

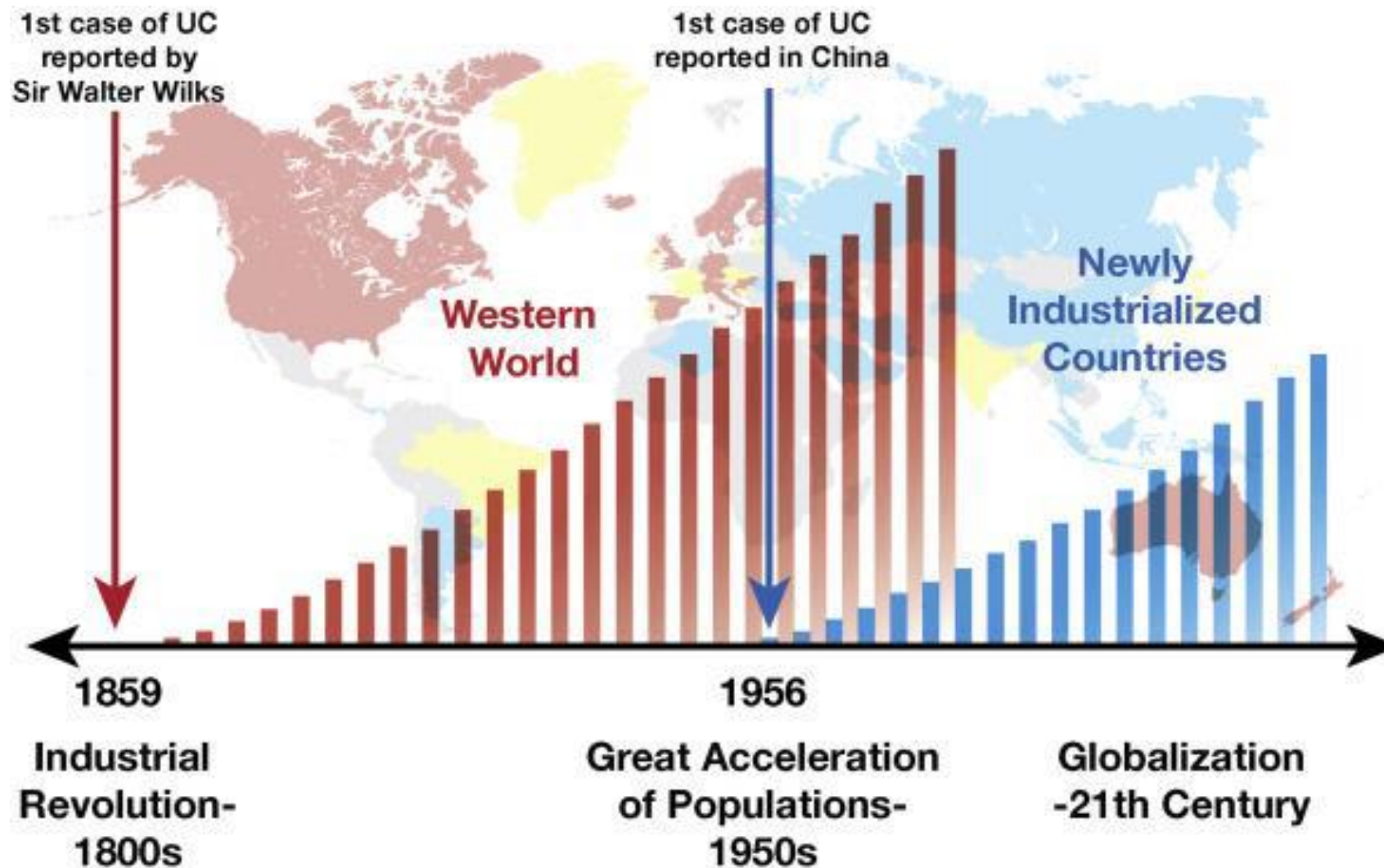
The microbiome in inflammatory bowel disease



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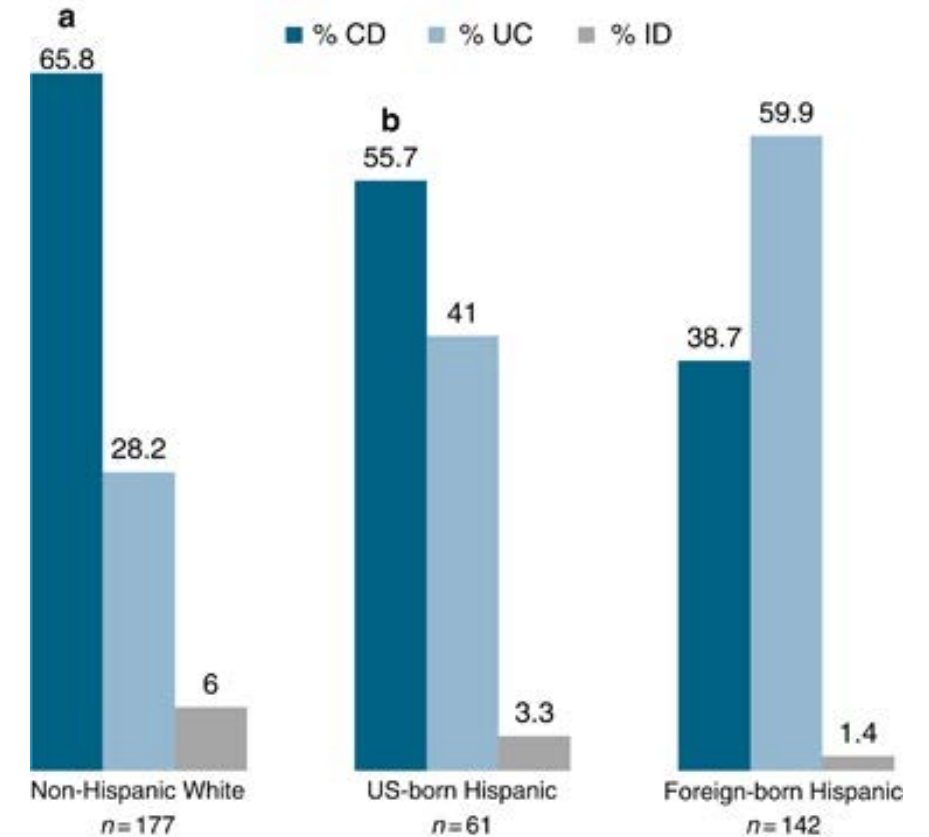
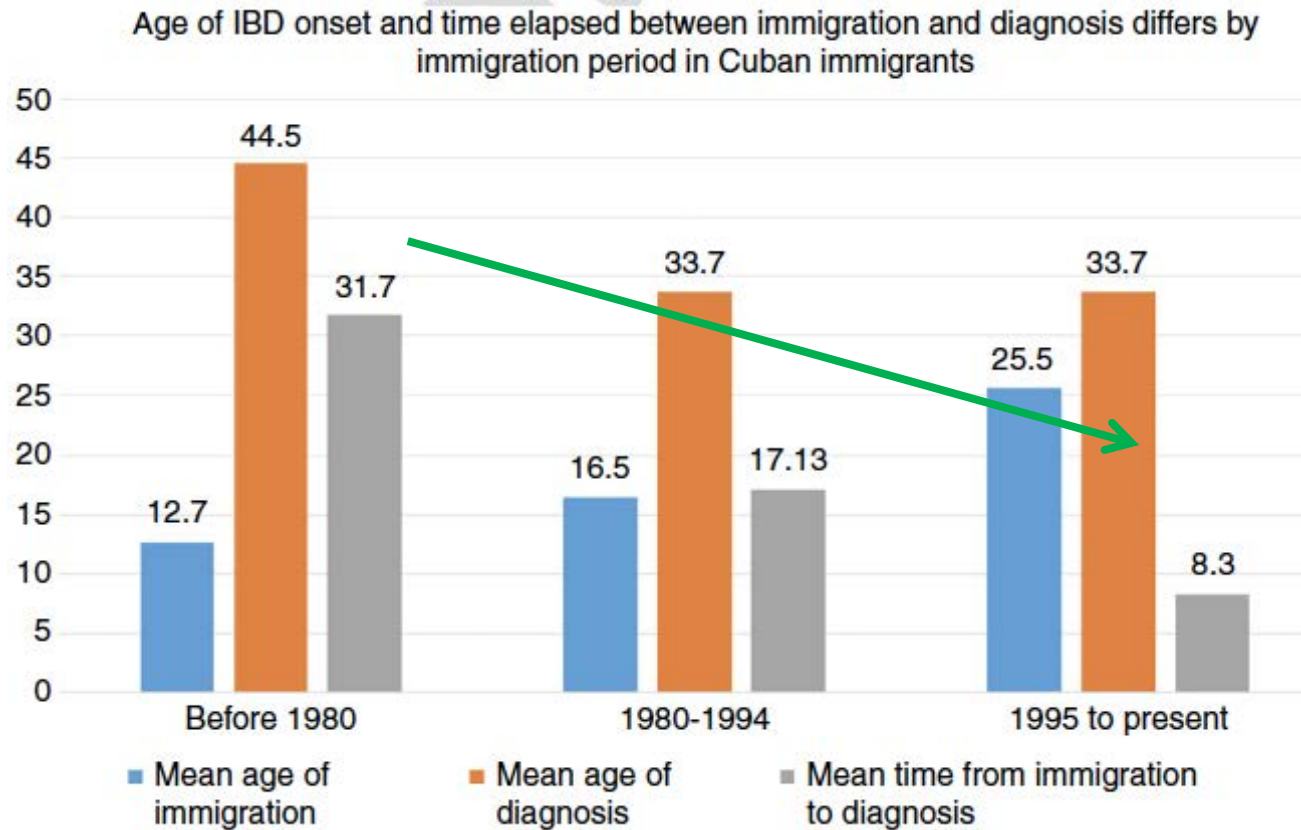
Objectives today

- ❑ Genetics vs environment: which one is more important?
- ❑ The role of the microbiome in IBD development
- ❑ Diet-microbiome relationships and their contribution to IBD risk
- ❑ What is the future of microbiome-based therapeutics in IBD



Kaplan et al. 2016

The environment plays a role in disease onset and disease phenotype among immigrant Hispanic patients with IBD



Damas, et al. APT. 2017, Damas O et al. AJG. 2013

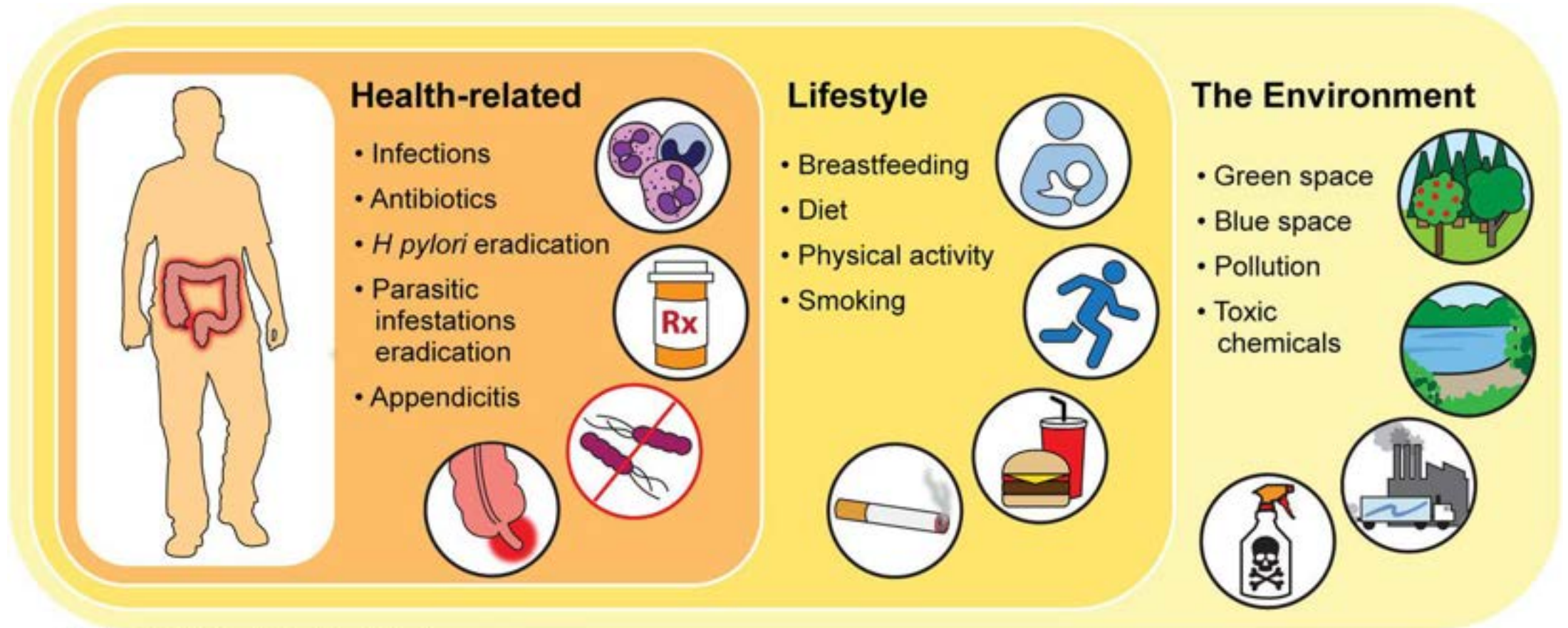
Hot off the press: Cumulative environment factors, more than genetic risk, impact age of IBD diagnosis

Ulcerative colitis	Non-Hispanic White (n=280)			Hispanic (n=265)		
	β	p-value	Standard Error	β	p-value	Standard Error
GRS	-2.87032	0.1712	2.093352	0.253158	0.9014	2.040721
AFR	-2.918479	0.5044	4.365642	0.684847	0.3253	0.694986
NAM	-14.9002	0.071	8.220544	-0.426184	0.425	0.533431
Weighted Environmental Score	-9.462907	<0.0001*	1.132007	-7.62588	<0.0001*	0.690408

- Environmental exposures influenced age of IBD diagnosis in both UC and CD and in both Hispanic and non-Hispanic individuals.
- Genetic predisposition influenced age of IBD diagnosis only in non-Hispanic individuals with IBD.

Crohn's disease	Non-Hispanic White (n=404)			Hispanic (n=402)		
	β	p-value	Standard Error	β	p-value	Standard Error
GRS	-3.025985	0.0242*	1.337178	-1.491706	0.2208	1.216512
AFR	-0.95961	0.7841	3.500131	-0.034395	0.939	0.449407
NAM	-6.240373	0.3366	6.486434	0.806365	0.1422	0.548392
Weighted Environmental Score	-7.169282	<0.0001*	1.065526	-9.569482	<0.0001*	0.948445

Environmental culprits implicated in IBD development



Preclinical stages and development of inflammatory bowel disease

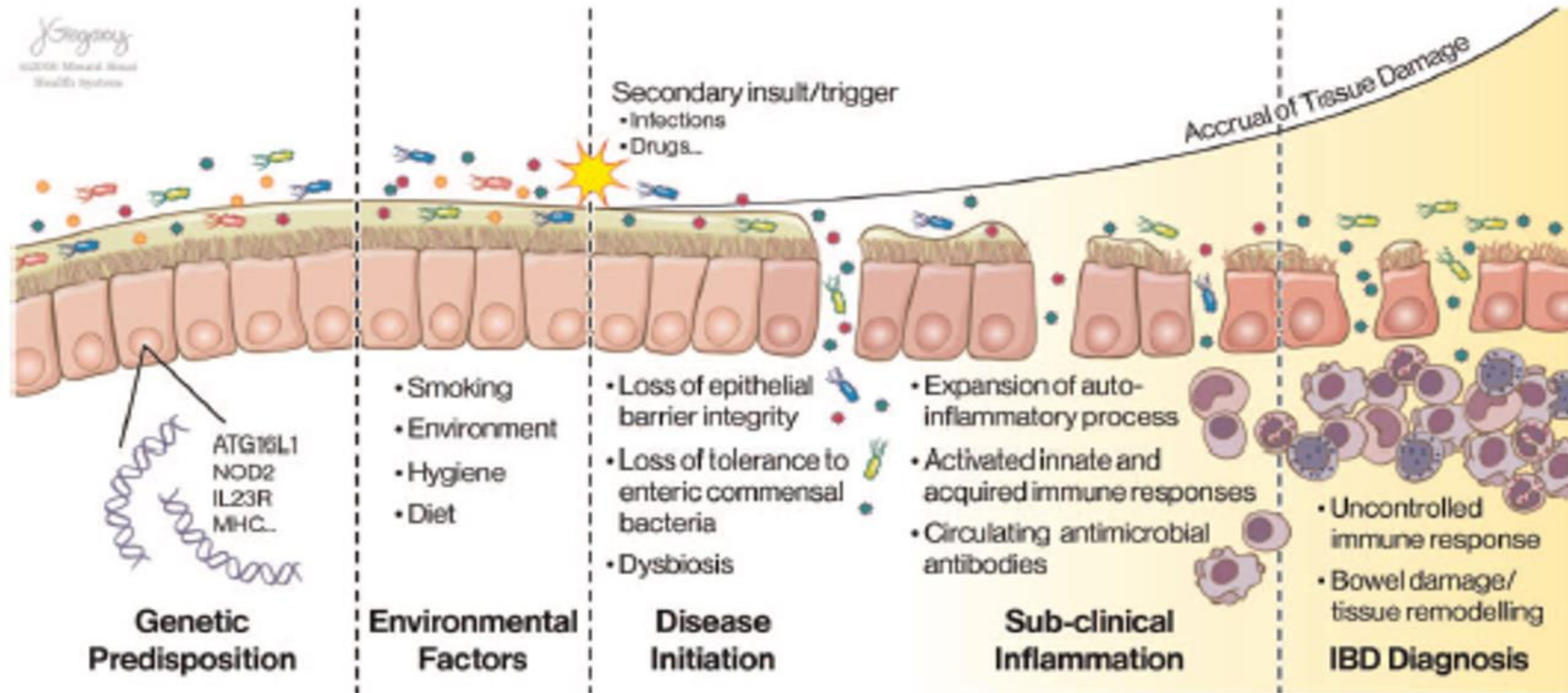
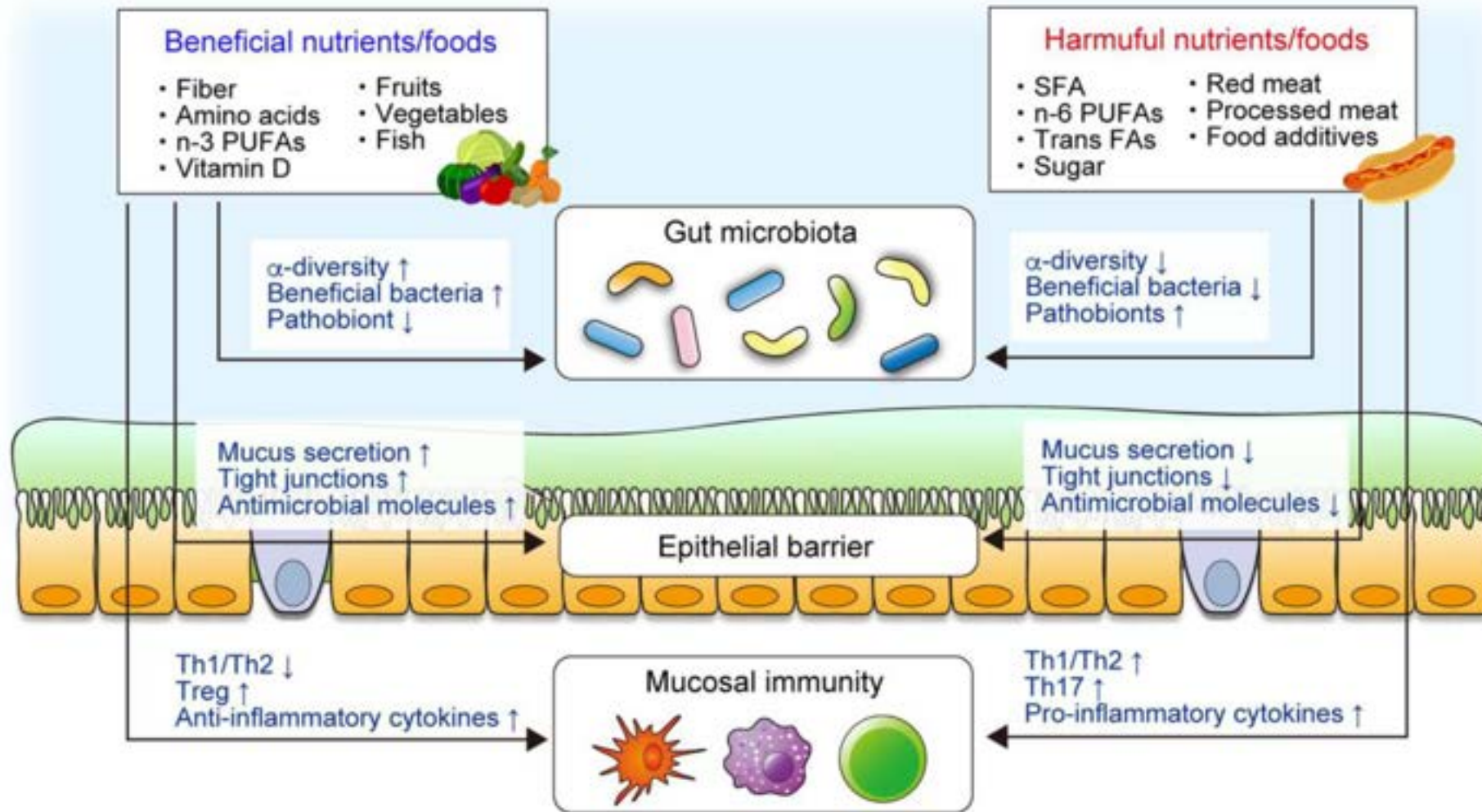


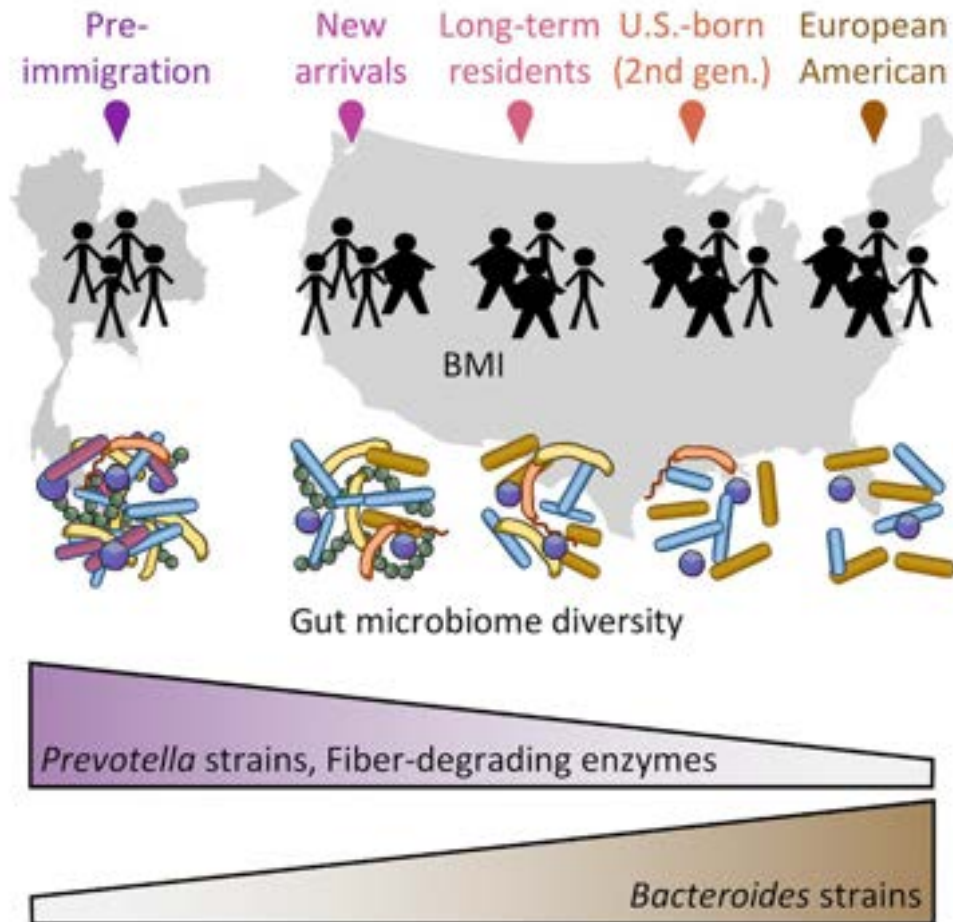
Figure 1 Proposed model of IBD pathogenesis and progression from preclinical to clinical disease.



