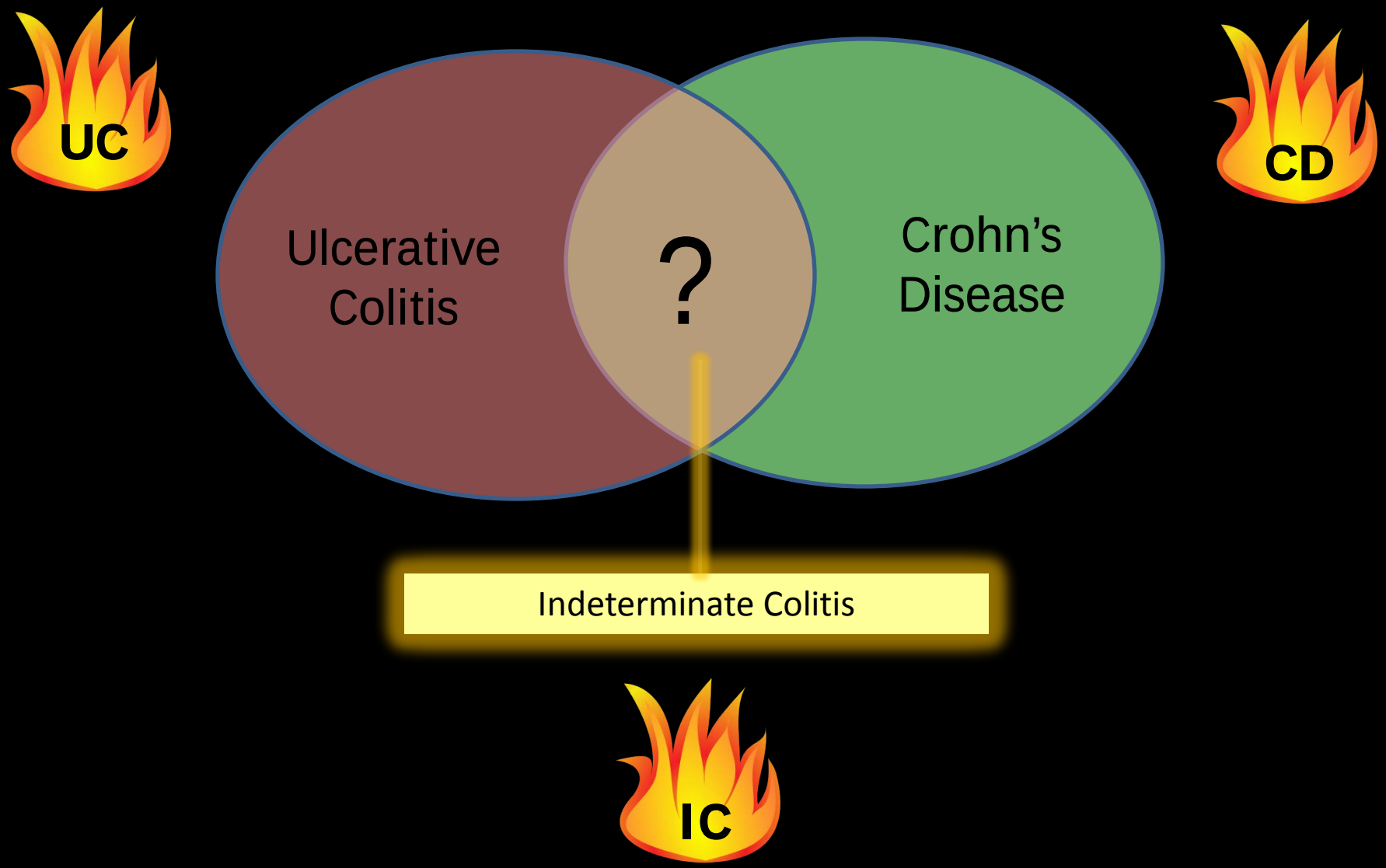
Pediatric Inflammatory Bowel Disease (IBD)

Disclaimer: I have no financial interests or conflicts of interest related to any of the material that I will present.


UC
Ulcerative Colitis
?
Crohn's Disease
CD
Indeterminate Colitis
IC

Data from several contemporary studies will referenced in this presentation and compared. For simplicity, an abbreviation is assigned to each and will be listed in brackets.

[CR] CEDATA-GPGE registry:

Buderus S, Scholz D, Behrens R, et al. for the CEDATA-GPGE study group: Inflammatory bowel disease in pediatric patients—characteristics of newly diagnosed patients from the CEDATA-GPGE registry. Dtsch Arztebl Int 2015; 112:
121–7.

[MN] Multi-National:

Isabelle Cleynen et al, “Inherited determinants of Crohn’s disease and ulcerative colitis phenotypes: a genetic association”, Lancet 2016; 387: 156–67.

[SA] Saudi Arabia:

El Mouzan MI, et al, “Incidence of pediatric inflammatory bowel disease in Saudi Arabia: a multicenter national study”, