705	finn-a-E4_LIPOPROT	Disorders of lipoprotein metabolism and other lipidaemias	FinnGen biobank analysis	European
Hyperlipidemia	endocrine/metabolic	1539	91366	3027	finn-a-E4_HYPERLIPNAS	Hyperlipidaemia, other/unspecified	FinnGen biobank analysis	European

Acute renal failure	genitourinary	584	94913	1161	finn-a-N14_ACUTERENFAIL	Acute renal failure	FinnGen biobank analysis	European

*For binary traits, N is the effective sample size (N_eff = 2/(1/cases + 1/controls) (see e.g. https://doi.org/10.1038/nprot.2014.071).

Supplementary Table 4. Information on outcomes tested in MR.

Outcome	Abbreviation	N case	N control	N*	Source	doi
Breast cancer		108067	88386	97241	Michailidou et al. 2017	10.1038/nature24284
Prostate cancer		79194	61112	68988	Schumacher et al. 2018	10.1038/s41588-018-0142-8
Attention-deficit/hyperactivity disorder	ADHD	20183	35191	25653	Demontis et al. 2019	10.1038/s41588-018-0269-7
Autism spectrum disorder	ASD	18381	27969	22183	Grove et al. 2019	10.1038/s41588-019-0344-8
Bipolar disorder	BPD	20352	31358	24684	Stahl et al. 2019	10.1038/s41588-019-0397-8
Major depressive disorder	MDD	135458	344901	194520	Wray et al. 2018	10.1038/s41588-018-0090-3
Schizophrenia	Schz	36989	113075	55743	Ripke et al. 2014	10.1038/nature13595
Type 2 diabetes	T2D	62892	596424	113786	Xue et al. 2018	10.1038/s41467-018-04951-w
Coronary artery disease	CAD	60801	123504	81486	Nikpay et al. 2015	10.1038/ng.3396
Stroke		40585	406111	73795	Malik et al. 2015	10.1038/s41588-018-0058-3
Type I diabetes	T1D	5913	8828	7082	Censin et al. 2017	10.1371/journal.pmed.1002362

*For binary traits, N is the effective sample size (N_eff = 2/(1/cases + 1/controls) (see e.g. https://doi.org/10.1038/nprot.2014.071).

Supplementary Table 5. Previously identified sentinel variants associated to CRP in the current UKB GWAS loci.

SNP	Chr	BP	Effect allele	Ref. allele	Beta	SE	P value	Closest Gene
rs4129267	1	154426264	C	T	0.094	0.002	< 4.94E-324	*IL6R*
rs2794520	1	159678816	C	T	0.173	0.002	< 4.94E-324	*CRP*
rs10925027	1	247612562	T	C	0.033	0.002	5.90E-56	*NLRP3*
rs75460349	1	27180088	A	C	0.097	0.007	4.50E-44	*ZDHHC18*
rs2293476	1	40036847	G	C	-0.029	0.002	1.70E-32	*PABPC4*
rs1805096	1	66102257	G	A	0.121	0.002	< 4.94E-324	*LEPR*
rs469772	1	91530305	C	T	0.035	0.003	6.90E-41	*ZNF644*
rs9284725	2	102744854	C	A	0.020	0.002	4.10E-16	*IL1R1*
rs13409371	2	113838145	G	A	-0.044	0.002	1.40E-95	*IL1F10*
rs1441169	2	214033530	A	G	0.021	0.002	3.60E-23	*IKZF2*
rs1260326	2	27730940	T	C	0.078	0.002	8.20E-291	*GCKR*
rs12995480	2	629881	T	C	-0.024	0.003	1.80E-18	*TMEM18*
rs4246598	2	88438050	C	A	-0.013	0.002	1.40E-09	*FABP1*
rs687339	3	135932359	C	T	0.026	0.003	3.90E-24	*MSL2*
rs1514895	3	170705693	A	G	-0.017	0.002	3.70E-14	*EIF5A2*
3:47431869_GTCT_G	3	47431869	GTCT	G	-0.010	0.002	1.80E-06	*PTPN23*
rs2352975	3	49891885	T	C	-0.021	0.002	4.50E-22	*TRAIP*
rs17658229	5	172191052	T	C	-0.038	0.005	2.30E-14	*DUSP1*
rs12202641	6	116314634	C	T	0.017	0.002	9.00E-17	*FRK*
rs1490384	6	126851160	C	T	0.029	0.002	4.50E-42	*C6orf173*
rs9385532	6	130371227	T	C	-0.023	0.002	4.50E-24	*L3MBTL3*
rs9271608*	6	32591588	A	G	-0.039	0.003	4.90E-48	*HLA-DQA1*
rs1880241	7	22759469	A	G	0.024	0.002	1.50E-29	*IL6*
rs2710804	7	36084529	T	C	-0.025	0.002	3.30E-30	*KIAA1706*
rs13233571	7	72971231	C	T	0.033	0.003	2.40E-24	*BCL7B*
rs7795281	7	74122854	A	G	0.013	0.002	5.90E-08	*GTF2I*
rs1736060	8	11664738	C	T	-0.023	0.002	7.40E-26	*FDFT1*
rs2064009	8	117007850	C	T	-0.026	0.002	3.20E-35	*TRPS1*
rs2891677	8	126344208	C	T	-0.022	0.002	1.90E-24	*NSMCE2*

