

Supplementary Material

Evidence for genetic correlation between appendix and inflammatory bowel disease: a bidirectional Mendelian randomization study

Dan Liu^{1,2,3}, Wanyue Dan^{1,2,3}, Bin Yan¹, Lihua Peng^{1*} & Fei Pan^{1*}

¹Department of Gastroenterology and Hepatology, the First Medical Center, Chinese PLA General Hospital, Beijing 100853, China. ²School of Medicine, Nankai University, Tianjin 300071, China. ³These authors contributed equally: Dan Liu and Wanyue Dan. *email: panfeisysu@163.com; penglihua301@126.com

Abstract: Observational studies highlighted an association between the appendix and inflammatory bowel disease (IBD). However, it's unclear whether the identified association is causal because of difficulties in establishing a clear temporal sequence. We investigated the association between acute appendicitis, appendectomy, and IBD by using two-sample bidirectional univariable Mendelian randomization (UVMR), multivariable MR (MVMR) and linkage disequilibrium score regression (LDSC) analyses. Eligible instrumental variables were screened from previous genome-wide association studies (GWAS) of European ancestry for analysis. The inverse variance-weighted (IVW) method was used for the primary analysis. Sensitivity analyses were used to detect and correct pleiotropy. LDSC analysis determined SNP-based heritability (h^2) for acute appendicitis, IBD, Crohn's disease (CD), and ulcerative colitis (UC). Following that, cross-trait LDSC analysis assessed genetic correlations (r_g) between these traits using GWAS summary data. Genetically predicted UC was associated with a significantly lower risk of acute appendicitis (OR = 0.933, $P < 0.001$) and appendectomy (OR = 0.954, $P < 0.001$), but conversely, acute appendicitis or appendectomy had no causal effect on IBD, UC or CD (all $P > 0.05$). CD had a suggestive association with appendectomy (OR = 0.981, $P = 0.018$) but was not significant after excluding the effect of UC by MVMR (OR = 0.999, $P = 0.889$). Furthermore, LDSC suggested a negative genetic correlation between UC and acute appendicitis ($r_g = -0.205$, $P = 0.005$). In conclusion, our study confirms UC casually leads to a decreased risk of acute appendicitis and appendectomy, but neither acute appendicitis nor appendectomy reduces the risk of IBD, UC, and CD.

Keywords: Mendelian randomization, inflammatory bowel disease, ulcerative colitis, acute appendicitis, appendectomy, genetic correlation

1 Supplementary Figures

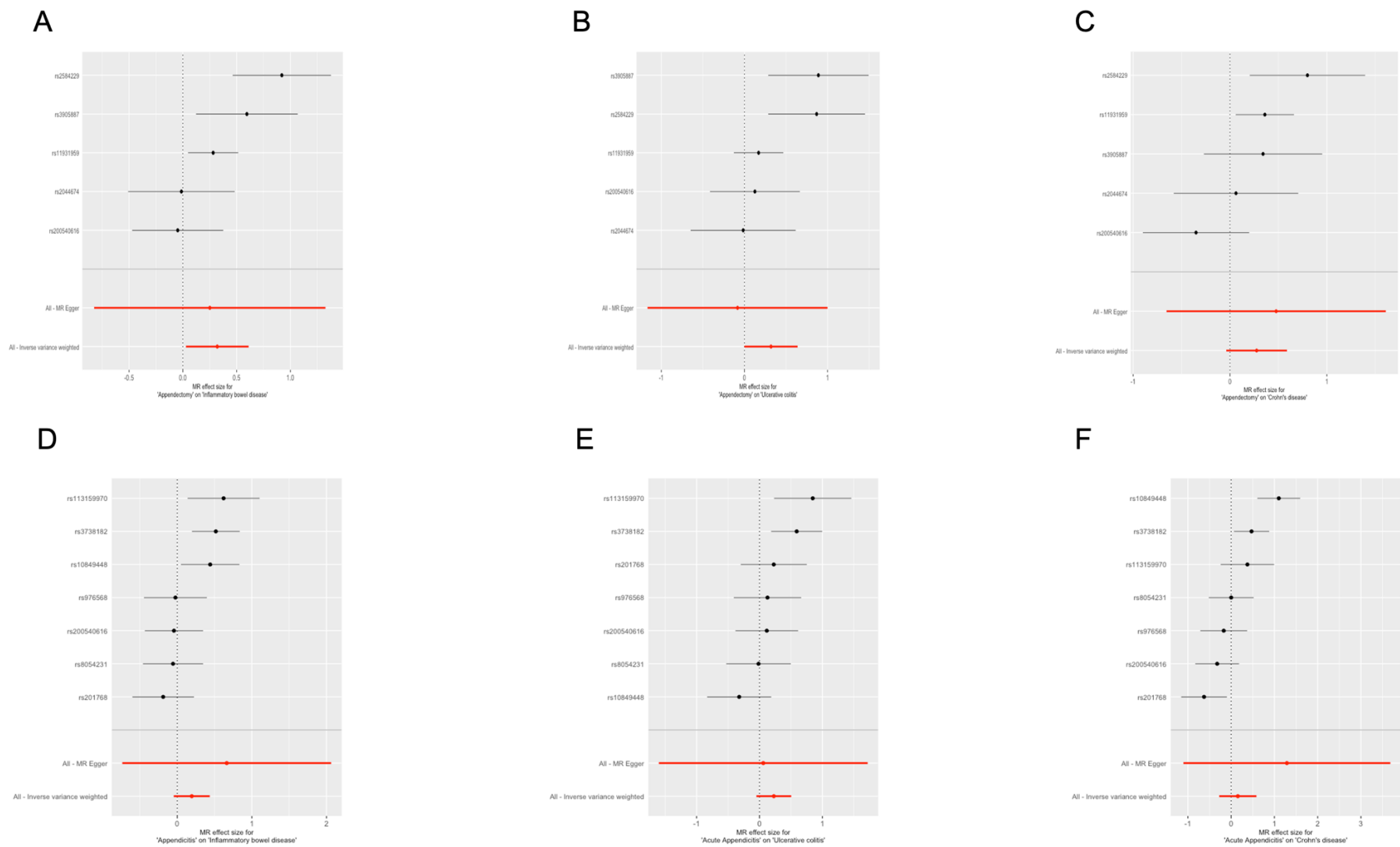
Supplementary Figure 1 MR forest plot for appendicitis and appendectomy on IBD, CD, and UC.

Supplementary Figure 2 MR leave-one-out plot for appendicitis and appendectomy on IBD, CD, and UC.

