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Intrinsic capacity, genetic susceptibility and incident inflammatory bowel disease: a prospective cohort study in UK Biobank

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Article

Keywords: intrinsic capacity, inflammatory bowel disease, Crohn's disease, polygenic risk score, UK Biobank, prospective cohort study

Posted Date: June 1st, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9582190/v1

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Additional Declarations: No competing interests reported.

Version of Record: A version of this preprint was published at Scientific Reports on September 4th, 2026. See the published version at https://doi.org/10.1038/s41598-026-68809-8.

Abstract

Inflammatory bowel disease (IBD) is a chronic immune-mediated disorder, but whether intrinsic capacity (IC), a multidomain measure of functional reserve, is associated with incident IBD remains unclear. We analysed 427,489 UK Biobank participants free of IBD at baseline and examined associations of baseline IC deficit burden with incident IBD, Crohn's disease (CD), and ulcerative colitis (UC), as well as joint effects with polygenic risk scores (PRS). During a median follow-up of 13.74 years, 3,719 participants developed IBD. Compared with participants with no IC deficits, those with 2, 3, and ≥ 4 deficits had progressively higher risks of incident IBD, and incidence rates increased from 0.556 to 1.067 per 1,000 person-years across IC categories. Associations were stronger for CD than for UC; participants with ≥ 4 deficits had hazard ratios of 2.44 for CD and 1.35 for UC. Poorer IC was most strongly associated with IBD among individuals with high PRS, with the highest risk observed for CD in those with both severe IC impairment and high PRS. These findings suggest that reduced IC is independently associated with increased IBD risk and may provide complementary information for risk stratification.

1. Introduction

Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), is a chronic immune-mediated disorder of the gastrointestinal tract characterized by relapsing–remitting inflammation, progressive bowel damage, and substantial impairment in quality of life[1, 2]. Over recent decades, the global incidence and prevalence of IBD have increased markedly[3, 4], particularly in newly industrialized regions, placing an increasing burden on health care systems worldwide [5–7]. Despite advances in medical therapy, IBD remains incurable, and patients often experience lifelong disease courses accompanied by complications, disability, and increased mortality risk[4]. The etiology of IBD is multifactorial, involving a complex interplay between genetic susceptibility, environmental exposures, gut microbiota dysbiosis, and host immune dysregulation[8–11]. Identifying factors associated with IBD susceptibility and progression is therefore essential for improving our understanding of disease pathogenesis and heterogeneity.

Conventional measures of aging often fail to capture multisystem functional decline and physiological reserve, underscoring the need for integrative frameworks to assess age-related vulnerability. Intrinsic capacity (IC), as proposed by the World Health Organization (WHO), refers to the composite of an individual's physical and mental capacities, including vitality, locomotion, cognition, sensory function, and psychological well-being [12, 13]. Unlike single biomarkers or disease-specific indicators, IC reflects multisystem physiological reserve and functional resilience, capturing the cumulative impact of biological aging, chronic inflammation, metabolic dysregulation, and psychosocial stress across the life course. Emerging evidence suggests that declines in IC are associated with a wide range of adverse health outcomes, including frailty, cardiovascular disease, cognitive impairment, and all-cause mortality[14–16]. Importantly, IC can be operationalized using routinely collected clinical and functional measures, rendering it a practical and potentially modifiable indicator for population-level risk stratification[17]. Because IBD involves chronic intestinal inflammation, immune dysregulation, and

extraintestinal manifestations, reduced IC may plausibly reflect a lower level of physiological reserve relevant to disease susceptibility. However, despite its conceptual relevance, the relationship between IC and incident IBD has not been systematically investigated.

Polygenic risk scores (PRS), which aggregate the cumulative effects of multiple genetic variants identified through genome-wide association studies (GWAS), are increasingly used to quantify individual-level genetic susceptibility to complex diseases, including IBD. Previous studies have demonstrated that individuals with higher PRS for CD or UC exhibit substantially elevated disease risk compared with those at low genetic risk[18, 19]. Growing epidemiological evidence suggests that genetic risk may interact with environmental and physiological factors, leading to heterogeneous disease susceptibility across populations[19, 20]. Integrative studies in other chronic diseases have shown that composite indicators of biological aging or multisystem dysregulation can synergize with PRS to markedly amplify disease risk. However, whether IC interacts with genetic susceptibility in shaping IBD risk remains unknown.

To address these knowledge gaps, we conducted a large prospective cohort study using UK Biobank data to examine the associations of intrinsic capacity with incident IBD, CD and UC. Furthermore, we examined the joint effects and potential interactions between intrinsic capacity and polygenic risk scores on IBD development. By integrating functional status and genetic susceptibility within a unified framework, this study aims to provide new insights into the multifactorial etiology of IBD and to inform risk stratification in the general population.

2. Materials and Methods

2.1 Study design and participants

UK Biobank has Research Tissue Bank ethics approval from the North West – Haydock Research Ethics Committee (REC reference: 21/NW/0157; favourable opinion dated 8 June 2021), which covers the majority of approved uses of the Resource. All participants provided written informed consent for data collection, analysis, and record linkage in accordance with the Declaration of Helsinki.

The study design and flowchart are shown in Fig. 1. Among the 502,129 participants enrolled in the UK Biobank, 61,229 individuals without available IC data were excluded. We then excluded 10,214 individuals without available PRS data, resulting in 430,686 participants. After further excluding 3,025 individuals with prevalent IBD at baseline, a total of 427,489 participants were included in the final analytic cohort.

2.2 Assessment of Intrinsic Capacity

The IC deficit score was developed using established approaches reported in previous studies[22] and was based on indicators representing four of the five domains proposed by Beard et al[23–25]. IC was assessed using a multidomain framework adapted from the Integrated Care for Older People (ICOPE) screening tool and previously applied in UK Biobank. IC was operationalized across four functional

domains: psychological, sensory, vitality, and locomotor capacity. Each domain was evaluated using routinely collected self-reported or objectively measured variables at baseline.

Psychological capacity was assessed using two self-reported indicators: exhaustion and sleep duration. Exhaustion was evaluated by responses to the question, “Over the past two weeks, how often have you felt tired or had little energy?”, with responses of “more than half of the days” or “nearly every day” classified as impaired (1 point), and “not at all” or “several days” classified as preserved (0 points). Sleep duration was assessed by self-reported total hours of sleep per 24 hours (including naps), with short (< 7 h/day) or long (> 9 h/day) sleep duration considered impaired (1 point), and a healthy duration of 7–9 h/day considered preserved (0 points). Sensory capacity included impairments in vision and hearing. Vision impairment was identified using self-reported data on eye or eyelid problems recorded as non-cancer illnesses. Hearing impairment was assessed by responses to the question, “Do you have any difficulty with your hearing?”, with complete deafness classified as impaired (1 point) and no hearing difficulty classified as preserved (0 points). Vitality was evaluated using handgrip strength and unintentional weight loss. Handgrip strength was measured using a hydraulic hand dynamometer (Jamar J00105), and the mean value of the left and right hands was calculated. Sex- and body mass index (BMI)-adjusted cut-off values proposed by Fried et al[26] were applied, with values below the cut-off classified as impaired (1 point) and those above as preserved (0 points). Weight loss was assessed by self-report using the question, “Compared with one year ago, has your weight changed?”, with responses indicating weight loss classified as impaired (1 point), and stable or increased weight classified as preserved (0 points). Locomotor capacity was assessed using self-reported usual walking pace. Participants reporting a slow walking pace were classified as impaired (1 point), whereas those reporting a steady average or brisk pace were classified as preserved (0 points). Each indicator was coded as 1 for deficit and 0 for no deficit. The total IC deficit score was calculated by summing the seven indicators across the four domains, yielding a score ranging from 0 (best intrinsic capacity) to 7 (worst intrinsic capacity)[14]. Due to the small number of participants with six or seven deficits, IC deficit scores were categorized as 0, 1, 2, 3, and ≥ 4 deficits for subsequent analyses, as previously described[22]. The ordinal categorization reflects the cumulative number of deficits rather than a continuous summary score and facilitates the identification of individuals with greater functional vulnerability.

2.3 Polygenic risk score assessment

Polygenic risk scores (PRS) for inflammatory bowel disease were obtained from the UK Biobank as part of the standardized PRS dataset (Category 301), which provides pre-calculated genetic risk scores derived from large-scale genome-wide association studies[27]. Specifically, PRS for Crohn’s disease (CD; field ID: 26229) and ulcerative colitis (UC; field ID: 26287) were used in the present analysis. Because a composite PRS for IBD was not directly available in the UK Biobank, an overall IBD PRS was constructed by summing the standardized PRS for CD and UC. These scores represent the weighted sum of disease-associated risk alleles across multiple single-nucleotide polymorphisms, with weights corresponding to effect sizes estimated from prior GWAS. For the primary analyses, PRS values were categorized into three genetic risk groups based on their distribution in the study population: low genetic risk (below the

25th percentile), intermediate genetic risk (25th–75th percentile), and high genetic risk (above the 75th percentile), as previously described[28].

2.4 Outcome ascertainment

The primary outcome of this study was incident IBD, including CD and UC. Ascertainment of IBD outcomes was based on linked primary care records and hospital inpatient data. Incident CD and UC cases were identified using the International Classification of Diseases, Tenth Revision (ICD-10) codes K50 and K51, respectively, while overall IBD was defined using codes K50-K51[18, 29].

Participants were followed from the baseline assessment until the first occurrence of an IBD diagnosis, death, loss to follow-up, or the end of available hospital record follow-up, whichever came first. The censoring dates for hospital records were October 31, 2022 for England (Hospital Episode Statistics), August 31, 2022 for Scotland (Scottish Morbidity Record), and May 31, 2022 for Wales (Patient Episode Database for Wales).

2.5 Covariates

Potential confounders were selected based on previous literature and biological plausibility. The analyses were adjusted for baseline age, sex (male or female), ethnicity (European or non-European), body mass index (BMI), smoking status (never, former, or current), alcohol consumption frequency (daily or almost daily, three or four times per week, once or twice per week, one to three times per month, on special occasions only, or never), physical activity level as defined by the International Physical Activity Questionnaire (IPAQ; high, moderate, or low), educational attainment (college or university degree vs. no degree), Townsend deprivation index (TDI), and dietary pattern (healthy or unhealthy).

Missing data were handled using indicator variables for categorical covariates, whereas continuous variables were imputed using sex-specific median values. Overall, the proportion of missing data was low (< 2%) for most covariates, except for IPAQ, which had a higher missing rate (18.79%).

2.6 Statistical analysis

Continuous variables are presented as mean (standard deviation [SD]) or median (interquartile range [IQR]), and categorical variables as number (%). Group differences were assessed using Student's *t* test or the Wilcoxon rank-sum test for continuous variables, and the chi-square test or fisher's exact test for categorical variables, as appropriate.

Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations between IC deficit burden and incident IBD, with participants with no IC deficits serving as the reference group, adjusting for age, sex, ethnicity, BMI, smoking status, alcohol intake frequency, educational attainment, TDI, IPAQ and diet group. The proportional hazards assumption was evaluated using Schoenfeld residuals, and no evidence of violation was observed.

Cumulative incidence across IC categories was visualized using Kaplan–Meier curves and compared with the log-rank test. To examine whether genetic susceptibility modified the association between IC and IBD risk, joint IC–PRS categories were constructed by cross-classifying IC deficit levels with PRS strata, using participants with preserved IC (IC = 0) and low PRS as the reference group. Additive interactions between IC and PRS were evaluated by calculating the relative excess risk due to interaction (RERI), the attributable proportion due to interaction (AP), and the synergy index (SI), together with their 95% CIs. Evidence of additive interaction was defined as 95% CIs excluding 0 for RERI and AP and excluding 1 for SI.

Beyond the primary analyses, a series of supplementary analyses were performed to further strengthen the robustness and comprehensiveness of the study. Subgroup analyses of IC and IBD risk were conducted by stratifying participants according to covariates. Effect modification was assessed by including interaction terms and comparing models with and without interaction terms using likelihood ratio tests. A series of sensitivity analyses was performed, including removing of participants who developed IBD within the first year of follow-up to reduce potential reverse causation, exclusion of participants who died within three years of baseline to account for early competing mortality, restricting the sample to individuals without functional bowel disorders at baseline (including irritable bowel syndrome and other functional intestinal disorders), and limiting analyses to participants with complete covariate data.

All analyses were performed using R software (version 4.5.1), and all tests were two-sided with $P < 0.05$ considered statistically significant.

3. Results

3.1 Baseline characteristics of study populations

A total of 427,489 participants were included in the incident IBD analysis (53.9% women; mean age, 56.5 years), of whom 3,719 developed IBD during a median follow-up of 13.74 years (Table 1, **Supplementary Table 1,2**). Compared with the general population, participants who developed IBD tended to be older and more often male, with higher prevalences of former or current smoking, greater adiposity, lower physical activity, and an unhealthy diet.

Table 1
Baseline characteristics of UK Biobank participants according to incident inflammatory bowel disease (IBD) status.

Characteristics	**Non-IBD**	**IBD Individuals**	***p* value**
	n = 423,770	**n = 3,719**	
Age, mean (SD), years	56.48 (8.08)	57.23 (7.98)	< 0.001
Sex, n (%)			< 0.001
Female	228,437 (53.9)	1,893(50.9)	
Male	195,333(46.1)	1,826 (49.1)	
BMI, mean (SD), kg/m²	27.36 (4.72)	27.56 (4.77)	0.010
Ethnicity, n (%)			0.918
Non-white	44,278 (10.4)	384 (10.3)	
White	379,492 (89.6)	3,335 (89.7)	
Smoking status, n (%)			< 0.001
Never	232,396 (54.8)	1,649 (44.3)	
Previous	146,664 (34.6)	1,579 (42.5)	
Current	43,467 (10.3)	484 (13%)	
Alcohol intake frequency, n (%)			0.068
Daily or almost daily	85,876 (20.2)	731 (19.7)	
Three or four times a week	97,263 (23.0)	896 (24.1)	
Once or twice a week	109,044 (25.7)	922 (24.8)	
One to three times a month	47,079 (11.1)	413 (11.1)	
Special occasions only	48,891 (11.6)	415 (11.2)	
Never	34,244 (8.1)	332 (8.9)	
Townsend deprivation index (TDI), mean (SD)	-1.40 (3.03)	-1.18 (3.13)	< 0.001
Education history, n (%)			< 0.001

Note: Values are presented as mean (standard deviation, SD) for continuous variables and number (percentage) for categorical variables. Percentages were calculated within each group (Non-IBD or incident IBD). Percentages may not sum to 100% because participants with unknown, missing, or non-quantifiable responses were not displayed as separate categories for some variables. P values were calculated using Student's t test for continuous variables and the chi-square test for categorical variables.

Characteristics	Non-IBD	IBD Individuals	*p* value
	n = 423,770	n = 3,719	
College or university degree	281,265 (66.4)	2,252 (60.6)	
Others	138,904 (32.8)	1,421 (38.2)	
Unknown	3,601(0.8)	46(1.2)	
Healthy diet counts, n (%)			< 0.001
Unhealthy	206,165(48.7)	1,926(51.8)	
Healthy	150,283(35.5)	1,195(32.1)	
Unknown	67,322	598	
IPAQ activity group, n (%)			0.001
Low	60,893 (14.4%)	565 (15.2)	
Moderate	137,623 (32.5)	1,137 (30.6)	
High	138,878 (32.8)	1,176 (31.6)	

Note: Values are presented as mean (standard deviation, SD) for continuous variables and number (percentage) for categorical variables. Percentages were calculated within each group (Non-IBD or incident IBD). Percentages may not sum to 100% because participants with unknown, missing, or non-quantifiable responses were not displayed as separate categories for some variables. P values were calculated using Student's t test for continuous variables and the chi-square test for categorical variables.

The distribution of individual biomarkers and IC deficit scores in the overall study population and according to incident IBD, CD, and UC is presented in Table 2 and **Supplementary Tables 3,4**. Participants who developed these outcomes exhibited a higher IC score compared with those who remained disease-free during follow-up ($P < 0.001$). Specifically, individuals with incident IBD were more likely to report fatigue, unhealthy sleep duration, hearing impairment, reduced grip strength, slow walking pace, and eye disease, with all differences reaching statistical significance (all $P < 0.001$). In contrast, no significant difference was observed for unintentional weight loss between the two groups ($P = 0.221$).

Table 2
Distribution of individual intrinsic capacity (IC) component deficits and IC deficit scores according to incident inflammatory bowel disease (IBD) status in the UK Biobank.

Variable	Level	Non-IBD	IBD	HR	*P* value
		n = 423,770	n = 3,719		
Fatigue_score (%)	0	373,178 (88.1)	3,135 (84.3)		< 0.001
	1	50,592 (11.9)	584 (15.7)	1.362(1.244–1.492)	
Sleep_score (%)	0	313,599 (74.0)	2,626 (70.6)		< 0.001
	1	110,171 (26.0)	1,093 (29.4)	1.146(1.067–1.230)	
Hearing_score (%)	0	316,114 (74.6)	2,666 (71.7)		< 0.001
	1	107,656 (25.4)	1,053 (28.3)	1.092(1.015–1.175)	
Grip_score (%)	0	342,060 (80.7)	2,872 (77.2)		< 0.001
	1	81,710 (19.3)	847 (22.8)	1.197(1.104–1.297)	
Weight_loss_score (%)	0	358,990 (84.7)	3,123 (84.0)		0.221
	1	64,780 (15.3)	596 (16.0)	1.065(0.976–1.163)	
Walk_score (%)	0	392,486 (92.6)	3,336 (89.7)		< 0.001
	1	31,284 (7.4)	383 (10.3)	1.334(1.192–1.494)	
Eye_disease (%)	0	405684 (95.7)	3511 (94.4)		< 0.001
	1	18086 (4.3)	208 (5.6)	1.308(1.136–1.506)	
IC score, n (%)					< 0.001
	0	144297(34.1)	1105 (29.7)		

Abbreviations: IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; HR, hazard ratio; CI, confidence interval; PY, person-years; BMI, body mass index; TDI, Townsend deprivation index; IPAQ, International Physical Activity Questionnaire; IC, intrinsic capacity.

Variable	Level	Non-IBD	IBD	HR	*P* value
		n = 423,770	n = 3,719		
	1	154014 (36.3)	1269 (34.1)		
	2	82128 (19.4)	772 (20.8)		
	3	30840 (7.3)	398 (10.7)		
	≥ 4	12491 (2.9)	175 (4.7)		

Abbreviations: IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; HR, hazard ratio; CI, confidence interval; PY, person-years; BMI, body mass index; TDI, Townsend deprivation index; IPAQ, International Physical Activity Questionnaire; IC, intrinsic capacity.

3.2 Association between intrinsic capacity and incident IBD

Higher IC deficit scores were consistently associated with increased incidence rates and risks of IBD, demonstrating a clear dose–response relationship (Table 3). The incidence rate of IBD increased from 0.556 per 1,000 person-years among participants with preserved IC (IC = 0) to 1.067 per 1,000 person-years among those with ≥ 4 deficits. Compared with the normal group, participants with IC deficit scores of 2, 3, and ≥ 4 had 17%, 58%, and 67% higher risks of incident IBD, respectively (HR = 1.17, 95% CI: 1.06–1.28; HR = 1.58, 95% CI: 1.40–1.78; HR = 1.67, 95% CI: 1.41–1.98; all $P < 0.001$), whereas no significant association was observed for a score of 1 ($P = 0.479$).

Table 3
Associations of intrinsic capacity (IC) deficit score categories with incident IBD in the UK Biobank.

Score	IR per 1000 PY (95% CI)	HR (95% CI)	*P* value
0	0.556 (0.524–0.590)	1.00 (ref)	
1	0.597 (0.564–0.632)	1.030 (0.949–1.119)	0.479
2	0.696 (0.647–0.748)	1.166 (1.060–1.282)	0.002
3	0.970 (0.875–1.073)	1.580 (1.401–1.782)	< 0.001
≥ 4	1.067 (0.909–1.245)	1.667 (1.405–1.979)	< 0.001

Abbreviations: IBD, inflammatory bowel disease; IR, incidence rate; PY, person-years; HR, hazard ratio; CI, confidence interval.

When exploring IBD subtypes, the association between IC deficits and disease risk was more pronounced for CD, whereas the association for UC was comparatively weaker but remained statistically

significant. Participants with ≥ 4 IC deficits had a 35% higher risk of UC compared with the reference group (HR = 1.35, 95% CI: 1.08–1.68; *P* = 0.007). In contrast, a substantially stronger association was observed for CD, with participants with ≥ 4 IC deficits had a more than twofold higher risk (HR = 2.44; 95% CI: 1.88–3.16; *P* < 0.001; **Supplementary Table 5,6**). Kaplan–Meier curves showed clear separation of cumulative incidence trajectories across IC deficit categories for IBD, CD, and UC (log-rank *P* < 0.001; Fig. 2).

To further clarify which IC components were related to IBD risk, we evaluated associations between individual IC deficits and incident IBD, CD, and UC (**Supplementary Table 7**). Impairments across multiple domains were independently associated with increased IBD risk, with generally stronger associations observed for CD than for UC. Fatigue and slow walking pace showed the strongest associations with CD risk, corresponding to a 76% (HR = 1.77, 95% CI: 1.54–2.03, *P* < 0.001) and 52% (HR = 1.52, 95% CI: 1.27–1.82, *P* < 0.001) higher risk, respectively. Reduced grip strength, abnormal sleep duration, hearing impairment, and eye disease were also associated with elevated CD risk, with more modest effect sizes. In contrast, associations with UC were weaker but remained significant for fatigue (HR = 1.22, 95% CI: 1.09–1.37, *P* < 0.001), slow walking pace (HR = 1.21, 95% CI: 1.06–1.39, *P* < 0.001), reduced grip strength (HR = 1.16, 95% CI: 1.06–1.28, *P* < 0.001), and eye disease (HR = 1.30, 95% CI: 1.10–1.54, *P* < 0.001), whereas no significant associations were observed for hearing impairment or unintentional weight loss.

3.3 Joint effects of genetic susceptibility and intrinsic capacity on incident IBD

Higher PRS were consistently associated with increased risks of incident IBD. Compared with individuals in the low PRS group, those with intermediate and high PRS had 63.1% and 235.5% increased risk (Intermediate: HR = 1.631, 95% CI: 1.473–1.805, *P* < 0.001; High: HR = 3.355, 95% CI: 3.032–3.713, *P* < 0.001), respectively. Similar associations were observed for CD (Intermediate: HR = 1.431, 95% CI: 1.210–1.692, *P* < 0.001; High: HR = 3.333, 95% CI: 2.827–3.931, *P* < 0.001), with a stronger effect for UC (Intermediate: HR = 1.696, 95% CI: 1.500-1.918, *P* < 0.001; High: HR = 3.581, 95% CI: 3.169–4.046, *P* < 0.001).

When stratified by PRS, the association between IC and incident IBD varied by genetic susceptibility (Fig. 3A). No significant associations were observed across IC deficit categories among individuals with low PRS. In contrast, among the high PRS group, participants with 3 IC deficits experienced a 36.7% increase in IBD risk (HR = 1.367, 95% CI 1.101–1.698, *P* = 0.005), while those with ≥ 4 IC deficits exhibited a 44.5% higher risk (HR = 1.445, 95% CI 1.068–1.956, *P* = 0.017), compared with individuals with preserved IC.

A more pronounced and consistent pattern was observed for CD (Fig. 3B). Across all PRS strata, severe IC impairment (≥ 3 deficits) was consistently associated with substantially increased CD risk, suggesting that advanced functional decline represents a dominant susceptibility factor that operates across different levels of genetic predisposition. In contrast, moderate IC impairment (score = 2) was associated with increased CD risk only in the high PRS group (HR = 1.461, 95% CI: 1.158–1.843, *P* =

0.001), with no significant associations observed in the low or medium PRS strata. For UC, associations were generally weaker and less consistent, with increased risk observed primarily among individuals with higher IC deficits in the medium and high PRS groups, while no significant associations were detected in the low PRS stratum (Fig. 3C).

In joint analyses using individuals with low PRS and preserved IC as the reference group, the risk of incident IBD increased progressively with higher PRS levels and a greater number of IC deficits, demonstrating a clear joint gradient effect (**Supplementary Table 8–10**). The pattern was most pronounced for CD. Severe IC impairment was consistently associated with a significantly increased CD risk across all levels of genetic susceptibility, with the highest risk observed in high PRS and ≥ 4 group (HR = 14.3, 95% CI: 9.70–21.1, $P < 0.001$). In contrast, associations between IC and UC were generally weaker, with additional effects of IC impairment mainly evident among individuals with medium or high PRS and of smaller magnitude than those observed for CD.

Additive interaction analyses further suggested that the combined effects of genetic susceptibility and IC impairment were more evident for CD than for UC or overall IBD (**Supplementary Tables 11–13**). For CD, significant positive additive interaction was observed in the high PRS group at IC deficit scores of 2 and 3, with corresponding RERI values of 1.08 (95% CI, 0.04–2.11) and 1.97 (95% CI, 0.12–3.82), and AP values of 0.23 (95% CI, 0.03–0.43) and 0.30 (95% CI, 0.07–0.53), respectively. For IBD, evidence of additive interaction was present primarily among participants with high PRS and an IC deficit score of 3 (RERI 1.20, 95% CI, 0.20–2.21; AP 0.21, 95% CI, 0.06–0.37), whereas the corresponding estimates for UC were weaker and less consistent, with only limited evidence observed in the medium PRS group with an IC deficit score of 3.

3.4 Subgroup and sensitivity analyses

Subgroup analyses showed that the association between IC deficit burden and incident IBD was generally consistent across most strata, with a clear dose–response pattern observed. Individuals with severe IC deficits (score ≥ 4) had markedly higher risks of IBD across subgroups, with significant effect modification observed for age, sex, smoking status, and educational attainment (all P for interaction < 0.05), whereas no substantial heterogeneity was detected across BMI, alcohol intake, physical activity, or socioeconomic deprivation categories. Of note, among current smokers, participants with incident CD who had IC deficit scores of 3 and ≥ 4 showed significantly increased risks, with the strongest association observed for those with a score of ≥ 4 (HR = 2.891, 95% CI: 1.345–6.218, P = 0.007). In contrast, no statistically significant associations were observed between IC deficit score and the risks of incident IBD or UC. When stratified by disease subtype, the associations were stronger and more consistent for CD, where severe IC deficits more than doubled the risk in most subgroups, while the corresponding estimates for UC were generally weaker and less consistent. (**Supplementary Table 14–22, Supplementary Fig. 1–3**).

In sensitivity analyses, the associations between IC deficit burden and incident IBD outcomes remained robust. Among individuals with complete covariate data, higher IC deficit scores were still significantly

associated with increased risks of IBD, CD, and UC (**Supplementary Table 23**). Similar results were observed after excluding participants who developed IBD within the first year of follow-up (**Supplementary Table 24**), as well as after excluding those who died within the first 3 years of follow-up (**Supplementary Table 25**). In addition, the associations remained materially unchanged after excluding participants with irritable bowel syndrome or functional bowel disorders at baseline (**Supplementary Table 26**), further supporting the robustness of the primary findings.

4. Discussion

In this large-scale prospective cohort study, we found that poorer IC, reflected by a greater burden of IC deficits, was independently associated with a higher risk of incident IBD, with a clear dose–response relationship across increasing deficit levels. This association was more pronounced for CD than for UC. We also observed a marked joint gradient between IC and genetic susceptibility, with the highest risks occurring among individuals with both severe functional impairment and high polygenic risk. Taken together, these findings suggest that multidomain functional vulnerability may represent an early systemic state associated with IBD development, particularly among genetically susceptible individuals.

IC, as proposed by the WHO within the healthy ageing framework, summarizes functional reserve across locomotor, vitality, psychological, and sensory domains[12]. Unlike a single biomarker or isolated clinical characteristic, it integrates signals from multiple functional systems and may therefore capture an overall vulnerability phenotype characterized by reduced physiological reserve and resilience. The association between IC and IBD is biologically plausible, as IBD represents a systemic rather than purely localized disorder. Pathologically, IBD involves a dysregulated mucosal immune response that is deeply intertwined with broader physiological homeostasis[30, 31]. This systemic complexity is exemplified by the bidirectional brain-gut axis, whereby neuroendocrine responses modulated by psychological status and systemic stress directly influence intestinal barrier integrity and mucosal inflammatory thresholds[32, 33].Previous cohort studies have shown that a higher burden of intrinsic-capacity deficits is associated with elevated risks of cardiovascular disease, functional decline, and all-cause mortality[15, 22, 34, 35]. In our study, IBD incidence increased from 0.556 per 1,000 person-years among participants with no IC deficits to 1.067 per 1,000 person-years among those with four or more deficits, and adjusted hazards rose progressively from IC scores of 2 onwards. The graded association, alongside the absence of a significant correlation at an IC score of one, supports the conceptualization of IC deficits as a cumulative marker of multisystem vulnerability that precedes the onset of IBD. A potential underlying mechanism is that a single deficit remains within the range of physiological compensation and is therefore insufficient to identify individuals in a state of stable vulnerability. In contrast, the accumulation of deficits across multiple domains more reliably indicates a diminution of physiological reserve as well as reduced resilience to the biological or environmental challenges associated with IBD development. At the same time, the clinical interpretation of these findings should consider both relative and absolute risk. Although the hazard ratios indicate a moderate increase in relative risk with increasing IC deficit burden, the absolute increase in incidence remained modest in population terms. This

suggests that IC may be more useful for population-level risk stratification and the identification of higher-risk subgroups than for individual-level prediction.

The stronger association observed for CD than for UC is particularly noteworthy. Compared with UC, CD more often involves transmural inflammation, a broader systemic inflammatory phenotype[1, 2], and a higher burden of extraintestinal manifestations[36, 37]. This may partly explain why CD susceptibility appears more sensitive to pre-existing reductions in physiological reserve. Consistent with this interpretation, our component-level analyses showed that the strongest associations with CD were observed for fatigue and slow walking pace, followed by reduced grip strength, suggesting that deficits in vitality and locomotor capacity may be particularly relevant to CD risk. These domains are closely related to energy balance, muscle function, and physical performance, and overlap substantially with the clinical construct of sarcopenia. Existing literature indicates that fatigue is highly prevalent in CD and is associated with inflammatory activity, nutritional disturbances, psychological burden, and gut-brain axis dysfunction, whereas sarcopenia and impaired muscle performance are increasingly recognized in IBD, particularly CD[38–41]. Although these prior studies largely concern established disease rather than incident risk, they are directionally consistent with our findings and support the possibility that deficits in vitality and locomotor capacity may capture a systemic vulnerability phenotype that is especially relevant to CD susceptibility.

As expected, polygenic risk showed a strong independent association with incident IBD, consistent with previous UK Biobank analyses highlighting genetic susceptibility as a major determinant of disease development[18]. However, the association between IC deficits and incident IBD was not uniform across genetic backgrounds. In our data, no clear association was observed across IC categories among individuals with low PRS, whereas in the high-PRS stratum, participants with 3 and ≥ 4 IC deficits had 36.7% and 44.5% higher risks of IBD, respectively. This pattern suggests that IC deficits may not represent a homogeneous exposure across the population, but rather a host vulnerability phenotype that modifies how genetic susceptibility is expressed clinically. In other words, reduced functional reserve may be especially relevant in individuals in whom inherited susceptibility is more likely to translate into overt disease. This joint gradient was particularly striking for CD, in which the highest risk was observed in the most extreme category defined by high PRS and severe IC impairment (HR 14.3), supporting the possibility that CD is especially sensitive to the combined influence of inherited liability and systemic functional vulnerability.

This study has several strengths. These include the large sample size, long follow-up duration, prospective design, and comprehensive adjustment for demographic, lifestyle, and socioeconomic factors. The availability of PRS data and detailed baseline phenotyping enabled us to evaluate overall IC, domain-specific deficits, and their joint effects with genetic susceptibility within a unified analytic framework. Multiple sensitivity analyses yielded consistent results, supporting the robustness of the observed associations.

Several limitations should also be considered. First, IC was assessed at baseline only, and longitudinal changes in functional status were not captured; such misclassification would most likely bias the associations toward the null. Second, although we adjusted for a broad range of potential confounders, residual confounding cannot be entirely excluded. Third, our IC construction was operationalized using variables available in UK Biobank and therefore represents an approximation of the WHO framework rather than a direct assessment of all original IC domains. Fourth, the UK Biobank cohort is predominantly European ancestry and is affected by healthy volunteer bias, which may limit generalizability to younger populations and other racial and ethnic groups.

5. Conclusion

In conclusion, poorer intrinsic capacity was independently and dose-dependently associated with a higher risk of incident IBD, particularly CD, and this association was most evident among individuals with high genetic susceptibility. These findings extend the IC framework to chronic intestinal inflammation and suggest that multidomain functional vulnerability may be relevant to the development of immune-mediated intestinal disease. Further studies with repeated IC assessments and external validation are needed to clarify temporality, refine risk prediction, and determine whether functional decline represents a modifiable pathway relevant to IBD susceptibility.

Declarations

Additional Information

Competing interests

The authors declare no competing interests.

Funding

This work was supported by the Jiangsu High-Level Key Discipline Construction Project of Traditional Chinese Medicine (k2025xk03) and the Jiangsu Provincial Project for Dominant Traditional Chinese Medicine Diseases.

Author Contribution

H.C. conceived and designed the study. B.Y. provided constructive comments on the analyses. S.W., Q.C. and M.L. performed the analyses and drafted the manuscript. W.G., Y.W., Z.L. and J.Z. revised the manuscript. All authors reviewed the manuscript and approved the final version.

Acknowledgements

This research has been conducted using the UK Biobank Resource under Application Number 468511. This work was supported by the Jiangsu High-Level Key Discipline Construction Project of Traditional Chinese Medicine (k2025xk03) and the Jiangsu Provincial Project for Dominant Traditional Chinese Medicine Diseases. We thank all UK Biobank participants and the management team for their participation and assistance.

Data Availability

The data analysed in this study are available from the UK Biobank Resource upon application under Application Number 468511. These data are not publicly available because they are subject to the UK Biobank controlled-access policy.

