

IBD: Tackling the Growing Problem of Immune Diseases - Causative Mechanisms and Related Therapies

*Epidemiology of Inflammatory Bowel Disease and its relationship to
IBD therapy and clinical management*

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Note that Dr. Darren Seril (IBD Faculty RWJMS) is PI of the Phase 3 SIBERITE-2 Trial (Roche)

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Off label medications discussed: VSL#3 or Visbiome for ulcerative colitis

Objectives:

- Describe the current epidemiology of IBD
- Describe the overall genetic and environmental factors that cause IBD
- Describe steps to ameliorate IBD onset and disease activity
- Novel therapies for IBD: they come from genetics

Inflammatory Bowel Disease

**Ulcerative
Colitis**



**Crohn's
Disease**



Idiopathic disorders of chronic inflammation of two major phenotypes, ulcerative colitis and Crohn's disease due to dysregulated immunity to the intestinal tract and its contents involving the intestinal epithelium in ulcerative colitis and transmurally in Crohn's disease, with a predilection to develop in genetically susceptible individuals

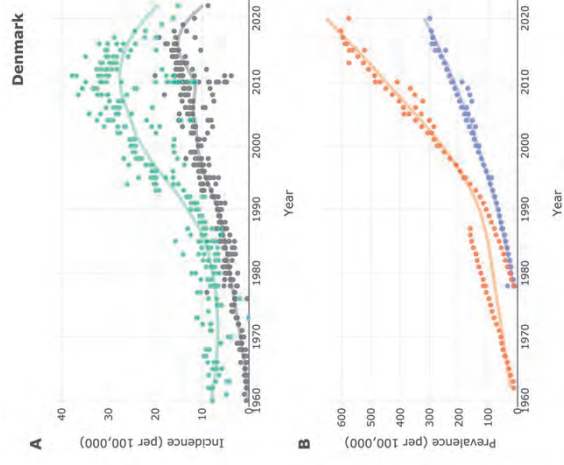
Rates of IBD Over Time: IBD Prevalence Still Increasing . . .

N. America and Western Europe:

- Incidence leveling off though increasing in older age groups
- *Compounding prevalence* due to an aging population – disease onset peaks in late 20s – but then have 50 more years with disease
- North-South gradient still observed

Asia and South America:

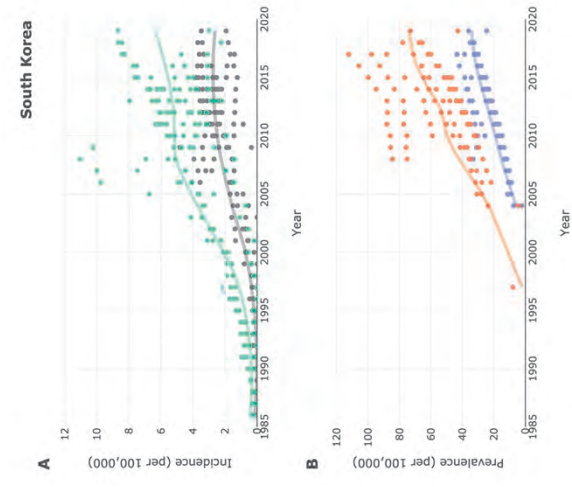
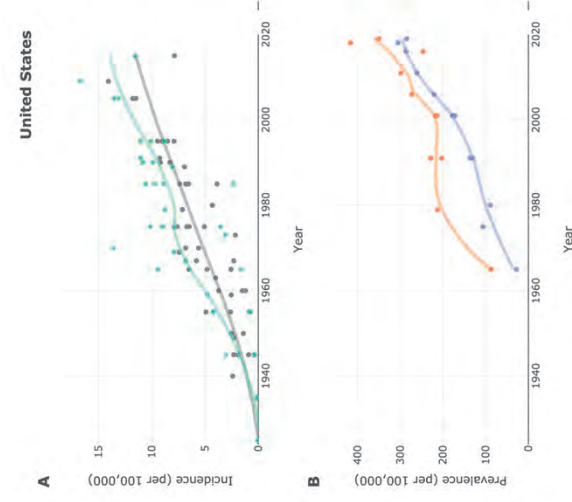
- Rapidly increasing incidence due to environmental factors & greater recognition
- East Asian population may have lower genetic risks, South Asian may be at greater risk



North South Gradient:

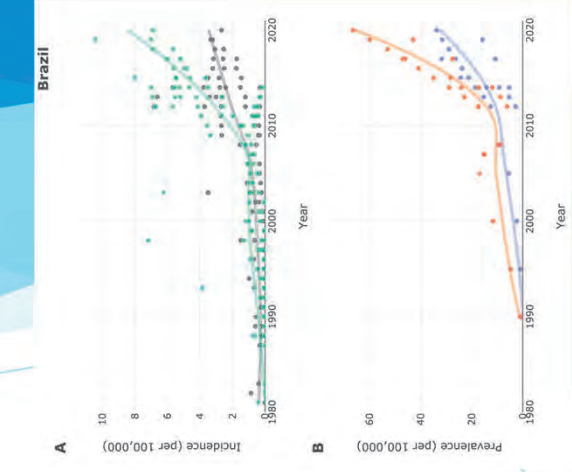
- Scandinavian countries highest incidence
- Incidence stabilizing, but prevalence increasing still
- Canada greater than US

US rates are similar to France



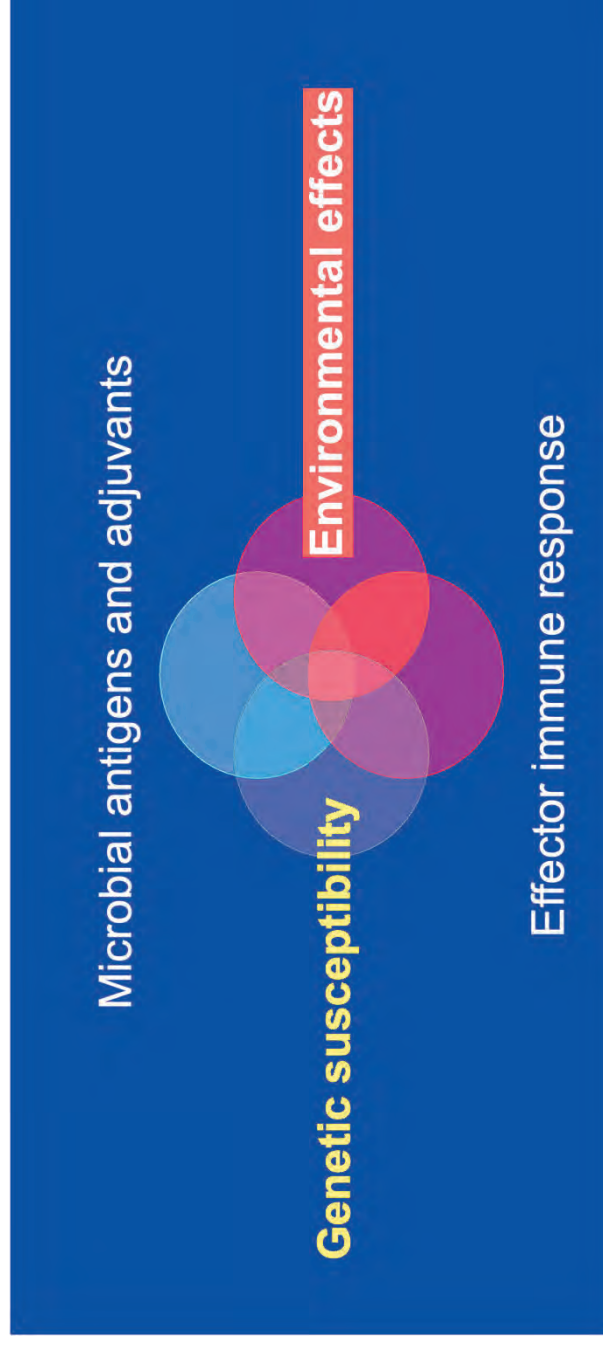
Rates in earlier developed Asian countries still much lower than US

- Environmental but also genetic factors (East Asians have much lower rate than whites or blacks in US. However, South Asians have a greater rate of UC than whites)



Brazil in early stage of increase

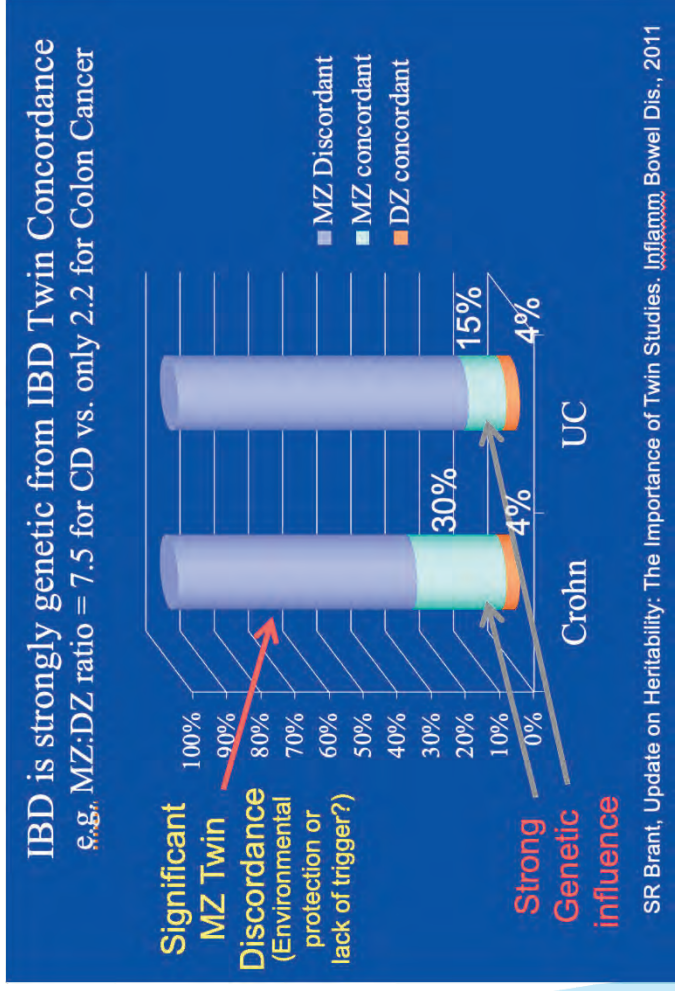
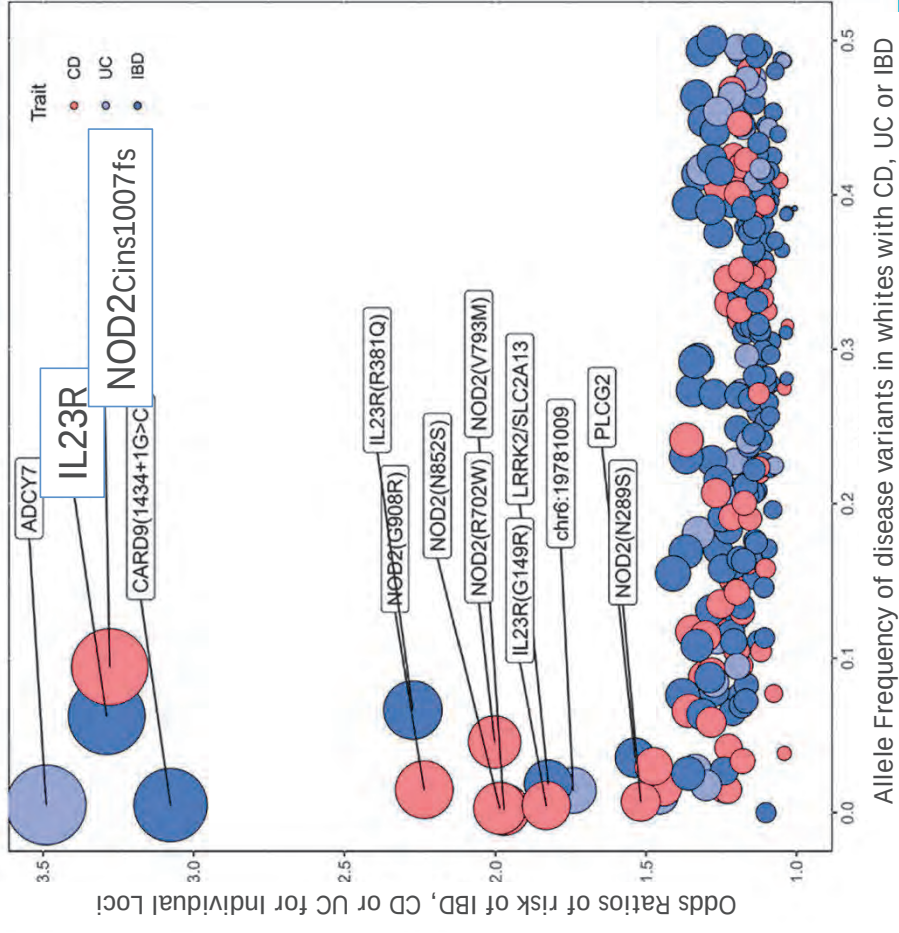
What are the mechanisms of IBD and how do they relate to therapy and prevention?



Genetic risk is the greatest IBD risk factor (for non-migrants) Over 300 IBD genetic risk loci identified in European studies

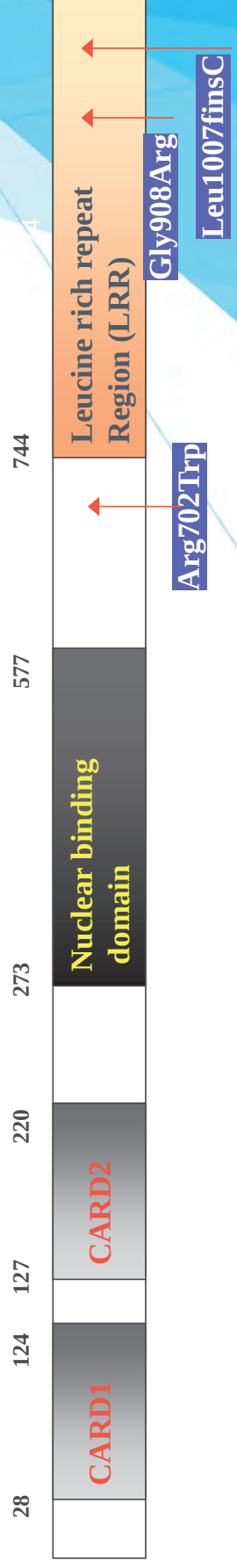
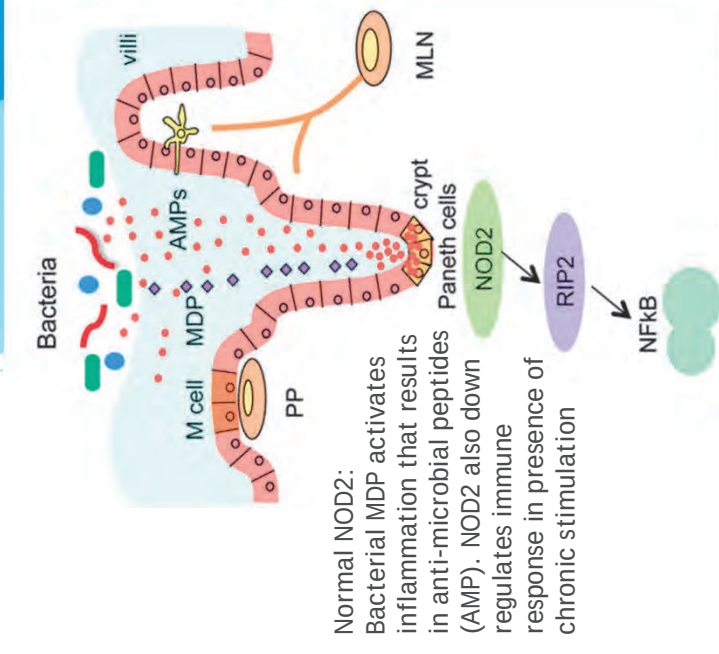
However:

- IBD may develop without identifiable increased genetic or known familial risks
- While 25% of IBD patients have IBD family history (10-fold risk), 75% do not



Mechanism of IBD elucidated from genetics: NOD2

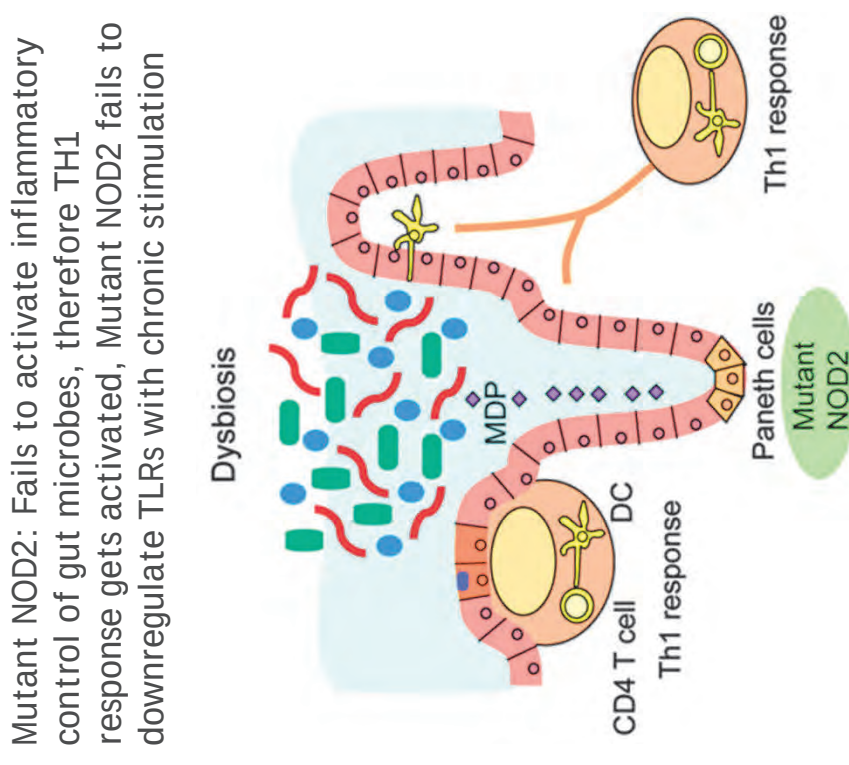
- ▶ NOD2 loss of function variants increase CD risk 3-fold in heterozygotes, 20-fold in homozygotes. They are associated with ileal disease location and penetrating and stricturing complications
- ▶ NOD2 binds bacterial cell-wall peptidoglycans, particularly MDP, and activates NFkB to promote an immune reaction to eliminate or control the bacteria, but downregulates immune response in chronic stimulation
- ▶ NOD2 is expressed in ileal Paneth cells in the ileal crypt.
 - ▶ Paneth cells protect the ileum from microbes. NOD2 mutation Paneth cells have defective bactericidal activity, reduced secretion of anti-microbial peptides (AMP) such as human defensins, natural antibiotics against gut microbes.



Mechanism of IBD elucidated from genetics: NOD2

- ▶ In NOD2 deficiency, bacterial killing ability is weakened. There is a hyperimmune response from other microbial protective pathways such as Toll-Like receptor activity
- ▶ The microbiome of the ileum in NOD2 deficiency is associated with
 - ▶ Increased load of commensal bacteria
 - ▶ Decrease ability to prevent colonization of pathogenic bacteria (including *Bacteroides vulgatus*),
 - ▶ Lower presence of protective firmicutes and SCFA producing species

- ▶ MECHANISM of CD RISK: A defect in overall control of intestinal microbes, leading to hyperactive immune system, elevated chronic stimulation of back-up immune defensive system, increased pathogenic microbes, decreased microbial diversity and presence of helpful microbes



Mutant NOD2: Fails to activate inflammatory control of gut microbes, therefore TH1 response gets activated, Mutant NOD2 fails to downregulate TLRs with chronic stimulation

IBD Therapy and NOD2: Concept that CD is microbial related to and depleting microbial exposure may help CD but not UC

- ▶ ANTIBIOTICS and EXCLUSIVE ENTERAL THERAPY REDUCE MICROBES OR PATHOGENIC MICROBES
 - ▶ Metronidazole is effective in preventing CD ileal recurrence post surgery (but much less than anti-TNF therapies) and a mild but significant improvement over placebo in disease activity assessments
 - ▶ Rifaximin has helped with CD – IBS symptoms and in maintaining remission in CD
 - ▶ EEN: used as first-line therapy in pediatric CD has been shown to decrease pathogenic *Bacteroidetes*, *Faecalibacterium prausnitzii*, and *Bifidobacterium* species, and enrich protective microbes.
- ▶ **However, NOD2 Mutations may make antibiotics less effective:**
 - ▶ Metronidazole and Ciprofloxacin can help heal perianal disease but are less effective in controlling perianal fistula in persons with NOD2 mutations
 - ▶ EEN is less effective in children with NOD2 mutations

Concept of healing dysbiosis epidemiologically related to IBD Microbiome related therapies:

- ▶ Fecal Microbial Transplant (FMT) for UC
 - ▶ In UC with up to 34% remission rates vs. 5 to 10% in 8-week placebo-controlled trials (meta-analyses OR 2.82, 95% CI 1.80-4.43; $p < 0.001$, $I^2 = 0\%$) [1]
 - ▶ However: need for continual therapy a challenge, safety and standardization concerns
 - ▶ Danger: prevents patients from getting more effective and safer therapies
- ▶ Conversely, in meta-analyses high dose probiotics (presently only VSL3-Visbiome has good efficacy, safer and can be given daily
 - ▶ 44% vs 25%, OR 2.4, $p = .0007$ at $3.6 \text{ CFU} \times 10^{12}$ (i.e. 4 packets DS/day)²
- ▶ Preferred: specific microbial therapies to correct the microbiome (in progress):
 - ▶ VE202, a live biotherapeutic product (LBP) composed of multiple Clostridia strains
 - ▶ SER-287 an investigational, oral microbiome therapeutic made of purified Firmicutes bacterial spores designed to treat mild-to-moderate ulcerative colitis
 - ▶ Challenges: difficult to get the strains to grow continuously in humans, inflammation is a barrier to engraftment
- ▶ Preclinical Progress: engineering into therapeutic bacterial strain *E Coli Nissle 1917 (EcN)* a bacterial operon *ttr* that allows EcN to use the inflammatory byproduct of inflammation, tetrathionate for sustenance

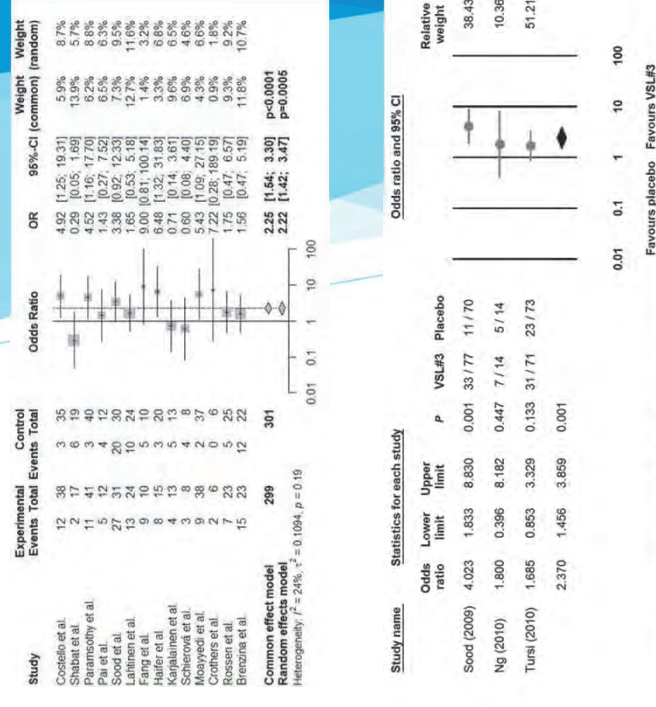


FIGURE 4. The efficacy of VSL#3 compared to placebo in achieving clinical remission.

¹ Gefen et al. Fecal microbiota transplantation for patients with ulcerative colitis: a systematic review and meta-analysis of randomized control trials. *Tech Coloproctol*. 2025; 29:103

² Mardini HE, Grigorian AY. Probiotic mix VSL#3 is effective adjunctive therapy for mild to moderately active UC: a meta-analysis. *Inflamm Bowel Dis* 2014;20:1562

Mechanism of IBD elucidated from genetics: IL23R

- R381Q reduced function variant **associated with 3-fold protection** from developing CD patients:
 - a natural experiment showing reducing IL23 activity lowers risk of getting IBD
- IL23 and the Th17 inflammation pathways recognized as a **major mechanism for chronic inflammation**

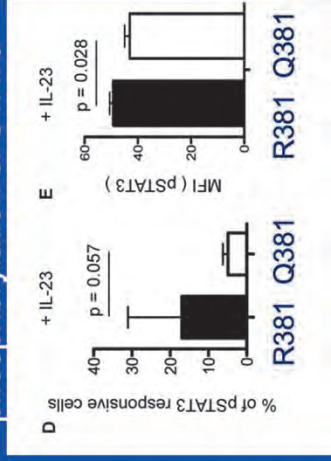
IL23 Receptor R381Q PROTECTIVE variant:

4% of whites with CD vs. 14% of healthy controls
3-fold protection from CD, 2-fold UC (IBD gene)

Wildtype variants is risk and has increased IL23R activity as compared to uncommon protective variant

Human, nucleotide	AGA	TCA	TTC	CGA	381	ACT	GG	g	t	a
Human, coding	Arg	Ser	Phe	Arg	Gln	Thr	Gly	-	-	-
Chimp	Arg	Ser	Leu	Arg	Arg	Thr	Gly	g	t	a
Rhesus	Arg	Ser	Leu	Arg	Arg	Thr	Gly	g	t	a
Mouse	Arg	Ser	Leu	Arg	Arg	Ile	Gly	g	t	a
Rat	Arg	Ser	Leu	Arg	Arg	Ile	Gly	g	t	a
Rabbit	Arg	Thr	Leu	Arg	Arg	Thr	Gly	g	t	a
Dog	Arg	Ser	Ile	Arg	Arg	Thr	Gly	g	t	a
Cow	Arg	Ser	Leu	Arg	Arg	Thr	Gly	g	t	a
Armadillo	Arg	Ala	Leu	Arg	Arg	Thr	Gly	g	t	a
Elephant	Arg	Ser	Val	Arg	Arg	Thr	Gly	g	t	a
Temrec	Lys	Ser	Leu	Arg	Arg	Thr	Gly	g	t	a
Opossum	Gln	Ser	Leu	Arg	Arg	Val	AG	g	t	a