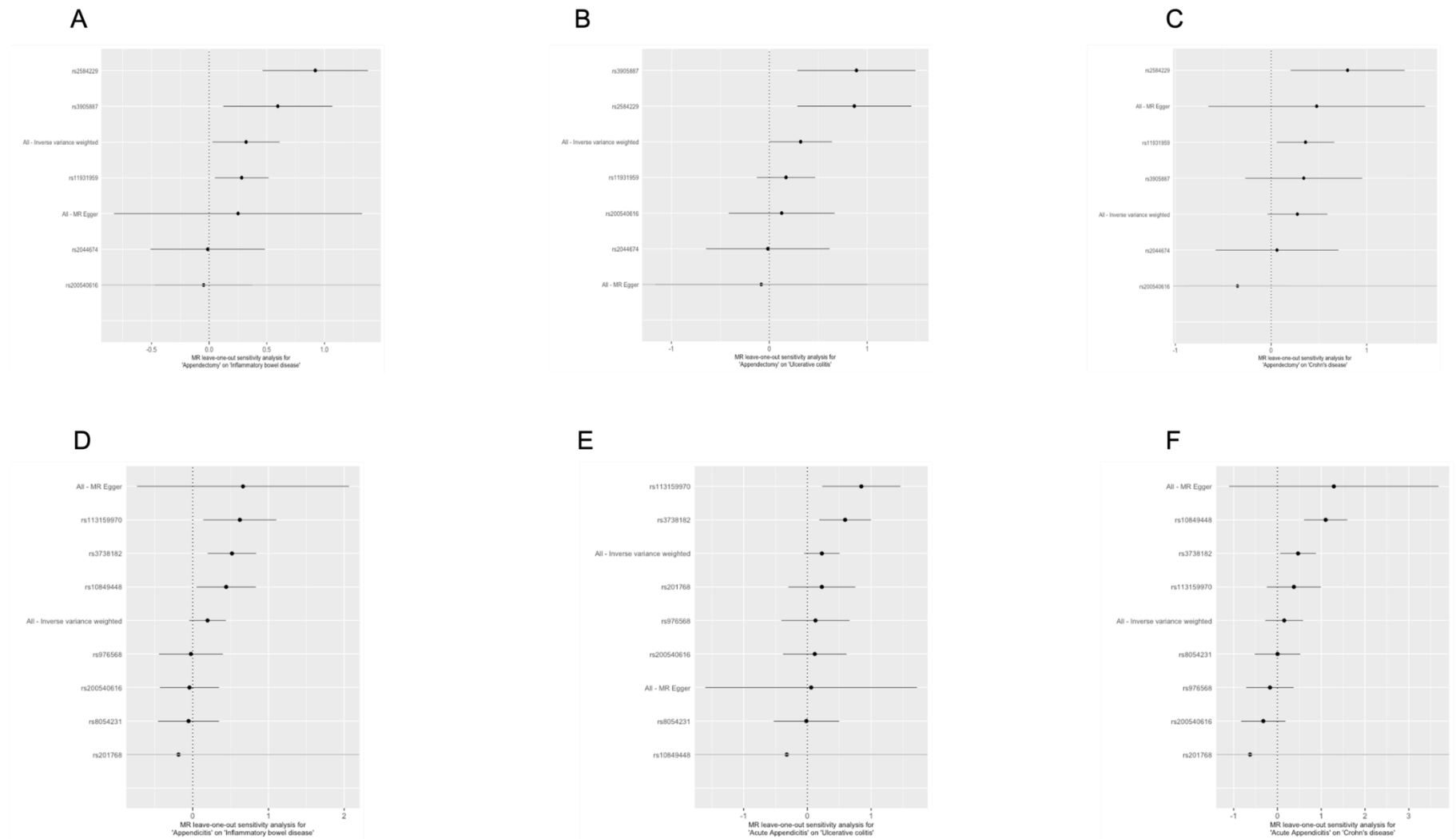
Supplementary Figure 3 MR forest plot for IBD, CD, and UC on appendicitis and appendectomy.

Supplementary Figure 4 MR leave-one-out plot for IBD, CD, and UC on appendicitis and appendectomy.

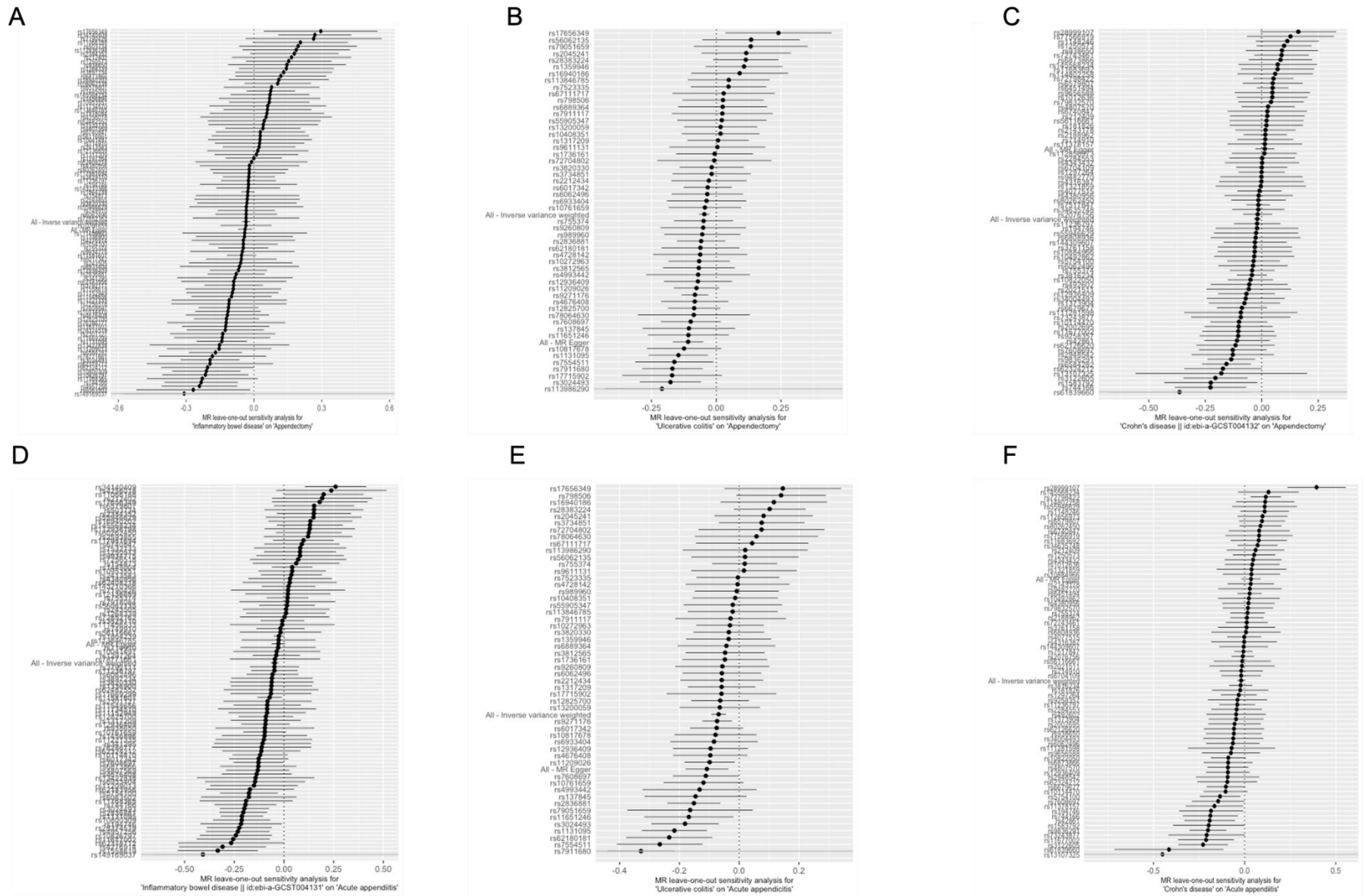
Supplementary Figure 5 MR funnel plot for IBD on appendicitis and appendectomy.