rs4841132	8	9183596	A	G	-0.083	0.004	3.00E-113	*PPP1R3B*
rs643434	9	136142355	G	A	-0.022	0.002	1.60E-23	*ABO*
rs1051338	10	91007360	T	G	-0.028	0.002	3.60E-33	*LIPA*
rs10832027	11	13357183	G	A	-0.030	0.002	2.50E-39	*ARNTL*
rs10838687	11	47312892	T	G	0.029	0.003	2.70E-27	*MADD*
rs1582763	11	60021948	G	A	0.020	0.002	3.80E-21	*MS4A4A*
rs7121935	11	72496148	G	A	0.015	0.002	1.10E-11	*STARD10*
rs10778215	12	103537266	T	A	0.018	0.002	2.90E-18	*ASCL1*
rs7310409	12	121424861	A	G	-0.150	0.002	< 4.94E-324	*HNF1A*
rs11108056	12	95855385	C	G	0.026	0.002	1.70E-35	*METAP2*
rs2239222	14	73011885	A	G	-0.035	0.002	2.50E-57	*RGS6*
rs112635299	14	94838142	G	T	0.096	0.007	2.00E-40	*SERPINA1/2*
rs4774590	15	51745277	G	A	0.006	0.002	0.0056	*DMXL2*
rs1189402	15	53728154	A	G	0.015	0.002	2.00E-12	*ONECUT1*
rs340005	15	60878030	G	A	-0.033	0.002	4.70E-52	*RORA*
rs10521222	16	51158710	C	T	0.107	0.005	4.90E-106	*SALL1*
rs1558902	16	53803574	T	A	-0.025	0.002	2.80E-31	*FTO*
rs178810	17	16097430	C	T	-0.015	0.002	2.70E-13	*NCOR1*
17:58001690_GA_G	17	58001690	GA	G	0.018	0.002	1.60E-17	*RPS6KB1*
rs10512597	17	72699833	T	C	-0.030	0.003	3.90E-29	*CD300LF,RAB37*
rs2852151	18	12841176	G	A	-0.019	0.002	8.70E-18	*PTPN2*
rs4092465	18	55080437	A	G	-0.027	0.002	1.40E-34	*ONECUT2*
rs12960928	18	57897803	T	C	-0.018	0.002	6.30E-14	*MC4R*
rs4420638	19	45422946	A	G	0.221	0.003	< 4.94E-324	*APOC1*
rs1800961	20	43042364	C	T	0.110	0.006	2.00E-72	*HNF4A*
rs2315008	20	62343956	T	G	-0.020	0.002	2.50E-18	*ZGPAT*
rs2836878	21	40465534	G	A	0.034	0.002	3.50E-46	*DSCR2*
rs6001193	22	39074737	A	G	0.030	0.002	4.70E-43	*TOMM22*
rs9611441	22	41339367	G	C	0.014	0.002	1.50E-11	*XPNPEP3*

* This variant is replicated in the UKB GWAS but HLA region was excluded in loci definition so was not found in UKB GWAS loci.

Variants listed were genome-wide significant variants replicated in current UKB GWAS at p <0.01 with concordant effect direction.

