Table 1 Association of genome-wide significant loci with CRP concentrations in previous studies.

SNP	Chr	Position	Gene	EA	BA	EAF	R^2	β[a]	SE	p-value	Study	LD exclusion[b]
rs2794520	1	159678816	CRP	C	T	0.67	1.01	0.160	0.006	2.0×10^{-186}		No
rs4420638	19	45422946	APOC1	A	G	0.83	0.84	0.236	0.009	8.8×10^{-139}		No
rs1183910	12	121420807	HNF1A	G	A	0.68	1.00	0.149	0.006	2.1×10^{-124}		No
rs4420065	1	66161461	LEPR	C	T	0.62	0.98	0.090	0.005	3.5×10^{-62}		No
rs4129267	1	154426264	IL6R	C	T	0.60	0.99	0.079	0.005	2.1×10^{-48}		No
rs1260326	2	27730940	GCKR	T	C	0.42	1.01	0.072	0.005	4.6×10^{-40}		No
rs6734238	2	113841030	IL1F10	G	A	0.41	1.00	0.050	0.006	1.8×10^{-17}		No
rs12239046	1	247601595	NLRP3	C	T	0.62	0.99	0.047	0.006	1.2×10^{-15}		No
rs9987289	8	9183358	PPP1R3B	A	G	0.08	1.00	0.069	0.011	3.4×10^{-13}	Dehghan et al (14)	No
rs10521222	16	51158710	SALL1	C	T	0.95	0.97	0.104	0.015	8.5×10^{-13}		No
rs10745954	12	103483094	ASCL1	A	G	0.52	0.99	0.039	0.006	1.6×10^{-11}		No
rs12037222	1	40064961	PABPC4	A	G	0.23	0.99	0.045	0.007	6.4×10^{-11}		No
rs1800961	20	43042364	HNF4A	C	T	0.97	0.88	0.088	0.015	2.2×10^{-9}		No
rs13233571	7	72971231	BCL7B	C	T	0.89	1.00	0.054	0.009	3.6×10^{-9}		No
rs340029	15	60894965	RORA	T	C	0.62	0.97	0.032	0.006	4.1×10^{-9}		No
rs4705952	5	131839618	IRF1	G	A	0.25	0.96	0.042	0.007	1.3×10^{-8}		No
rs2847281	18	12821593	PTPN2	A	G	0.60	0.99	0.031	0.006	2.2×10^{-8}		No
rs6901250	6	117114025	GPRC6A	A	G	0.32	0.99	0.035	0.006	4.8×10^{-8}		No
rs2075650	19	45395619	TOMM40	A	G	0.86	1.00	0.220	0.020	1.83×10^{-38}		Yes
rs1205	1	159682233	CRP	C	T	0.67	1.01	0.170	0.010	1.03×10^{-31}		Yes
rs1800947	1	159683438	CRP	C	G	0.94	0.85	0.300	0.030	3.1×10^{-25}		No
rs2650000	12	121388962	HNF1A	C	A	0.65	1.00	0.120	0.010	2.62×10^{-23}		Yes
rs2228145	1	154426970	IL6R	A	C	0.60	0.99	0.100	0.010	1.47×10^{-18}	Kocarnik et al (21)	Yes
rs780094	2	27741237	GCKR	T	C	0.41	1.00	0.100	0.010	1.53×10^{-16}		Yes
rs7310409	12	121424861	HNF1A	G	A	0.60	1.00	0.180	0.030	1.57×10^{-10}		Yes
rs6857	19	45392254	PVRL2	C	T	0.84	0.97	0.230	0.040	2.07×10^{-10}		Yes
rs429358	19	45411941	APOE	T	C	0.86	0.96	0.240	0.040	2.41×10^{-10}		Yes

Chr: chromosome; EA: effect allele; BA: baseline allele; EAF: effect allele frequency; SE: standard error

[a] β coefficient represents one unit increase in the natural log-transformed CRP (mg/L) per copy increment in the effect allele. Outcome is CRP concentration.

[b] SNPs that are in linkage disequilibrium (LD; $r^2>0.2$) with other SNPs are excluded in the analysis.