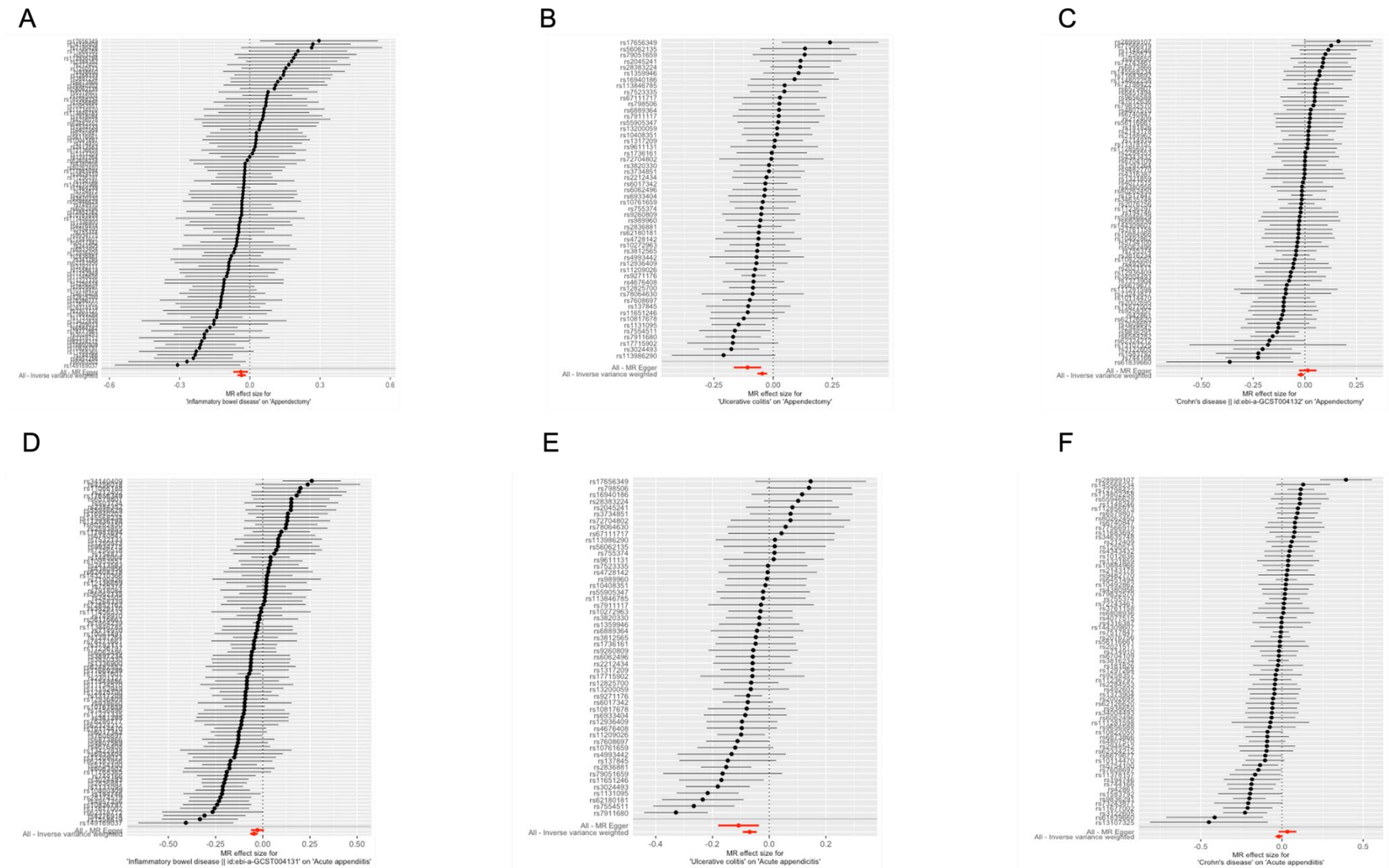
Supplementary Figure 1 MR forest plot for appendicitis and appendectomy on IBD, CD, and UC.



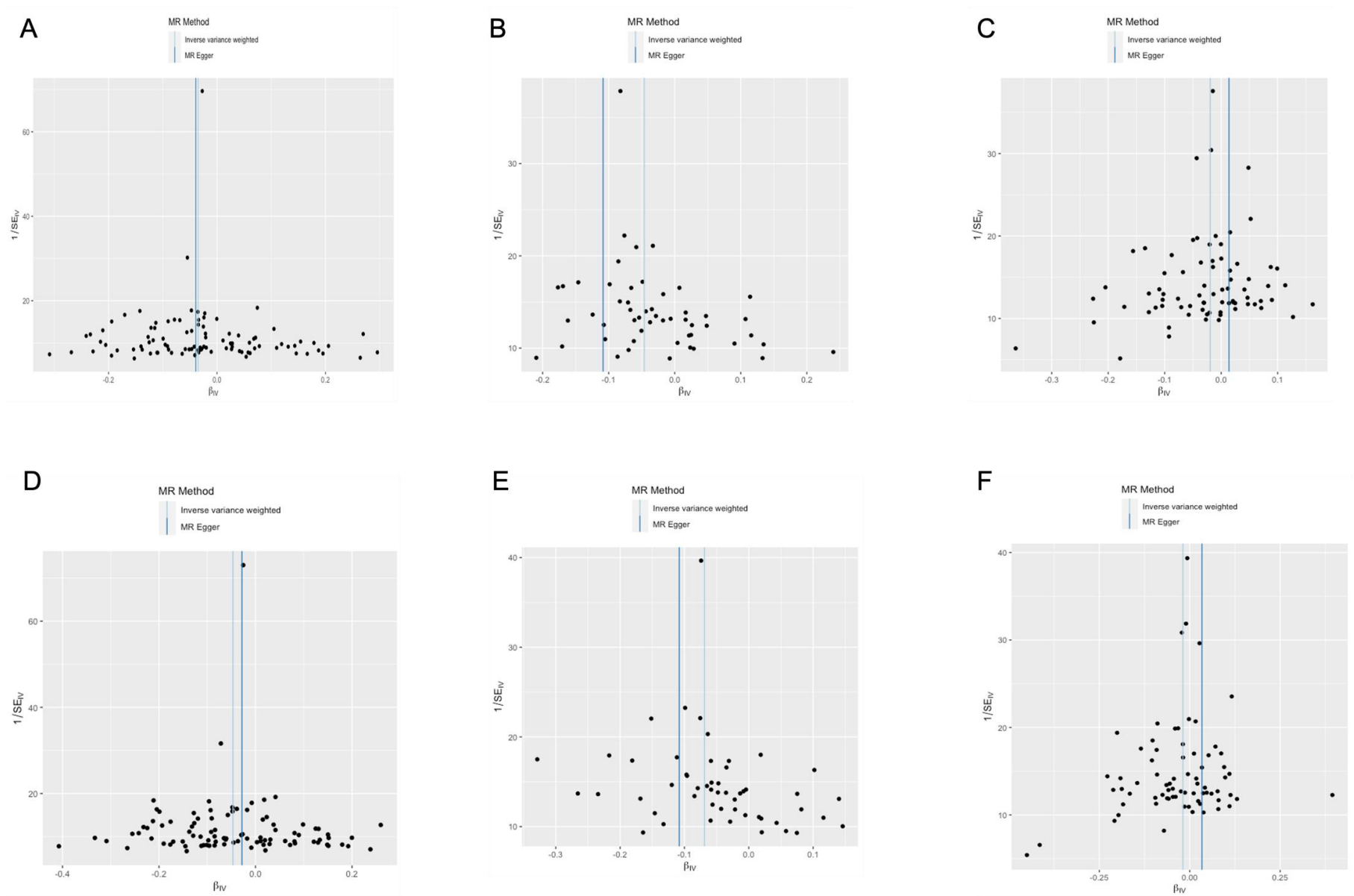
Supplementary Figure 2 MR leave-one-out plot for appendicitis and appendectomy on IBD, CD, and UC.



Supplementary Figure 3 MR forest plot for IBD, CD, and UC on appendicitis and appendectomy.



Supplementary Figure 4 MR leave-one-out plot for IBD, CD, and UC on appendicitis and appendectomy.



Supplementary Figure 5 MR funnel plot for IBD on appendicitis and appendectomy.

2 Supplementary Tables

Supplementary Table 1 Genetic variants used as instrumental variables for acute appendicitis and appendectomy.

Supplementary Table 2 Genetic variants used as instrumental variables for IBD.

Supplementary Table 3 Multivariable MR estimates for UC and CD using IVW method.

Supplementary Table 4 LDSC Regression Estimates of IBD, UC, CD, and appendicitis.

Supplementary Table 5 Genetic Correlation Estimates between IBD and appendicitis from LDSC Regression.

Supplementary Table 1 Genetic variants used as instrumental variables for appendicitis and appendectomy.

SNP	other allele	Effect allele	eaf	se	beta	pval	R2	F
Appendicitis								
rs3738182	G	A	0.239914	0.0103513	-0.0979872	2.90E-21	0.00350177	1317.86784
rs1550771	T	C	0.795866	0.0106842	-0.0624286	5.12E-09	0.00126635	475.514953
rs200540616	C	T	0.216786	0.0104351	0.079808	2.04E-14	0.00216289	812.898367
rs976568	G	T	0.599276	0.00887135	-0.0618654	3.09E-12	0.00183822	690.650495
rs7697491	A	T	0.530804	0.00868103	-0.155711	6.07E-72	0.01207694	4584.53538
rs2348650	C	G	0.658643	0.009235	0.0716928	8.28E-15	0.00231121	868.77289
rs9273368	G	A	0.278145	0.0096078	0.0644853	1.92E-11	0.00166983	627.277708
rs10748784	G	A	0.542511	0.00875832	0.0512173	4.98E-09	0.00130212	488.967296
rs10849448	A	G	0.756301	0.0103436	0.0799734	1.06E-14	0.0023576	886.249525
rs201768	T	C	0.724155	0.00980694	0.0641906	5.93E-11	0.00164615	618.367131
rs113159970	G	A	0.255019	0.0100646	-0.0548815	4.96E-08	0.00114446	429.693091
rs8054231	G	A	0.192681	0.0112047	-0.0744085	3.12E-11	0.0017225	647.096804

Appendectomy

rs2484697	A	G	0.497538	0.00912702	0.054711	2.04E-09	0.00149661	526.490339
rs200540616	C	T	0.21676	0.0109459	0.0735558	1.82E-11	0.00183712	646.498615
rs2044674	C	T	0.389458	0.00932122	0.0533642	1.03E-08	0.00135427	476.349702
rs11931959	A	G	0.307617	0.00973014	0.115885	1.05E-32	0.00572059	2020.98877
rs3905887	C	T	0.646222	0.00958465	0.0539003	1.87E-08	0.00132839	467.232869
rs7983949	T	A	0.267565	0.010399	0.0586683	1.68E-08	0.00134907	474.51818
rs2584229	T	C	0.17522	0.0121503	-0.072019	3.08E-09	0.00149915	527.386124

Supplementary Table 2 Genetic variants used as instrumental variables for IBD.

SNP	other allele	effect_allele	eaf	se	beta	pval	R2	F
IBD								
rs12136659	T	C	0.2515	0.0142	0.087	1.02E-09	0.00284969	171.341702
rs2488398	G	C	0.1899	0.0149	0.0985	3.63E-11	0.00298515	179.510491
rs10746475	T	A	0.83	0.0164	0.1308	1.58E-15	0.00482806	290.87057
rs4654925	G	C	0.4443	0.0124	-0.1172	4.80E-21	0.00678269	409.433201
rs112936798	A	C	0.0219	0.0332	-0.1844	2.89E-08	0.00145673	87.465689
rs35730213	G	C	0.2744	0.014	-0.1346	7.50E-22	0.00721442	435.683832
rs3024493	C	A	0.166	0.0165	0.1911	4.04E-31	0.01011173	612.441679
rs11209013	A	G	0.5249	0.0124	0.0773	4.46E-10	0.00298024	179.214121
rs11581607	G	A	0.0616	0.0294	-0.6578	4.59E-111	0.05002493	3157.18217
rs1336900	G	A	0.4095	0.0128	-0.0848	2.98E-11	0.00347773	209.234794
rs10800309	A	G	0.6998	0.0133	-0.123	1.94E-20	0.0063566	383.54798
rs1268339	T	C	0.2167	0.0163	0.0907	2.75E-08	0.00279275	167.908077

rs1317209	G	A	0.1809	0.016	0.1164	3.79E-13	0.00401524	241.704181
rs3820330	C	A	0.3002	0.014	-0.0892	1.72E-10	0.00334306	201.105544
rs4276914	G	A	0.494	0.0125	0.0783	3.15E-10	0.003065	184.327253
rs7532133	A	G	0.6769	0.0134	0.0789	3.83E-09	0.00272299	163.70241
rs11677002	T	C	0.4592	0.0126	-0.0931	1.37E-13	0.00430495	259.219088
rs55946629	C	A	0.1233	0.018	0.1298	5.45E-13	0.00364245	219.181379
rs4676408	G	A	0.5119	0.013	0.1011	7.63E-15	0.00510771	307.80494
rs7608697	A	C	0.3628	0.0126	0.1395	1.67E-28	0.00899749	544.342333
rs13422838	T	C	0.0954	0.0205	-0.1143	2.56E-08	0.0022549	135.498104
rs62180107	G	C	0.3688	0.0132	-0.0797	1.55E-09	0.00295736	177.834582
rs3792111	C	T	0.5368	0.0124	0.1391	5.12E-29	0.009622	582.491693
rs1558619	G	T	0.493	0.0123	-0.0843	8.90E-12	0.00355255	213.752415
rs76286777	T	C	0.2048	0.0151	0.0996	4.65E-11	0.00323113	194.350624
rs72852162	A	C	0.1103	0.0202	-0.1129	2.30E-08	0.00250171	150.366202

rs6740847	A	G	0.5447	0.0125	-0.0924	1.22E-13	0.00423476	254.974888
rs62183956	C	T	0.5	0.0125	-0.078	4.49E-10	0.003042	182.939612
rs1131095	T	C	0.3241	0.0131	0.1635	1.22E-35	0.01171189	710.507758
rs56116661	C	T	0.1938	0.0163	-0.1	9.27E-10	0.00312483	187.936525
rs77272631	G	C	0.0408	0.0417	0.2293	3.72E-08	0.00411536	247.755788
rs503734	A	G	0.5139	0.0124	-0.0692	2.67E-08	0.00239247	143.784513
rs2593855	C	T	0.325	0.014	-0.0832	2.54E-09	0.00303713	182.646017
rs11734570	G	A	0.4473	0.0127	0.0694	4.80E-08	0.00238143	143.119293
rs62324212	C	A	0.4642	0.0127	0.0886	2.67E-12	0.00390486	235.033555
rs4957256	C	T	0.2326	0.0155	-0.1179	3.37E-14	0.00496237	299.002633
rs17656349	C	T	0.5646	0.0125	0.0731	5.17E-09	0.00262721	157.929019
rs6579807	C	T	0.16	0.0189	0.125	4.01E-11	0.0042	252.873067
rs1445004	C	T	0.5895	0.0127	0.1689	3.48E-40	0.01380659	839.362524
rs62378712	T	C	0.2634	0.0142	-0.0776	4.23E-08	0.00233669	140.42432
rs6873866	T	C	0.5954	0.0128	-0.0919	6.15E-13	0.00406908	244.958163

rs10041497	T	C	0.6203	0.0129	0.0819	1.95E-10	0.00315966	190.037794
rs755374	C	T	0.327	0.0134	0.1767	1.59E-39	0.01374251	835.412564
rs56235845	T	G	0.341	0.0138	0.0877	1.77E-10	0.00345676	207.968824
rs11739135	G	C	0.3738	0.0125	0.1366	1.10E-27	0.00873542	528.347399
rs341295	C	T	0.4652	0.0124	0.0702	1.45E-08	0.00245208	147.376068
rs11152949	A	G	0.3032	0.0133	0.1019	1.56E-14	0.00438749	264.21092
rs1267496	G	C	0.7694	0.0159	0.1053	3.39E-11	0.00393458	236.829483
rs145568234	T	G	0.0139	0.0476	0.86	4.73E-73	0.02027508	1240.74894
rs6457681	G	T	0.2197	0.0153	-0.1687	3.75E-28	0.0097578	590.793626
rs4712528	G	C	0.7932	0.0152	0.1043	7.14E-12	0.00356888	214.738531
rs143210366	T	G	0.0398	0.036	0.2836	3.14E-15	0.00614734	370.843461
rs62408218	C	T	0.3757	0.0129	-0.0818	2.40E-10	0.00313885	188.78256
rs212402	G	A	0.6431	0.013	-0.0743	1.06E-08	0.00253415	152.321095
rs34140409	C	T	0.1272	0.0237	-0.1583	2.28E-11	0.00556408	335.461188

rs6933404	T	C	0.169	0.0149	0.0863	6.64E-09	0.00209189	125.682315
rs35171809	A	G	0.4473	0.0123	0.1088	1.16E-18	0.00585297	352.980681
rs10953551	A	G	0.6034	0.0127	-0.1033	4.94E-16	0.00510727	307.778163
rs243505	A	G	0.4185	0.0128	-0.0805	3.04E-10	0.00315404	189.698672
rs149169037	G	A	0.0755	0.0242	-0.1338	3.26E-08	0.00249917	150.213246
rs1456896	C	T	0.6869	0.0133	0.0879	4.50E-11	0.00332341	199.919649
rs62482552	G	A	0.5726	0.0131	-0.0737	1.97E-08	0.00265859	159.820464
rs11768365	A	G	0.1968	0.0152	-0.0837	3.88E-08	0.00221478	133.081609
rs78771661	C	T	0.0249	0.0669	-0.3848	8.95E-09	0.00719033	434.218211
rs4380956	G	A	0.6302	0.0127	0.0907	1.12E-12	0.00383433	230.772319
rs938650	G	A	0.1044	0.0189	-0.1074	1.41E-08	0.00215702	129.603384
rs1887428	G	C	0.6282	0.0131	-0.1643	2.46E-36	0.01260992	765.683149
rs10114470	T	C	0.675	0.0137	0.1475	4.10E-27	0.00954556	577.819337
rs3829110	A	G	0.3936	0.0125	0.1574	3.52E-36	0.01182643	717.539656
rs1250573	G	A	0.2863	0.0138	-0.098	1.11E-12	0.00392482	236.23948

rs10826797	G	T	0.3101	0.0136	-0.099	3.99E-13	0.00419361	252.486868
rs6584282	A	G	0.507	0.0124	-0.152	1.19E-34	0.01154974	700.555643
rs11195128	C	T	0.3201	0.0133	0.0792	2.74E-09	0.0027303	164.143564
rs2384352	A	G	0.3419	0.0131	0.0951	3.12E-13	0.00406988	245.00704
rs10761659	A	G	0.503	0.0126	0.1585	2.30E-36	0.01256067	762.654593
rs7918084	C	T	0.5398	0.0125	0.071	1.38E-08	0.00250453	150.536101
rs111456533	G	A	0.167	0.017	-0.1031	1.18E-09	0.00295739	177.83633
rs11221335	T	C	0.2445	0.0148	0.0827	2.44E-08	0.0025267	151.872267
rs11236797	C	A	0.4503	0.0125	0.1488	7.19E-33	0.01096134	664.470463
rs11066188	G	A	0.4135	0.013	0.0874	1.76E-11	0.00370507	222.963554
rs117981694	G	A	0.0229	0.0411	0.3452	4.53E-17	0.00533269	321.435342
rs12825700	G	A	0.3598	0.0127	0.1324	1.27E-25	0.00807575	488.123474
rs3897234	T	C	0.2336	0.0145	0.0971	1.90E-11	0.00337596	203.091074
rs140933577	T	C	0.0368	0.0305	-0.1857	1.13E-09	0.00244466	146.928655