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Figures

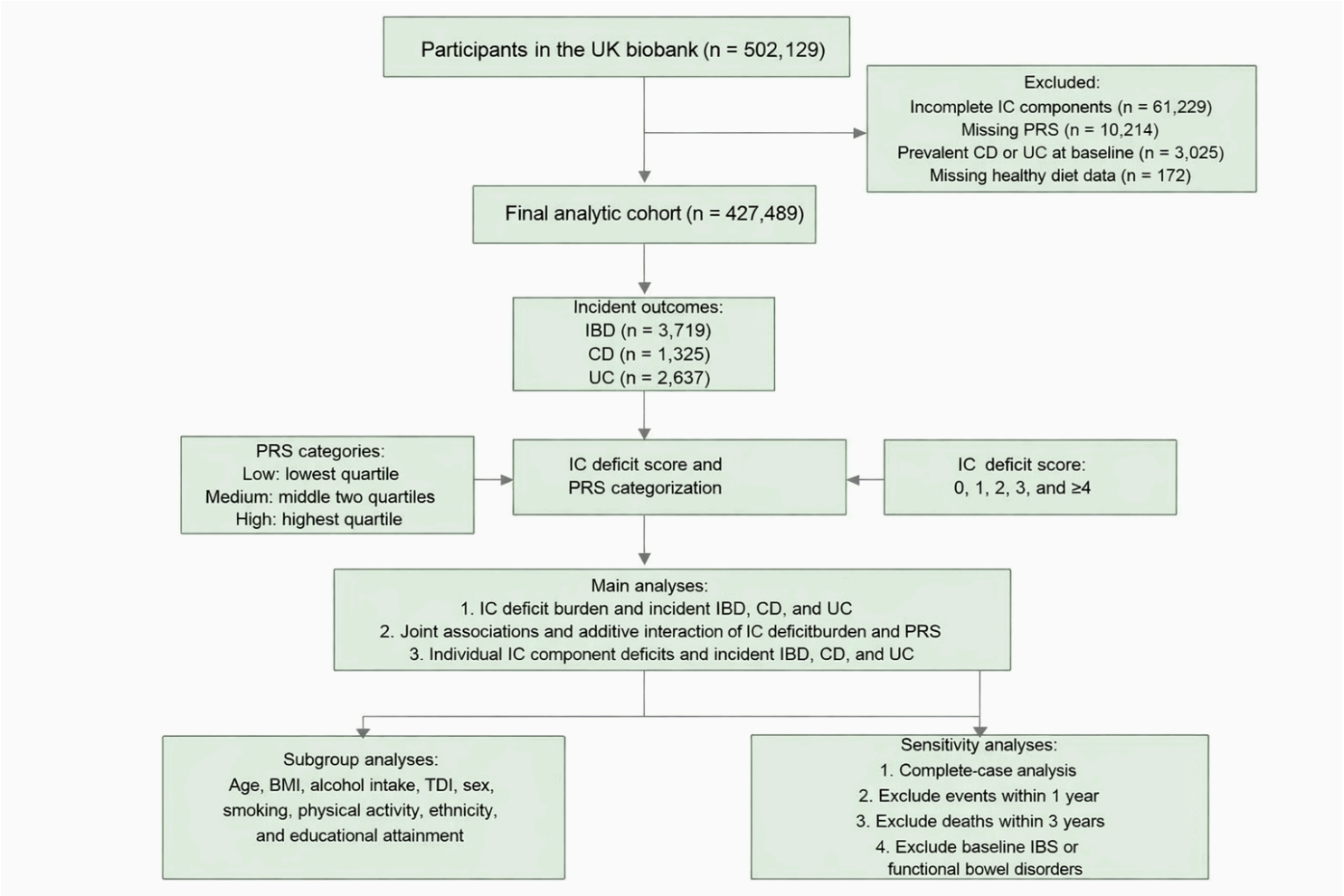


Figure 1

Flowchart of participant selection and analytical framework in the UK Biobank

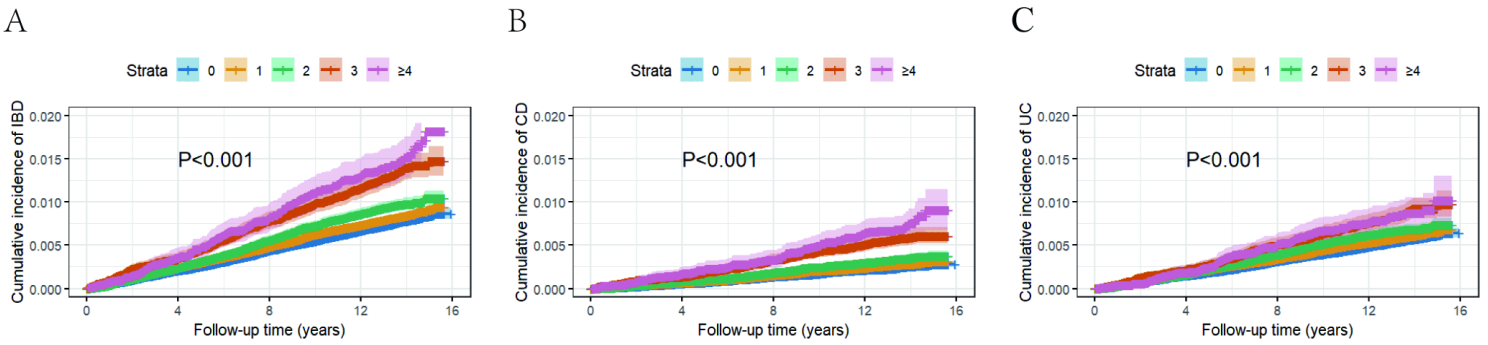


Figure 2

Cumulative incidence of incident IBD, CD, and UC according to IC deficit score categories. Kaplan–Meier curves showing cumulative incidence of incident IBD, CD, and UC according to IC deficit score categories (0, 1, 2, 3, and ≥4 deficits)

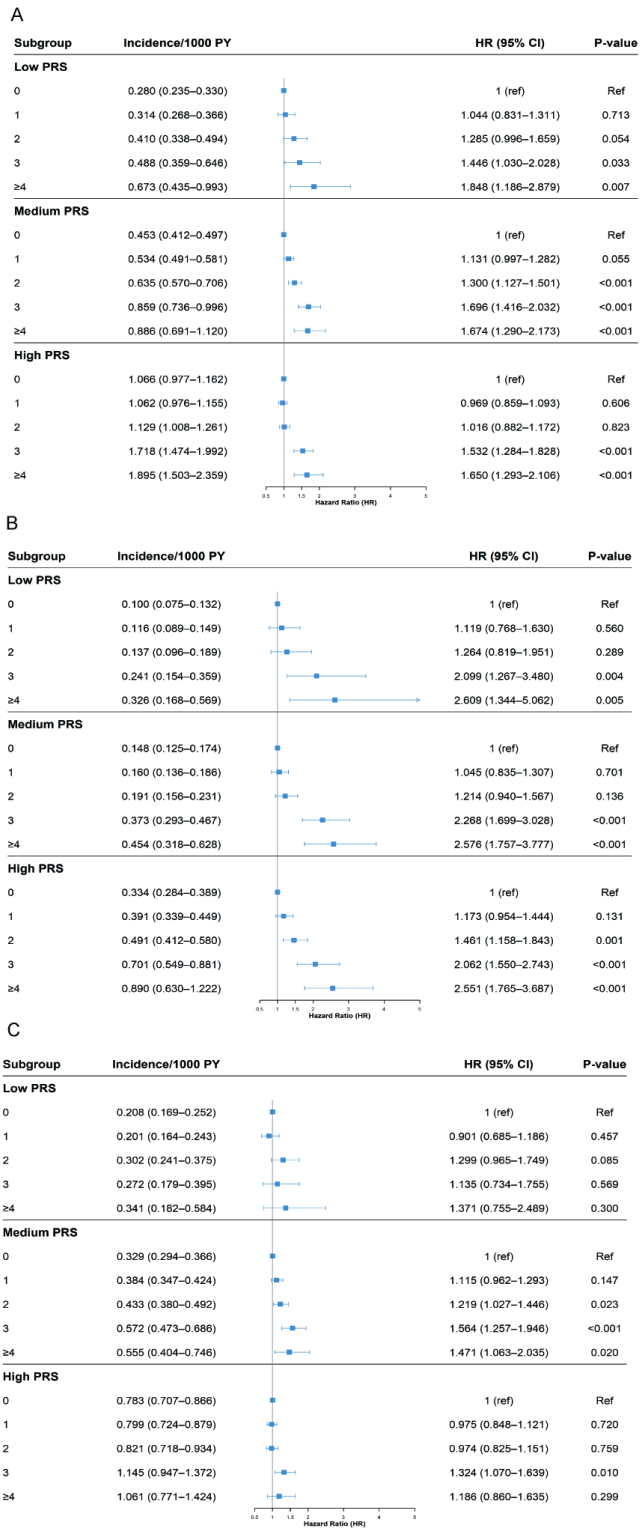


Figure 3

Associations of IC deficit score categories with incident IBD, CD, and UC within strata of polygenic risk. Forest plots showing incidence rates per 1,000 person-years and adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) for incident IBD, CD, and UC according to IC deficit score categories within low, medium, and high PRS strata

Supplementary Files

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