Diet-Induced Microbial Changes in IBD



Thai immigrants change their microbiome after living in US

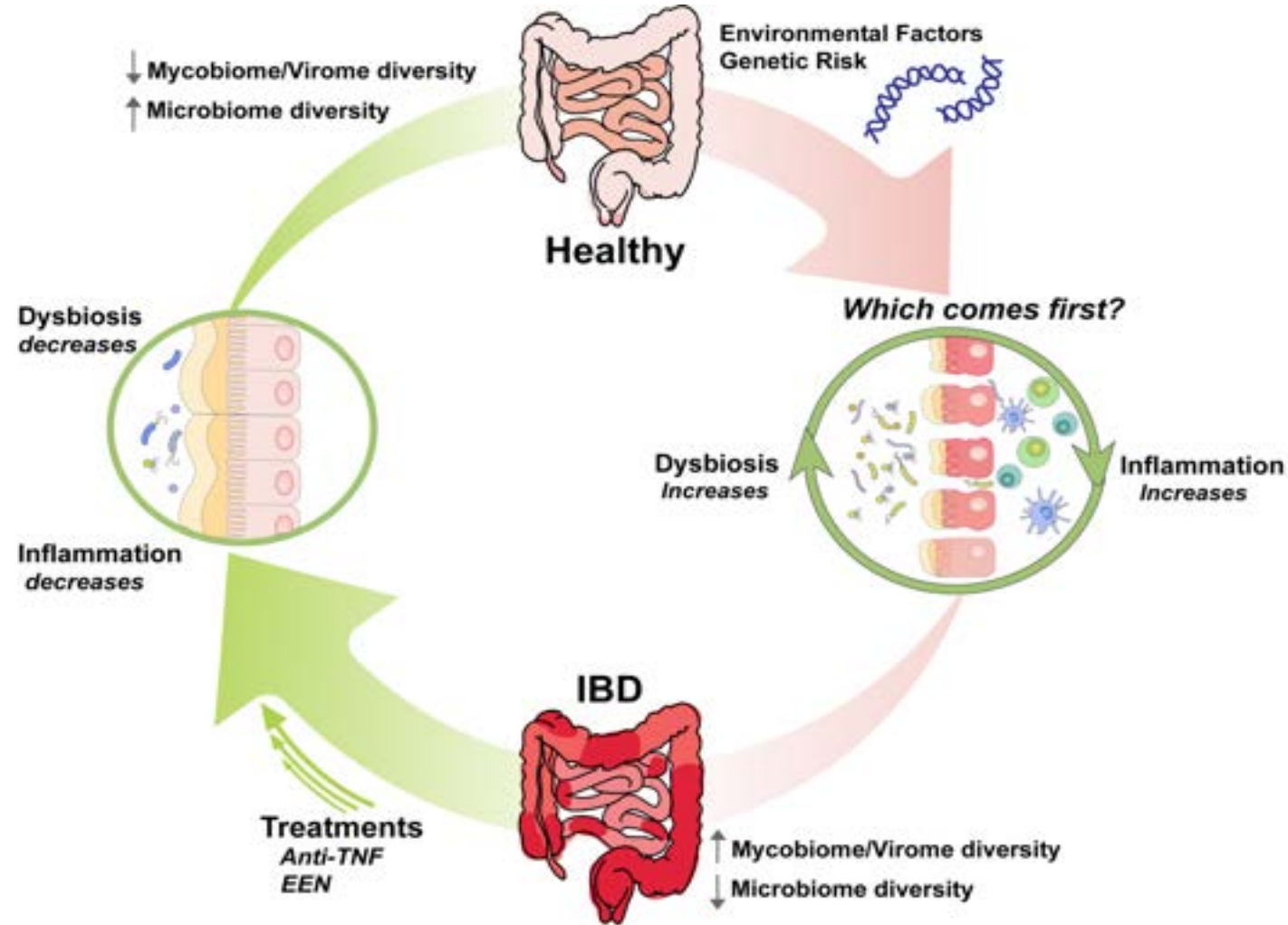


↓ Bacterial diversity with Western immigration → eating less fiber

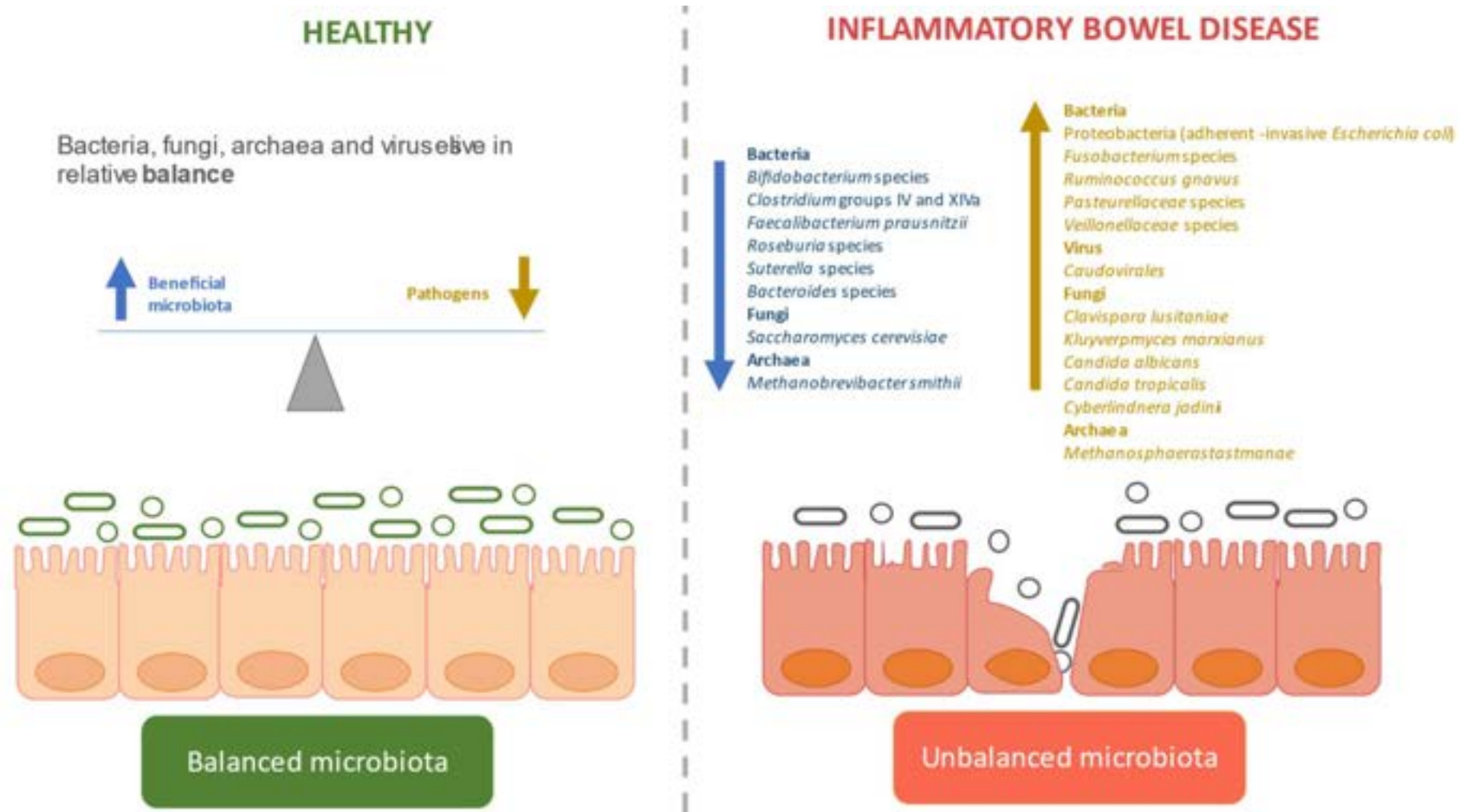
★ We lose fiber-degrading bacteria when we change our lifestyle to Westernized diets: “the loss of bacteria in generations of immigrants”

★ Studies show that lower bacterial diversity → **more disease** and **less resilient**.

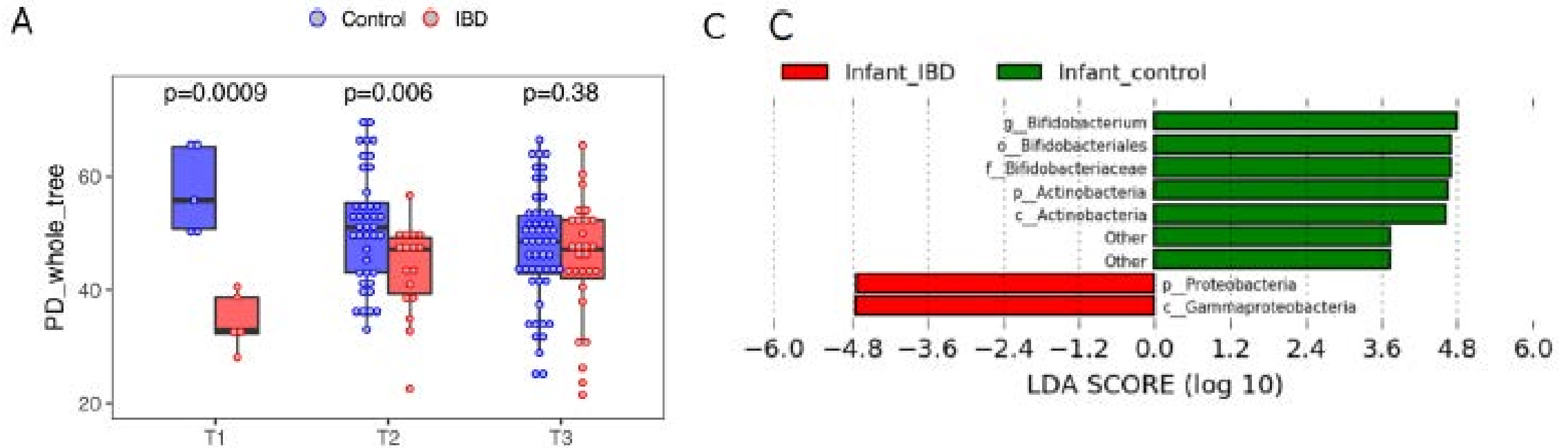
The vicious cycle of the microbiome in IBD



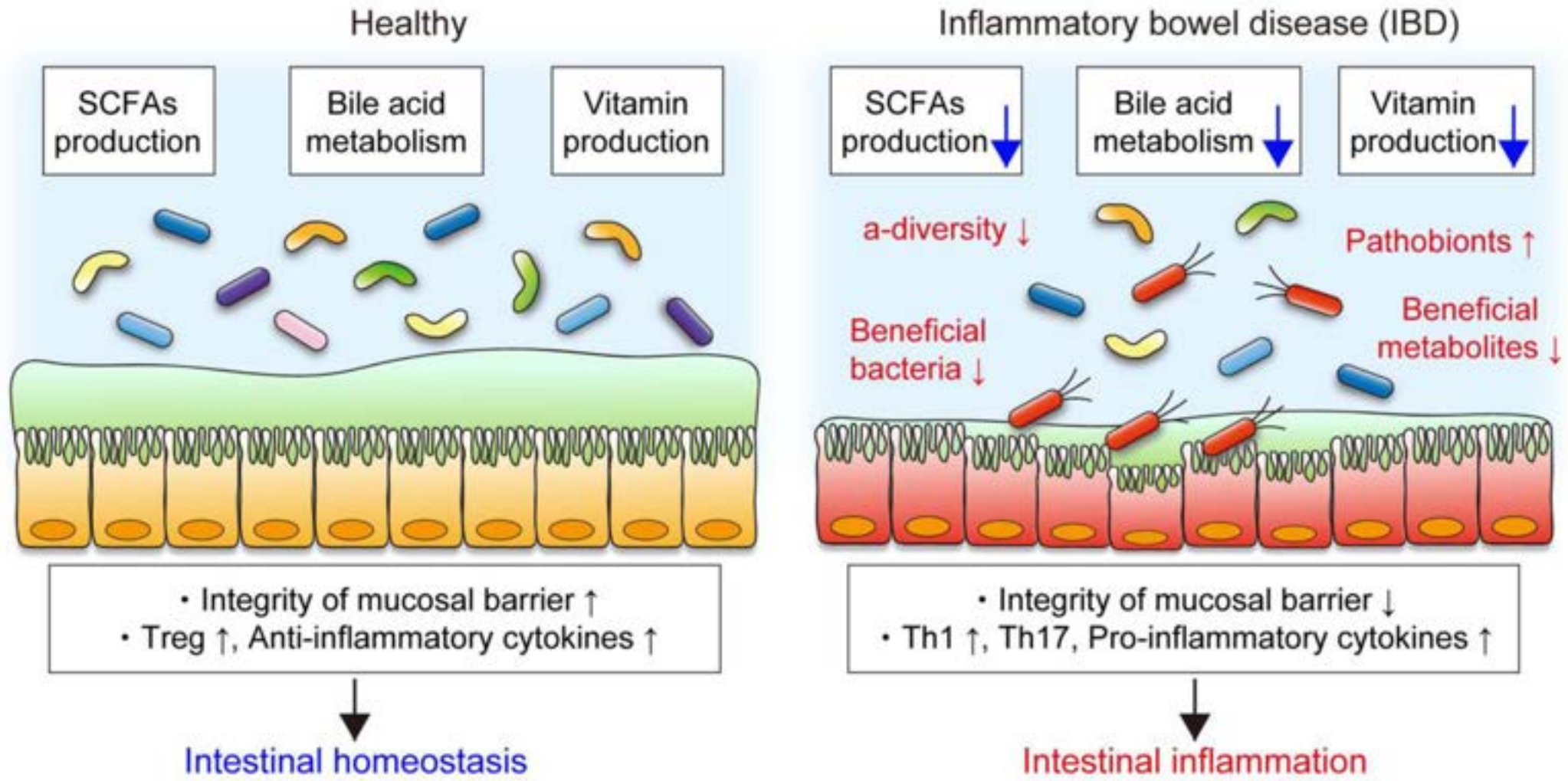
Microbiota Alterations in IBD



Infants born to mothers with IBD present with altered gut microbiome that transfers abnormalities of the adaptive immune system to germ-free mice



Functional changes of the gut microbiota in IBD



Can we identify microbiome signatures
that predict development of IBD?

Pre-disease cohorts

- The GEM Project
- Meconium study
- Tooth Fairy Study
- PREDICT
- Predicts Cohort



The CCC GEM Project

- Aiming to identify Genetic, Environmental, and Microbial determinants of CD
- 5,122 Healthy first-degree relatives (FDR) of CD-affected individuals

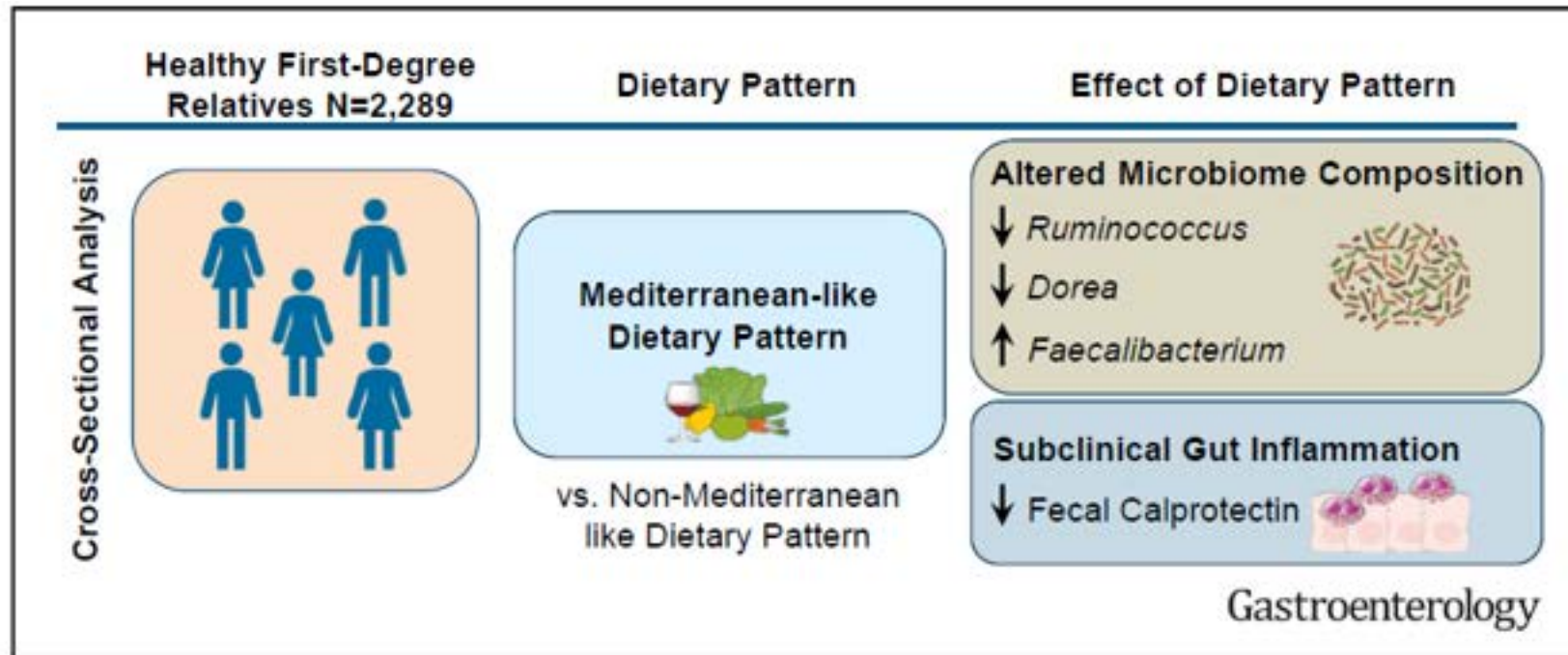


The MECONIUM Study

Exploring **ME**chanisms **O**f disease tra**N**smision
In Utero through the **M**icrobiome