rs194746	C	T	0.4712	0.0124	0.0833	1.84E-11	0.00345793	208.039834
rs3850378	T	C	0.1054	0.0207	0.1536	1.10E-13	0.0044492	267.943924
rs1864239	A	G	0.0189	0.1782	1.3366	6.27E-14	0.06625337	4254.06724
rs56062135	C	T	0.2147	0.0145	0.1382	1.37E-21	0.00644041	388.637955
rs7190426	A	C	0.1879	0.0155	-0.0872	2.06E-08	0.00232059	139.454861
rs28374519	G	A	0.4612	0.0137	-0.1105	6.55E-16	0.00606836	366.049931
rs9934775	C	T	0.1581	0.0172	-0.1116	8.77E-11	0.00331551	199.442851
rs8056255	T	A	0.0368	0.0327	0.2765	2.99E-17	0.00541982	326.715821
rs11548656	A	G	0.0398	0.0362	-0.2374	5.18E-11	0.00430761	259.379959
rs749910	G	A	0.2256	0.0138	0.1961	7.83E-46	0.01343661	816.563632
rs2301127	G	A	0.5209	0.0126	0.0783	4.96E-10	0.00306009	184.030783
rs16940202	T	C	0.1889	0.0169	0.113	2.50E-11	0.00391285	235.516486
rs12936409	C	T	0.4722	0.0124	0.1406	7.73E-30	0.00985362	596.65325
rs744166	A	G	0.4145	0.0126	-0.1109	1.34E-18	0.00596959	360.056171
rs714910	A	C	0.3201	0.0139	-0.0959	6.23E-12	0.00400311	240.971317

rs113846785	C	CG	0.1352	0.018	-0.1319	2.47E-13	0.00406829	244.910727
rs1319951	C	G	0.2475	0.0147	-0.0851	7.50E-09	0.00269756	162.169564
rs80262450	G	A	0.0895	0.019	0.1581	1.04E-16	0.00407377	245.242062
rs4807569	A	C	0.1988	0.0152	0.1281	4.24E-17	0.0052274	315.055574
rs7256518	G	A	0.9503	0.0276	-0.1665	1.63E-09	0.00261864	157.412693
rs62126610	A	G	0.174	0.0166	0.1407	2.60E-17	0.00569046	343.124151
rs11669299	C	T	0.172	0.0157	-0.1107	1.84E-12	0.00349047	210.004196
rs6062496	G	A	0.5994	0.0129	0.137	2.83E-26	0.00901361	545.32641
rs4256018	T	G	0.2783	0.0138	0.0786	1.23E-08	0.00248168	149.159021
rs6017342	A	C	0.5199	0.0135	0.1156	1.07E-17	0.0066711	402.651686
rs6063502	A	G	0.4016	0.0134	-0.0734	4.55E-08	0.00258945	155.653487
rs154873	G	A	0.3519	0.0132	-0.0813	7.38E-10	0.0030149	181.304721
rs1297264	A	G	0.4384	0.0126	-0.1462	3.98E-31	0.01052501	637.738991
rs2836881	G	T	0.2575	0.0146	-0.1643	1.96E-29	0.01032236	625.331723

rs2838517	T	C	0.6163	0.0125	-0.128	1.83E-24	0.00774879	468.206752
rs2413583	C	T	0.165	0.0171	-0.1732	4.60E-24	0.00826602	499.719621
rs5754100	T	C	0.1839	0.016	0.1293	7.14E-16	0.00501825	302.386532
rs5763793	G	T	0.3628	0.013	0.0734	1.47E-08	0.00249095	149.717899
CD								
rs12131079	C	T	0.6779	0.0174	-0.1088	3.99E-10	0.00516945	209.224216
rs35730213	G	C	0.2744	0.0181	-0.1166	1.17E-10	0.00541388	219.170955
rs3122605	G	A	0.8489	0.0227	-0.1748	1.24E-14	0.00783852	318.103468
rs114802258	C	T	0.0646	0.0384	-0.2245	5.11E-09	0.00609106	246.753254
rs4316387	T	C	0.8042	0.0189	-0.1292	7.74E-12	0.00525693	212.783414
rs6679677	C	A	0.0915	0.0286	-0.2275	1.77E-15	0.00860476	349.469205
rs6704109	C	T	0.2336	0.0181	0.1748	5.10E-22	0.0109406	445.385147
rs7517847	T	G	0.4205	0.0165	-0.3447	5.84E-97	0.05790713	2474.88601
rs11378157	A	AG	0.7793	0.0185	-0.1376	9.29E-14	0.00651289	263.954186
rs11683692	T	C	0.0547	0.038	-0.2144	1.75E-08	0.00475375	192.319318

rs4343432	A	G	0.4473	0.0162	0.1123	3.50E-12	0.0062356	252.645374
rs11677002	T	C	0.4592	0.0163	-0.1124	4.57E-12	0.00627482	254.244638
rs34004493	A	G	0.2465	0.0179	0.1258	2.00E-12	0.00587884	238.105297
rs3816234	G	A	0.5427	0.0162	0.2704	1.51E-62	0.03629146	1516.26671
rs55946629	C	A	0.1233	0.0231	0.1755	2.85E-14	0.00665884	269.908651
rs7608697	A	C	0.3628	0.0163	0.1229	4.03E-14	0.00698356	283.163509
rs6740847	A	G	0.5447	0.0161	-0.104	9.72E-11	0.00536478	217.172476
rs1583792	C	T	0.5507	0.016	-0.0882	3.26E-08	0.00384963	155.600388
rs56116661	C	T	0.1938	0.0212	-0.1312	5.67E-10	0.00537891	217.747655
rs6808936	A	G	0.4235	0.0161	0.0904	1.93E-08	0.00399043	161.314345
rs9836291	G	A	0.3241	0.017	0.1722	3.77E-24	0.01299145	529.973033
rs2581828	C	G	0.6103	0.0162	-0.0941	6.46E-09	0.00421195	170.307206
rs73243877	A	G	0.1799	0.0212	0.1164	4.12E-08	0.00399792	161.618326
rs13107325	C	T	0.0795	0.0284	0.2006	1.66E-12	0.00588956	238.54211

rs62324212	C	A	0.4642	0.0163	0.106	8.02E-11	0.0055892	226.308391
rs6579807	C	T	0.16	0.0244	0.1993	3.44E-16	0.01067687	434.532851
rs755374	C	T	0.327	0.0174	0.1969	1.38E-29	0.01706413	698.998075
rs6451494	T	C	0.5895	0.0166	0.2605	8.26E-56	0.03284297	1367.29538
rs112856973	T	C	0.1312	0.0243	-0.1612	3.61E-11	0.00592398	239.944632
rs6873866	T	C	0.5954	0.0164	-0.1314	1.35E-15	0.0083187	337.753788
rs2188962	C	T	0.3867	0.016	0.2004	5.59E-36	0.01904902	781.883732
rs181826	C	A	0.6203	0.0167	0.1162	3.24E-12	0.0063604	257.73456
rs1012636	G	T	0.7942	0.0198	0.1291	7.01E-11	0.00544826	220.570419
rs1321859	C	T	0.3628	0.0172	-0.1049	1.18E-09	0.00508773	205.899906
rs73516754	A	C	0.3151	0.0169	0.1423	4.04E-17	0.00874008	355.013392
rs35171809	A	G	0.4473	0.0159	0.1566	9.07E-23	0.01212556	494.216275
rs111281598	T	C	0.0586	0.0316	0.2745	4.17E-18	0.00831355	337.54295
rs6941902	T	C	0.1133	0.0273	0.163	2.39E-09	0.00533841	216.099316
rs7753014	C	G	0.4801	0.0163	-0.0989	1.39E-09	0.00488286	197.568095

rs145568234	T	G	0.0139	0.0633	0.8602	4.31E-42	0.02028452	833.645819
rs9482770	T	C	0.4105	0.0162	0.0987	1.01E-09	0.00471478	190.735105
rs9501641	C	T	0.0417	0.0432	0.3027	2.57E-12	0.00732306	297.030717
rs9258357	T	C	0.829	0.0216	-0.1179	5.00E-08	0.00394102	159.308925
rs212409	G	A	0.5586	0.0162	-0.1096	1.49E-11	0.00592358	239.928318
rs9656588	T	C	0.6849	0.0173	0.1183	8.73E-12	0.00604053	244.693986
rs938650	G	A	0.1044	0.0247	-0.1747	1.65E-12	0.0057073	231.117619
rs4380956	G	A	0.6302	0.0165	0.132	1.15E-15	0.00812126	329.671571
rs79832570	T	C	0.0934	0.0344	0.2234	8.90E-11	0.00845199	343.211708
rs10114470	T	C	0.675	0.0177	0.1687	1.76E-21	0.01248669	509.121285
rs1887428	G	C	0.6282	0.0169	-0.166	8.54E-23	0.01287222	525.045612
rs4077515	C	T	0.3966	0.0162	0.1848	3.14E-30	0.01634526	669.061709
rs10884966	G	A	0.3201	0.0171	0.1131	4.13E-11	0.00556783	225.438285
rs61839660	C	T	0.0696	0.0261	0.1468	1.98E-08	0.00279101	112.691661

rs2002695	A	G	0.2525	0.0189	-0.1293	8.31E-12	0.00631102	255.720809
rs10822050	T	C	0.3767	0.0162	0.1827	2.35E-29	0.01567472	641.177268
rs2675670	G	C	0.5865	0.0161	0.1074	2.89E-11	0.00559477	226.535154
rs1148246	C	T	0.6392	0.0167	-0.1323	2.09E-15	0.00807334	327.710481
rs1250573	G	A	0.2863	0.0179	-0.1522	1.92E-17	0.00946665	384.808061
rs6584282	A	G	0.507	0.016	-0.1658	3.44E-25	0.01374213	561.022605
rs11236797	C	A	0.4503	0.0161	0.176	8.51E-28	0.01533497	627.063352
rs28999107	G	T	0.4374	0.0178	0.1083	1.06E-09	0.00577252	233.774195
rs77566919	G	A	0.6879	0.0185	-0.1089	4.13E-09	0.00509219	206.081455
rs34635748	C	T	0.0229	0.0504	0.4794	1.95E-21	0.01028491	418.41503
rs1373904	A	G	0.2256	0.0189	0.141	9.11E-14	0.00694661	281.654684
rs194746	C	T	0.4712	0.0161	0.0975	1.24E-09	0.00473736	191.6528
rs3850378	T	C	0.1054	0.0267	0.199	8.31E-14	0.00746802	302.954957
rs72743461	C	A	0.2147	0.0187	0.1684	2.26E-19	0.00956273	388.75121
rs2021511	C	T	0.2962	0.0182	-0.1082	2.63E-09	0.00488111	197.497127

rs42861	A	G	0.3946	0.0167	0.1243	8.87E-14	0.00738196	299.437718
rs2076756	A	G	0.2256	0.0174	0.385	1.80E-108	0.05179119	2199.22076
rs7195228	C	G	0.1879	0.0209	-0.1327	2.09E-10	0.00537413	217.553111
rs72798422	T	C	0.0378	0.0382	0.5495	6.05E-47	0.02196456	904.242401
rs10492862	C	A	0.2823	0.0176	0.1067	1.26E-09	0.00461331	186.611218
rs2948542	A	G	0.6173	0.0163	0.1016	5.15E-10	0.00487722	197.338762
rs714910	A	C	0.3201	0.0181	-0.1531	2.49E-17	0.01020261	415.032115
rs12936409	C	T	0.4722	0.016	0.1426	4.31E-19	0.01013595	412.292828
rs744166	A	G	0.4145	0.0162	-0.1142	1.80E-12	0.00633015	256.500632
rs80262450	G	A	0.0895	0.0244	0.2268	1.34E-20	0.00838338	340.402077
rs144309607	C	T	0.0308	0.047	-0.3712	2.69E-15	0.0082264	333.975361
rs62126620	G	A	0.2018	0.0201	0.144	8.61E-13	0.00668018	270.779436
rs4807570	G	A	0.1998	0.0193	0.1811	6.03E-21	0.01048723	426.73321
rs492602	A	G	0.4414	0.0162	0.1084	2.33E-11	0.00579458	234.672722

rs6062496	G	A	0.5994	0.0167	0.1223	2.62E-13	0.00718308	291.311977
rs3761158	G	A	0.4155	0.0165	-0.1098	2.65E-11	0.00585585	237.168921
rs1297264	A	G	0.4384	0.0163	-0.1769	1.59E-27	0.01540931	630.150812
rs2284553	A	G	0.6193	0.0165	0.1277	1.14E-14	0.00768946	312.007519
rs2838517	T	C	0.6163	0.0162	-0.1456	2.03E-19	0.01002621	407.783766
rs2143178	T	C	0.167	0.0223	-0.2087	6.84E-21	0.01211815	493.910522
rs5754100	T	C	0.1839	0.0206	0.1687	3.02E-16	0.00854251	346.919
UC								
rs10272963	T	C	0.455467	0.016	-0.1512	4.11E-21	0.01134004	527.315575
rs10408351	A	G	0.183473	0.0204	0.1548	2.92E-14	0.00717984	332.465724
rs10761659	G	A	0.52802	0.016	0.1276	1.33E-15	0.00811531	376.137794
rs10817678	A	G	0.678839	0.017	0.1332	4.42E-15	0.00773621	358.429488
rs11209026	A	G	0.0456299	0.0358	-0.483	1.99E-41	0.02031845	953.473254
rs1131095	C	T	0.411965	0.0168	0.1593	2.18E-21	0.0122949	572.269491
rs113846785	CG	C	0.1431	0.0229	-0.1627	1.15E-12	0.00649195	300.404429

rs113986290	T	C	0.0182714	0.0531	-0.3066	7.59E-09	0.00337239	155.563424
rs11645239	G	C	0.160382	0.02	-0.1174	4.14E-09	0.00371196	171.285849
rs11651246	G	T	0.185268	0.0219	0.147	2.01E-11	0.00652349	301.873572
rs12825700	A	G	0.32278	0.0161	0.1889	7.33E-32	0.0156002	728.553811
rs12936409	T	C	0.514831	0.0158	0.1365	5.62E-18	0.00930793	431.933799
rs1317209	A	G	0.220176	0.0203	0.1818	2.90E-19	0.0113497	527.76972
rs13200059	A	G	0.0488116	0.0436	0.2944	1.48E-11	0.00804813	372.998806
rs1359946	A	G	0.176467	0.0202	0.1571	6.58E-15	0.00717343	332.166881
rs137845	G	A	0.569785	0.0158	0.1011	1.50E-10	0.00501105	231.533297
rs16940186	C	T	0.145411	0.0214	0.1357	2.18E-10	0.00457661	211.368009
rs1736161	A	G	0.398844	0.0161	-0.1227	2.22E-14	0.00721954	334.31741
rs17656349	T	C	0.607584	0.0159	0.09	1.54E-08	0.0038625	178.259056
rs17715902	A	G	0.351665	0.0166	0.0974	4.62E-09	0.0043259	199.738672
rs1811711	G	C	0.148141	0.0223	-0.1299	6.09E-09	0.00425884	196.629046