Table 2 Mendelian randomization estimates of the causal effect of genetically elevated CRP and colorectal cancer risk.

Study	N Cases	N Controls	OR (95% CI)[a,b]	p-value	p-het[c]
GECCO	10,644	10,729	1.07 (0.96, 1.20)	0.217	
CORECT	19,836	12,115	1.02 (0.93, 1.12)	0.654	
Combined[d]	30,480	22,844	1.04 (0.97, 1.12)	0.256	0.509

OR: Odds ratio; 95% CI: 95% confidence interval;

[a] Final set includes 19 SNPs identified from both studies, excluding the SNPs that are in linkage disequilibrium (r^2>0.8).

[b] Inverse-variance weighted method was used to estimate causal effect of genetically elevated CRP and CRC risk, and corresponding 95% CIs. Odds ratios represent the change in odds of colorectal cancer risk with one unit increase in the log-transformed genetically elevated CRP concentration (mg/L).

[c] P-het is p-value for heterogeneity of differences between GECCO and CORECT estimates.

[d] Fixed-effects meta-analysis was used to combine estimates from GECCO and CORECT.

Table 3 Mendelian randomization estimates of the causal effect of genetically elevated CRP and CRC risk by subgroups.

Subgroups	GECCO			CORECT			Combined[b]			
	Cases/ Controls	OR[a] (95% CI)	p-value	Cases/ Controls	OR[a] (95% CI)	p-value	Cases/ Controls	OR[a] 95% CI	p-value	p-het[c]
Sex										
Male	5,027/4,940	1.12 (0.95, 1.32)	0.172	10,854/6,181	1.03 (0.91, 1.17)	0.653	15,881/11,121	1.06 (0.96, 1.18)	0.229	0.431
Female	5,617/5,789	1.03 (0.88, 1.20)	0.717	8,913/5,934	1.01 (0.89, 1.16)	0.859	14,530/11,723	1.02 (0.92, 1.13)	0.710	0.876
BMI										
Normal	3,249/3,875	1.18 (0.98, 1.43)	0.087	3,672/3,139	0.99 (0.82, 1.20)	0.934	6,921/7,014	1.08 (0.95, 1.24)	0.245	0.205
Overweight	3,959/3,935	0.99 (0.82, 1.18)	0.872	4,637/3,503	0.97 (0.82, 1.16)	0.779	8,596/7,438	0.98 (0.86, 1.11)	0.754	0.936
Obese	2,216/1,757	1.01 (0.78, 1.31)	0.921	2,772/1,748	1.19 (0.93, 1.51)	0.171	4,988/3,505	1.10 (0.92, 1.31)	0.286	0.388
Smoking										
Never	4,612/5,107	1.12 (0.95, 1.33)	0.169	3,031/2,983	1.02 (0.87, 1.19)	0.836	10,139/9,279	1.07 (0.95, 1.20)	0.269	0.399
Ever	5,855/5,654	1.03 (0.89, 1.20)	0.670	7,025/4,515	1.08 (0.92, 1.28)	0.342	11,425/9,789	1.06 (0.94, 1.18)	0.338	0.681
NSAID use										
Yes	2,847/3,722	1.04 (0.85, 1.27)	0.732	3,031/2,983	1.05 (0.86, 1.29)	0.635	5,878/6,705	1.04 (0.90, 1.20)	0.563	0.926
No	5,855/5,924	1.03 (0.89, 1.19)	0.693	7,025/4,515	1.02 (0.88, 1.19)	0.790	13,478/10,439	1.03 (0.92, 1.14)	0.639	0.936
Aspirin use										
Yes	2,182/2,882	1.02 (0.81, 1.28)	0.880	2,518/2,448	1.07 (0.86, 1.34)	0.538	4,700/5,330	1.05 (0.89, 1.23)	0.582	0.751
No	7,034/6,695	1.05 (0.92, 1.21)	0.472	6,938/4,949	1.03 (0.89, 1.20)	0.676	13,972/11,644	1.04 (0.94, 1.15)	0.418	0.852
Non-aspirin NSAID use										
Yes	1,192/1,539	0.97 (0.71, 1.34)	0.864	680/766	1.05 (0.68, 1.62)	0.831	1,872/2,305	1.00 (0.77, 1.29)	0.990	0.784
No	7,681/7,682	1.03 (0.91, 1.18)	0.635	9,226/6,623	1.00 (0.88, 1.14)	0.972	16,907/14,305	1.02 (0.93, 1.11)	0.721	0.752
Family History of CRC										
Yes	1,715/1,312	0.88 (0.64, 1.21)	0.425	2,023/1,089	0.92 (0.68, 1.25)	0.610	3,738/2,401	0.90 (0.72, 1.12)	0.358	0.821
No	8,299/7,835	1.08 (0.95, 1.23)	0.247	8,867/6,819	1.00 (0.88, 1.14)	0.960	17,166/14,654	1.04 (0.95, 1.14)	0.399	0.427
History of endoscopy										
Yes	2,842/3,809	1.11	0.321	7,792/3,086	1.00	0.986	10,634/6,895	1.04	0.538	0.437

		(0.90, 1.37)			(0.84, 1.19)			(0.91, 1.19)		
No	5,774/4,826	1.09 (0.93, 1.28)	0.293	1,581/4,105	1.15 (0.90, 1.47)	0.272	7,355/8,931	1.11 (0.97, 1.27)	0.139	0.730

[a] Inverse-variance weighted method was used to estimate causal effect of genetically elevated CRP and CRC risk, and corresponding 95% CIs. Odds ratio represents the change in odds of colorectal cancer risk with one unit increase in the log-transformed genetically elevated CRP concentration.

[b] Fixed-effects meta-analysis was used to combine estimates from GECCO and CORECT.

[c] P-het is p-value for heterogeneity of differences between GECCO and CORECT estimates.

Table 4 Mendelian randomization estimates of the causal effect of genetically elevated CRP and CRC risk by subgroups.

Subgroups	GECCO			CORECT			Combined[b]			
	Cases/ Controls	OR[a] (95% CI)	p-value	Cases/ Controls	OR[a] (95% CI)	p-value	Cases/ Controls	OR[a] (95% CI)	p-value	p-het[c]
Subsite										
Colon	7,662/10,729	1.13 (1.00, 1.27)	0.062	11,964/12,115	1.02 (0.92, 1.13)	0.748	19,626/22,844	1.06 (0.98, 1.15)	0.131	0.199
Proximal	4,180/10,729	1.17 (0.98, 1.32)	0.084	5,815/12,115	1.01 (0.89, 1.14)	0.907	9,995/22,844	1.06 (0.96, 1.17)	0.226	0.215
Distal	3,343/10,729	1.12 (0.96, 1.32)	0.155	5,448/12,115	1.03 (0.90, 1.17)	0.651	8,791/22,844	1.07 (0.96, 1.18)	0.213	0.412
Rectal	2,780/10,729	0.92 (0.77, 1.11)	0.385	6,617/12,115	1.06 (0.93, 1.20)	0.410	9,397/22,844	1.01 (0.91, 1.12)	0.867	0.237
Stage										
Local	2,653/10,729	1.11 (0.93, 1.32)	0.270	2,780/12,115	1.04 (0.88, 1.24)	0.624	5,433/22,844	1.07 (0.95, 1.21)	0.263	0.652
Regional	5,002/10,729	1.09 (0.94, 1.25)	0.254	7,484/12,115	1.04 (0.91, 1.18)	0.586	12,486/22,844	1.06 (0.96, 1.16)	0.242	0.630
Distant	1,118/10,729	1.26 (0.98, 1.63)	0.069	1,206/12,115	1.13 (0.89, 1.43)	0.320	2,324/22,844	1.19 (1.00, 1.42)	0.049	0.524

[a] Inverse-variance weighted method was used to estimate causal effect of genetically elevated CRP and CRC risk, and corresponding 95% CIs. Odds ratio represents the change in odds of colorectal cancer risk with one unit increase in the log-transformed genetically elevated CRP concentration (mg/L).

[b] Fixed-effects meta-analysis was used to combine estimates from GECCO and CORECT.

[c] P-het is p-value for heterogeneity of differences between GECCO and CORECT estimates.