Diet, intestinal inflammation and microbiome in high-risk individuals



- Part of GEM study
- 2289 healthy FDRs of CD patients
- Stool samples
- Food frequency questionnaire
- Importance of dietary patterns over individual food items

Gut barrier function predicts disease onset and an abnormal gut barrier function is associated with an abnormal microbiome composition

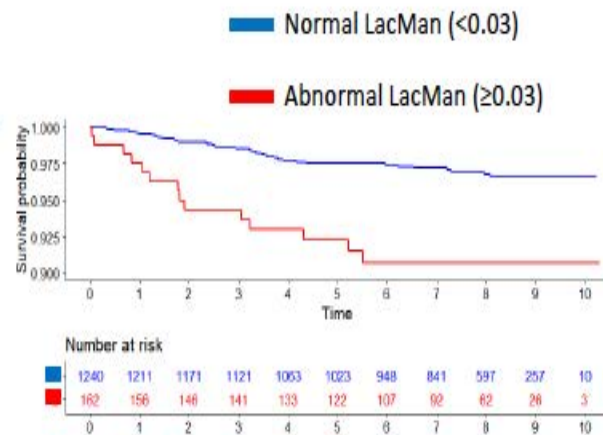
Abnormal Gut Barrier Function is a Predictor of Disease Onset

Gastroenterology 2019;156:2063-2100

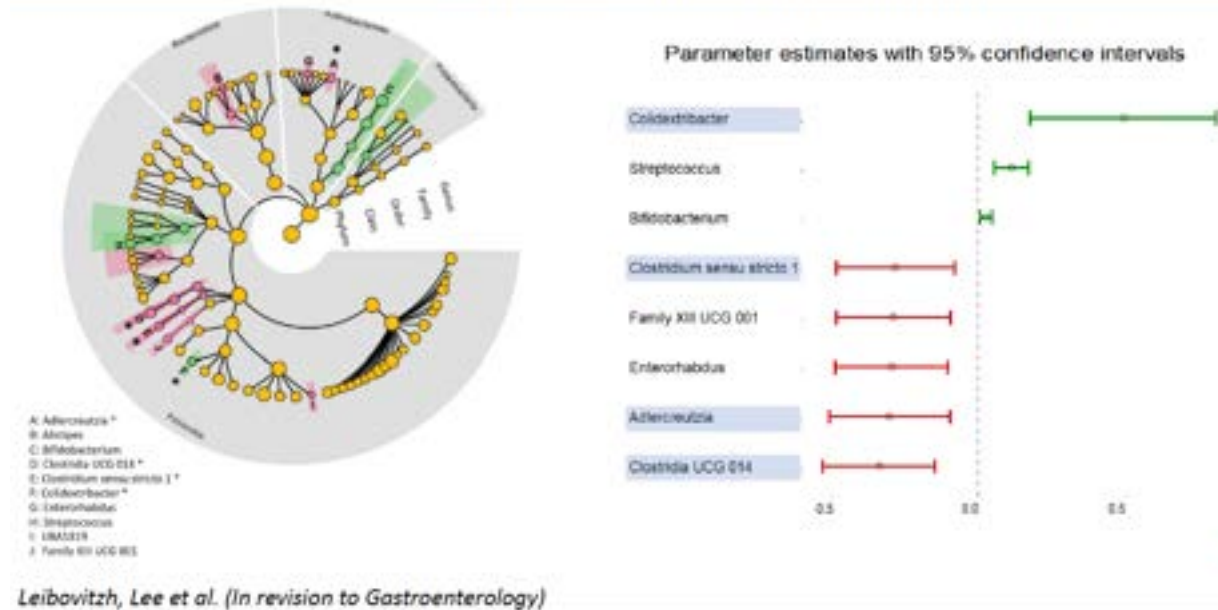
Increased Intestinal Permeability Is Associated With Later Development of Crohn's Disease

Williams Turpin,^{1,2,*} Sun-Ho Lee,^{1,2,*} Juan Antonio Raygoza Garay,^{1,2} Karen L. Madsen,³ Jonathan B. Meadings,⁴ Lari Bedrani,⁵ Namita Power,⁶ Osvaldo Espin-Garcia,⁶ Wei Xu,⁶ Michelle I. Smith,⁶ Anne M. Griffiths,⁶ Paul Moayyedi,⁶ Dan Turner,⁷ Ernest G. Seidman,⁸ A. Hilary Steinbart,^{1,2} John K. Marshall,^{1,2} Kevin Jacobson,^{1,2} David Mack,^{1,2} Hien Huynh,⁴ Charles N. Bernstein,^{1,2} Andrew D. Peterson,^{9,10} The Crohn's and Colitis Canada Genetic Environmental Microbial Project Research Consortium, and Kenneth Croitoru^{1,2}

- Abnormal barrier increase risk of CD onset
- p-value = 4.1×10^{-4} , Adjusted HR = 3.03
95% CI [1.63-5.61]



Gut Barrier Function is Associated with Microbiome Composition



Are we ready to modulate
the gut microbiome in IBD?

Conclusion Remarks

- Environmental factors play a crucial role in the rise and development of IBD
- Pre-disease cohorts yield important information on disease evolution and biologic pathways for disease
- Future goals of predicting disease development are near. A way to “Predict” and “Prevent” IBD?
 - Microbiome score
 - Serologic and proteomic markers
 - Intestinal permeability
 - Fecal calprotectin
- Still unclear is the ‘internal dose’ necessary to trigger pre-disease states and in whom?

Thank you!

