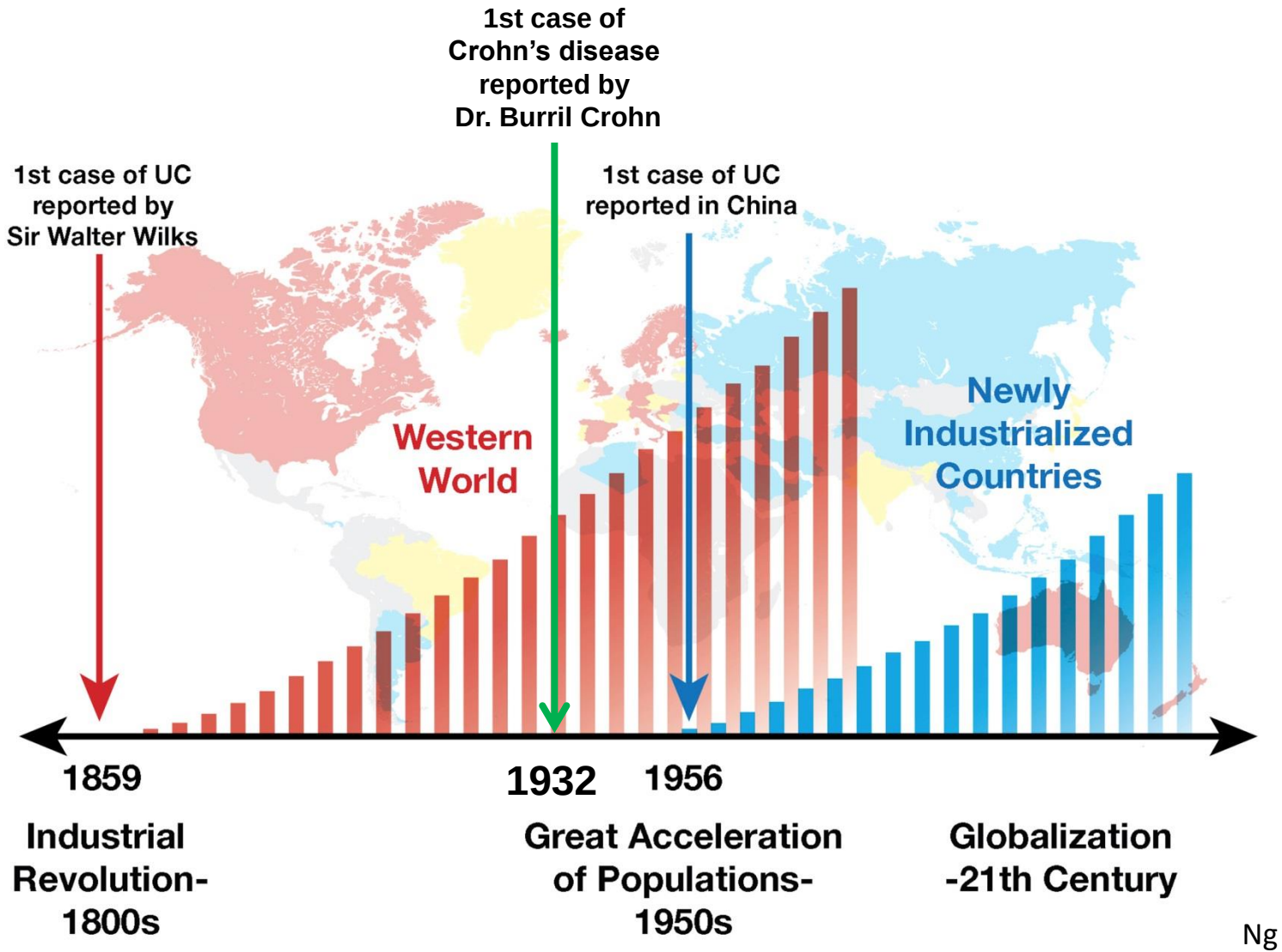
INFLAMMATORISK TARMSYKDOM

Epidemiologi, patogenese og immunologi

Marte Lie Høivik
Overlege/Førsteamanuensis
Gastromedisinsk avdeling OUS/UiO

Oslo universitetssykehus

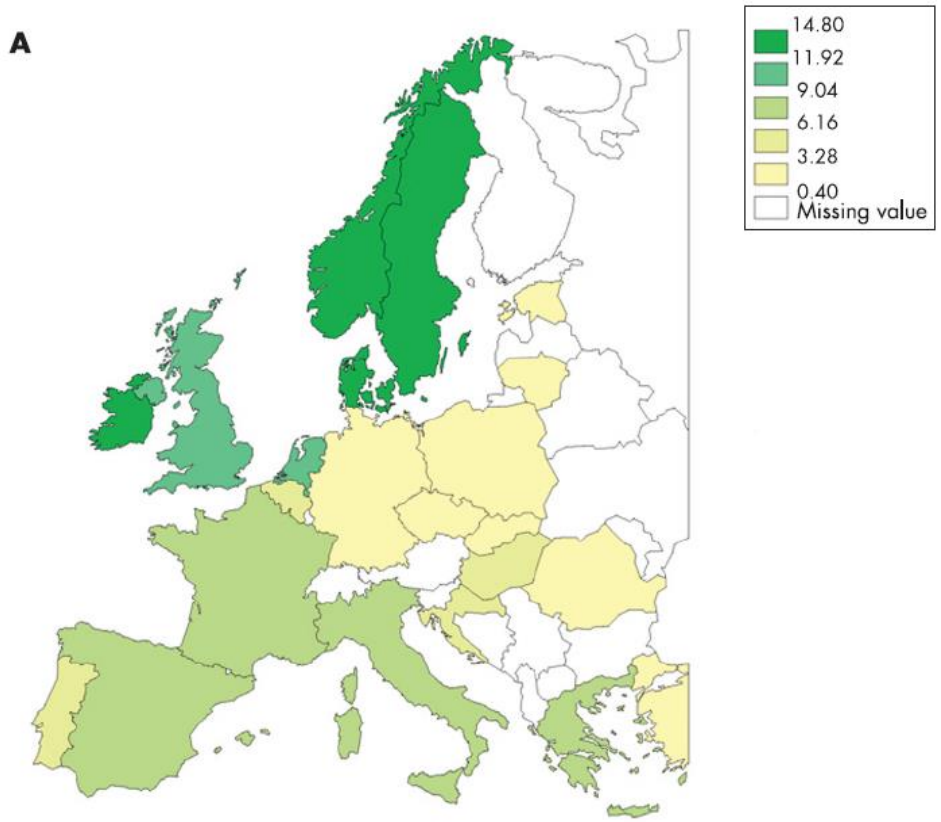
«Nye» sykdommer



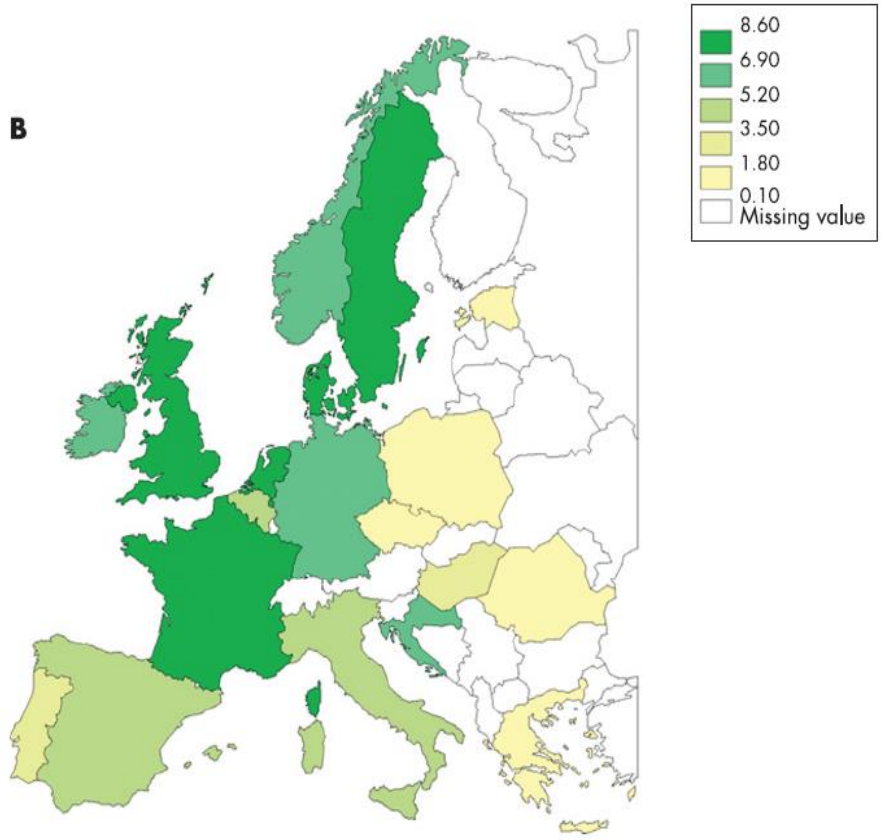
Ng et al. Gastroenterology 2017

Geografisk gradient

Ulcerative colitis

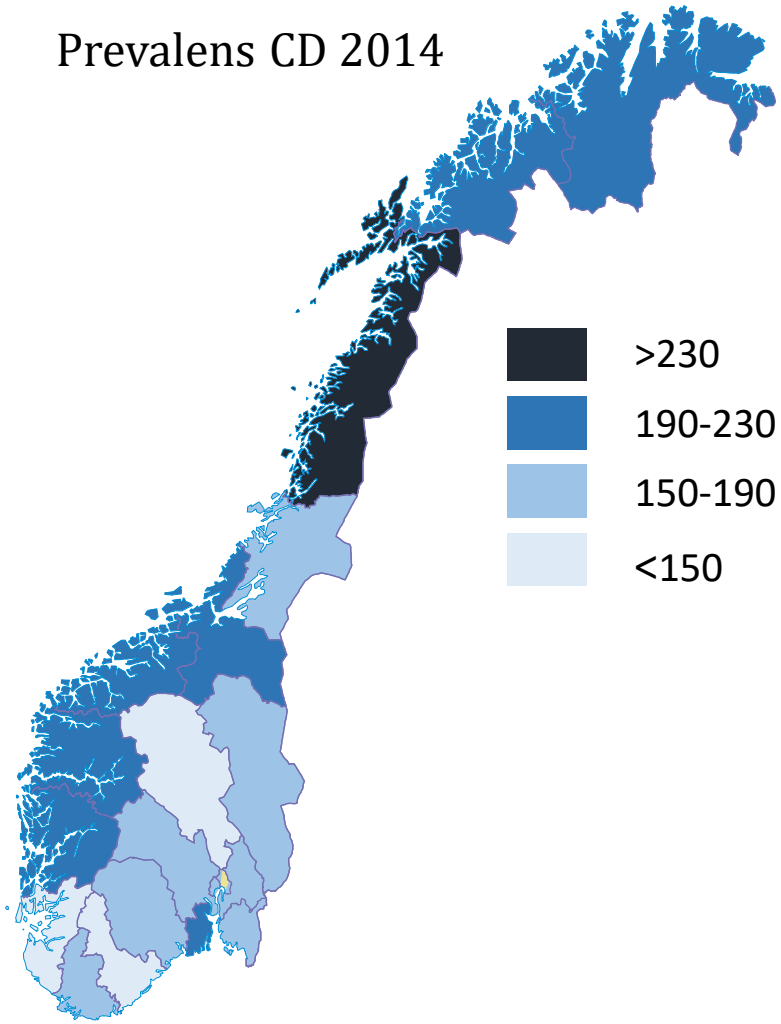


Crohn's disease

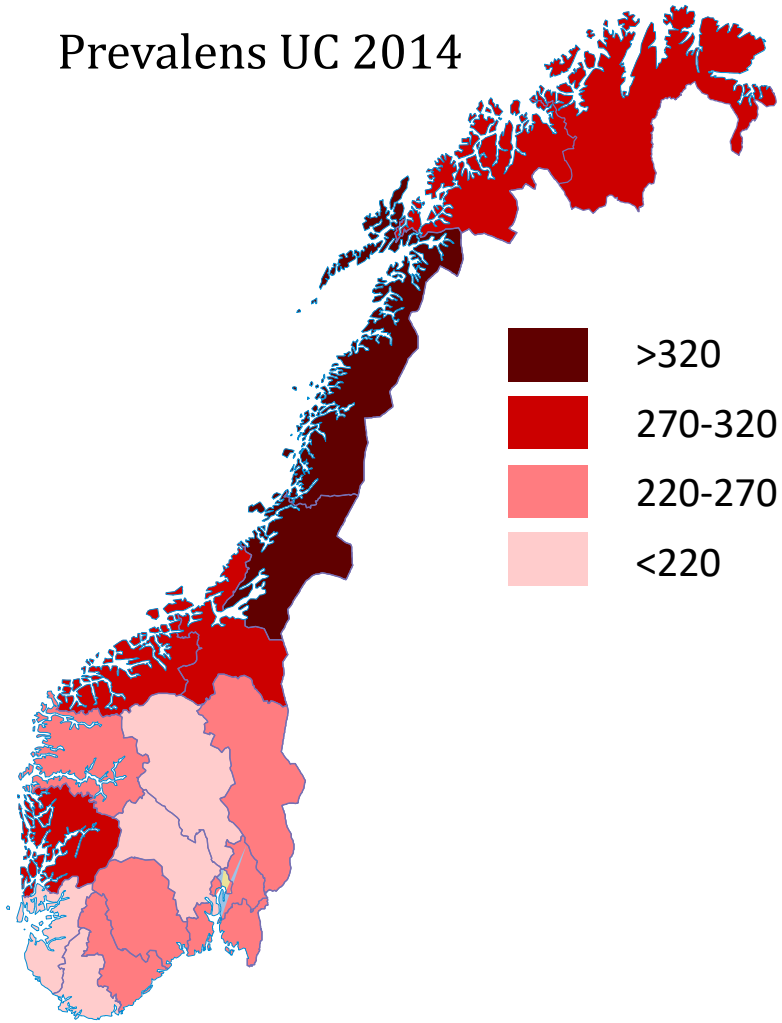


Constatinos et al Gut 2007

Prevalens CD 2014

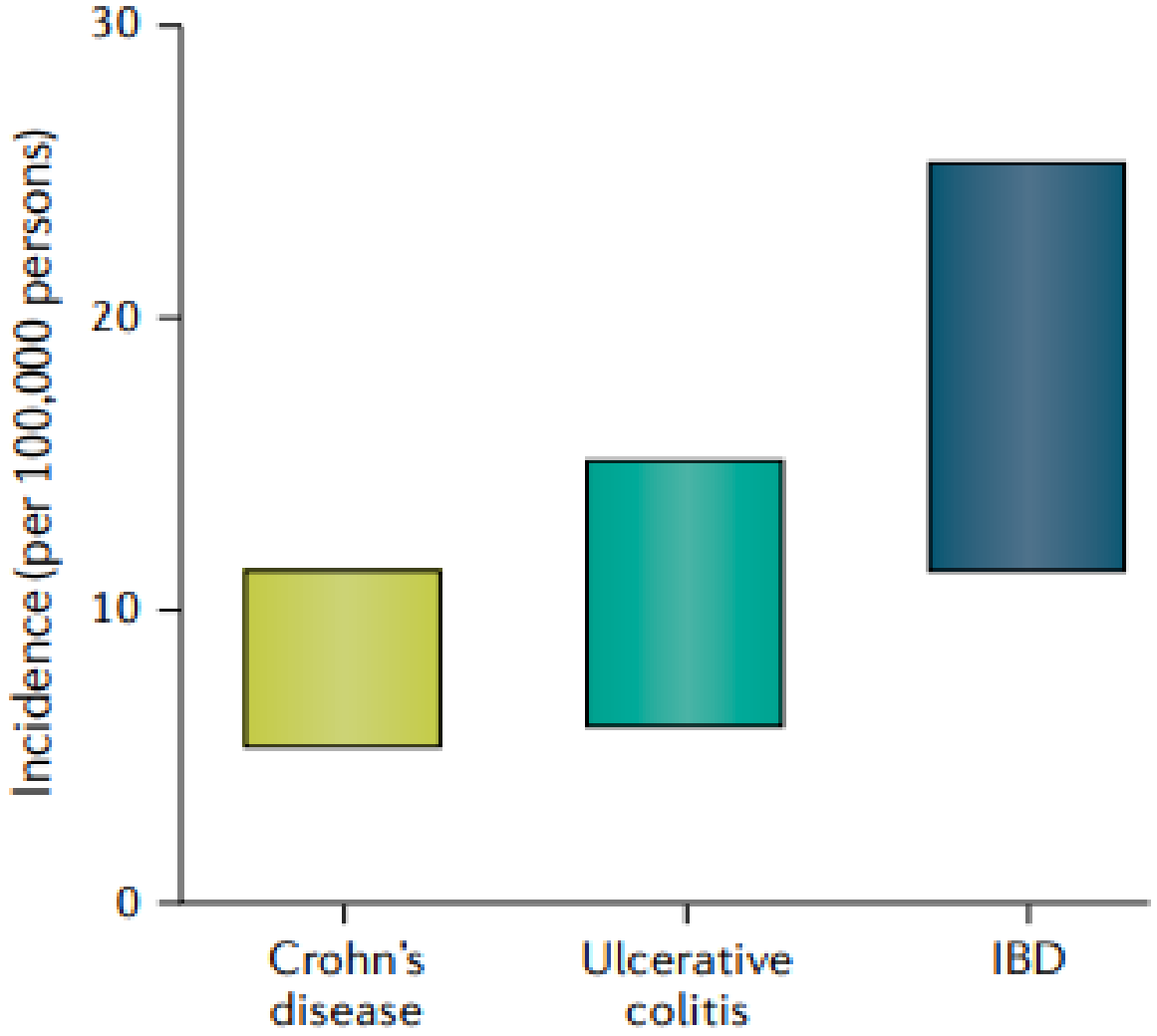


Prevalens UC 2014



Høivik et al, abstrakt Lillehammer 2016

Gjennomsnittlig insidens (vestlige land)



Kaplan G, Nature Reviews 2020

Clinical Epidemiology