rs1887428	C	G	0.616203	0.0166	-0.167	9.65E-24	0.01319132	614.551392
rs2045241	A	G	0.392643	0.0169	-0.1063	2.83E-10	0.00538938	249.108287
rs2212434	T	C	0.405242	0.0159	0.1252	2.80E-15	0.00755603	350.017889
rs2816954	A	T	0.81276	0.0229	0.1375	1.80E-09	0.00575435	266.075871
rs2836881	T	G	0.247334	0.0186	-0.2217	1.11E-32	0.01829985	856.981582
rs28383224	G	A	0.625696	0.0165	-0.1468	4.65E-19	0.01009415	468.790616
rs2838517	C	T	0.3186	0.016	-0.1177	1.78E-13	0.00601493	278.197874
rs3024493	A	C	0.156104	0.0209	0.21	7.46E-24	0.01161907	540.443172
rs3734851	A	G	0.0141207	0.0584	0.5033	6.58E-18	0.00705284	326.543119
rs3812565	C	T	0.37036	0.016	0.1335	6.50E-17	0.00831206	385.333465
rs3820330	A	C	0.293937	0.0178	-0.1587	3.91E-19	0.01045398	485.677973
rs4654925	C	G	0.503578	0.0159	-0.2217	2.61E-44	0.02457419	1158.21117
rs4676408	A	G	0.631831	0.0167	0.1433	1.19E-17	0.00955368	443.447719
rs4728142	A	G	0.420958	0.0158	0.0995	3.23E-10	0.00482642	222.961048
rs4993442	T	G	0.711456	0.0179	-0.0988	3.54E-08	0.00400778	184.991119

rs55905347	A	G	0.424761	0.0166	0.1054	2.09E-10	0.0054288	250.940721
rs56062135	T	C	0.262157	0.0184	0.1078	4.66E-09	0.00449565	207.612081
rs6017342	C	A	0.559163	0.017	0.1944	3.95E-30	0.01863112	872.789564
rs6062496	A	G	0.64519	0.0163	0.1359	8.97E-17	0.00845575	392.051514
rs62180181	T	C	0.378764	0.0171	0.1226	8.08E-13	0.00707353	327.508067
rs6658353	C	G	0.494944	0.016	-0.1569	1.17E-22	0.01230755	572.865398
rs67111717	G	A	0.360294	0.0171	0.0944	3.27E-08	0.00410782	189.62778
rs6889364	A	G	0.193595	0.0228	0.1318	7.87E-09	0.00542386	250.710759
rs6933404	C	T	0.18927	0.0188	0.1486	2.69E-15	0.00677682	313.676249
rs7203363	A	T	0.820284	0.0189	0.1071	1.41E-08	0.00338189	156.003375
rs72704802	T	C	0.12633	0.0206	-0.1223	2.89E-09	0.00330169	152.291602
rs7523335	A	G	0.265783	0.021	-0.1389	3.42E-11	0.00752985	348.796013
rs7544646	G	C	0.475468	0.016	-0.1168	2.53E-13	0.0068047	314.975774
rs755374	T	C	0.299928	0.0171	0.1714	9.73E-24	0.01233705	574.255857

rs7554511	A	C	0.212908	0.0178	-0.1448	4.27E-16	0.00702724	325.349472
rs7608697	C	A	0.370039	0.0161	0.1597	3.03E-23	0.01189052	553.221145
rs78064630	A	G	0.059641	0.0308	0.1759	1.08E-08	0.00347057	160.107985
rs79051659	A	G	0.069621	0.0264	0.1605	1.30E-09	0.00333718	153.934092
rs7911117	G	T	0.136773	0.0239	-0.1342	1.84E-08	0.00425266	196.342404
rs7911680	C	A	0.529894	0.0159	-0.1525	6.71E-22	0.01158656	538.913027
rs798506	C	T	0.337922	0.0179	-0.1206	1.47E-11	0.00650804	301.154061
rs9260809	G	A	0.404441	0.0184	-0.1102	1.96E-09	0.00585023	270.53545
rs9267798	C	G	0.068899	0.028	0.2486	6.54E-19	0.00792943	367.45337
rs9271176	G	A	0.579337	0.0173	-0.3495	4.20E-91	0.05953741	2910.39045
rs9611131	C	T	0.118251	0.0227	-0.1494	5.11E-11	0.00465459	214.985918
rs989960	T	C	0.507834	0.016	-0.1214	3.28E-14	0.00736717	341.204666

IBD, Inflammatory Bowel Disease; CD, Crohn's disease; UC, ulcerative colitis.

Supplementary Table 3 Multivariable MR estimates for UC and CD using IVW method.

exposure	outcome	nsnp	se	pval	OR	Lower CI	Upper CI
Crohn's disease	Appendectomy	69	0.010	0.889	0.999	0.978	1.019
Ulcerative colitis	Appendectomy	45	0.013	0.002*	0.961	0.937	0.986
Crohn's disease	Acute appendicitis	69	0.013	0.884	1.002	0.976	1.029
Ulcerative colitis	Acute appendicitis	45	0.017	1.083E-04*	0.937	0.907	0.969

UC, ulcerative colitis; CD, Crohn's disease; IVW, inverse variance weighted; nsnp, number of single nucleotide polymorphisms; se, standard error; OR, odds ratio; CI, confidence interval.

Supplementary Table 4 LDSC Regression Estimates of IBD, UC, CD, and acute appendicitis.

Trait	mean_chi_sq	lambda_gc	intercept	intercept_se	ratio	ratio_se	h2_observed	h2_observed_se	h2_Z	h2_p
Acute appendicitis	1.166534895	1.142851278	1.08871423	0.011942205	0.53270656	0.07170993	0.010353145	0.001879858	5.50740779	3.64E-08
IBD	1.471732501	1.296497642	1.15697075	0.014689344	0.33275373	0.03113914	0.258761704	0.025747405	10.0500109	9.19E-24
CD	1.413160249	1.262446476	1.13065246	0.013632123	0.31622707	0.03299476	0.339025847	0.034798122	9.74264781	1.98E-22
UC	1.314055181	1.212451883	1.11433632	0.015614965	0.36406443	0.04972045	0.215536707	0.027026715	7.97495015	1.52E-15

IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis.

Supplementary Table 5 Genetic Correlation Estimates between IBD and acute appendicitis from LDSC Regression.

Trait 1	Trait 2	rg	rg_se	rg_p
Acute appendicitis	IBD	-0.1616012	0.06838992	0.01813067
Acute appendicitis	CD	-0.0994235	0.06974028	0.15397651
Acute appendicitis	UC	-0.2052475	0.07344349	0.00519589

IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis.