

Supplementary Information

Associations of Polygenic Risk Scores with Intestinal Surgery, Gastrointestinal Cancer, and All-Cause Mortality in 5,021 Individuals with Inflammatory Bowel Disease

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Supplementary Tables S1–S10

Supplementary Table S1. Outcome definitions and diagnostic/procedure codes

Outcome/category	Coding system	Codes or definition
Intestinal surgery	OPCS-4	Prespecified gastrointestinal procedures; episode-level indication unavailable G581, G582, G583, G584, G585, G588, G589, G591, G631, G633, G634, G671, G691, G692, G693, G694, G698, G699, G702, G703, G708, G709, G781, G784, G788, G789, G822; prefixes G49, G58, G69
Small-bowel resection	OPCS-4	G721, G722, G723, G724, H051, H101, H112, H113
Ileal/ileocolic/ileorectal anastomosis	OPCS-4	H051, H052, H053, H058, H059, H114, H115, H298, H299
Total/subtotal colectomy	OPCS-4	H061, H062, H063, H064, H068, H069, H071, H072, H073, H074, H078, H079
Ileocaecal/right-hemicolon resection	OPCS-4	G74.* (all subcodes; prefix match)
Ileostomy creation	OPCS-4	1510, 1511, 1512, 1513, 1514, 1515, 1516, 1518, 1519
Gastric cancer	ICD-9	C160, C161, C162, C163, C164, C165, C166, C168, C169
Gastric cancer	ICD-10	1520, 1521, 1522, 1523, 1528, 1529
Small-intestinal cancer	ICD-9	C170, C171, C172, C173, C178, C179
Small-intestinal cancer	ICD-10	1530–1539, 1540, 1541
Colorectal cancer	ICD-9	C180–C189, C19, C20
Colorectal cancer	ICD-10	40000
All-cause mortality	UK Biobank field	

Procedure categories are not mutually exclusive (e.g., H051 describes colectomy with ileorectal anastomosis). G74.* denotes every G74 subcode after punctuation normalization, matching the prefix rule used in the analysis. OPCS-4 labels follow the NHS Classifications Browser (<https://classbrowser.nhs.uk/OPCS-4.9/>); UK Biobank operative-procedure records use field 41272 and Data-Coding 240 (<https://biobank.ctsu.ox.ac.uk/crystal/coding.cgi?id=240>). The endpoint is termed intestinal surgery because episode-level indications were unavailable and unrelated indications cannot be completely excluded. ICD, International Classification of Diseases; OPCS-4, Office of Population Censuses and Surveys Classification of Interventions and Procedures, fourth revision.

Supplementary Table S2. Definitions of covariates used in the study

Covariate	UK Biobank Field ID	Definition
Age	21022	Age at the initial assessment-centre visit, truncated to whole years.
Sex	31	Registry-recorded or participant-updated sex.
Townsend Deprivation Index	22189	Area-level deprivation score assigned from the residential postcode before recruitment.
Household income	738	Self-reported total annual household income before tax.
Education	6138	Self-reported qualifications, categorized as college/university degree versus below college degree.
Ethnicity	21000	Self-reported ethnicity, categorized as White versus other ethnicities.
Body mass index	21001	Body mass index derived from measured height and weight at baseline.
Smoking status	20116	Never versus previous or current smoking.
Alcohol use	20117	Never versus previous or current alcohol use.
Diet quality	1289, 1299, 1309, 1319, 1329, 1339, 1349, 1359, 1369, 1379, 1389, 1408, 1418, 1428, 1438, 1448, 1458, 1468, 2654, 6144	Healthy-diet score derived from the touchscreen food-frequency questionnaire using fruit, vegetables, fish, whole grains, refined grains, processed meat, and unprocessed meat.
Physical activity	884, 894, 904, 914	Adequate activity was defined using reported moderate and vigorous activity frequency and duration.
C-reactive protein	30710	Serum high-sensitivity C-reactive protein measured by immunoturbidimetry.
Crohn's disease duration	131626	Time from the first recorded Crohn's disease diagnosis to recruitment.
Ulcerative colitis duration	131628	Time from the first recorded ulcerative colitis diagnosis to recruitment.
Previous intestinal surgery	Derived	Indicator of a qualifying intestinal-surgery OPCS-4 code before recruitment; qualifying codes are listed in Supplementary Table S1.
Baseline aminosalicylate use	20003	Self-reported treatment/medication code at the baseline assessment, mapped to aminosalicylates.

Supplementary Table S2. Definitions of covariates used in the study

Covariate	UK Biobank Field ID	Definition
Baseline corticosteroid use	20003	Self-reported treatment/medication code at the baseline assessment, mapped to corticosteroids.
Baseline immunomodulator use	20003	Self-reported treatment/medication code at the baseline assessment, mapped to immunomodulators.
Crohn's disease PRS	26229	Released UK Biobank Standard PRS for Crohn's disease, re-standardized within the CD analytic cohort.
Ulcerative colitis PRS	26287	Released UK Biobank Standard PRS for ulcerative colitis, re-standardized within the UC analytic cohort.

Field 20003 records self-reported treatment/medication use at the assessment-centre visit. BMI, body mass index; CD, Crohn's disease; OPCS-4, Office of Population Censuses and Surveys Classification of Interventions and Procedures, fourth revision; PRS, polygenic risk score; UC, ulcerative colitis.

Supplementary Table S3. Multiple-imputation missingness, integrity audit, and pooled nested-model estimates

Panel A. Pre-imputation missingness by disease		
Variable	CD, missing n (%)	UC, missing n (%)
Age	0 (0.0%)	0 (0.0%)
Sex	0 (0.0%)	0 (0.0%)
Townsend Deprivation Index	4 (0.3%)	2 (0.1%)
Annual household income	231 (16.2%)	521 (14.5%)
Education	19 (1.3%)	38 (1.1%)
Ethnicity	3 (0.2%)	12 (0.3%)
Body mass index	4 (0.3%)	19 (0.5%)
C-reactive protein	63 (4.4%)	161 (4.5%)
Smoking status	4 (0.3%)	10 (0.3%)
Alcohol consumption	411 (28.8%)	922 (25.7%)
Diet quality	46 (3.2%)	70 (1.9%)
Physical activity	363 (25.4%)	852 (23.7%)
Disease duration	0 (0.0%)	0 (0.0%)
Previous intestinal surgery	0 (0.0%)	0 (0.0%)
Baseline aminosalicylate use	0 (0.0%)	0 (0.0%)
Baseline corticosteroid use	0 (0.0%)	0 (0.0%)
Baseline immunomodulator use	0 (0.0%)	0 (0.0%)

Panel B. Observed-value integrity audit		
Variable	Observed values checked, n	Values changed, n
Age	5,021	0
Sex	5,021	0
Townsend Deprivation Index	5,015	0
Annual household income	4,269	0
Education	4,964	0
Ethnicity	5,006	0
Body mass index	4,998	0
C-reactive protein	4,797	0
Smoking status	5,007	0
Alcohol consumption	3,688	0
Diet quality	4,905	0
Physical activity	3,806	0

Panel C. Rubin-pooled nested-model estimates					
Model	Disease	Outcome	Events	Adjusted HR (95% CI)	FDR
Model 1	CD	Intestinal surgery	110	1.49 (1.23–1.80)	<0.001
Model 1	CD	Gastrointestinal cancer	28	1.12 (0.74–1.69)	0.677
Model 1	CD	All-cause mortality	186	1.02 (0.88–1.19)	0.757
Model 1	UC	Intestinal surgery	145	1.07 (0.91–1.27)	0.593
Model 1	UC	Gastrointestinal cancer	104	1.22 (1.00–1.49)	0.102
Model 1	UC	All-cause mortality	394	1.11 (1.00–1.22)	0.102
Clinical Model 2	CD	Intestinal surgery	110	1.61 (1.31–1.99)	<0.001

Panel C. Rubin-pooled nested-model estimates					
Model	Disease	Outcome	Events	Adjusted HR (95% CI)	FDR
Clinical Model 2	CD	Gastrointestinal cancer	28	1.11 (0.69–1.76)	0.762
Clinical Model 2	CD	All-cause mortality	186	0.99 (0.85–1.16)	0.929
Clinical Model 2	UC	Intestinal surgery	145	1.06 (0.90–1.25)	0.723
Clinical Model 2	UC	Gastrointestinal cancer	104	1.21 (0.99–1.48)	0.130
Clinical Model 2	UC	All-cause mortality	394	1.10 (1.00–1.22)	0.130

Twenty imputations with 10 iterations were created separately in CD and UC; estimates were pooled with Rubin's rules. Model 1 included demographic, socioeconomic, and lifestyle covariates. Model 2 additionally included disease duration, log(CRP+1), previous intestinal surgery, and three baseline medication indicators. No observed pre-imputation value differed from the corresponding observed value in the supplied completed table. No participant-level imputed data are distributed. CD, Crohn's disease; CRP, C-reactive protein; FDR, false-discovery rate; UC, ulcerative colitis.