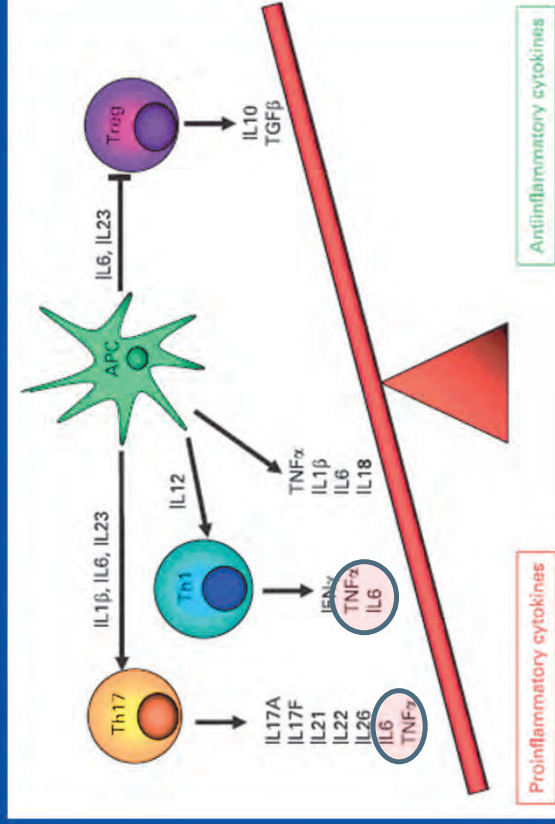
381Q associated with decreased phosphorylation of STAT3



Pidasheva et al., *PLoS One*, 2011

Inflammation in Crohn's disease:

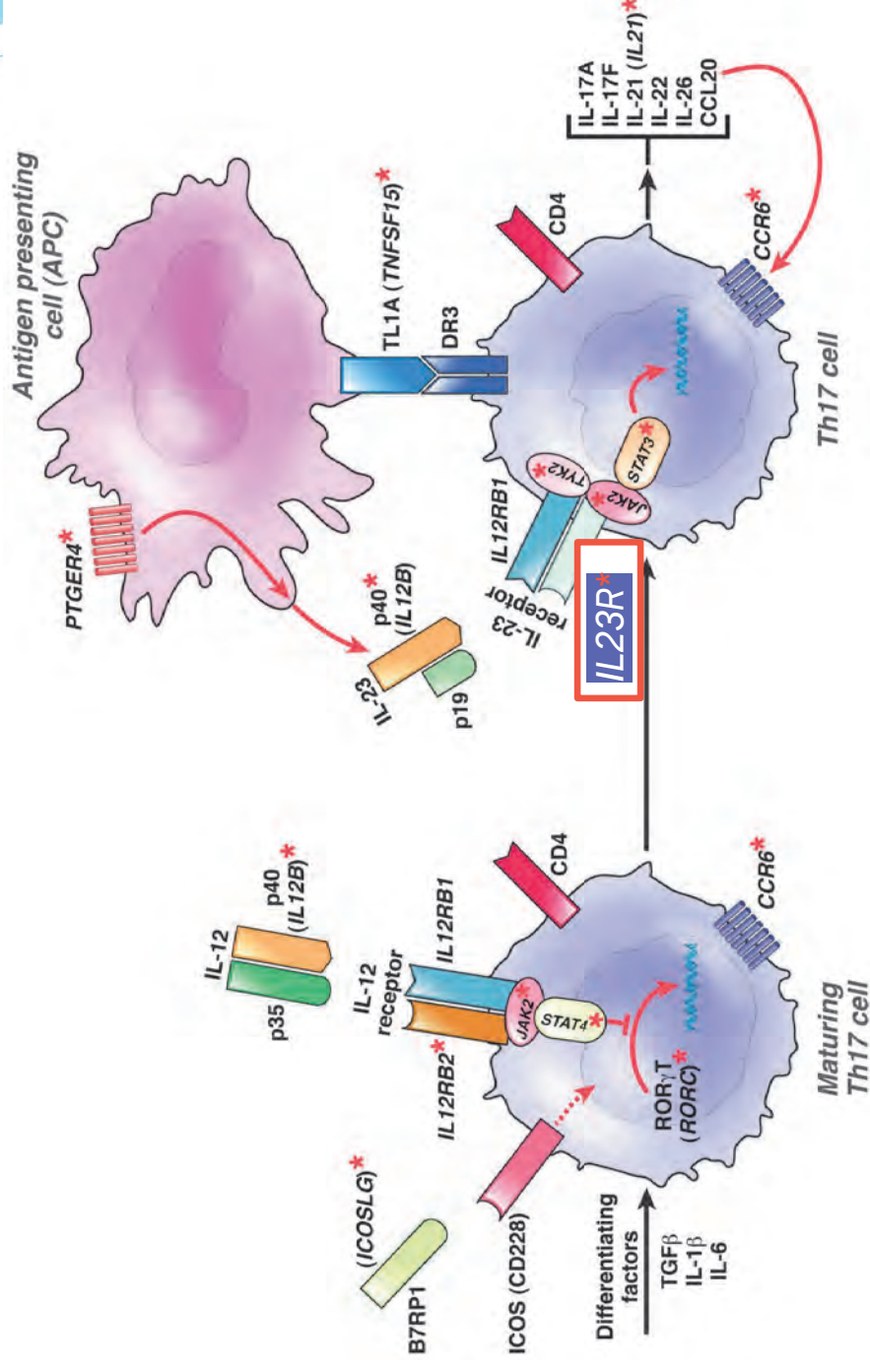
Up-regulation of pro-inflammatory **Th17 and Th1** cells and cytokine
Down-regulation of anti-inflammatory T-regulatory cells and cytokines



ation in IBD:

IL-17A
IL-17F
IL-21 (IL21)*
IL-22
IL-26
CCL20

astro, 2013

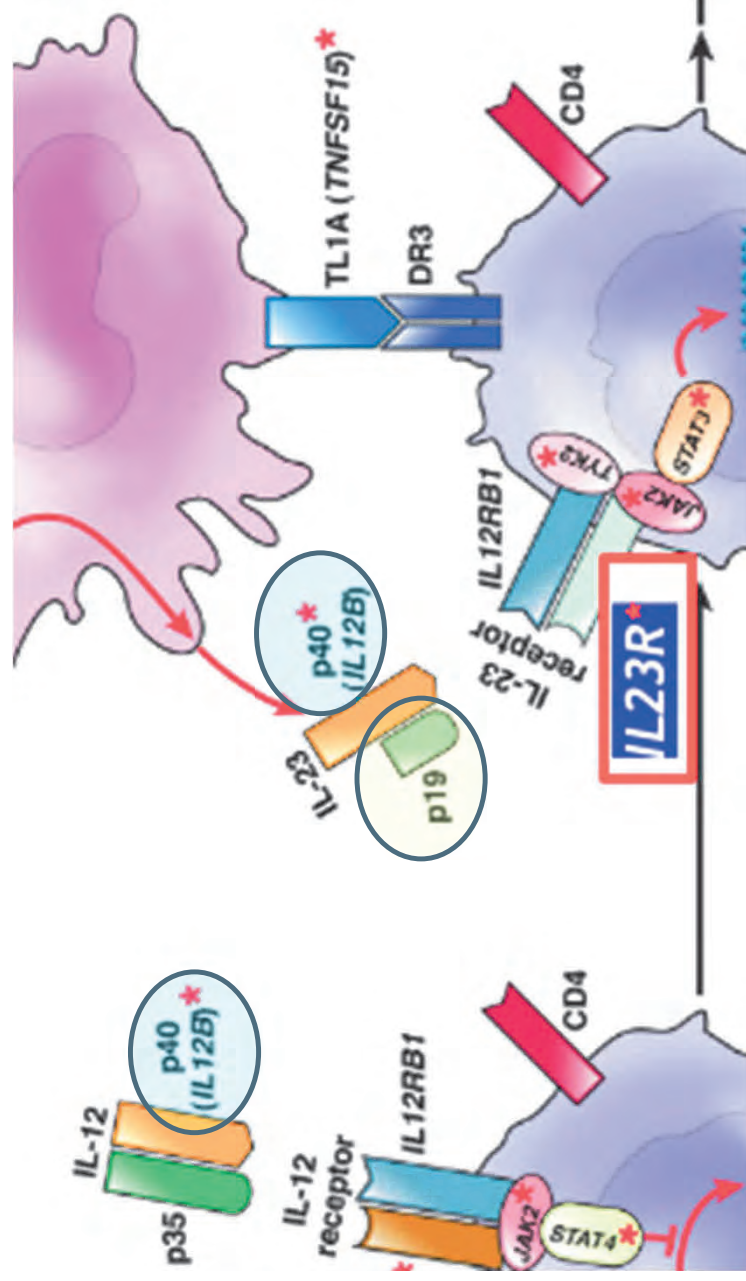


SR Brant, A

SR Brant, Am J Gastro, 2013

IL23R activated by IL23 cytokine, composed of two subunits, p40 (ustekinumab target) and p19 (risankizumab, mirikizumab, guselkumab target). p40 also is part of IL12, a TH1 cytokine