Dovepress

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ORIGINAL RESEARCH

Incidence and Prevalence of Inflammatory Bowel Disease in Norway and the Impact of Different Case Definitions: A Nationwide Registry Study

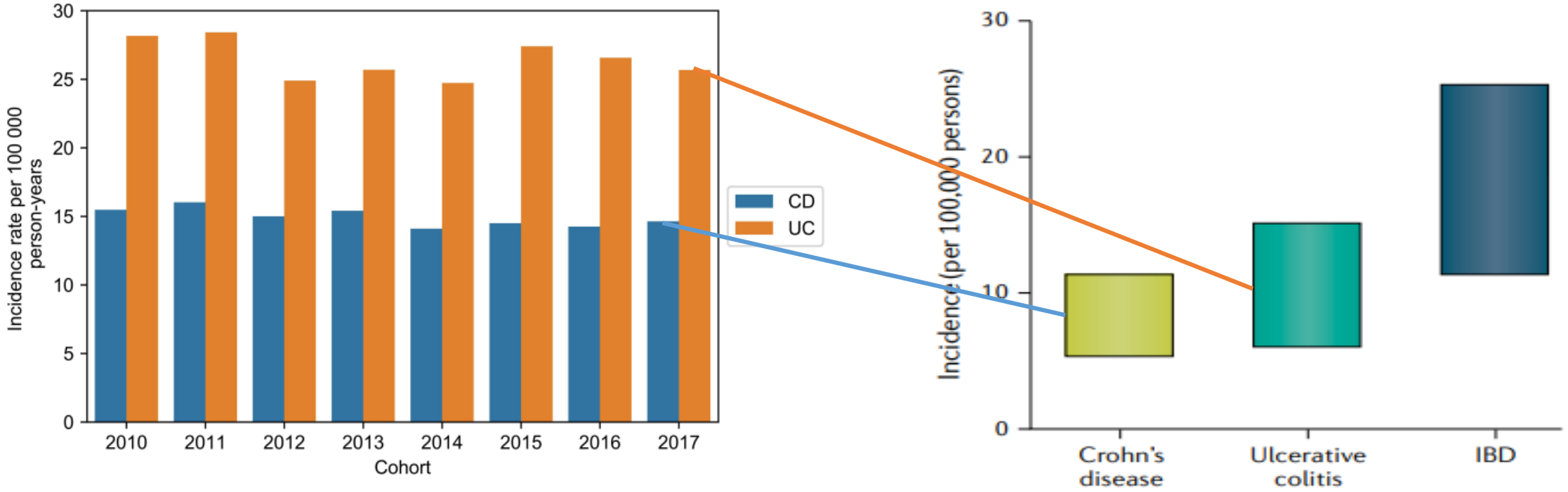
Sandre Svatun Lirhus[1]
Marte Lie Høivik[2,3]
Bjørn Moum[2,3]
Karoline Anisdahl[2,3]
Hans Olav Melberg[1]

Background: Countries have different diagnostic procedures and treatment regimens for inflammatory bowel disease (IBD) patients. In addition to differences in population characteristics, completeness of data and health registries, different follow-up time and case definitions can have a large impact on estimates of the incidence and prevalence of IBD.

Aim: The aim of this study was to use hospital and prescription data to estimate incidence and prevalence of Crohn's disease (CD) and ulcerative colitis (UC), using different case

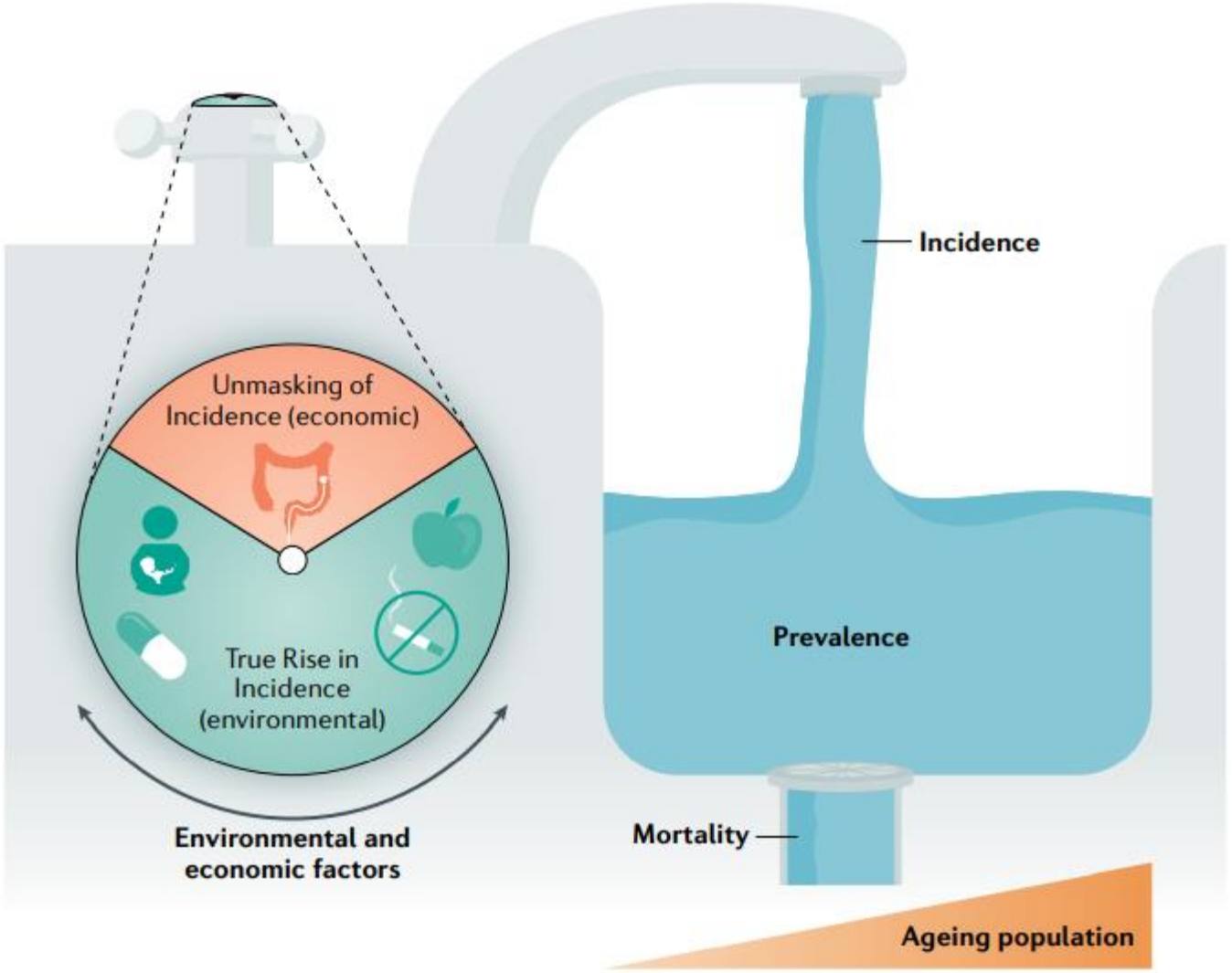
Lirhus et al, Clin Epid 2021

Norske **insidenstall** - basert registerdata (norsk pasientregister og reseptregisteret)



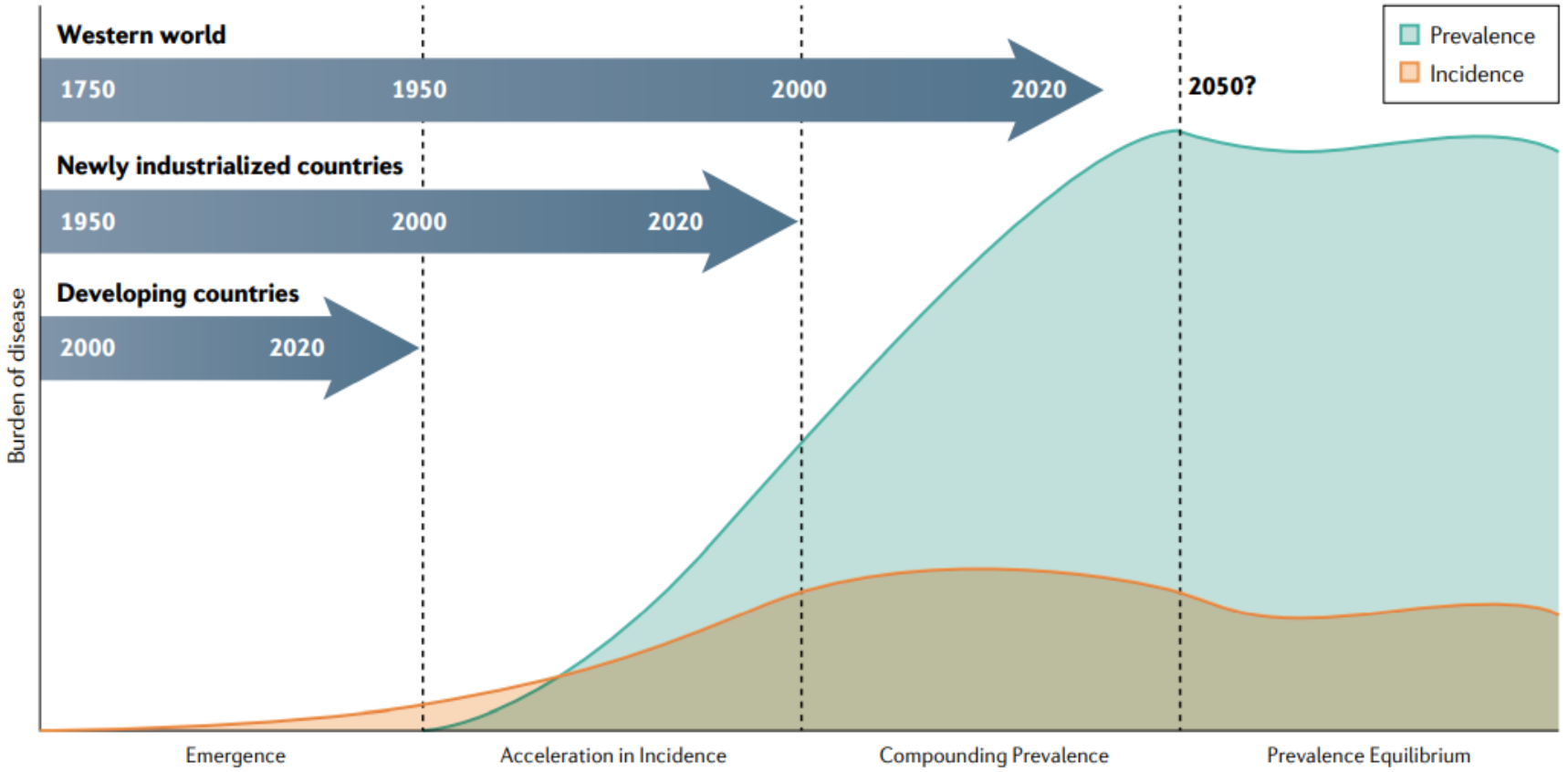
Lirhus et al, Clin Epid 2021
Kaplan G, Nature Reviews 2020

Insidens - prevalens



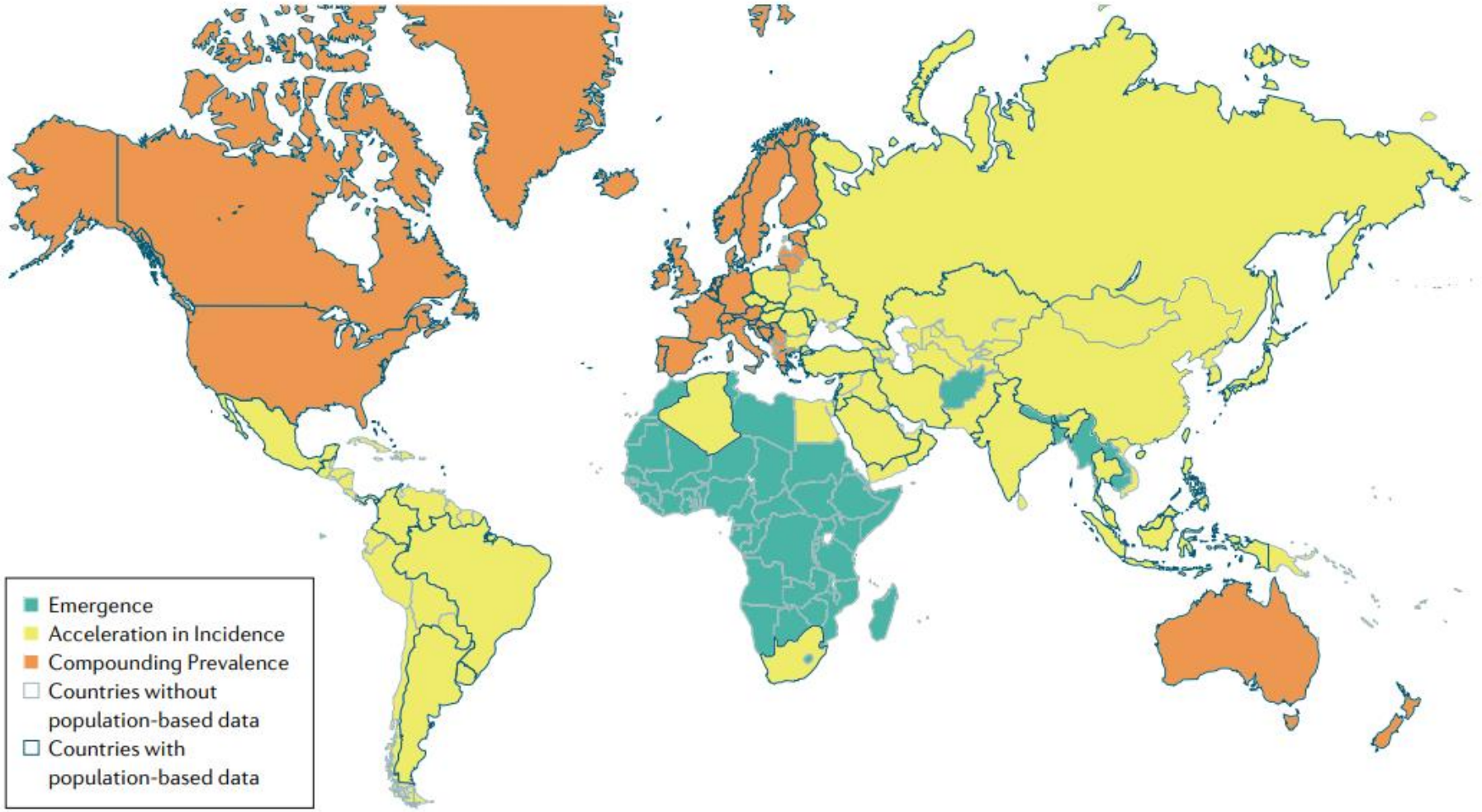
Kaplan G, Nature Reviews 2020

Fire stadier for «sykdomsbyrde»



Kaplan G, Nature Reviews 2020

Fire stadier for sykdomsbyrde



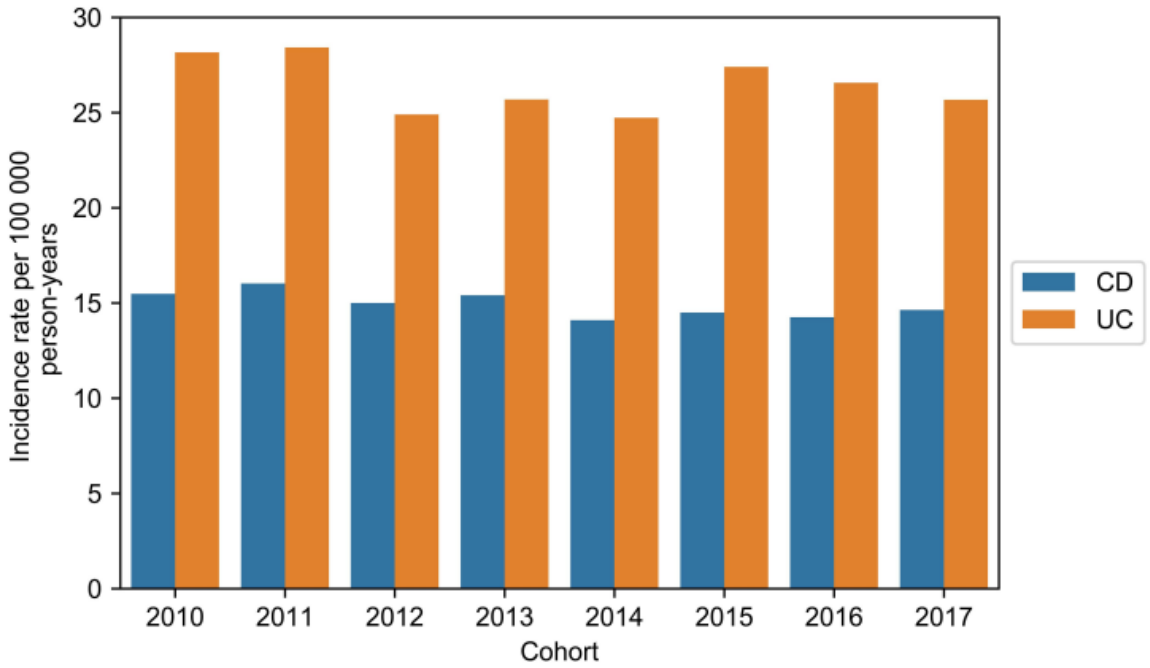
Kaplan G, Nature Reviews 2020

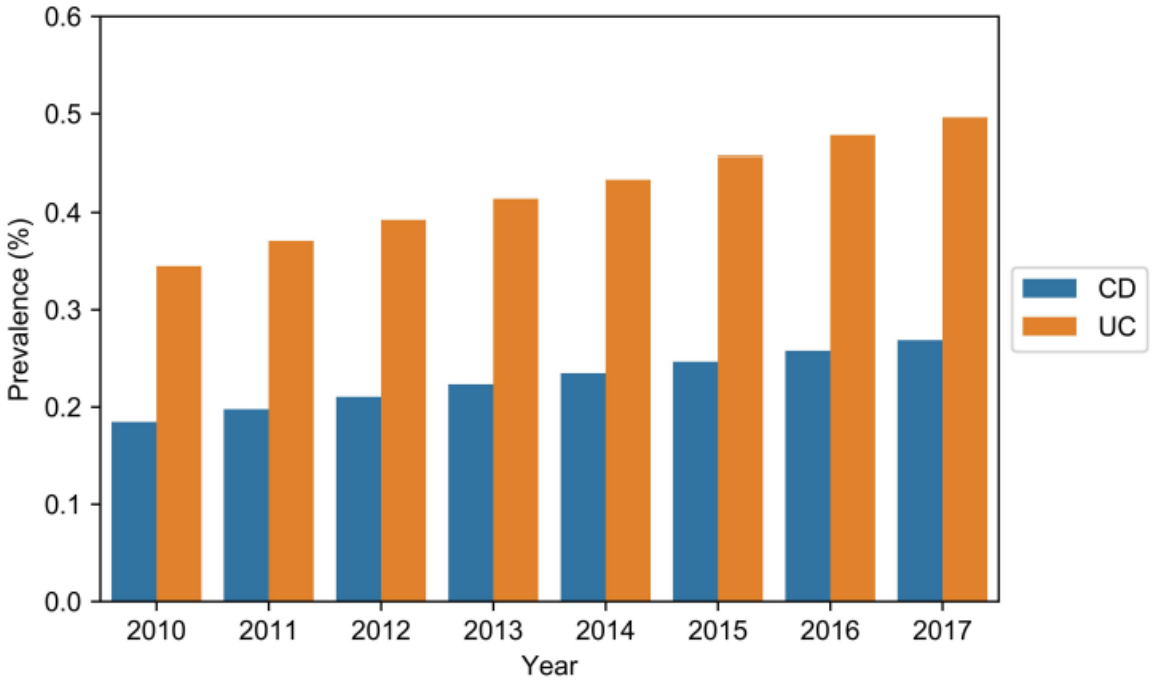
Table 1 | **Projected IBD population in selected industrialized countries of the Western world**

Region	Prevalent IBD population			Increase 2010–2030 (%)
	2010 (0.5%)	2020 (0.75%)	2030 (1%)	
Australia	110,158	192,060	283,930	258
Austria	41,817	66,622	90,170	216
Belgium	54,477	86,535	119,040	219
Canada	170,024	282,630	402,853	237
Denmark	27,738	43,800	60,470	218
Finland	26,816	41,610	56,560	230
France	325,137	505,822	695,090	214
Germany	408,884	620,085	815,200	199[a]
Greece	55,606	79,987	103,550	186[a]
Hungary	50,000	72,712	90,920	182[a]
Ireland	22,800	36,997	52,550	230
Italy	296,387	451,875	591,960	200
Netherlands	83,077	129,975	177,390	214
New Zealand	21,753	37,282	53,420	246
Norway	24,446	40,665	58,540	239
Portugal	52,865	76,462	98,320	186[a]
Spain	232,884	350,332	462,740	199[a]
Sweden	46,890	77,392	109,330	233
Switzerland	39,124	64,807	91,450	234
UK	313,831	504,180	702,770	224
USA	1,546,630	2,489,362	3,544,480	229

Kaplan G, Nature Reviews 2020

Norske **prevalenstall-** basert på registerdata (norsk pasientregister og reseptregisteret)





Lirhus et al, Clin Epid 2021

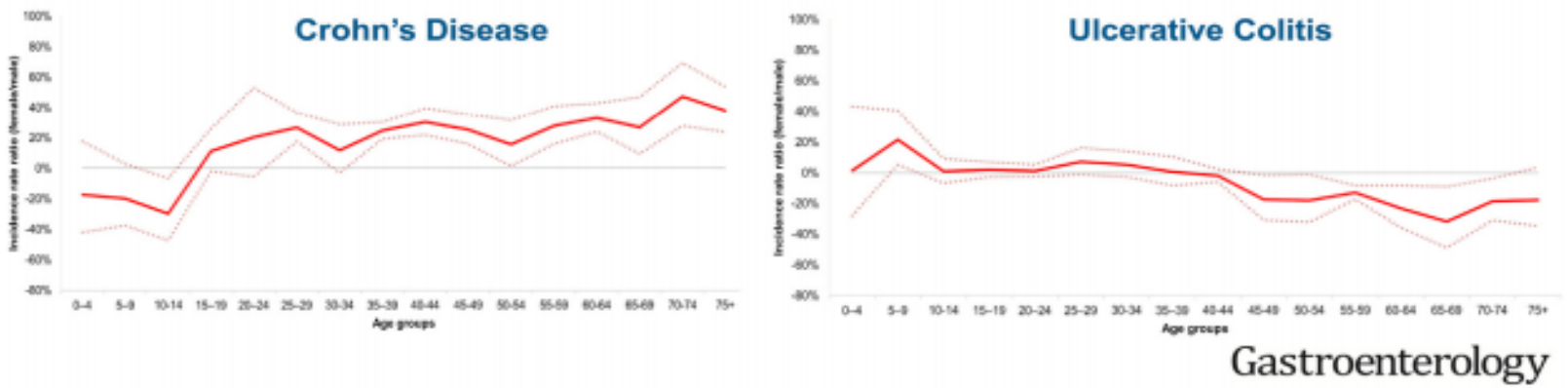
Gastroenterology 2018;155:1079–1089

Sex-Based Differences in Incidence of Inflammatory Bowel Diseases—Pooled Analysis of Population-Based Studies From Western Countries

Shailja C. Shah,[1,2,*] **Hamed Khalili**,[3,*] Corinne Gower-Rousseau,[4] Ola Olen,[5] Eric I. Benchimol,[6,7] Elsebeth Lynge,[8] Kári R. Nielsen,[9] Paul Brassard,[10] Maria Vutcovici,[11] Alain Bitton,[11] Charles N. Bernstein,[12] Desmond Leddin,[13] Hala Tamim,[13] Tryggvi Stefansson,[14] Edward V. Loftus Jr,[15] Bjørn Moum,[16] Whitney Tang,[17] Siew C. Ng,[17] Richard Gearry,[18] Brankica Sincic,[19] Sally Bell,[20] Bruce E. Sands,[1] Peter L. Lakatos,[21] Zsuzsanna Végh,[21] Claudia Ott,[22] Gilaad G. Kaplan,[23] Johan Burisch,[24,§] and Jean-Frederic Colombel[1,§]

CLINICAL AT

There are sex-based differences in incidence of Crohn's disease and ulcerative colitis, based on a pooled analysis from Western countries



Kjønnsforskjeller i forekomst UC

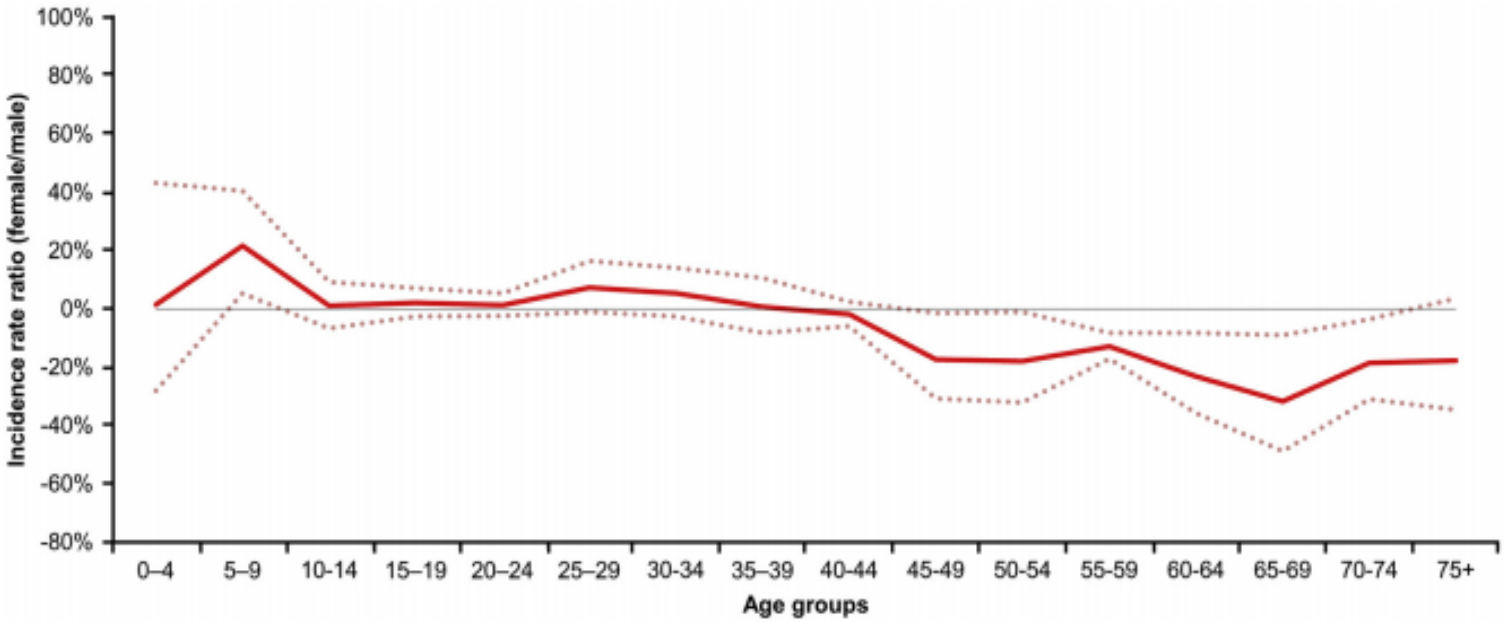


Figure 3. Trend of UC incidence according to sex ratio (F:M) for the full age spectrum.

Flere kvinner

Flere menn

Kjønnsforskjeller i forekomst CD

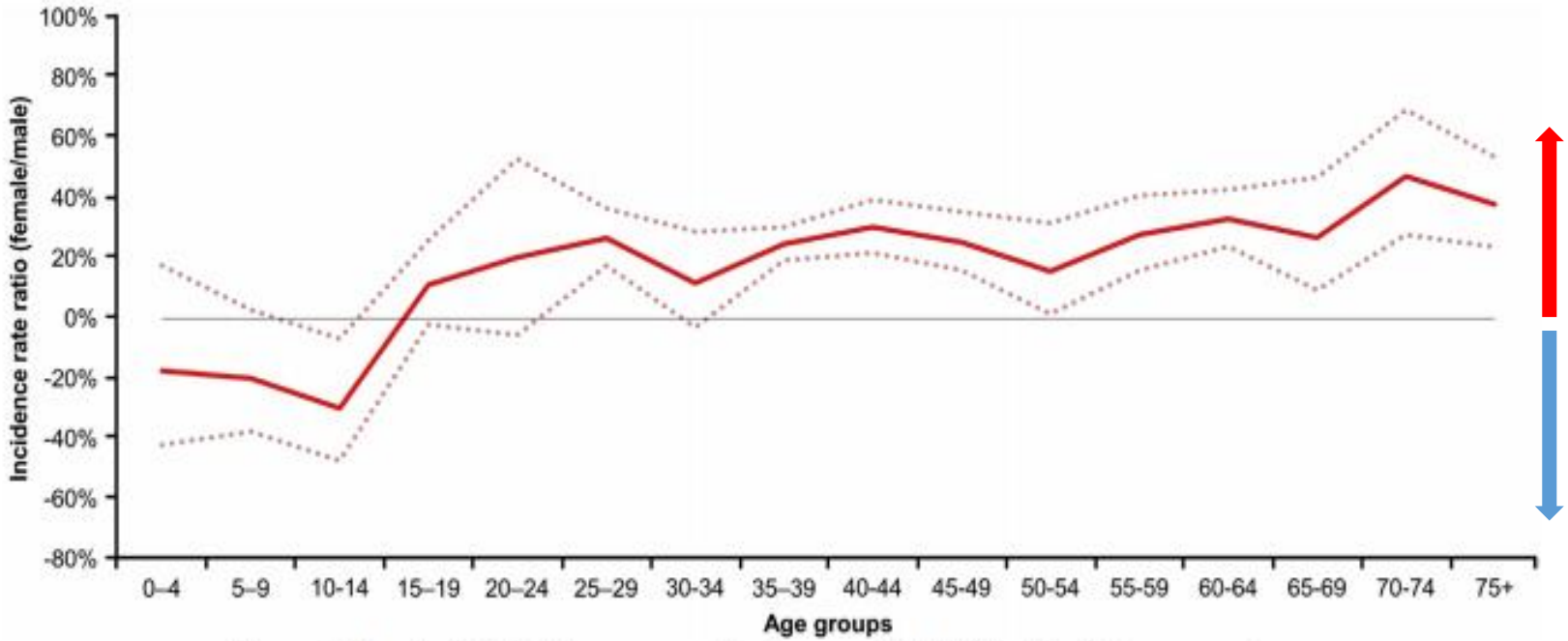


Figure 2. Trend of CD incidence according to sex ratio (F:M) for the full age spectrum.

Flere kvinner

Flere menn

Oppsummering - epidemiologi

- Pågående endringer i IBD-epidemiologi
  - Økende insidens særlig i nyindustrialiserte land
  - Økende prevalens – på vei til å stabiliseres i vestlige land?

- Høy og økende forekomst (prevalens) også i Norge

➡ økt byrde på helsevesenet

Patogenese og immunologi

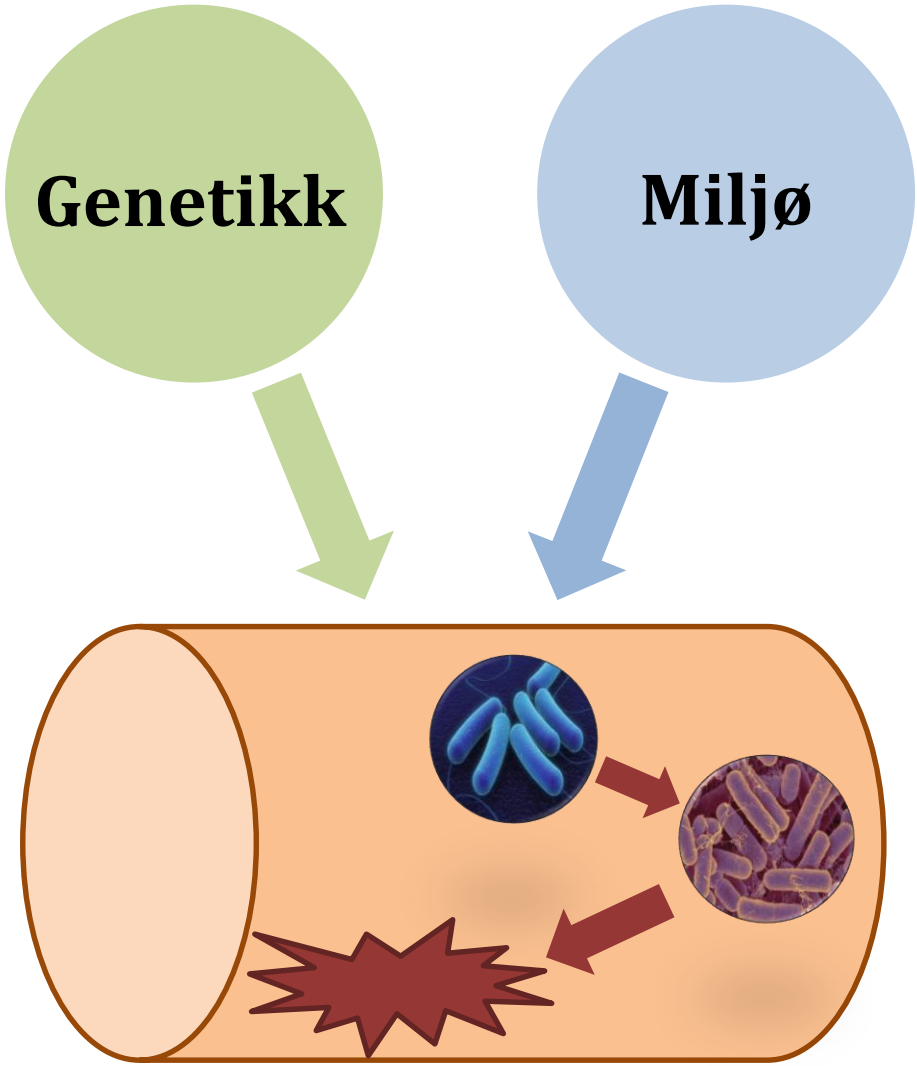
Although still not completely clear, scientific evidences support a multifactorial pathogenesis characterized by a dysregulated immune response to gut microbiota which leads to progressive destructive damage and defective repair of the gastrointestinal tract, in genetically susceptible individuals exposed to environmental factors….

….. ok, men

Patogenese og immunologi

Although still not completely clear, scientific evidences support a multifactorial pathogenesis characterized by a dysregulated immune response to gut microbiota which leads to progressive destructive damage and defective repair of the gastrointestinal tract, in genetically susceptible individuals exposed to environmental factors….

….. ok, da går vi igang☺


Genetikk
Miljø

Genetikk

Etniske forskjeller i forekomst

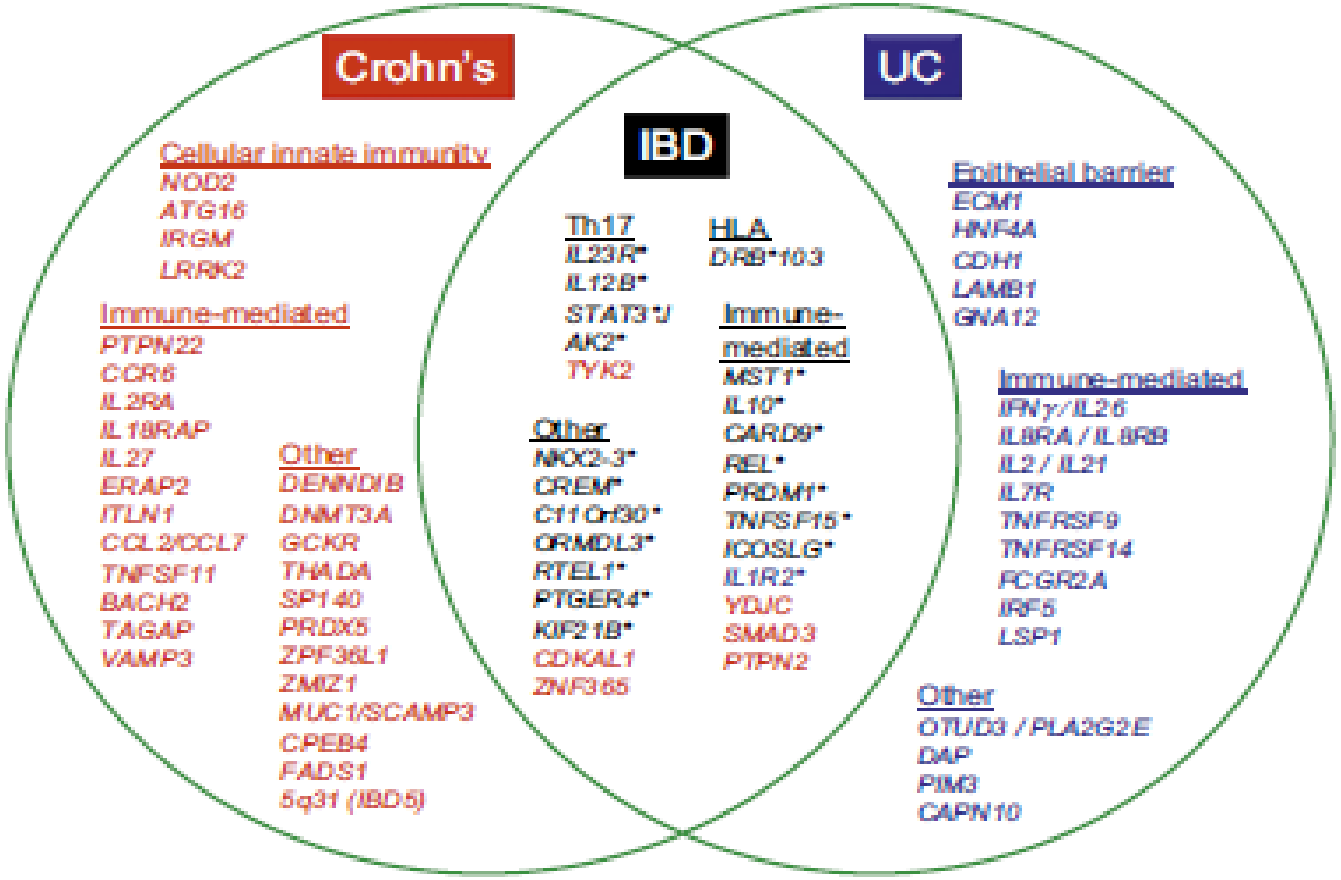
Familiær opphopning: ↑ risiko hos 1.gradsslektninger

Tvillingstudier – konkordans rater

- Eneggede (CD 37%; UC 10%)
- Toeggede (CD 7%; UC 3%)

Genetikk

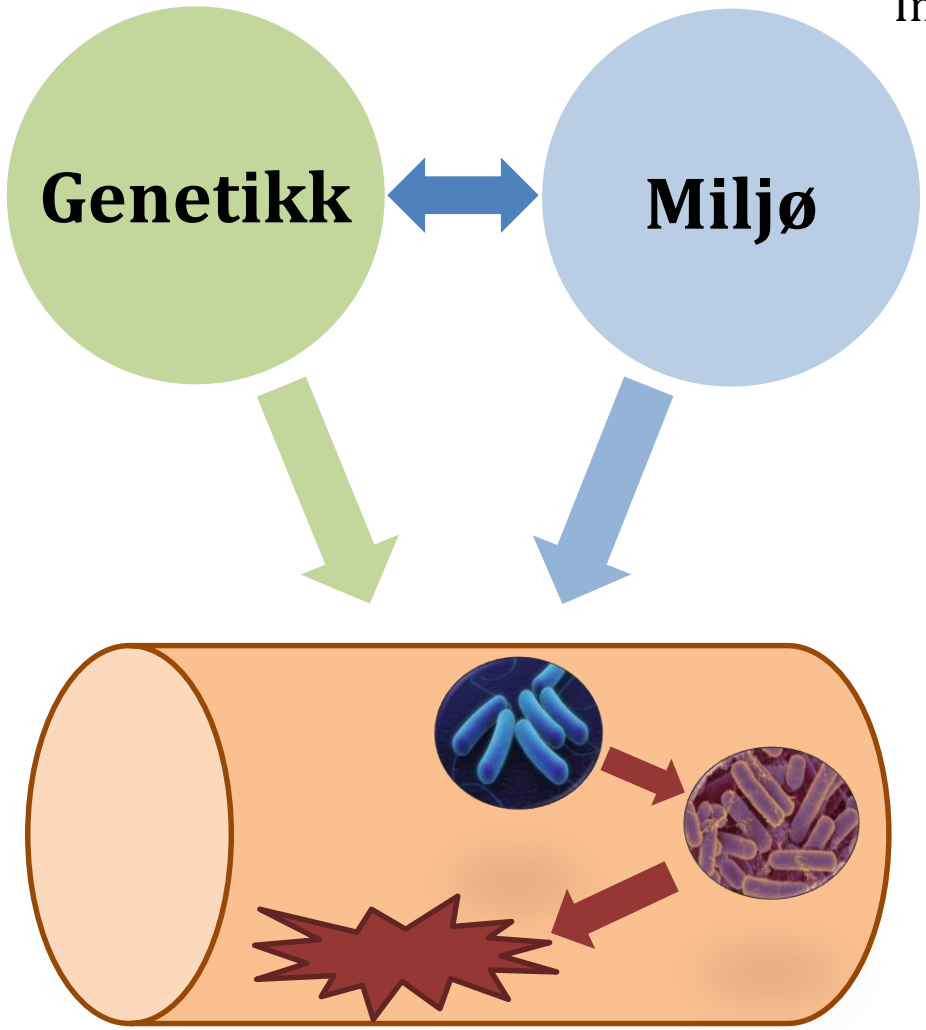
GWAS studier: 240 ++ genetiske loci (alleler)
Forklarer ca. 8-13 % av arveligheten



Diaz Obrero et al, JCC 2021
deLange et al, Nat Genetics 2017
Lees et al, Gut 2011

240 ++ genetiske loci

8-13% av arveligheten



Medisinbruk

Infeksjoner

Bakterieflora

Diett

Pre og periantale faktorer

Røyking

Stress

Fysisk aktivitet

Miljø

Pre- og periantale faktorer

- Forløsningsmetode: Ikke økt risiko ved keisersnitt
- Amming: Mulig beskyttende effekt, men heterogene studier
- Intrauterin eksponering tungmetaller: Økt risiko for CD (melketenner, bly, kopper, sink, krom)

Torres et al, JCC 2021

Miljø

Medisinbruk

- Antibiotika: Assosiert med økt risiko for CD men ikke UC
  - dose respons, høyere risiko for pediatric onset enn adult onset
  - antibiotika under svangerskap – økt risiko for CD hos barna

- P-piller: Assosiert med økt risiko for CD

Torres et al, JCC 2021

Miljø

Livsstil

- Røyking: Påvirker barriereintegritet, immunrespons, diversitet av mikrobiota, epigenetiske effekter og kan påvirke genekspresjon. Røykere: 2-4 økt risiko for CD , røykestopp øker risiko for UC

Torres et al, JCC 2021

Miljø

Livsstil

- Fysisk aktivitet: Redusert risiko for CD

www.helsedirektoratet.no

- Diet: Økning av forekomst i land som går over til mer vestlig diett

Torres et al, JCC 2021

Stress?

Box 1
Highlights of brain-gut axis and stress in inflammatory bowel disease

1. The vagus nerve has an anti-inflammatory role; enhanced cholinergic activity is anti-inflammatory, whereas sympathetic activity is proinflammatory.
2. Stress increases intestinal permeability, which can allow bacteria to cross the epithelial barrier to activate the mucosal immune response and ultimately the innate immune system.
3. In mouse models, behavioral traits of donor mice can be transferred to adult germ-free mice of a different strain by transplanting gut microbiota, underscoring that the gut microbiota can impact mental processes.
4. Persons with IBD have a 2 -to 3-fold elevated rate of depression and anxiety than the general population. These conditions may antedate the diagnosis of IBD by years and hence are not only sequelae of having a chronic disease.
5. Psychiatric comorbidity in IBD negatively impacts clinical outcomes and increases rates of disability, health care utilization, and ultimately, health care costs.
6. High perceived stress is a predictor of increased symptoms in persons with IBD. The relationship between stress and symptoms is bidirectional.
7. There are limited data suggesting that stress exacerbates frank intestinal inflammation; however, this requires further study.
8. In persons with active symptoms, only up to 30% may rate their IBD as being stressful, whereas in asymptomatic patients as little as 2% rate their IBD as being stressful. Persons with IBD suffer from the usual life stressors as the general population does: finances, work, and family being the leading stressors reported.
9. There are few controlled studies exploring the management of psychiatric comorbidity in IBD or the impact of psychotropic drugs on IBD outcomes.
10. Clinicians must engage patients with IBD on issues of mental health because they impact greatly on symptoms, and improving mental health may improve outcomes in terms of both the IBD and general well-being.

Bernstein C, Gastroenterol Clin N Am 2017

Immunologisk dysregulering ved IBD karakteriseres av:

1. Forstyrret barrierefunksjon

-epitelskade, ødelagte tight junctions og abnorm slimproduksjon (årsak eller virkning?)

2. Ukontrollert inflammasjonsrespons

-drevet av tarmfloraen (?)

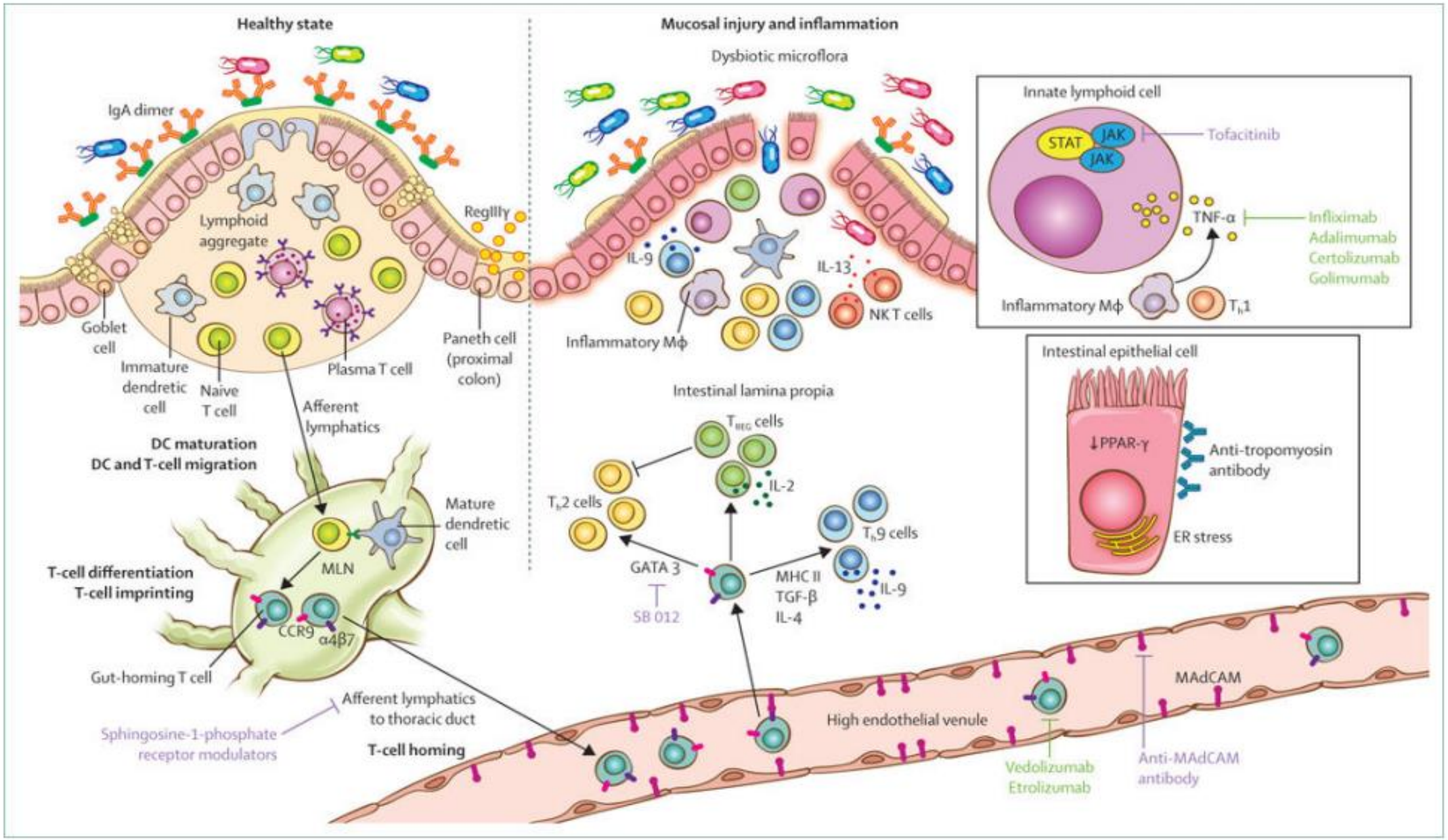
-aktivering av store mengder celler som infiltrerer lamina propria (T-celler, B-celler, makrofager, dendritiske celler, neutrofile)

-produksjon av store mengder proinflammatoriske cytokiner i vevet (feks: TNF, IL1beta, INF gamma, IL23/th17 pathway)

3. Svikt i immunreguleringsmekanismer som skal kontrollere responsen

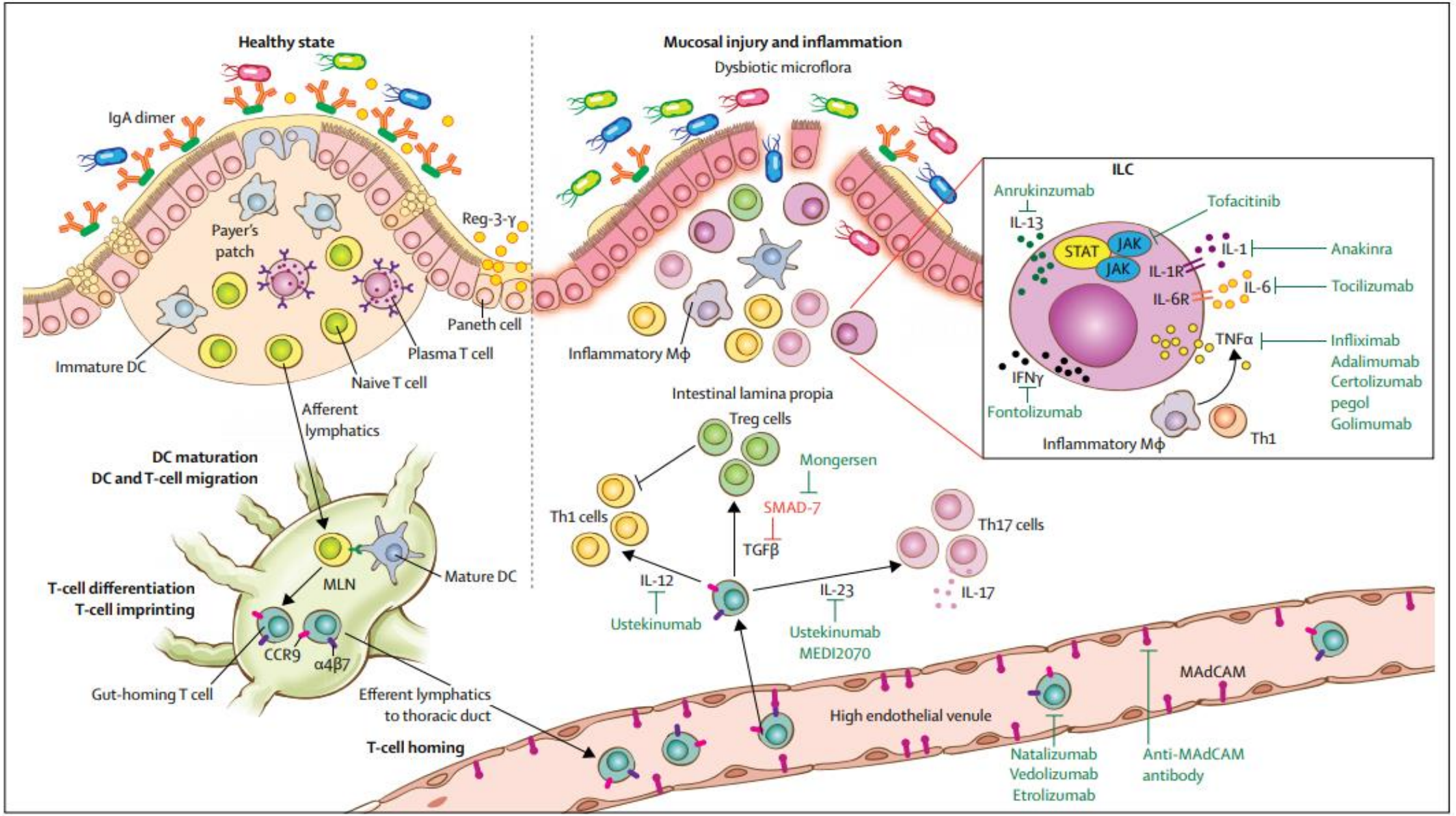
Torres et al, JCC 2021

Ulcerøs kolitt



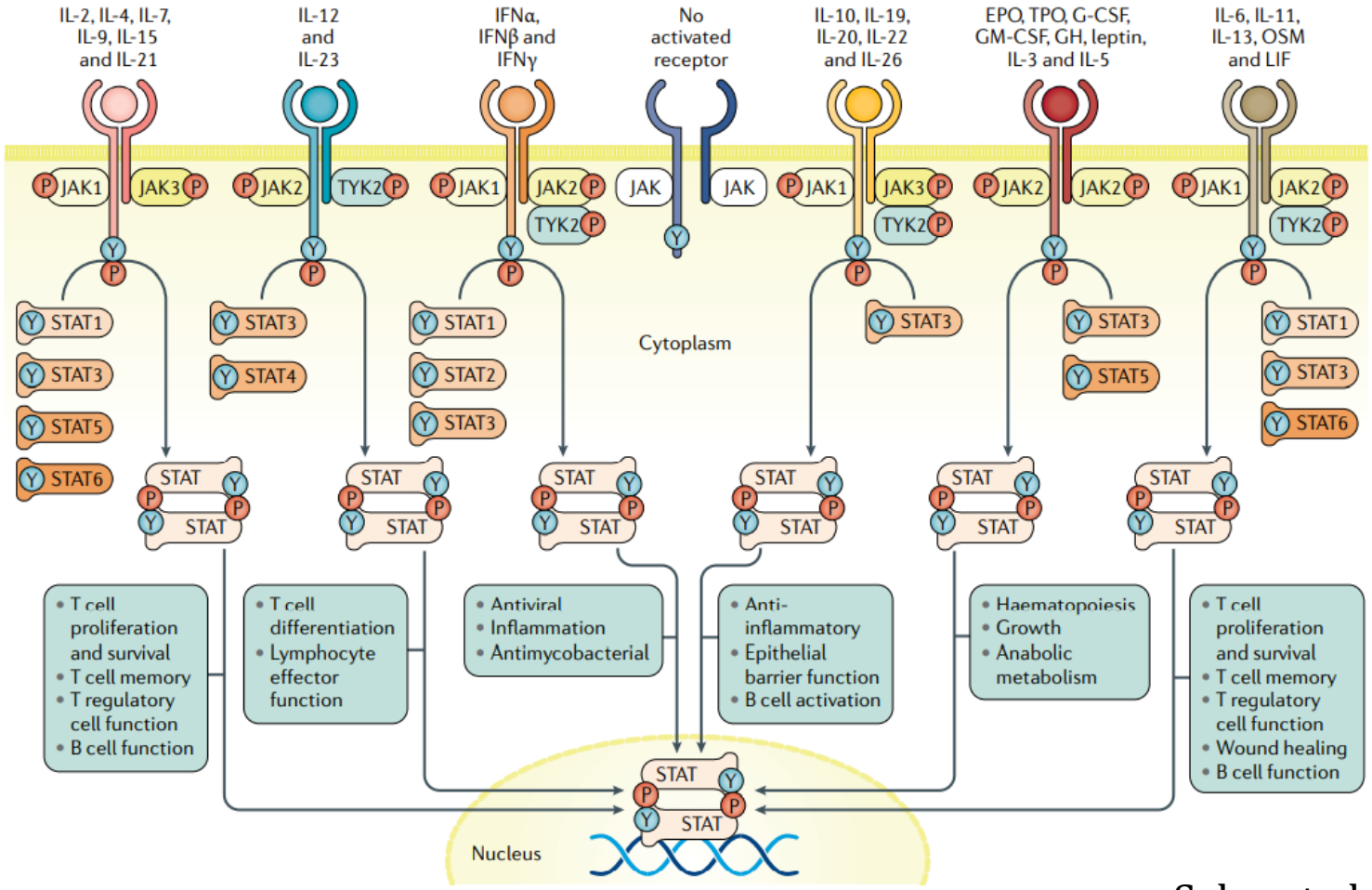
Ungaro et al, Lancet 2017

Mb Crohn



Torres et al, Lancet 2017

JAK/STAT -intracellulære signalsystemer som bla overfører cytokinmedierte signaler fra reseptor og inn i cellen



Salas et al, Nature Reviews 2020

Mikrobiomets rolle

Mange case kontroll studier

IBD mikrobiota karakterisert ved:

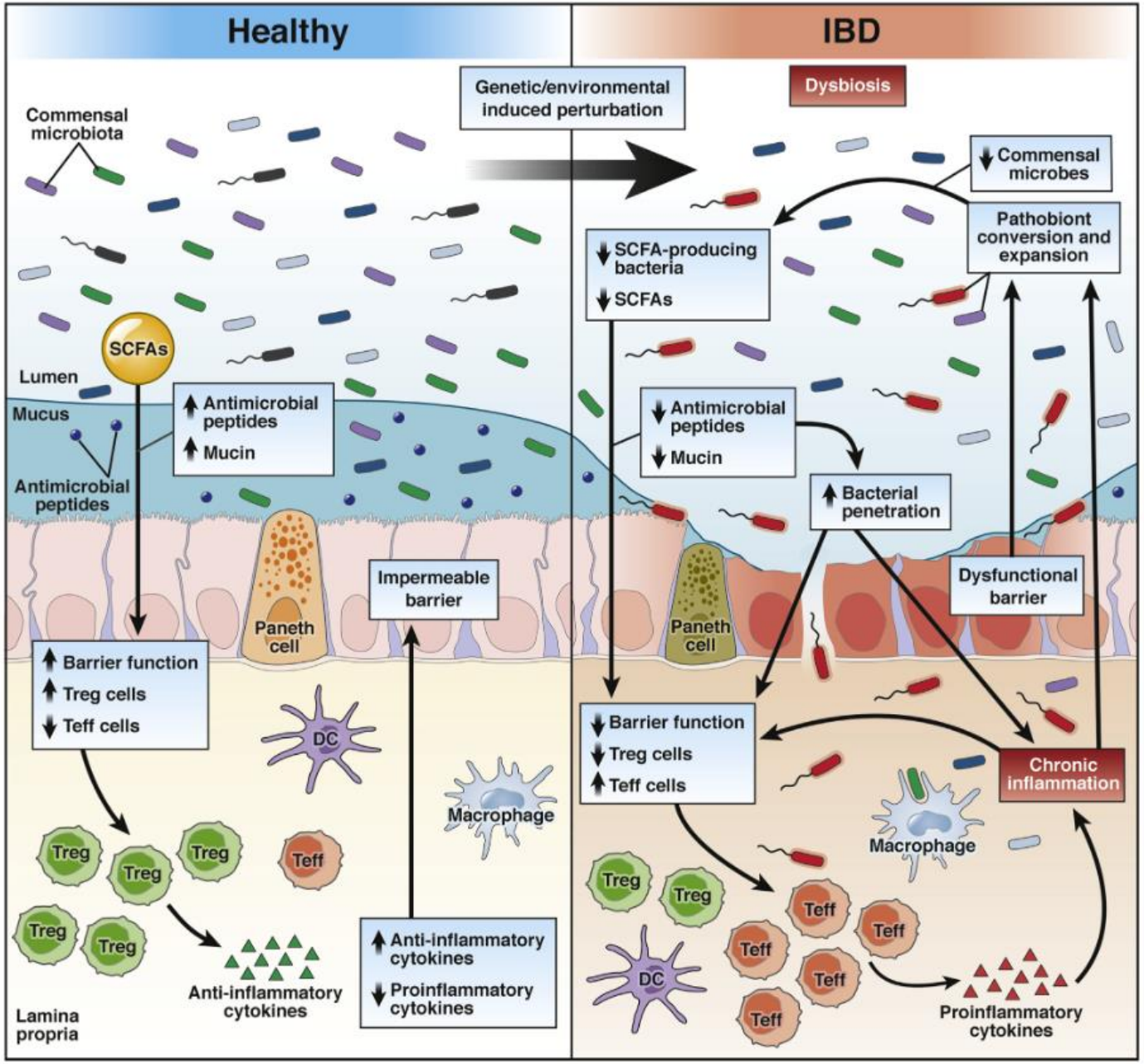
- Nedsatt diversitet
- Økt ustabilitet
- Reduksjon av phyla med anti-inflammatoriske egenskaper (feks butyrate produsenter (Firmicutes).

- årsak eller konsekvens?

TABLE II. Microbiota changes associated with IBD

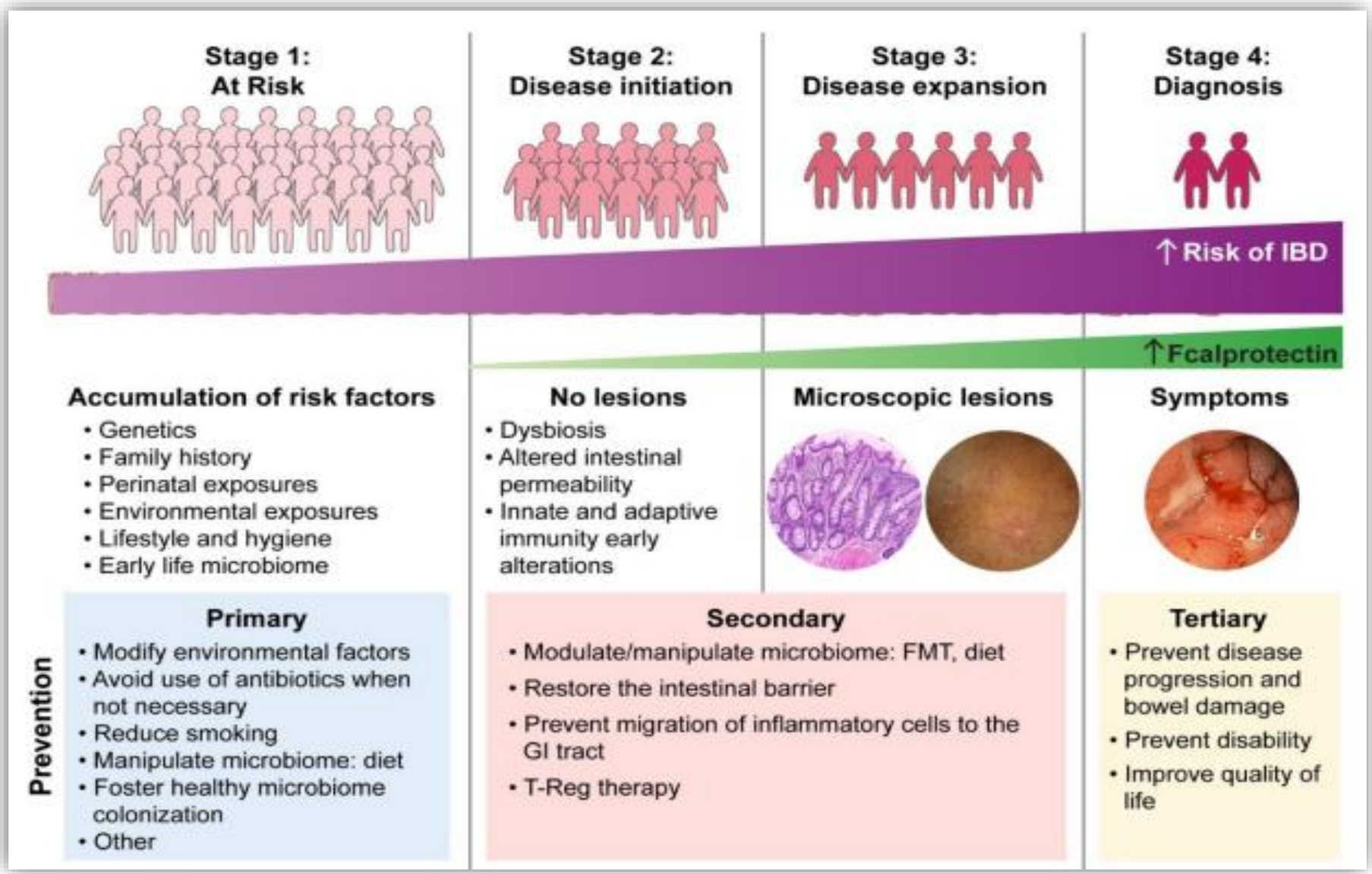
Increased	Decreased
Bacteria: ● *Fusobacterium* species ● Pasturellaceae ● Proteobacteria (adherent invasive *Escherichia coli*) ● *Ruminococcus gnavus* ● Veillonellaceae	Bacteria: ● *Bacteroides* species ● *Bifidobacterium* species ● *Clostridium* XIVa, IV ● *Faecalibacterium prausnitzii* ● *Roseburia* species ● *Suterella* species
Fungi: ● *Candida albicans* ● *Candida tropicalis* ● *Clavispora lusitaniae* ● *Cyberlindnera jadinii* ● *Kluyveromyces marxianus*	Fungi: ● *Saccharomyces cerevisiae*
Viruses: ● Caudivirales	

Glasner et al, J Allergy clin immunol 2019



Lee et al, Gastroenterology 2021

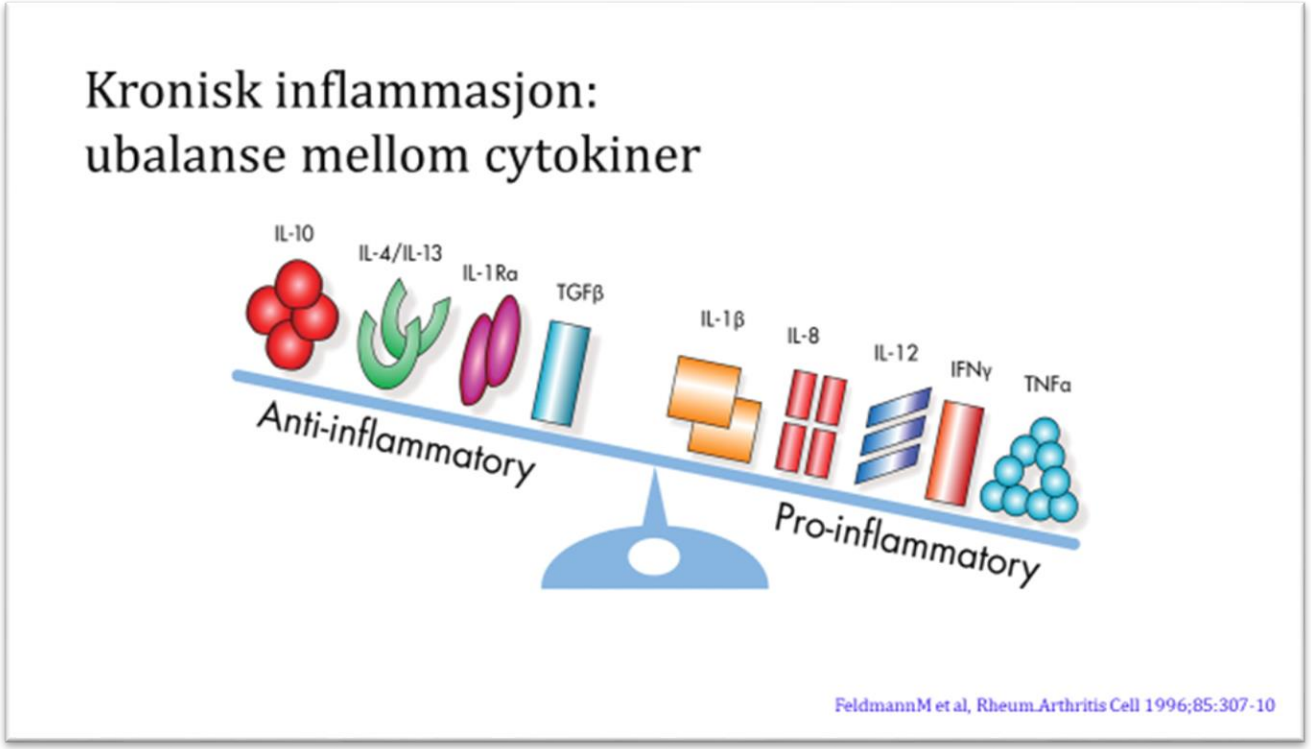
Mulighet for å forebygge IBD?



Torres et al, JCC 2021

Oppsummering patogenese og immunologi

- Mye mer komplekst enn for ti år siden….men hovedlinjene er ganske like



Aktuelle referanser

- **The four epidemiological stages in the global evolution of inflammatory bowel disease** Gilaad G. Kaplan and Joseph W. Windsor, Nature reviews Gastroenterology and Hepatology 2020
- **Ulcerative colitis** Ryan Ungaro, Saurabh Mehandru, Patrick B Allen, Laurent Peyrin-Biroulet, Jean-Frédéric Colombel, Lancet 2017; 389: 1756–70
- **Crohn's disease** Joana Torres, Saurabh Mehandru, Jean-Frédéric Colombel, Laurent Peyrin-Biroulet, Lancet 2017; 389: 1741–55
- **Precision medicine in IBD- prediction and prevention of inflammatory bowel disease** Joana Torresa,b, Jonas Halfvarson , Iago Rodríguez-Lagod , Charlotte RH Hedine,f, Tine Jessg,h, Marla Dubinskyi , Kenneth Croitoruj , Jean-Frédéric Colombelk , on behalf of the Scientific Workshop Steering Committee*, JCC 2021
- **Incidence and Prevalence of Inflammatory Bowel Disease in Norway and the Impact of Different Case Definitions: A Nationwide Registry Study** Sandre Svatun Lirhus, Marte Lie Høivik, Bjørn Moum, Karoline Anisdahl, Hans Olav Melberg, J Clin Epidemiology 2021
- **JAK–STAT pathway targeting for the treatment of inflammatory bowel disease** Azucena Salas, Cristian Hernandez-Rocha, Marjolijn Duijvestein , William Faubion, Dermot McGovern, Severine Vermeire , Stefania Vetrano, and Niels Vande Casteele Nature reviews Gastroenterology and Hepatology 2020