Supplementary Table 6. MAGMA gene set analysis Bonferroni significant results for curated gene sets.

Gene sets*	N Genes	Beta	Beta STD	SE	P value
GO_bp:go_positive_regulation_of_gene_expression	1825	0.283	0.083	0.036	2.55E-15
GO_bp:go_positive_regulation_of_biosynthetic_process	1844	0.274	0.081	0.036	1.09E-14
GO_bp:go_positive_regulation_of_rna_biosynthetic_process	1505	0.299	0.080	0.039	1.53E-14
GO_bp:go_positive_regulation_of_transcription_by_rna_polymerase_ii	1123	0.339	0.080	0.046	4.71E-14
GO_bp:go_regulation_of_lipid_localization	134	0.876	0.073	0.137	8.87E-11
GO_bp:go_negative_regulation_of_biosynthetic_process	1420	0.244	0.064	0.040	8.19E-10
GO_mf:go_regulatory_region_nucleic_acid_binding	890	0.308	0.065	0.051	8.84E-10
Curated_gene_sets:roversi_glioma_copy_number_up	97	1.123	0.080	0.188	1.15E-09
GO_mf:go_dna_binding_transcription_factor_activity	1603	0.238	0.066	0.041	2.23E-09
Curated_gene_sets:reactome_interleukin_36_pathway	7	4.275	0.082	0.742	4.21E-09
GO_bp:go_regulation_of_interleukin_1_mediated_signaling_pathway	7	3.588	0.069	0.647	1.46E-08
GO_bp:go_negative_regulation_of_interleukin_1_mediated_signaling_pathway	5	4.412	0.071	0.811	2.66E-08
GO_mf:go_sequence_specific_dna_binding	1060	0.254	0.058	0.047	3.30E-08
GO_bp:go_negative_regulation_of_rna_biosynthetic_process	1138	0.240	0.057	0.045	4.77E-08
GO_mf:go_sequence_specific_double_stranded_dna_binding	821	0.275	0.056	0.053	1.04E-07
GO_bp:go_t_cell_differentiation_involved_in_immune_response	63	1.015	0.058	0.196	1.15E-07
GO_bp:go_circadian_regulation_of_gene_expression	54	1.020	0.054	0.198	1.28E-07
GO_bp:go_negative_regulation_of_receptor_signaling_pathway_via_stat	20	1.721	0.056	0.335	1.36E-07
GO_bp:go_negative_regulation_of_transcription_by_rna_polymerase_ii	771	0.273	0.054	0.053	1.68E-07
GO_mf:go_double_stranded_dna_binding	900	0.256	0.054	0.050	1.78E-07
GO_bp:go_inflammatory_response	658	0.297	0.054	0.060	3.63E-07
GO_bp:go_t_cell_activation_involved_in_immune_response	96	0.837	0.059	0.169	3.67E-07
GO_bp:go_positive_regulation_of_lipid_localization	80	0.838	0.054	0.170	3.95E-07
GO_bp:go_regulation_of_lipid_transport	105	0.787	0.058	0.160	4.18E-07
GO_bp:go_regulation_of_glucocorticoid_receptor_signaling_pathway	7	3.113	0.060	0.636	4.97E-07
GO_bp:go_t_helper_17_type_immune_response	26	1.434	0.053	0.297	7.08E-07
GO_mf:go_proximal_promoter_sequence_specific_dna_binding	515	0.324	0.052	0.068	8.20E-07
GO_bp:go_negative_regulation_of_relaxation_of_muscle	5	4.148	0.067	0.867	8.53E-07
GO_mf:go_interleukin_1_receptor_binding	16	1.977	0.057	0.416	1.02E-06

GO_mf:go_complement_component_c1q_binding	7	3.043	0.058	0.641	1.05E-06
GO_bp:go_positive_regulation_of_t_cell_mediated_immunity	37	1.253	0.055	0.266	1.26E-06
GO_bp:go_positive_regulation_of_t_cell_mediated_immunity	1698	0.173	0.049	0.037	1.41E-06
Curated_gene_sets:reactome_signaling_by_leptin	11	2.112	0.051	0.456	1.78E-06
GO_bp:go_response_to_lipid	879	0.230	0.048	0.050	1.86E-06
GO_bp:go_interleukin_6_mediated_signaling_pathway	19	1.446	0.046	0.313	1.98E-06
GO_bp:go_positive_regulation_of_lipid_transport	60	0.935	0.052	0.203	2.07E-06
Curated_gene_sets:pid_il12_2pathway	59	0.906	0.050	0.198	2.26E-06
GO_bp:go_response_to_molecule_of_bacterial_origin	326	0.372	0.048	0.081	2.28E-06
GO_bp:go_lymphocyte_activation_involved_in_immune_response	166	0.572	0.053	0.125	2.42E-06
Curated_gene_sets:dacosta_uv_response_via_ercc3_common_dn	453	0.344	0.052	0.076	2.89E-06
GO_bp:go_regulation_of_lipid_storage	45	1.022	0.050	0.226	2.95E-06
Curated_gene_sets:biocarta_circadian_pathway	6	3.097	0.055	0.684	3.00E-06

GO, Gene ontology; bp, biological processes; mf, molecular functions.

* The gene sets in bold represent the previously reported MAGMA gene sets from prior CRP GWAS

Bonferroni significance at $p < 3.23 \times 10\text{-}6$

Supplementary Table 7. MAGMA Gene-set association for tissue specific gene expression results, 53 tissue.

Tissue	Beta	SE	P value
Liver	**0.050**	**0.011**	**3.04E-06**
Whole_Blood	**0.033**	**0.010**	**4.42E-04**
Spleen	0.028	0.012	0.013
Brain_Cerebellum	0.024	0.011	0.017
Fallopian_Tube	0.036	0.020	0.036
Brain_Cerebellar_Hemisphere	0.018	0.011	0.050
Pituitary	0.024	0.016	0.061
Cells_EBV-transformed_lymphocytes	0.011	0.009	0.104
Uterus	0.024	0.019	0.105
Small_Intestine_Terminal_Ileum	0.017	0.016	0.144
Cells_Transformed_fibroblasts	0.012	0.012	0.145
Adrenal_Gland	0.017	0.017	0.165
Ovary	0.012	0.016	0.236
Lung	0.010	0.016	0.257
Stomach	0.011	0.020	0.298
Testis	0.005	0.010	0.309
Cervix_Endocervix	0.008	0.020	0.350
Colon_Transverse	0.007	0.019	0.365
Kidney_Cortex	0.004	0.016	0.408
Thyroid	0.001	0.017	0.468
Adipose_Subcutaneous	-0.001	0.019	0.516
Brain_Cortex	-0.001	0.012	0.530
Cervix_Ectocervix	-0.002	0.022	0.538
Bladder	-0.003	0.020	0.564
Colon_Sigmoid	-0.005	0.021	0.596
Skin_Sun_Exposed_Lower_leg	-0.004	0.014	0.627
Skin_Not_Sun_Exposed_Suprapubic	-0.006	0.014	0.659
Artery_Aorta	-0.010	0.018	0.715
Esophagus_Gastroesophageal_Junction	-0.013	0.022	0.716
Artery_Coronary	-0.012	0.020	0.729
Adipose_Visceral_Omentum	-0.012	0.019	0.737
Prostate	-0.013	0.021	0.739
Brain_Frontal_Cortex_BA9	-0.008	0.012	0.762
Pancreas	-0.011	0.015	0.774
Artery_Tibial	-0.016	0.018	0.823
Breast_Mammary_Tissue	-0.021	0.022	0.835
Esophagus_Muscularis	-0.022	0.021	0.849
Nerve_Tibial	-0.018	0.018	0.852
Vagina	-0.021	0.019	0.861
Brain_Anterior_cingulate_cortex_BA24	-0.014	0.013	0.870
Brain_Nucleus_accumbens_basal_ganglia	-0.016	0.013	0.888
Brain_Hypothalamus	-0.017	0.014	0.888
Brain_Caudate_basal_ganglia	-0.018	0.014	0.904

Brain_Hippocampus	-0.018	0.014	0.907
Muscle_Skeletal	-0.016	0.012	0.912
Brain_Putamen_basal_ganglia	-0.020	0.014	0.924
Brain_Amygdala	-0.019	0.014	0.924
Brain_Spinal_cord_cervical_c-1	-0.023	0.015	0.935
Esophagus_Mucosa	-0.021	0.013	0.946
Heart_Atrial_Appendage	-0.027	0.017	0.947
Brain_Substantia_nigra	-0.027	0.015	0.965
Minor_Salivary_Gland	-0.035	0.017	0.981
Heart_Left_Ventricle	-0.038	0.016	0.992

Bonferroni significant tissue in bold with $p < 9.43 \times 10\text{-}4$

Supplementary Table 8. Significant enriched tissue from DEPICT analysis.

MeSH term*	Name	MeSH first level term	MeSH second level term	P value	False discovery rate
A11.118.637.555.567.562.440	**Precursor Cells B Lymphoid**	**Cells**	**Blood Cells**	**8.21E-07**	<0.01
A11.872.378.294	**Lymphoid Progenitor Cells**	**Cells**	**Stem Cells**	**8.21E-07**	<0.01
A02.835.583.443.800.800	**Synovial Fluid**	**Musculoskeletal System**	**Skeleton**	**1.46E-05**	<0.01
A03.620	**Liver**	**Digestive System**	**Liver**	**2.11E-05**	<0.01
A15.145	**Blood**	**Hemic and Immune Systems**	**Blood**	**2.66E-05**	<0.01
A15.145.229	**Blood Cells**	**Hemic and Immune Systems**	**Blood**	**6.51E-05**	<0.01
A15.378.316	**Bone Marrow Cells**	**Hemic and Immune Systems**	**Hematopoietic System**	**0.000122**	<0.01
A15.378	**Hematopoietic System**	**Hemic and Immune Systems**	**Hematopoietic System**	**0.000122**	<0.01
A15.382.490.315.583	Neutrophils	Hemic and Immune Systems	Immune System	0.000401	<0.01
A11.118.637.415	Granulocytes	Cells	Blood Cells	0.000433	<0.01
A15.382.680	Phagocytes	Hemic and Immune Systems	Immune System	0.000549	<0.01
A11.627	Myeloid Cells	Cells	Myeloid Cells	0.000642	<0.01
A11.066	Antigen Presenting Cells	Cells	Antigen-Presenting Cells	0.000789	<0.01
A15.382.812.260	Dendritic Cells	Hemic and Immune Systems	Immune System	0.000789	<0.01
A06.407.071.140	Adrenal Cortex	Endocrine System	Endocrine Glands	0.000815	<0.01
A02.835.232.043.300	Foot Bones	Musculoskeletal System	Skeleton	0.00104	<0.01
A02.835.232.043.300.710	Tarsal Bones	Musculoskeletal System	Skeleton	0.00104	<0.01
A02.835.232.043	Bones of Lower Extremity	Musculoskeletal System	Skeleton	0.00108	<0.01
A11.118.637	Leukocytes	Cells	Blood Cells	0.00112	<0.01
A15.382.520.604.800	Palatine Tonsil	Hemic and Immune Systems	Immune System	0.00113	<0.01
A04.623.603	Oropharynx	Respiratory System	Pharynx	0.00113	<0.01
A05.810.890	Urinary Bladder	Urogenital System	Urinary Tract	0.00117	<0.01
A15.145.300	Fetal Blood	Hemic and Immune Systems	Blood	0.0014	<0.01
A15.378.316.580	Monocytes	Hemic and Immune Systems	Hematopoietic System	0.00142	<0.01
A06.407.071	Adrenal Glands	Endocrine System	Endocrine Glands	0.00188	<0.01
A09.371.337	Eyelids	Sense Organs	Eye	0.00193	<0.01
A09.371.337.168	Conjunctiva	Sense Organs	Eye	0.00193	<0.01
A09.371.060	Anterior Eye Segment	Sense Organs	Eye	0.00221	<0.01

A15.382.812	Mononuclear Phagocyte System	Hemic and Immune Systems	Immune System	0.0024	<0.01
A05.360.319.114.373	Fallopian Tubes	Urogenital System	Genitalia	0.00432	<0.05
A15.382.520.604.700	Spleen	Hemic and Immune Systems	Immune System	0.00538	<0.05
A10.272	Epithelium	Tissues	Epithelium	0.00545	<0.05
A15.145.229.637.555	Leukocytes Mononuclear	Hemic and Immune Systems	Blood	0.00578	<0.05
A15.382.490.555.567.537	Killer Cells Natural	Hemic and Immune Systems	Immune System	0.00614	<0.05
A09.531	Nose	Sense Organs	Nose	0.00683	<0.05
A10.615.550.760	Respiratory Mucosa	Tissues	Membranes	0.00683	<0.05
A04.531.520	Nasal Mucosa	Respiratory System	Nose	0.00683	<0.05
A11.118.637.555.567.569	T Lymphocytes	Cells	Blood Cells	0.00831	<0.05
A02.165	Cartilage	Musculoskeletal System	Cartilage	0.00969	<0.05
A11.436	Epithelial Cells	Cells	Epithelial Cells	0.01	<0.05