- IL23R genetic risk variants have not shown to affect outcomes for ustekinumab

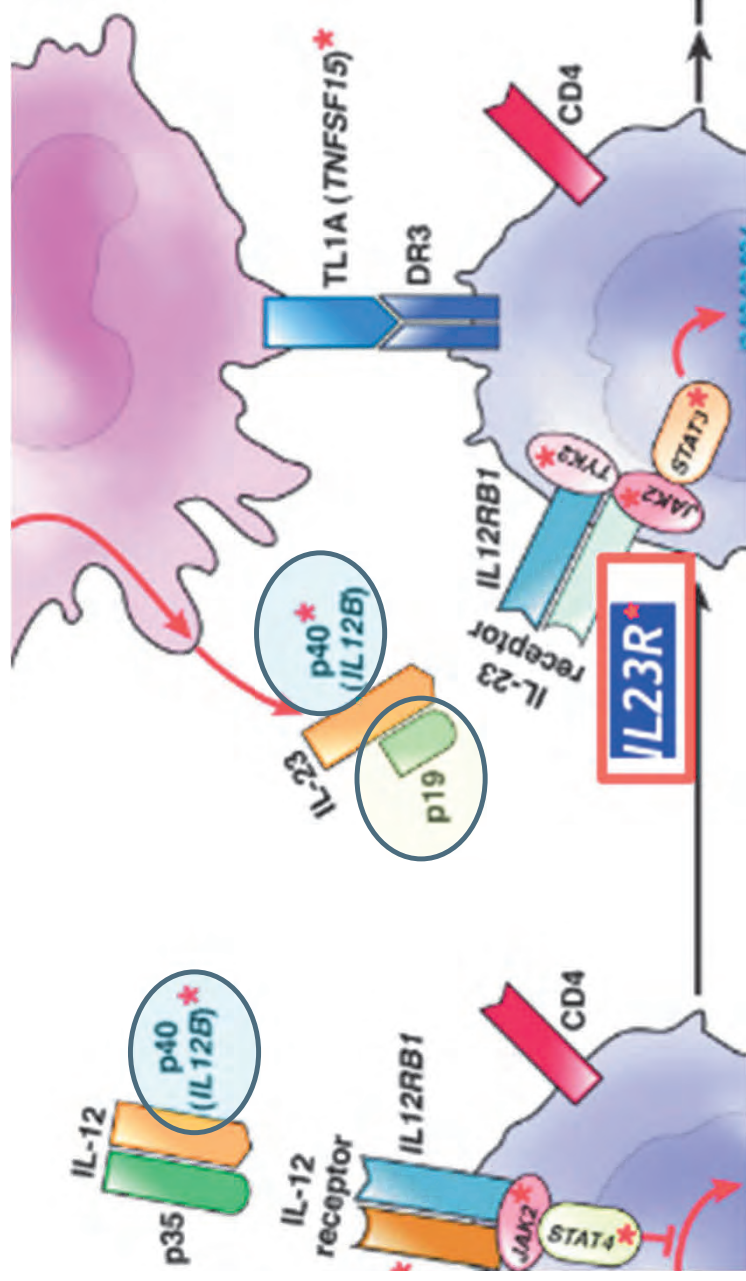


* Proteins within Established Associated Loci

SR Brant, *Am J Gastro*, 2013

So: what's more important for controlling IBD?

- blocking IL23 alone (**p19**) [mirikizumab, risankizumab or guselkumab – p19 specific]
- or blocking both IL12 and IL23 (**p40**) [Ustekinumab – p40 specific]



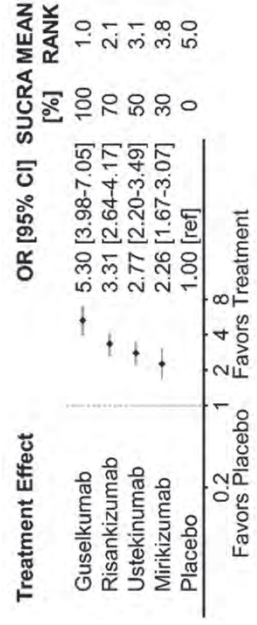
* Proteins within Established Associated Loci

SR Brant, Am J Gastro, 2013

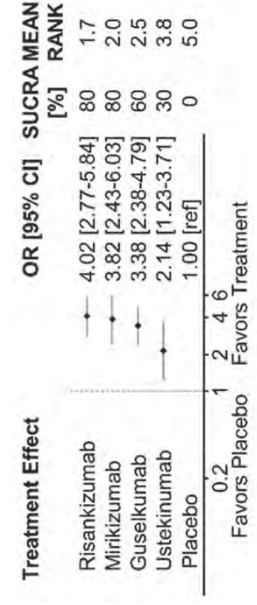
Advantages of IL23 specific anti-p19 therapy vs. IL23 plus IL12 anti-p40 specific therapy (ustekinumab)

- IL23 is more important for ongoing chronic inflammation in IBD than IL12
- The newer p19 – IL23 specific therapies inhibit IL23 to a greater extent than Ustekinumab
 - Comparison studies show greater effectiveness in meta-analyses (and in selected head-to-head analyses), but not by all that much!

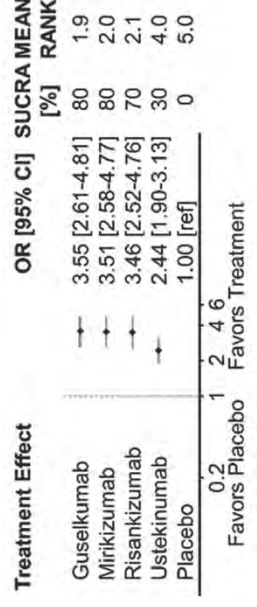
Clinical Response (Induction)



Endoscopic Response (Induction)

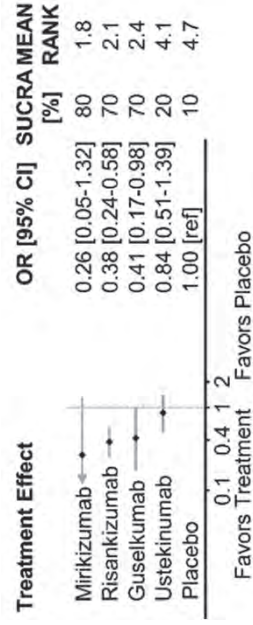


Clinical Remission (Maintenance)

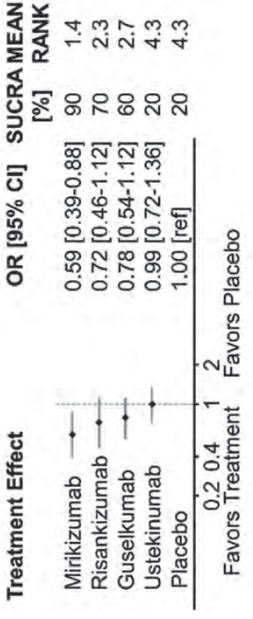


- IL23 specific inhibition has a trend to lower *serious adverse events* than combined IL23 – IL12 inhibition in large part due to (1) greater effectiveness (most events related to CD complications) and (2) IL12 inhibition *theoretically* has a greater risk for acute infections
- However, infections vs. placebo similar for all treatments, and these agents have the lowest infection risk of IBD immunosuppressives

Serious Adverse Events - Induction



Serious Adverse Events - Maintenance



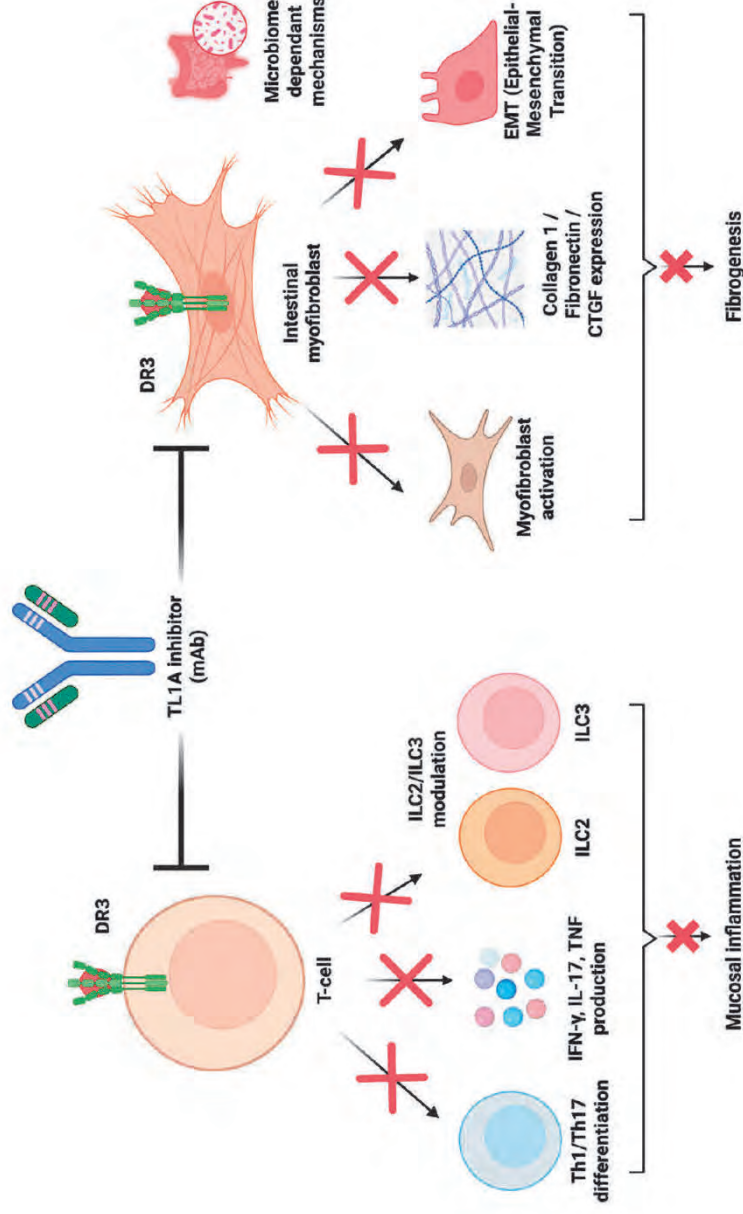
*Kaneke and Sakuraba, Efficacy and safety of IL-23p19 and IL-12/23p40 inhibitors in moderate-to-severe Crohn's disease. *Annals of Medicine*, 2025

IL23 therapy may show greater effectiveness, but can it be given post-ustekinumab failure?

