

Inflammatory Bowel Disease Is Not Genetically Determined, Not Classically Autoimmune, and Not Idiopathic: A Critical Reframing of Pathogenesis

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Abstract

Background: Inflammatory bowel disease (IBD) is conventionally explained as a genetically determined disorder, a classical autoimmune disease, or a largely idiopathic condition. Current evidence challenges all three.

Methods: Literature was searched from inception through January 2026 across epidemiology, genetics, immunology, and toxicology. IBD-associated antibodies were evaluated against the Rose and Bona criteria for classical autoimmunity. For mold and mycotoxin exposure, converging mechanisms were drawn from immunology and toxicology literature.

Results: First, IBD is not genetically determined. Heritability is modest ($h^2=0.25$), only 20–40% of NOD2 homozygotes develop CD, twin concordance is 20–50%/10–19% for CD/UC, and immigrant children develop IBD at host-population rates within one generation. Prevalence has compounded from 2–4 to >1,000 per 100,000 (1950s–2035) in

early industrialized countries, incompatible with monogenic determinism. Second, IBD fails classical autoimmune criteria. IBD-associated antibodies (ASCA, pANCA, anti-OmpC, anti-CBir1, anti-glycan ALCA/ACCA/AMCA) target microbial and environmental antigens, not self. Pathogenic transfer is not demonstrated, supporting an immune-mediated rather than autoimmune classification. Third, IBD is not idiopathic. Smoking (OR 1.76), antibiotic exposure (OR 1.74), urbanization, oral contraceptives, ultra-processed food, air pollution, and psychological stress are confirmed contributors. Shared mechanisms point to mold and mycotoxin exposure via Th17/Th1 polarization, NF- κ B activation, and barrier disruption.

Conclusions: IBD is environmentally driven, immune-mediated rather than classically autoimmune, and partially heritable but not genetically determined. This reframing supports a prevention-oriented clinical and public health agenda.

Keywords: Inflammatory bowel disease, immune-mediated disease, genetic determinism, classical autoimmunity criteria, environmental triggers, mycotoxins

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Introduction

Inflammatory bowel disease (IBD) affects more than 7 million people worldwide and is one of the fastest-growing chronic diseases globally. (1,2) It is conventionally placed into three categories: a genetic disorder of inherited susceptibility (>240 risk loci identified); (3–8) a chronic autoimmune disease driven by an immune system attacking its own tissues; (3–8) and a condition with a large idiopathic component. (3–8) These framings shape which re-

search questions get funded, how clinicians counsel patients, and whether prevention is considered possible.

This perspective argues that each of the three framings is now contradicted by converging evidence. The aim is not to deny that genetics matter, that immune dysregulation occurs, or that some triggers remain to be identified. It is to reject three stronger claims: that IBD is genetically determined, that IBD is classically autoimmune in the Witebsky-Rose-Bona sense, (9) and that the remaining disease burden is idiopathic. A synthesis then proposes a unified model: genes establish susceptibility, environmental exposures determine expression through epigenetic and microbiome-mediated pathways, and the resulting immune response is mediated rather than autoimmune. (10–17)

Position relative to prior work

Each of the three pillars has been engaged separately in the recent literature, but never jointly. Cadwell and Loke (2025) (12) and Bai and colleagues (2025) (11) establish gene-environment interactions but do not engage the autoimmune classification or the idiopathic residual. Fiocchi (2015) (18) and Wen and Fiocchi (2004) (19) question whether IBD meets autoimmune criteria, but do not address genetic determinism. Piovani and colleagues (2019) (20) catalog environmental risk factors but engage neither the autoimmune nor genetic framings. Noble and colleagues (2023) (10) and the IOIBD consensus (21) integrate genome, epigenome, and environment but retain the conventional pathogenic categories. No prior review has evaluated all three framings simultaneously and concluded that the conventional pathogenic model fails as a coherent whole. The implication is not that the conventional model needs updating; it needs replacing.

Methods

This perspective synthesizes evidence across immunology, genetics, epidemiology, toxicology, and gastroenterology to test each conventional pathogenic framing of IBD. Systematic reviews are the right method to ask whether any single exposure is associated with IBD; such reviews already exist. (11,20,22–25) A perspective is the right method to ask whether the three framings jointly survive current evidence, because that question requires cross-disciplinary conceptual integration that systematic methods are not designed to deliver. This work uses systematic reviews and meta-analyses as inputs, but

its claim is about how IBD should be classified rather than which factors associate with it.

Literature Search

PubMed, Scopus, Web of Science, and Embase were searched from inception to January 2026. Search terms combined “inflammatory bowel disease,” “Crohn’s disease,” and “ulcerative colitis” with key terms covering heritability, autoimmune criteria, serologic markers, gene-environment interactions, environmental triggers, stress, pollution, mycotoxin, mold, microbiome, and antibiotics. Priority was given to meta-analyses, systematic reviews, umbrella reviews, genome-wide association studies, and large prospective cohorts.

Evaluation Frameworks

Pillar 1 (genetic determination) was evaluated using pooled heritability estimates, penetrance data, twin concordance, immigrant cohort studies, and time-series epidemiology. Pillar 2 (classical autoimmunity) was evaluated using the Rose and Bona criteria (Witebsky’s postulates revisited): (9) direct evidence (pathogenic antibody or T-cell transfer reproduces disease), indirect evidence (the disease is reproduced in animals using a defined autoantigen), and circumstantial evidence (HLA association, lymphocytic infiltration, response to immunosuppression, co-occurrence with autoimmune disease). Each IBD serologic marker was mapped onto these criteria. Pillar 3 (idiopathy) was evaluated using umbrella reviews and meta-analyses of environmental risk factors. For mold and mycotoxin exposure, where direct meta-analytic evidence is unavailable, a mechanistic pathway convergence approach was applied (explicitly hypothesis-generating).

Results

Pillar 1: IBD is not genetically determined

Pooled heritability of IBD is approximately 0.25 (95% CI 0.20–0.30; $I^2=75\%$), meaning genetics explain roughly a quarter of disease risk. (26,27) Genome-wide association studies have identified more than 240 risk loci that together account for only about 13% of CD heritability and 8% of UC heritability; (26–28) the remainder is attributable to environmental factors and gene-environment interaction. (10–12) Only 20–40% of individuals homozygous for NOD2 risk variants develop Crohn’s disease, (26–29) inconsistent with deterministic genetic causation. Monozygotic twin pairs are dis-

cordant for IBD in most cases, with concordance just 20–50% for CD and 10–19% for UC. (30,31) And in population-based cohorts in Canada and Denmark, children of immigrants from low-incidence countries develop IBD at host-population rates within one generation, (32,33) a window too short for population genetic architecture to shift.

In early industrialized countries, IBD incidence has compounded from approximately 2–4 per 100,000 in the 1950s (34,35) to current US prevalence of 721 per 100,000 (~1 in 139 people, ~2.4 million Americans), (36) with intermediate data points documented in Olmsted County. (35,37–39) Canadian prevalence rose from ~400 per 100,000 in 2002 to 825 per 100,000 in 2023 and is projected to exceed 1,098 per 100,000 (>1% of the population) by 2035 (**Figure 1**). (40,41) Scotland projects similar 1% prevalence by 2028. (42) Newly industrialized countries across Asia, Latin America, Africa, and the Middle East are now experiencing the same accelerated incidence. (43–47) Human population genetics do not shift on this timescale, and the magnitude of increase exceeds what any plausible change in genetic architecture could produce. The trajectory is incompatible with primarily genetic causation and consistent with environmental drivers acting on a stable susceptible-genotype background.

Pediatric-onset IBD incidence is rising worldwide, (48) and sex-based differences in incidence patterns shift with industrialization and reproductive-hormone exposure. (49) Both observations are difficult to reconcile with fixed genetic causation alone, but readily reconciled with environmental drivers acting on susceptible genotypes.

Pillar 2: IBD does not meet classical autoimmune criteria

Rose and Bona, revisiting Witebsky's postulates, defined three categories of evidence required to establish a human disease as autoimmune: (9) direct evidence (transfer of pathogenic autoantibody or T cells reproduces disease in a naive recipient), indirect evidence (the disease is reproduced in experimental animals using a defined autoantigen), and circumstantial evidence (HLA association, lymphocytic infiltration, response to immunosuppression, co-occurrence with autoimmune disease). Diseases that meet category (3) (e.g., myasthenia gravis, Graves' disease) are unambiguously autoimmune. Diseases meeting only category (5) are more accurately termed immune-mediated inflammatory diseases. (18)

Pathogenic transfer of IBD by purified antibody, or

by adoptive transfer of patient T cells into a naive recipient, has not been demonstrated. Animal models of colitis depend on barrier disruption, microbial dysbiosis, or genetic disruption of regulatory immunity. They do not depend on the introduction of a defined autoantigen-specific lymphocyte clone. (2,3,18,30) This is a real failure of the criterion, not a technical limitation.

No defined autoantigen reliably reproduces IBD when used to immunize experimental animals. Where animal models do reproduce IBD-like inflammation, the trigger is microbial or environmental (chemical colitogens, microbiota transfer, gnotobiotic dysbiosis) rather than autoantigen exposure. (12,18,50) This pattern is more consistent with an antigen-driven, environmentally activated immune response against luminal targets than with classical autoreactivity.

T-cell transfer colitis (CD45RBhi naive T cells into immunodeficient hosts) and IL-10 knockout reproduce colitis but depend on absence of regulatory T cells in a microbially replete environment, not on introduction of an autoantigen-specific clone. (4,12,50) Disease can be prevented by regulatory T-cell transfer, germ-free rearing, or microbiota depletion, none of which would rescue a classical autoimmune disease driven by a defined autoantigen. These models reproduce IBD-like inflammation through tolerance failure to luminal antigens, not autoreactivity.

The serologic markers historically cited as evidence of IBD autoimmunity recognize microbial or environmental targets rather than self (**Table 2**). ASCA (anti-Saccharomyces cerevisiae antibodies) recognize mannan, a fungal cell-wall glycan, and is by definition an anti-microbial response, not autoreactivity; (51) sensitivity for CD is ~50–60%, with specificity rising only when combined with additional anti-microbial markers. (52,53) pANCA in IBD lacks a consistent self-antigen with established pathogenic transfer, shows heterogeneous reactivity patterns, and has not been demonstrated to appear before clinical disease; reactivity also occurs in conditions such as ankylosing spondylitis without IBD. (19,52,54,55) Anti-OmpC and anti-CBir1 target bacterial outer membrane porin C of Escherichia coli and commensal bacterial flagellin, respectively, both microbial antigens. (51,52) Anti-glycan antibodies ALCA, ACCA, and AMCA target laminaribioside, chitobioside, and mannobioside, all carbohydrate epitopes of fungal cell walls; Dotan and colleagues established these as serologic markers of Crohn's disease, (56) and Mitsuyama and colleagues documented them as fungal-antigen re-

sponses within the IBD antibody panel. (53) None of these markers are autoantibodies in the classical sense.

Anti-tropomyosin antibodies (anti-hTM5) reported in ulcerative colitis have been proposed as evidence of self-reactivity. (18,19) However, pathogenic transfer has not been demonstrated, antibody titer does not consistently predict disease activity or onset, and tropomyosin reactivity does not satisfy the direct-evidence criterion. (9) The pattern is consistent with epitope spreading from chronic mucosal inflammation, not primary autoreactivity initiating disease, a distinction Witebsky himself emphasized. (9)

IBD shows some features of category (5) circumstantial evidence, such as modest HLA associations, lymphocytic infiltration, response to immunosuppression, and co-occurrence with classical autoimmune conditions in a subset of patients. However, these features are shared by many immune-mediated inflammatory diseases that are not autoimmune, including immune-mediated reactive arthritides and granulomatous disorders of microbial origin. Circumstantial evidence alone, without categories, (3,4) is insufficient to support classical autoimmune classification under the Rose-Bona framework. (9)

Pillar 3: IBD is not idiopathic

An umbrella review of 53 meta-analyses spanning 71 risk factors identified a coherent panel of modifiable exposures that contribute to IBD risk (**Table 1**). (20) Smoking confers OR 1.76 for CD and is protective for UC (OR 0.58), interacting with NOD2 and ATG16L1 variants. (11,20,57) Antibiotic exposure confers OR 1.74 for CD via dysbiosis-driven amplification of NOD2/IRGM defects, with independent meta-analyses reporting OR 1.7–2.8 depending on timing and class. (20,24,25,58) Urban environment confers OR 1.17–1.20, (20) oral contraceptives OR 1.28–1.46, (57,59) and appendectomy is protective for UC (OR 0.40). (20) Breast-feeding shows consistent protective effects (OR 0.67 for CD, 0.77 for UC), (60) though one recent multi-cohort analysis found no association with duration alone, suggesting a more nuanced relationship. (61)

Ultra-processed food intake is significantly associated with increased IBD risk and promotes dysbiosis with altered ATG16L1/IRGM expression. (11,23,62,63) Mediterranean-pattern adherence was associated with favorable microbiome composition and reduced subclinical inflammation, (64) and

healthy lifestyle adherence was associated with substantially reduced IBD risk in a Nurses' Health Study analysis. (65) Air pollution exposure is associated with IBD incidence, flares, and hospitalizations through oxidative stress, barrier disruption, and dysbiosis, (22,66) with Mendelian randomization providing support for causal inference. (67)

Treatment-naïve microbiome analysis of new-onset Crohn's disease identifies distinct microbial signatures before any therapeutic exposure. (50) Faecal microbiota from IBD patients induce inflammatory Th17 responses in animal models. (12) Dysbiosis is therefore not merely a consequence of disease. It is a contributor to its initiation.

A systematic review of 38 prospective studies found that perceived stress preceded IBD exacerbation, (68,69) and bidirectional meta-analysis demonstrated approximately two-fold increased risk of subsequent IBD with depression (HR ~2.0). (70) The IOIBD formally recognizes stress as a modifiable factor warranting clinical attention. (21) Chronic stress activates the HPA axis, suppresses regulatory T cells, promotes NF- κ B and Th17 polarization through IL-6 and IL-1 β , and skews immunity toward Th2 dominance via STAT6, the same pathways dysregulated in IBD. (12,71)

The exposures above rest on quantified meta-analytic and prospective-cohort data. The category that follows (mold and mycotoxin exposure) is explicitly hypothesis-generating and represents a dedicated research target rather than a confirmed exposure.

Mold and mycotoxin exposure: dedicated research target with mechanistic pathway convergence

No published meta-analysis directly quantifies the relationship between mold or mycotoxin exposure and IBD onset, but mechanistic pathway convergence supports biological plausibility warranting epidemiological investigation. Deoxynivalenol (DON) induces Th17 differentiation and increases susceptibility to intestinal inflammatory disease in animal models. (72,73) DON and ochratoxin A enhance IL-1 β , IL-6, and TNF- α (the same cytokines targeted by IBD biologics), drive Th1/Th17 differentiation via STAT signaling, disrupt Th1/Th2 balance through IL-12 suppression, promote NF- κ B-driven inflammation, and compromise barrier integrity. (72,73) CARD9, a top IBD risk locus critical for antifungal immunity, provides a plausible genetic link, (12,29) and the anti-glycan antibodies ALCA, ACCA, and AMCA in IBD patients are themselves fungal-antigen responses. (53,56) This

convergence supports mold and mycotoxin exposure as a biologically plausible, currently unconfirmed environmental contributor requiring dedicated epidemiological study.

Therapeutic-pathway concordance

The immune pathways activated by mycotoxin exposure are the same pathways targeted by FDA-approved IBD biologics. Mycotoxin-activated Th17 (72,73) is targeted by ustekinumab and risankizumab. Mycotoxin-driven TNF- α (73) is targeted by infliximab, adalimumab, certolizumab, and golimumab. Mycotoxin-driven barrier disruption and altered chemokine signaling (72) align with vedolizumab. STAT signaling targeted by JAK inhibitors (tofacitinib, upadacitinib) is the same pathway mycotoxins use to drive Th1/Th17 polarization. (73) Equivalent concordance maps to stress, ultra-processed diet, and dysbiosis, each of which activates Th17, NF- κ B, and barrier-disruption pathways targeted by existing therapies. (12,62,63,71) This is supportive mechanistic evidence, not proof of causation.

Maternal smoking during pregnancy is associated with offspring CD via oxidative stress and epigenetic modification. (74,75) Breastfeeding shows consistent protective effects in long-running meta-analyses, (60,76) though one recent cohort analysis adds nuance. (61) Early antibiotic exposure confers OR 1.7–2.8 for new-onset CD, depending on timing and class. (20,25,58) Khakoo and colleagues demonstrated that early-life environmental exposures, more than genetic predisposition, influenced age of IBD diagnosis in a diverse cohort of 2,952 patients. (77) Early disruption of the developing microbiome compounds functional defects in NOD2/IRGM pathways. (11,12)

Discussion

A unified model

The three pillars converge on a single coherent model: IBD is a partially heritable, environmentally activated, immune-mediated inflammatory disease. Genes establish baseline susceptibility (h^2 around 0.25). Environmental exposures that induce dysbiosis, disrupt the barrier, or polarize immunity determine whether and when disease becomes clinically manifest. (10–12) The resulting immune response is mediated rather than autoimmune, driven by aberrant reactivity to luminal microbial and environmental antigens rather than to defined self-antigens. (9,18,19,51,52,54,55) This model fits the data more

simply than the three conventional framings alone and explains the modest heritability, twin discordance, immigrant-cohort effects, the global compounding of prevalence, the antigen targets of the IBD antibody panel, the failure of pathogenic transfer, the environmental rather than autoantigen dependence of animal models, and the mechanistic convergence of stress, mycotoxins, dysbiosis, and ultra-processed diet on shared immune pathways. (12,71–73)

The mucosal mechanism connecting the three pillars is loss of tolerance to luminal antigens through barrier disruption and altered short-chain fatty acid signaling: environmental triggers reduce microbial diversity and impair butyrate production, weakening the epithelial barrier and Treg-mediated tolerance to luminal microbial and dietary antigens. Genetically susceptible immune systems respond to the resulting antigen leak with the aberrant Th17/Th1 inflammation described across the three pillars.

Testable predictions

Four predictions distinguish the unified model from the conventional framings and can be tested with available methods.

- Prediction 1. Patients carrying CARD9 risk variants with elevated anti-glycan antibody titers (ALCA, ACCA, AMCA) should show higher rates of documented fungal/mycotoxin exposure than antibody-negative IBD patients and non-IBD controls. Testable with existing biobanks linked to exposure questionnaires and urinary or indoor-air mycotoxin measurement.
- Prediction 2. IBD patients stratified by serologic profile and exposure history should show differential responses to immune-modulating therapies. Anti-glycan/CARD9-positive subgroups should respond preferentially to Th17-axis therapies and antigen-source modification. Testable through post hoc analyses of existing biologic-trial cohorts.
- Prediction 3. Prospective trials reducing identified environmental triggers (antibiotic stewardship, breastfeeding support, ultra-processed food reduction, mold remediation, microbiome-supportive interventions) should measurably reduce population-level IBD incidence over 5–10 years. The conventional framings do not predict this; the unified model does.
- Prediction 4. The compounding-prevalence tra-

jectory in newly industrialized countries should track measurable environmental transitions rather than any shift in population genetic architecture. Testable using existing population-based registries. (43,44)

Implications for clinical communication, therapeutic logic, and public health

- Clinical communication. Patients are commonly told IBD is “genetic, autoimmune, and idiopathic.” A more accurate framing is: genes raised your risk, environmental exposures activated it, and your immune system is reacting to luminal microbial and environmental antigens rather than attacking itself. This framing identifies levers patients can act on.
- Therapeutic logic. Classical autoimmunity implies suppressing self-reactivity. The immune-mediated reframing implies restoring tolerance to luminal antigens. This makes sense of biologic therapy (anti-TNF, anti-IL-12/23, anti-integrin) and creates explicit space for antigen-source modification (microbiome restoration, barrier repair, removal of mycotoxin or mold exposure, dietary deprocessing) as primary rather than add-on intervention. (18)
- Public health. If multiple environmental factors carry OR 1.5–2.0 and are widely prevalent, the share of disease they could account for is substantial. Reducing unnecessary antibiotic prescribing, supporting breastfeeding, minimizing ultra-processed food consumption, addressing air pollution and indoor mold exposure, and integrating stress management could measurably reduce population-level IBD incidence, a target unreachable under any framing of the disease as genetic, autoimmune, or idiopathic.
- These findings align with Noble and colleagues, (10) Bai and colleagues, (11) Cadwell and Loke, (12) Piovani and colleagues, (20) and the IOIBD consensus, (21) all of which converge on environmental and gene-environment causation. The contribution here is to make the three-pillar reframing explicit and to apply the Rose-Bona criteria (9) directly to the IBD serologic panel.

Limitations

As a perspective rather than a systematic review, this work synthesizes evidence through expert interpretation. The mold and mycotoxin pathway-convergence analysis is hypothesis-generating and does not replace direct epidemiological evidence. The stress-IBD relationship lacks a single pooled odds ratio for primary disease onset due to heterogeneity in stress measurement. (68) Most included studies are observational, with potential for recall bias for early-life exposures. No randomized trials have shown that removing identified environmental triggers prevents IBD onset; Mendelian randomization (67) and prospective intervention studies may strengthen causal inference. The relative contribution of each factor likely varies by individual, population, and disease phenotype.

Conclusions

Inflammatory bowel disease is not genetically determined, does not meet the classical criteria for autoimmunity, and is not idiopathic. It is a partially heritable, environmentally activated, immune-mediated inflammatory disease in which luminal microbial and environmental antigens drive an aberrant immune response in genetically susceptible hosts. The therapeutic implication is that treatment goals shift from suppressing self-directed autoimmunity to restoring tolerance to luminal antigens through barrier repair, microbiome restoration, and removal of identifiable environmental triggers. This reframing is consistent with current epidemiology, genetics, immunology, and toxicology. It directly supports a prevention-oriented clinical and public-health agenda that the three conventional framings preclude.

Conflicts of Interest

Josh Dech provides clinical services focused on inflammatory bowel disease. Yusuf JP Saleeby provides clinical services in integrative medicine. No external funding was received, and no proprietary interests are associated with the conclusions of this manuscript.

Table 1. Selected IBD risk genes with effect sizes and representative environmental triggers

Gene	Function	Risk effect (Odds Ratio)	Environmental Triggers
NOD2	Bacterial sensing, autophagy	CD ~2–4 (heterozygous); ~17–40 (compound/homozygous); UC ~1	Dysbiosis, smoking, antibiotics, Western diet (8,12,20,29)
ATG16L1	Autophagy	CD ~1.3–1.5; UC ~1	Western diet, smoking, dysbiosis (12,20)
IL23R	Immune regulation (Th17)	Protective variant (R381Q) ~0.2–0.5 CD; risk variants ~1.3–1.5 CD/UC	Psychological stress, dysbiosis (20,68,71)
IRGM	Autophagy, immunity	CD ~1.3–1.4; UC ~1	Antibiotics, diet, microbiome disruption (12,20,25,58)
TLR4	Pathogen recognition	CD ~1.2–1.4; UC ~1.2–1.4	Air pollution, environmental toxins (13,22,66)
HLA-DRB1*01:03	Antigen presentation	CD ~1.5; UC ~3–5	Dysbiosis, environmental antigens (12,27)
FUT2	Microbiome composition (secretor status)	CD ~1.3–1.5; UC ~1	Antibiotics, dietary changes (12,25,58)
CARD9	Fungal immunity	CD ~1.3–1.5; UC ~1.3–1.5	Mycotoxins, fungal dysbiosis (12,72)
PTPN22	T-cell regulation	CD ~1.3–1.5; UC variable	Psychological stress, brain-gut axis dysregulation (3,68,71)
MST1	Macrophage function	CD ~1.2–1.4; UC ~1.2–1.4	Pollutants, oxidative stress (13,22,66)

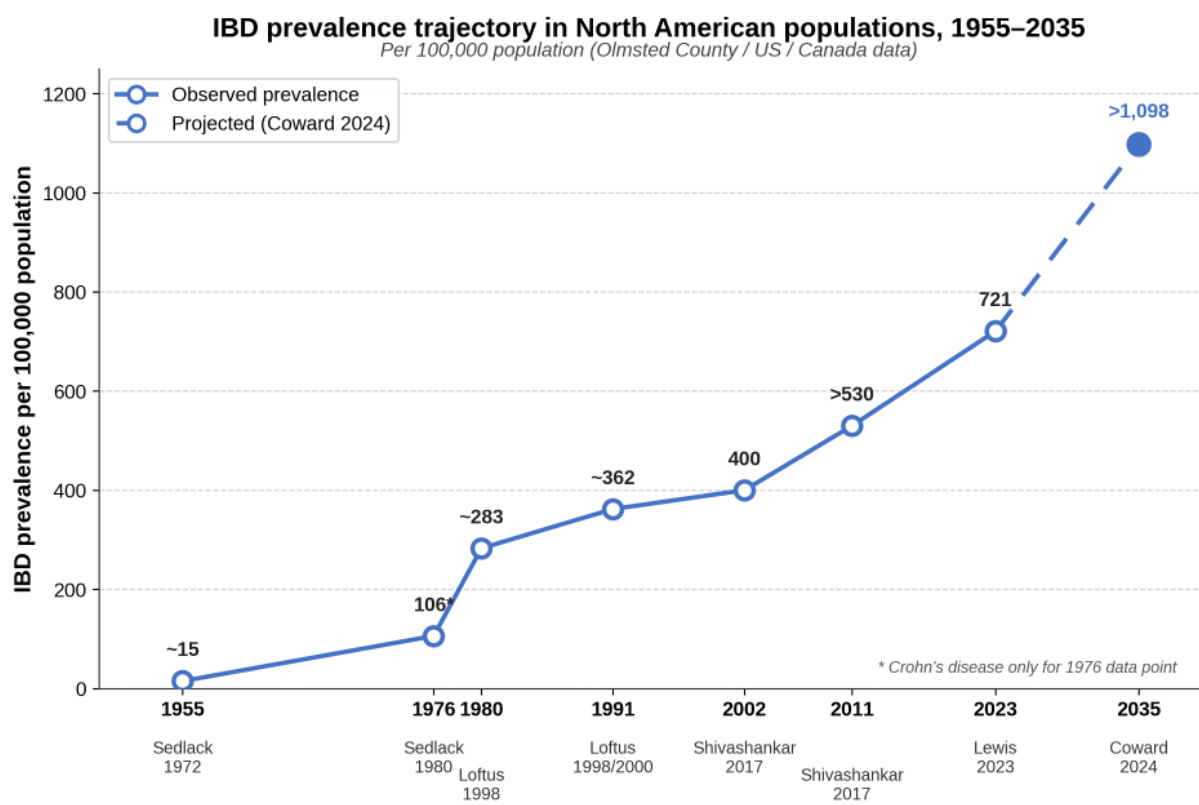
Odds ratios compiled from IBD genome-wide association study literature. Effect sizes for common risk variants are modest (mostly OR 1.2–2), consistent with genetics contributing to susceptibility rather than determining disease. The NOD2 compound heterozygous state is the outlier with high OR but low population frequency. Environmental triggers are cited from gene-environment interaction studies, IBD-specific environmental risk factor reviews, and mechanistic literature relevant to each gene's function.

Table 2. IBD-associated serologic markers, prevalence in Crohn's disease and ulcerative colitis, and environmental/microbial correlates

Marker	Prevalence (CD / UC)	Environmental/Microbial Correlates
ASCA	~40–70% CD / ~5–15% UC	Anti-Saccharomyces cerevisiae antibodies cross-reacting with Candida and related fungal antigens; (51,52,53) Western and ultra-processed dietary patterns altering microbiota; (23,62,63) antibiotic exposure disrupting commensal balance; (25,58) prenatal and early-life environmental exposures (24,74,75)
pANCA	~10–25% CD / ~50–80% UC	Neutrophil-directed antibodies documented in IBD serologic-marker literature; (52,53) antibiotic exposure altering gut barrier and microbiome; (25,58) environmental pollution and benzene exposure increasing oxidative and inflammatory burden; (13,22,66) prenatal maternal smoking and perinatal exposures (74,75)
Anti-OmpC	~40–55% CD / ~5–10% UC	Response to bacterial outer membrane porin epitopes documented in IBD serologic literature; (52,53) antibiotic-driven microbiome disruption; (25,58) prenatal and early-life environmental exposures (24,74,75)
Anti-CBir1, Anti-A4-Fla2, Anti-FlaX	~40–60% CD (each) / <10% UC	Antibody responses to bacterial flagellin variants documented in IBD serologic literature; (52,53) Western and ultra-processed dietary patterns altering microbiota composition toward flagellated species; (23,62,63) antibiotic exposure altering commensal-pathobiont balance; (25,58) prenatal and early-life environmental exposures (24,74,75)
Anti-I2	~30–55% CD / ~5–10% UC	Antibody response to Pseudomonas fluorescens I2-associated sequence documented in IBD serologic literature; (52,53) antibiotic exposure permitting pathobiont expansion; (25,58) Western and ultra-processed dietary patterns altering microbiota; (23,62,63) prenatal and early-life environmental exposures (24,74,75)
PAB (anti-GP2)	~30–40% CD / <5% UC	Antibodies to glycoprotein-2, a receptor for bacterial FimH on Peyer's patch M cells, documented in IBD serologic literature; (52,53) microbial adhesion and pathobiont expansion driven by antibiotic exposure and dysbiosis; (25,58) Western and ultra-processed dietary patterns altering microbiota; (23,62,63) prenatal and early-life environmental exposures (24,74,75)
ALCA / ACCA / AMCA	~15–30% CD / <5% UC	Anti-glycan antibodies to fungal cell-wall components (laminaribioside, chitobioside, mannobioside); (55,56) mold and mycotoxin exposure with dysregulated immunity; (72) antibiotic exposure disrupting bacterial-fungal balance (25,58)

Prevalence ranges compiled from IBD serologic-marker systematic reviews. Each marker targets a microbial or environmentally-derived antigen (or, in the case of PAB, a host receptor for bacterial adhesion), consistent with an antigen-driven rather than classically autoimmune pathogenesis. Individual prevalence estimates vary by cohort and assay across the cited literature.

Figure 1. Compounding prevalence of IBD in North American populations, 1955–2035



Data from Olmsted County, Minnesota (1955–2011), national US estimates (2023), and Canadian forecasting models (2035 projection, dashed line). *Crohn's disease only for 1976 data point. Sources: Sedlack 1972/1980, (34,35) Loftus 1998/2000, (38,39) Shivashankar 2017, (37) Lewis 2023, (36) Coward 2024. (41)

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