*Medical Subject Heading (MeSH)

Significance determined by FDR q<0.05

Supplementary Table 9. Disease outcomes associated with weighted GRS of CRP in PheWAS analysis.

Phecode	Outcome description	Group	OR	Beta	SE	Lower	Upper	P value	N total	N cases	N controls	Bonferroni	False discover rate
496	Chronic airway obstruction	respiratory	1.046	0.045	0.008	1.030	1.062	1.19E-08	327982	17567	310415	TRUE	TRUE
496.21	Obstructive chronic bronchitis	respiratory	1.083	0.080	0.014	1.054	1.114	1.71E-08	315551	5136	310415	TRUE	TRUE
496.2	Chronic bronchitis	respiratory	1.078	0.075	0.014	1.050	1.108	3.79E-08	315919	5504	310415	TRUE	TRUE
411	Ischemic Heart Disease	circulatory system	1.025	0.025	0.006	1.014	1.036	7.92E-06	327162	40105	287057	TRUE	TRUE
519.8	Other diseases of respiratory system, NEC	respiratory	1.039	0.038	0.009	1.021	1.056	9.47E-06	328108	14515	313593	TRUE	TRUE
714	Rheumatoid arthritis and other inflammatory polyarthropathies	musculoskeletal	1.063	0.061	0.014	1.033	1.093	1.89E-05	322471	5112	317359	TRUE	TRUE
411.3	Angina pectoris	circulatory system	1.032	0.032	0.007	1.017	1.047	2.16E-05	307501	20444	287057	TRUE	TRUE
519	Other diseases of respiratory system, not elsewhere classified	respiratory	1.036	0.036	0.008	1.019	1.054	2.21E-05	328573	14980	313593	TRUE	TRUE
440	Atherosclerosis	circulatory system	1.109	0.103	0.025	1.056	1.164	3.02E-05	317387	1660	315727	TRUE	TRUE
440.2	Atherosclerosis of the extremities	circulatory system	1.123	0.116	0.028	1.063	1.186	3.36E-05	317029	1302	315727	TRUE	TRUE
714.1	Rheumatoid arthritis	musculoskeletal	1.064	0.062	0.015	1.033	1.096	3.93E-05	321884	4525	317359	TRUE	TRUE
411.8	Other chronic ischemic heart disease, unspecified	circulatory system	1.031	0.030	0.007	1.016	1.046	4.11E-05	308289	21232	287057	TRUE	TRUE
362.29	Macular degeneration (senile) of retina NOS	sense organs	1.058	0.057	0.014	1.030	1.088	5.15E-05	317190	5314	311876	FALSE	TRUE
428	Congestive heart failure; nonhypertensive	circulatory system	1.047	0.046	0.011	1.024	1.070	5.47E-05	327840	8256	319584	FALSE	TRUE