- ▶ Multiple studies including “real-world” studies show IL23 specific therapies are effective after IL12-23 (ustekinumab) failure (both primary and secondary)
- ▶ Choosing an IL23-specific inhibitor *especially* makes sense in those who initially had a satisfactory response to Ustekinumab but subsequently had a loss of response (LOR)
 - ▶ Makes sense as the Ustekinumab initial response was most likely from IL23 inhibition!
 - ▶ *Patients who had endoscopic remission on ustekinumab but than had LOR *showed 3.8-fold greater likelihood to achieve* endoscopic response when given risankisumab as compared to those who has no remission from ustekinumab
- ▶ BUT BEWARE:
 - There are no studies comparing initial dosage of higher frequency ustekinumab vs. p19-IL23 specific therapies
 - A search provided no studies of Ustekinumab after IL23 failure
 - There is significant heterogeneity among studies, some biases and uncertainty in measurements and initial head-to-head studies were from Pharma controlled
 - Cost of Ustekinumab (brand and biosimilars) are significantly lower although programs can be helpful though primarily for patients who are not on Medicare or Medicaid

TL1A: target for inflammation *and* fibrosis via DR3 (death domain receptor 3)

promising for the 1/3rd of CD patients with a fibrostenotic phenotype who are generally non-responsive to present medical therapies and major indication for CD surgery



*Quaishi et al., *Inflamm Bowel Dis*, 2026

Effect on Th17 cell activation

- ▶ Effect TH17 differentiation
- ▶ IFN γ , IL17, TNF α ,
- ▶ Innate lymphoid cells (ILC2, ILC3)

Effect on Intestinal myofibroblasts (via TGF β / SMAD3)

- ▶ Myofibroblast activation
- ▶ Collagen1/ fibronectin
- ▶ Epithelial-Mesenchymal Transition

TL1A transgenic mice

- ▶ Develop fibrosis but not in germ free conditions, suggesting fibrosis is microbial related, replicating Crohn's microbial driven fibrosis

Initial trials of anti-TL1A biologics

- ▶ TL1A inhibitor therapy suppresses TH1 and TH17 driven fibrosis gene expression signatures

Furthermore: *TNFSF15* risk polymorphisms show higher rates of fibrostenotic complications and CD stenosis surgeries

Promise from initial anti-TL1A biologics UC and CD trials

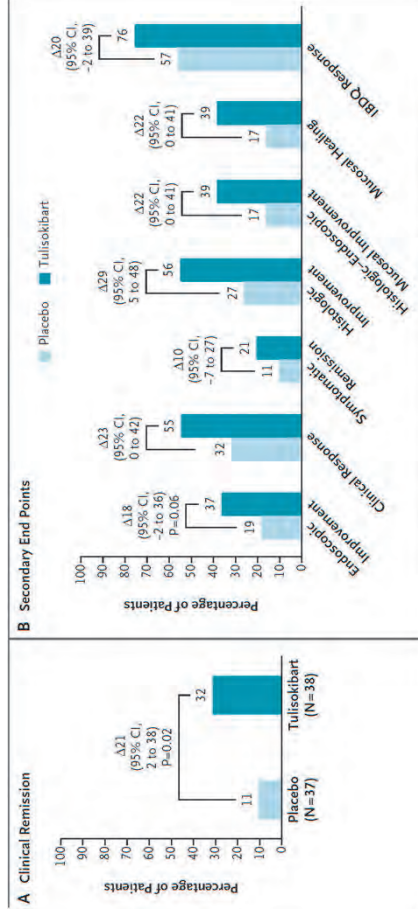
- ▶ **Tulisokibart (MK-7240 humanized IgG1 κ monoclonal antibody [Merck])**
 - ▶ ARTEMIS-UC Phase 2, 135 adults (steroid dependent or failed conventional therapy)
 - ▶ Week 12 clinical remission: 26% treatment arm, 1% placebo; symptomatic remission 47% vs. 13% placebo ($p < 0.001$)
 - ▶ APOLLO CD Phase 2a [open label, 55 adults] moderate to severe CD, SES-CD score > 6 or > 4 ileal disease
 - ▶ Endoscopic Response 50% SES-CD achieved in 26% vs. 14% historical placebo estimate $P = 0.002$
 - ▶ Clinical remission in 49% vs. 16% historical placebo estimate ($P < 0.001$)
- ▶ **Afimkibart (RO7790121 fully human IgG1 monoclonal antibody [Roche/Genentech])**
 - ▶ TUSCANY UC phase 2b, 246 adults (Mayo score 6 - 12); 3 doses: 50 mg, 150 mg, 450 mg
 - ▶ Week 14 clinical remission (tMS ≤ 2 , no subscore > 1) not statistically significant for any doses vs placebo (26%, 23%, 24% vs 12%). Concern with high placebo rate (expected 6%). By modified Mayo score (FDA preferred) 30%, 35%, 32% vs. 12%.
 - ▶ Week 56 Endoscopic improvement 38%, 39%, 26% vs. 5% (an expected rate of endoscopic improvement seen in Phase 2A)
- ▶ **Duvakitug (Teva/Sanofi) human IgG1 monoclonal antibody blocking TL1A-DR3 binding**
 - ▶ RELIEVE UCCD 14-week phase 2b randomized, double-blind, dose-ranging basket study (UC 137, CD 138)
 - ▶ UC: clinical remission (MMS ≤ 2) at week 14: 36% (450mg) and 48% (900mg) vs 20% placebo.
 - ▶ CD: ($\geq 50\%$ reduction in SES-CD) at week 14 achieved by 26% (450mg) and 48% (900mg) vs 13% placebo
 - ▶ Bayesian analysis demonstrated $> 90\%$ posterior probability of treatment effectiveness

From summary provided by Quaishi et al., Targeting the TL1A pathway in inflammatory bowel disease. Inflamm Bowel Dis, 2026

Results by stratification of those with hypothesized greater Likelihood of Response based on genetic risk (ARTEMIS-UC)

High Likelihood Analysis

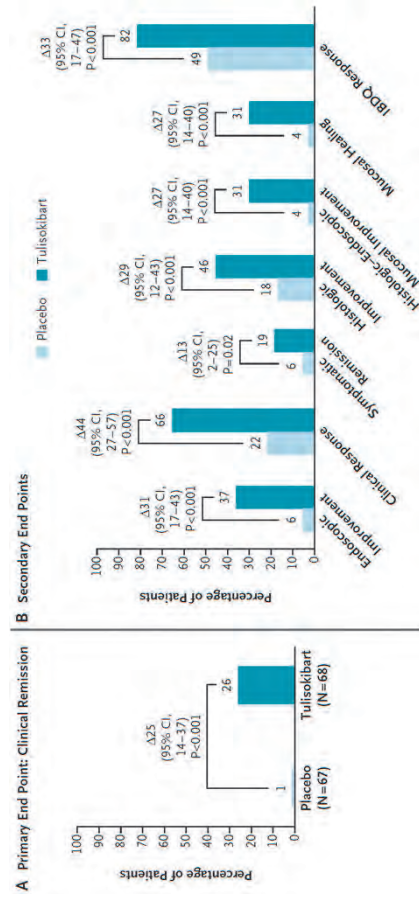
n=32 from Cohort 1;
n=43 Cohort 2 subjects
(recruited with a high
likelihood genetic score)



In “High Likelihood” Study,
primary endpoint of Clinical
Remission increased in treatment
relative to non-selected subjects
but so did placebo!