Supplementary Table S4. Baseline characteristics of UK Biobank participants with CD stratified by PRS

Characteristic	Low (N = 476)	Intermediate (N = 475)	High (N = 476)
Duration time of disease [y, median (IQR)]	10.25 (4.64, 21.66)	16.68 (6.99, 28.35)	20.70 (11.32, 30.81)
Age [y, median (IQR)]	58 (51.00, 64.00)	57 (49.00, 62.00)	56 (49.00, 62.00)
Sex [n (%)]			
Female	248 (52.10)	261 (54.95)	290 (60.92)
Male	228 (47.90)	214 (45.05)	186 (39.08)
TDI [median (IQR)]	-2.28 (-3.66, 0.61)	-1.94 (-3.43, 0.99)	-1.72 (-3.50, 1.16)
Income [n (%)]			
<£31,000	271 (56.93)	242 (50.95)	262 (55.04)
>=£31,000	205 (43.07)	233 (49.05)	214 (44.96)
Education [n (%)]			
Below College degree	349 (73.32)	349 (73.47)	357 (75.00)
College degree	127 (26.68)	126 (26.53)	119 (25.00)
Ethnicity [n (%)]			
White	462 (97.06)	459 (96.63)	458 (96.22)
Others	14 (2.94)	16 (3.37)	18 (3.78)
BMI [kg/m ² , median (IQR)]	26.75 (24.07, 29.63)	26.17 (23.76, 28.92)	25.87 (23.18, 28.74)
Physical activity [n (%)]			
Inadequate	107 (22.48)	98 (20.63)	109 (22.90)
Adequate	369 (77.52)	377 (79.37)	367 (77.10)
Smoking status [n (%)]			
Never	266 (55.88)	250 (52.63)	273 (57.35)
Previous or current	210 (44.12)	225 (47.37)	203 (42.65)
Alcohol consumption [n (%)]			
Never	136 (28.57)	136 (28.63)	121 (25.42)
Previous or current	340 (71.43)	339 (71.37)	355 (74.58)
Diet [n (%)]			
Unhealthy	141 (29.62)	142 (29.89)	142 (29.83)
Healthy	335 (70.38)	333 (70.11)	334 (70.17)
Previous intestinal surgery, n (%)	47 (9.87)	61 (12.84)	107 (22.48)
CRP [mg/L, median (IQR)]	2.04 (0.93, 5.17)	2.12 (0.94, 4.45)	2.24 (1.05, 4.44)
PRS of CD [median (IQR)]	-0.25 (-0.67, 0.04)	0.68 (0.44, 0.89)	1.59 (1.33, 2.01)

Median (IQR) values and number (percentage) are reported for continuous and categorical variables, respectively. CD, Crohn's disease; IBD, inflammatory bowel disease; TDI, Townsend deprivation index; BMI, Body mass index; CRP, C-reactive protein; PRS, Polygenic risk score.

Supplementary Table S5. Baseline characteristics of UK Biobank participants with UC stratified by PRS

Characteristic	Low (N = 1,198)	Intermediate (N = 1,198)	High (N = 1,198)
Duration time of disease [y, median (IQR)]	11.74 (5.88, 23.71)	13.83 (6.39, 24.70)	15.33 (7.64, 27.83)
Age [y, median (IQR)]	60 (52.00, 64.00)	59 (51.00, 64.00)	58 (50.00, 63.00)
Sex [n (%)]			
Female	613 (51.17)	581 (48.50)	597 (49.83)
Male	585 (48.83)	617 (51.50)	601 (50.17)
TDI [median (IQR)]	-2.08 (-3.46, 0.42)	-2.16 (-3.64, 0.50)	-2.23 (-3.74, 0.53)
Income [n (%)]			
<£31,000	641 (53.51)	648 (54.09)	607 (50.67)
>=£31,000	557 (46.49)	550 (45.91)	591 (49.33)
Education [n (%)]			
Below College degree	851 (71.04)	882 (73.62)	814 (67.95)
College degree	347 (28.96)	316 (26.38)	384 (32.05)
Ethnicity [n (%)]			
White	1,149 (95.91)	1,147 (95.74)	1,132 (94.49)
Others	49 (4.09)	51 (4.26)	66 (5.51)
BMI [kg/m ² , median (IQR)]	26.67 (24.11, 29.66)	26.75 (24.16, 29.83)	26.40 (23.95, 29.52)
Physical activity [n (%)]			
Inadequate	262 (21.87)	232 (19.37)	251 (20.95)
Adequate	936 (78.13)	966 (80.63)	947 (79.05)
Smoking status [n (%)]			
Never	630 (52.59)	608 (50.75)	626 (52.25)
Previous or current	568 (47.41)	590 (49.25)	572 (47.75)
Alcohol consumption [n (%)]			
Never	357 (29.80)	353 (29.47)	370 (30.88)
Previous or current	841 (70.20)	845 (70.53)	828 (69.12)
Diet [n (%)]			
Unhealthy	407 (33.97)	406 (33.89)	419 (34.97)
Healthy	791 (66.03)	792 (66.11)	779 (65.03)
Baseline history of intestinal surgery [n (%)]	56 (4.67)	58 (4.84%)	72 (6.01%)
CRP [mg/L, median (IQR)]	1.74 (0.83, 3.45)	1.67 (0.83, 3.63)	1.83 (0.87, 3.95)
PRS of UC [median (IQR)]	-0.08 (-0.54, 0.20)	0.86 (0.66, 1.06)	1.81 (1.52, 2.24)

Median (IQR) values and number (percentage) are reported for continuous and categorical variables, respectively. UC, Ulcerative colitis; TDI, Townsend deprivation index; BMI, Body mass index; CRP, C-reactive protein; PRS, Polygenic risk score.

Supplementary Table S6. Clinical Model 2 PRS tertile and trend analyses

Disease	Outcome	Contrast	Adjusted HR (95% CI)	P	FDR
CD	Intestinal surgery	Intermediate	1.50 (0.86–2.64)	0.153	0.276
CD	Intestinal surgery	High	2.70 (1.58–4.62)	<0.001	0.004
CD	Intestinal surgery	P for trend	—	<0.001	0.004
CD	Gastrointestinal cancer	Intermediate	0.77 (0.25–2.34)	0.594	0.710
CD	Gastrointestinal cancer	High	0.85 (0.28–2.63)	0.754	0.754
CD	Gastrointestinal cancer	P for trend	—	0.742	0.754
CD	All-cause mortality	Intermediate	1.13 (0.78–1.63)	0.525	0.710
CD	All-cause mortality	High	1.10 (0.75–1.61)	0.628	0.710
CD	All-cause mortality	P for trend	—	0.631	0.710
UC	Intestinal surgery	Intermediate	1.60 (1.04–2.46)	0.031	0.155
UC	Intestinal surgery	High	1.53 (0.99–2.36)	0.056	0.168
UC	Intestinal surgery	P for trend	—	0.066	0.169
UC	Gastrointestinal cancer	Intermediate	1.30 (0.77–2.19)	0.315	0.473
UC	Gastrointestinal cancer	High	1.67 (1.02–2.76)	0.043	0.155
UC	Gastrointestinal cancer	P for trend	—	0.041	0.155
UC	All-cause mortality	Intermediate	1.14 (0.89–1.46)	0.286	0.467
UC	All-cause mortality	High	1.20 (0.94–1.54)	0.149	0.276
UC	All-cause mortality	P for trend	—	0.149	0.276

The low PRS tertile was the reference group. Trend tests used the median PRS value within each disease-specific tertile. All models used 20 imputations and the full clinical Model 2 covariate set. Benjamini–Hochberg FDR was calculated across the 18 intermediate-tertile, high-tertile, and trend tests. CD, Crohn's disease; CI, confidence interval; FDR, false-discovery rate; HR, hazard ratio; PRS, polygenic risk score; UC, ulcerative colitis.

Supplementary Table S7. Sensitivity analyses of continuous PRS

Disease	Outcome	Sensitivity analysis	N/events	Adjusted HR (95% CI)	P	Descriptive FDR
CD	Intestinal surgery	Clinical Model 2 MI: surgery-free at baseline	1212/92	1.62 (1.29–2.04)	<0.001	<0.001
CD	Gastrointestinal cancer	Clinical Model 2 MI: surgery-free at baseline	1212/24	1.30 (0.75–2.25)	0.277	0.415
CD	All-cause mortality	Clinical Model 2 MI: surgery-free at baseline	1212/150	1.08 (0.91–1.28)	0.398	0.477
UC	Intestinal surgery	Clinical Model 2 MI: surgery-free at baseline	3408/126	1.06 (0.88–1.27)	0.547	0.547
UC	Gastrointestinal cancer	Clinical Model 2 MI: surgery-free at baseline	3408/103	1.21 (0.98–1.48)	0.071	0.143
UC	All-cause mortality	Clinical Model 2 MI: surgery-free at baseline	3408/367	1.12 (1.01–1.25)	0.031	0.092
CD	Intestinal surgery	Surgery-free at baseline	1212/92	1.55 (1.26–1.90)	<0.001	—
CD	Intestinal surgery	Formal 1-year landmark (time origin reset)	1420/104	1.53 (1.26–1.86)	<0.001	—
CD	Intestinal surgery	Additional adjustment: baseline aminosalicylate	1427/110	1.50 (1.24–1.81)	<0.001	—
CD	Intestinal surgery	Additional adjustment: baseline corticosteroid	1427/110	1.49 (1.23–1.80)	<0.001	—
CD	Intestinal surgery	Additional adjustment: baseline immunomodulator	1427/110	1.48 (1.22–1.79)	<0.001	—
CD	Intestinal surgery	Additional adjustment: CRP	1427/110	1.59 (1.31–1.93)	<0.001	—
CD	Intestinal surgery	Additional adjustment: prior intestinal surgery	1427/110	1.50 (1.24–1.81)	<0.001	—
CD	Intestinal surgery	Additional adjustment: IBD duration	1427/110	1.53 (1.26–1.85)	<0.001	—
CD	Gastrointestinal cancer	Surgery-free at baseline	1212/24	1.30 (0.87–1.96)	0.202	—
CD	Gastrointestinal cancer	Formal 1-year landmark (time origin reset)	1426/28	1.11 (0.76–1.62)	0.578	—
CD	Gastrointestinal cancer	Additional adjustment: baseline aminosalicylate	1427/28	1.11 (0.76–1.62)	0.582	—
CD	Gastrointestinal cancer	Additional adjustment: baseline corticosteroid	1427/28	1.11 (0.76–1.61)	0.592	—

Supplementary Table S7. Sensitivity analyses of continuous PRS (continued)

Disease	Outcome	Sensitivity analysis	N/events	Adjusted HR (95% CI)	P	Descriptive FDR
CD	Gastrointestinal cancer	Additional adjustment: baseline immunomodulator	1427/28	1.12 (0.77–1.63)	0.562	—
CD	Gastrointestinal cancer	Additional adjustment: CRP	1427/28	1.12 (0.76–1.63)	0.571	—
CD	Gastrointestinal cancer	Additional adjustment: prior intestinal surgery	1427/28	1.10 (0.76–1.61)	0.608	—
CD	Gastrointestinal cancer	Additional adjustment: IBD duration	1427/28	1.11 (0.75–1.65)	0.594	—
CD	All-cause mortality	Surgery-free at baseline	1212/150	1.07 (0.90–1.25)	0.447	—
CD	All-cause mortality	Formal 1-year landmark (time origin reset)	1426/186	1.01 (0.88–1.17)	0.843	—
CD	All-cause mortality	Additional adjustment: baseline aminosalicylate	1427/186	1.01 (0.88–1.17)	0.845	—
CD	All-cause mortality	Additional adjustment: baseline corticosteroid	1427/186	1.02 (0.88–1.18)	0.840	—
CD	All-cause mortality	Additional adjustment: baseline immunomodulator	1427/186	1.01 (0.88–1.18)	0.843	—
CD	All-cause mortality	Additional adjustment: CRP	1427/186	1.02 (0.88–1.18)	0.797	—
CD	All-cause mortality	Additional adjustment: prior intestinal surgery	1427/186	0.99 (0.85–1.15)	0.917	—
CD	All-cause mortality	Additional adjustment: IBD duration	1427/186	1.01 (0.87–1.18)	0.870	—
UC	Intestinal surgery	Surgery-free at baseline	3408/126	1.07 (0.90–1.28)	0.456	—
UC	Intestinal surgery	Formal 1-year landmark (time origin reset)	3584/135	1.06 (0.89–1.26)	0.502	—
UC	Intestinal surgery	Additional adjustment: baseline aminosalicylate	3594/145	1.07 (0.90–1.26)	0.448	—
UC	Intestinal surgery	Additional adjustment: baseline corticosteroid	3594/145	1.07 (0.91–1.26)	0.441	—
UC	Intestinal surgery	Additional adjustment: baseline immunomodulator	3594/145	1.06 (0.90–1.25)	0.503	—
UC	Intestinal surgery	Additional adjustment: CRP	3594/145	1.07 (0.91–1.26)	0.440	—
UC	Intestinal surgery	Additional adjustment: prior intestinal surgery	3594/145	1.06 (0.90–1.25)	0.461	—
UC	Intestinal surgery	Additional adjustment: IBD duration	3594/145	1.09 (0.93–1.29)	0.289	—
UC	Gastrointestinal cancer	Surgery-free at baseline	3408/103	1.22 (1.00–1.49)	0.051	—