362.2	Degeneration of macula and posterior pole of retina	sense organs	1.058	0.056	0.014	1.029	1.087	5.64E-05	317193	5317	311876	FALSE	TRUE
740.11	Osteoarthrosis, localized, primary	musculoskeletal	1.035	0.035	0.009	1.018	1.053	6.38E-05	283671	14428	269243	FALSE	TRUE
411.2	Myocardial infarction	circulatory system	1.035	0.034	0.009	1.017	1.053	1.08E-04	301218	14161	287057	FALSE	TRUE
428.2	Heart failure NOS	circulatory system	1.053	0.051	0.013	1.026	1.081	1.16E-04	325426	5842	319584	FALSE	TRUE
318	Tobacco use disorder	mental disorders	1.036	0.035	0.010	1.016	1.056	3.41E-04	322768	10831	311937	FALSE	TRUE
244.4	Hypothyroidism NOS	endocrine/ metabolic	1.027	0.026	0.007	1.012	1.042	4.06E-04	324451	20075	304376	FALSE	TRUE
375	Disorders of lacrimal system	sense organs	1.065	0.063	0.018	1.028	1.103	4.28E-04	323395	3188	320207	FALSE	TRUE
272.11	Hypercholesterolemia	endocrine/ metabolic	1.018	0.018	0.005	1.008	1.029	4.78E-04	324759	47440	277319	FALSE	TRUE
411.4	Coronary atherosclerosis	circulatory system	1.023	0.023	0.007	1.010	1.037	5.27E-04	313406	26349	287057	FALSE	TRUE
272	Disorders of lipoid metabolism	endocrine/ metabolic	1.017	0.017	0.005	1.007	1.027	5.63E-04	328652	51333	277319	FALSE	TRUE
272.1	Hyperlipidemia	endocrine/ metabolic	1.017	0.017	0.005	1.007	1.027	6.45E-04	328449	51130	277319	FALSE	TRUE
585.1	Acute renal failure	genitourinary	1.031	0.031	0.009	1.013	1.050	9.30E-04	313931	12682	301249	FALSE	TRUE
244	Hypothyroidism	endocrine/ metabolic	1.024	0.024	0.007	1.009	1.039	1.12E-03	325419	21043	304376	FALSE	TRUE

Significance determined at FDR q<0.05. In addition Bonferroni threshold p<4.47 x 10-5

Supplementary Table 10. Reverse causality MR assessment with CRP as outcome.

Exposure	Method	N SNPs*	Beta	SE	P value	heterogeneity	p_heterogeneity	intercept	p_pleiotropy	p_distortion
Schz	IVW	95	-0.004	0.003	0.160	513.354	5.05E-59			
Schz	IVW-RE	95	-0.004	0.007	0.548	513.354	5.05E-59			
Schz	MR-Egger	95	-0.012	0.031	0.702	512.999	2.47E-59	0.000614589	0.800	
Schz	Weighted median	95	1.26E-05	0.006	0.998					
Schz	Weighted mode	95	0.010	0.014	0.473					
Schz	MR PRESSO	81	-0.006	0.005	0.227					0.776
BC	IVW	295	0.005	0.002	0.020	1319.647	1.31E-129			
BC	IVW-RE	295	0.005	0.005	0.272	1319.647	1.31E-129			
BC	MR-Egger	295	0.006	0.011	0.576	1319.628	6.21E-130	-4.60E-05		
BC	Weighted median	295	0.009	0.004	0.033					
BC	Weighted mode	295	0.012	0.005	0.028					
BC	MR PRESSO	278	0.005	0.003	0.096					0.975
prca	IVW	290	0.003	0.002	0.069	790.456	3.41E-48			
prca	IVW-RE	290	0.003	0.003	0.271	790.456	3.41E-48			
prca	MR-Egger	290	0.006	0.006	0.319	789.625	2.68E-48	-0.000316886	0.582	
prca	Weighted median	290	0.006	0.003	0.049					
prca	Weighted mode	290	0.010	0.005	0.034					
prca	MR PRESSO	278	0.002	0.002	0.495					0.234
COPD*	IVW	13	-0.004	0.004	0.293	52.870	4.34E-07			
COPD	IVW-RE	13	-0.004	0.008	0.616	52.870	4.34E-07			
COPD	MR-Egger	13	0.021	0.026	0.428	48.156	1.34E-06	-0.004922581	0.322	
COPD	Weighted median	13	-0.006	0.006	0.362					
COPD	Weighted mode	13	-0.005	0.009	0.595					
COPD	MR PRESSO	11	-0.011	0.004	0.030					0.469

* COPD exposure variants selected at lowered threshold 1e-5 due to low number of genome wide significant SNPs harmonised with CRP summary statistics.

*N SNPs for MR PRESSO reported number of variants in MR after outlier correction

Significance determined by Bonferroni threshold $p < 0.0125$

p_pleiotropy= global p value from MR PRESSO, intercept p value from MR Egger

Abbreviations

"BC" = Breast Cancer

"PrC" = Prostate Cancer

"Schz" = Schizophrenia

"COPD"=Chronic Obstructive Pulmonary Disease

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