Main analysis: Cohort 1

135 subjects independent
of genetic likelihood
status



Multiple anti-TL1A trials now in progress:

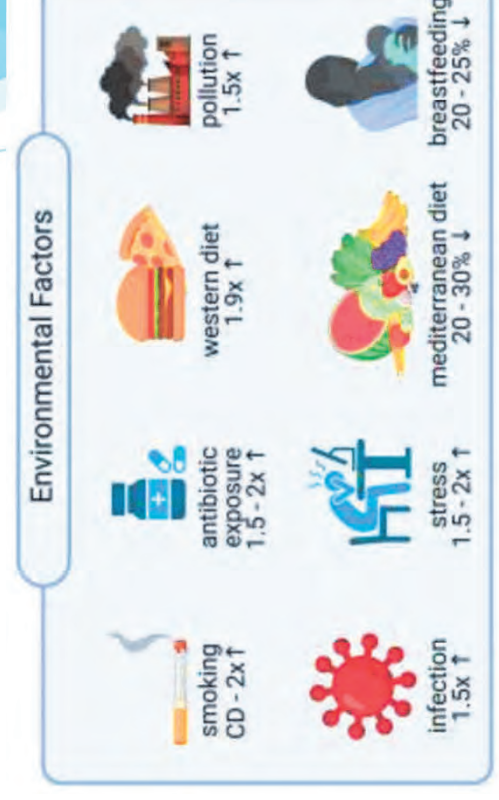
32/34

fibrosis

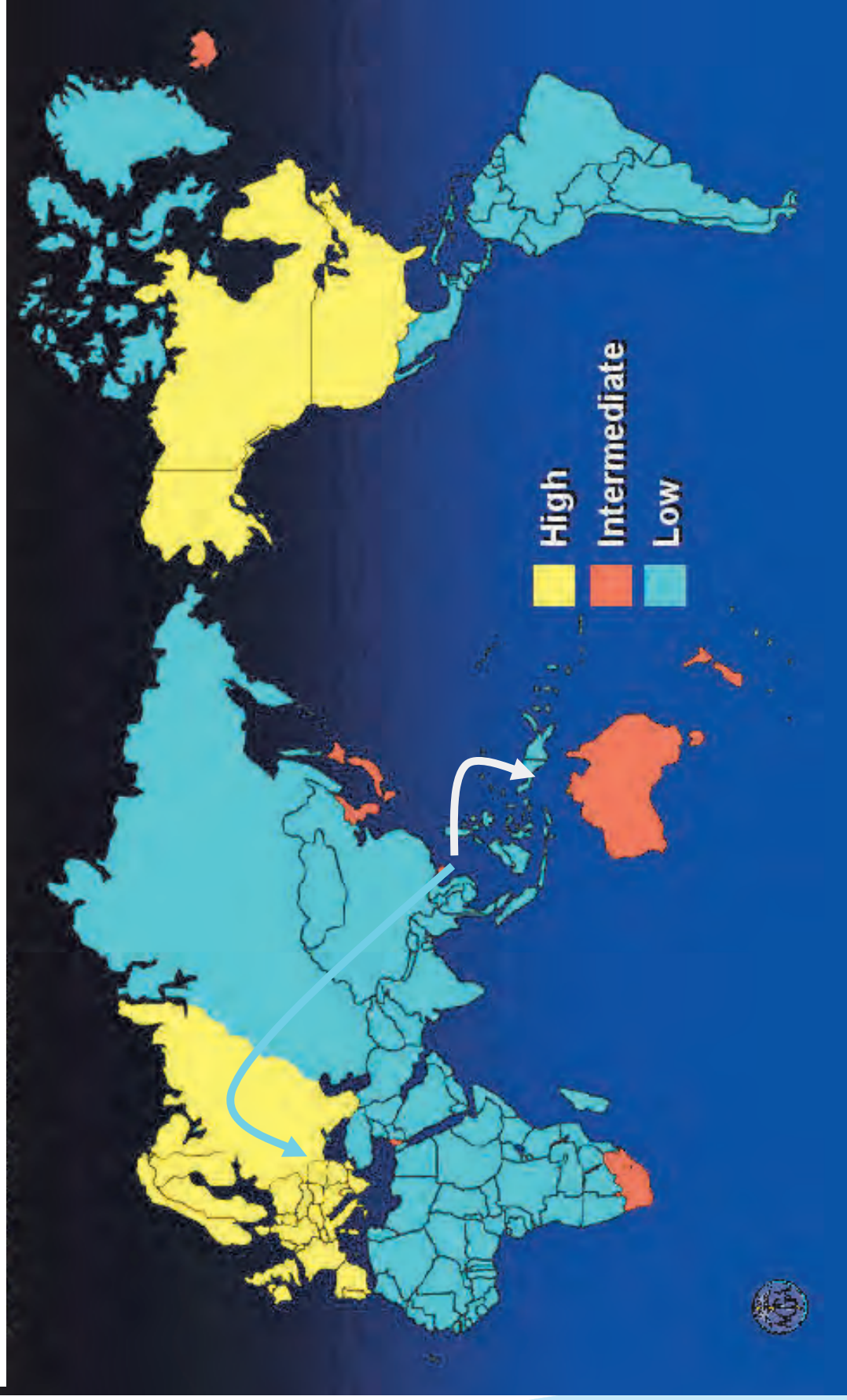
	Preclinical	Phase 1	Phase 2	Phase 3
First-generation anti-TL1A mAb				UC and Crohn's
				UC and Crohn's
				UC and Crohn's
Long-acting anti-TL1A				Crohn's
				UC
				UC
				UC
				UC
Bispecific antibody				TL1A x p40
				TL1A x IL-23p19
				TL1A x IL-23
				TL1A x alpha4-beta7
				TL1A x IL-23p19
				TL1A x IL-23p19
				TL1A x IL-23p19
				TL1A x IL-23p19
				TL1A x IL-23p19
				TL1A x IL-23p19
Oral TL1A modality				
DR3 receptor antagonist				

Other epidemiological factors and IBD:

- Westernization as a risk



Migration to Industrialized Countries or to Tropical Countries Changes IBD Prevalence



Migration effect on UC: Diet or “Hygeine” related (or both)?
 Risk 3x greater in South Asians in UK than India; Risk 2x *lower* in Singapore
 Risk much lower in ethnic Chinese in Singapore (Genetic factors likely at play)

Location	Ethnicity	Prevalence: cases/100,000	
		UC	Crohn's
England	European	128	76
	South Asian	172	33
Northern India	South Asian	43	
Singapore	South Asian	24	8
	Chinese	8	1

Yang, Inflamm Bowel Dis, 2001
 Lee, J Gastroenterol Hepatol, 2000

Environmental risk: the Hygiene Hypothesis

- ▶ Hygiene Effect?
 - ▶ IBD most rare in developing countries, particularly with high risk of varied and repeated infectious diseases in childhood
 - ▶ Hypothesis: our ancestral immune system learns tolerance to a healthy microbiome)
 - ▶ Crohns disease lower in US Veterans served in Vietnam vs. Non-deployed Veterans ¹
 - ▶ Helminths can protect from chronic inflammation in animal models ²
 - ▶ IBD risk lower in children growing up with dogs (greater with birds) ³
- ▶ IBD RECOMMENDATIONS? Consider getting owning a dog to decrease IBD risk in offspring of parents with IBD

¹Delco and Sonnenberg, *Am J Gastro* 1998

²Weinstock & Elliot, *Inflamm Bowel Dis.*, 2008

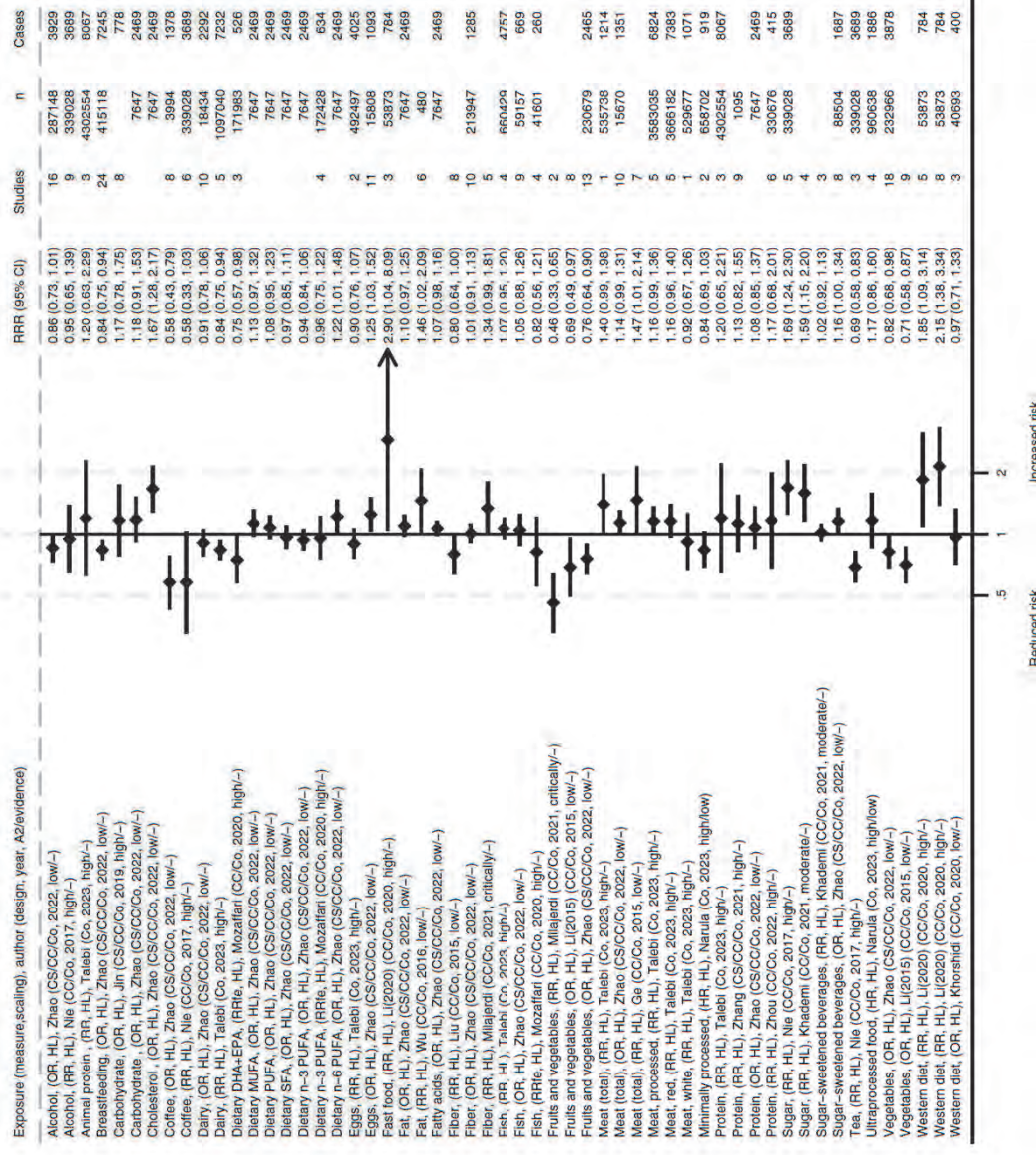
³Xue et al., *Clin Gastroenterol Hepatol* 2024