Supplementary Table S7. Sensitivity analyses of continuous PRS (continued)

Disease	Outcome	Sensitivity analysis	N/events	Adjusted HR (95% CI)	P	Descriptive FDR
UC	Gastrointestinal cancer	Formal 1-year landmark (time origin reset)	3594/104	1.22 (1.00–1.49)	0.045	—
UC	Gastrointestinal cancer	Additional adjustment: baseline aminosalicylate	3594/104	1.21 (1.00–1.48)	0.055	—
UC	Gastrointestinal cancer	Additional adjustment: baseline corticosteroid	3594/104	1.22 (1.00–1.49)	0.048	—
UC	Gastrointestinal cancer	Additional adjustment: baseline immunomodulator	3594/104	1.20 (0.99–1.47)	0.064	—
UC	Gastrointestinal cancer	Additional adjustment: CRP	3594/104	1.23 (1.01–1.50)	0.043	—
UC	Gastrointestinal cancer	Additional adjustment: prior intestinal surgery	3594/104	1.23 (1.01–1.49)	0.044	—
UC	Gastrointestinal cancer	Additional adjustment: IBD duration	3594/104	1.24 (1.02–1.52)	0.032	—
UC	All-cause mortality	Surgery-free at baseline	3408/367	1.13 (1.02–1.26)	0.019	—
UC	All-cause mortality	Formal 1-year landmark (time origin reset)	3594/394	1.10 (1.00–1.22)	0.054	—
UC	All-cause mortality	Additional adjustment: baseline aminosalicylate	3594/394	1.10 (1.00–1.22)	0.054	—
UC	All-cause mortality	Additional adjustment: baseline corticosteroid	3594/394	1.10 (0.99–1.21)	0.065	—
UC	All-cause mortality	Additional adjustment: baseline immunomodulator	3594/394	1.10 (0.99–1.22)	0.066	—
UC	All-cause mortality	Additional adjustment: CRP	3594/394	1.10 (0.99–1.22)	0.064	—
UC	All-cause mortality	Additional adjustment: prior intestinal surgery	3594/394	1.10 (1.00–1.22)	0.052	—
UC	All-cause mortality	Additional adjustment: IBD duration	3594/394	1.11 (1.01–1.23)	0.040	—

The first six rows are multiple-imputation Model 2 analyses restricted to participants without previous intestinal surgery; previous surgery was omitted because it was constant. Their descriptive FDR values apply the Benjamini–Hochberg procedure across these six secondary tests. Remaining rows are complete-data exploratory models in which each additional covariate was added separately to Model 1; their nominal P values are descriptive and were not used to define the principal findings. The formal landmark analysis excluded events/censoring at or before 1 year and reset time zero to 1 year. CD, Crohn's disease; CI, confidence interval; CRP, C-reactive protein; FDR, false-discovery rate; HR, hazard ratio; IBD, inflammatory bowel disease; MI, multiple imputation; PRS, polygenic risk score; UC, ulcerative colitis.

Supplementary Table S8. Clinical Model 2 complexity and proportional-hazards diagnostics

Disease	Outcome	Events/coefficients	Events per coefficient	PRS PH tests across 20 imputations	Global PH tests across 20 imputations	All coefficients finite
CD	Intestinal surgery	110/18	6.1	0.463–0.495; median 0.473; 0/20 <0.05	0.343–0.884; median 0.775; 0/20 <0.05	TRUE
CD	Gastrointestinal cancer	28/18	1.6	0.591–0.634; median 0.618; 0/20 <0.05	0.541–0.784; median 0.655; 0/20 <0.05	TRUE
CD	All-cause mortality	186/18	10.3	0.051–0.069; median 0.059; 0/20 <0.05	0.009–0.119; median 0.073; 8/20 <0.05	TRUE
UC	Intestinal surgery	145/18	8.1	0.709–0.729; median 0.717; 0/20 <0.05	0.433–0.663; median 0.568; 0/20 <0.05	TRUE
UC	Gastrointestinal cancer	104/18	5.8	0.244–0.256; median 0.251; 0/20 <0.05	0.073–0.192; median 0.136; 0/20 <0.05	TRUE
UC	All-cause mortality	394/18	21.9	0.310–0.336; median 0.326; 0/20 <0.05	0.038–0.160; median 0.099; 2/20 <0.05	TRUE

Model 2 contained 18 fitted coefficients. Proportional-hazards (PH) diagnostics used Schoenfeld residuals in each of 20 completed datasets. The PRS-specific test was nonsignificant in every completed dataset. Global-model tests indicated isolated covariate-level departures for mortality models; these do not establish a time-varying PRS association. The CD gastrointestinal-cancer model had only 28 events (1.6 events per fitted coefficient) and should be regarded as imprecise and potentially overfit. CD, Crohn's disease; PRS, polygenic risk score; UC, ulcerative colitis.

Supplementary Table S9. Procedure and gastrointestinal-cancer subtype characterization

Disease	Endpoint	Subtype/category	n	% of cohort
CD	Intestinal surgery	Small-bowel resection	40	2.80
CD	Intestinal surgery	Ileal/ileocolic/ileorectal anastomosis	11	0.77
CD	Intestinal surgery	Total/subtotal colectomy	12	0.84
CD	Intestinal surgery	Ileocaecal/right hemicolon resection	43	3.01
CD	Intestinal surgery	Ileostomy creation	17	1.19
UC	Intestinal surgery	Small-bowel resection	37	1.03
UC	Intestinal surgery	Ileal/ileocolic/ileorectal anastomosis	2	0.06
UC	Intestinal surgery	Total/subtotal colectomy	53	1.47
UC	Intestinal surgery	Ileocaecal/right hemicolon resection	28	0.78
UC	Intestinal surgery	Ileostomy creation	58	1.61
CD	Gastrointestinal cancer	Gastric cancer	4	0.28
CD	Gastrointestinal cancer	Small-intestinal cancer	3	0.21
CD	Gastrointestinal cancer	Colorectal cancer	21	1.47
UC	Gastrointestinal cancer	Gastric cancer	13	0.36
UC	Gastrointestinal cancer	Small-intestinal cancer	5	0.14
UC	Gastrointestinal cancer	Colorectal cancer	86	2.39
UC	Exploratory Cox model	Colorectal cancer, per 1-SD PRS: 1.17 (0.94–1.45); P=0.164	87	—

Note: Procedure categories are non-mutually exclusive; cancer subtypes sum to the released composite totals. Episode-level surgical indications were unavailable. The UC colorectal-cancer model was exploratory.

Supplementary Table S10. Corrected restricted cubic spline tests

Disease	Outcome	N	Events	Overall P	Nonlinear P
CD	Intestinal surgery	1427	110	<0.001	0.953
CD	Gastrointestinal cancer	1427	28	0.781	0.663
CD	All-cause mortality	1427	186	0.720	0.513
UC	Intestinal surgery	3594	145	0.056	0.033
UC	Gastrointestinal cancer	3594	104	0.055	0.105
UC	All-cause mortality	3594	394	0.079	0.270

Four knots were placed at the 5th, 35th, 65th, and 95th percentiles of within-disease standardized PRS. The same clinical Model 2 covariates, cohorts, outcome definitions, exposure transformation, and time scales were used in all 20 completed datasets. Overall P is the pooled D1 test of all three PRS spline coefficients versus the covariate-only model; nonlinear P is the pooled D1 test of the two nonlinear coefficients versus the linear-PRS model. Spline tests are exploratory and nominal P values are descriptive.