Meta-analyses of Dietary Exposures and UC Risk

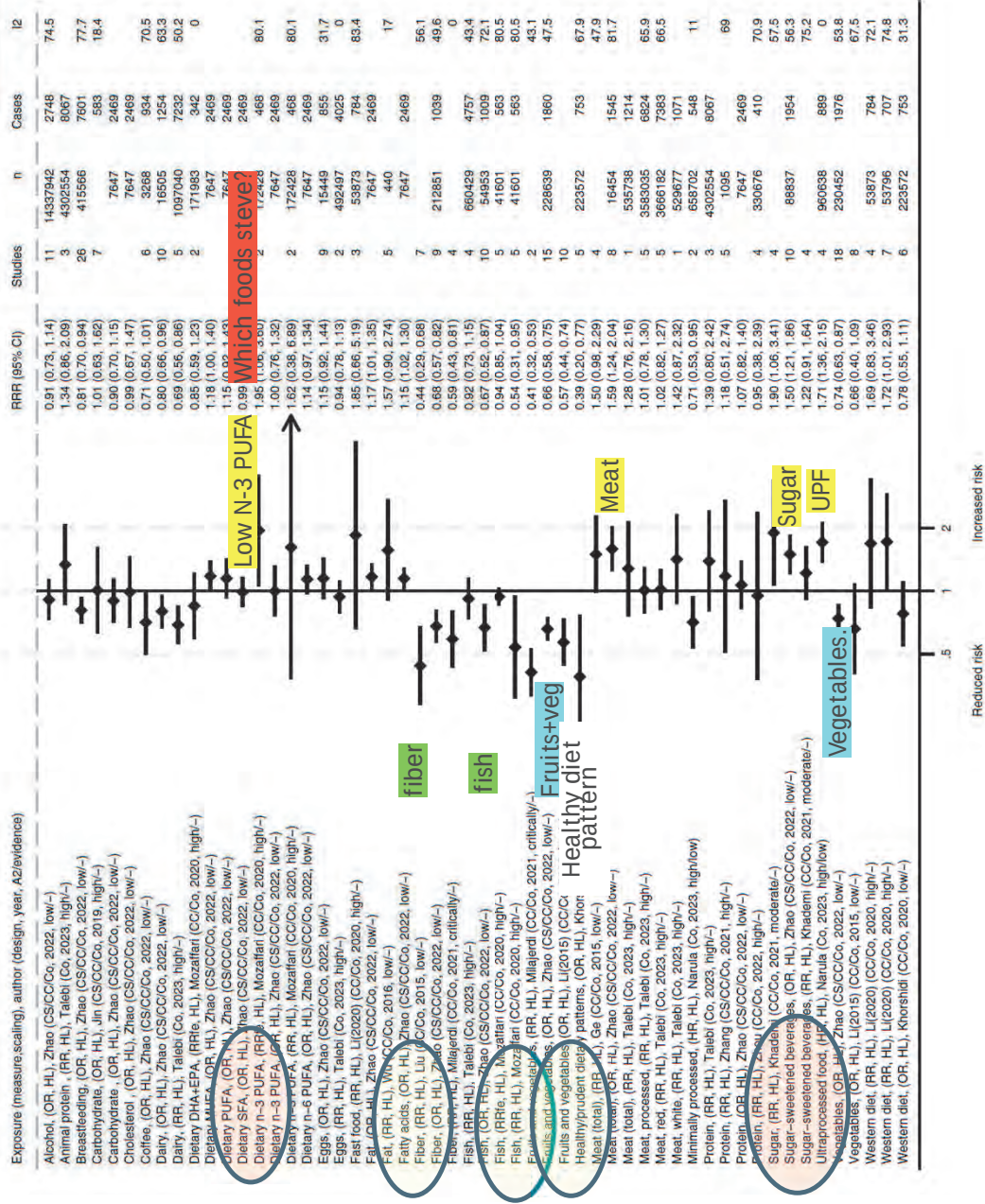
Sugar intake and Western Diet

most consistent risks

Coffee may be beneficial



Meta-analysis of Dietary Exposures and CD Risk



Sugar intake again risks

N-3 Polyunsaturated Fatty Acids (PUFA) lowers risk (anti-inflammatory and c/w animal research)

Western Diet uncertain

Fruits, vegetables and fiber lower risk but is this bias?

Dietary emulsifiers* and ultra-processed foods (UPF):

- Carrageenan
- Carboxymethylcellulose (CMC)
- Polysorbate-80 (P80)
- Xanthan Gum

- *associated with Crohn's disease and eliminating may be beneficial*

- Emulsifiers are detergents to allows thorough and stable mixing of oil-based (non-polar) and water-based (polar) food ingredients, commonly added to baked goods, ice cream and UPF.
- UPFs in meta-analysis associated with CD, not UC (HR 1.70, 95% CI 1.23 – 2.35)
- Emulsifier risk of colitis and flares in animal studies include
 - Disruption of mucus barrier
 - Increased bowel wall permeability (a pre-diagnostic CD risk demonstrated in the GEM study of siblings of CD patients monitored for development of CD)
 - Altered intestinal microbiome

▪ **What about human studies?** Two studies (24 subjects and 60 subjects randomized to emulsifier restricted diets for 4 and 6 wks, respectively)

- No significant difference in outcomes of activity or markers of inflammation (e.g. calprotectin, CRP, etc.)
- However, in the 6 week study of 60 subjects, short-chain fatty-acid concentrations were lower in some emulsifier groups, and carrageenan increased transcellular intestinal permeability relative to baseline.
- Conclusion: needs further study, but epidemiologically, a diet lower in UPF and dietary emulsifiers that were common when IBD was rare in the US may be helpful for CD and probably can't hurt!

REVISE SLIDE:

IBD and Diet / Nutritional Therapies and Avoidance:

Rationale:

- Greater IBD incidence in higher latitudes (maximal in Scandinavia and Canada among white populations)
- Mediterranean populations at lower risk of IBD than other European populations.
- UPFs and dietary emulsifiers have shown association in some studies with CD risk

Vitamin D: prospective studies (including our own) found unrelated to IBD risk nor an effect of dietary additives on alterations and restrictions:

However, vitamin D (ergocalciferol) supplementation is associated with better disease control

- Mediterranean Diet: Supportive evidence epidemiologically and in unblinded studies
- Restriction of Dietary Emulsifier Trials: Supported in preliminary studies
- Obesity: May be associated with worse disease course, incidence association unclear
But, small studies of GLP-1 agonists are showing positive effects on improved disease control with lower than expected GI side effects including Crohn's disease

Obesity: although fat is proinflammatory, uncertain obesity is a risk for IBD (meta-analyses are conflicting). However, patients may have lower response to immunosuppressive therapy and worse disease course:

Analysis	Finding
Meta-analysis of anti-TNF studies	Obesity associated with increased odds of treatment failure
Ulcerative colitis	OR 1.41 (95% CI 1.01-1.98)
Crohn's disease	OR 1.10 (95% CI 0.93-1.30), not statistically significant
Fixed-dose anti-TNF	OR 1.12 (95% CI 1.03-1.22)
Weight-based anti-TNF	OR 1.45 (95% CI 1.01-2.09)

Take home points:



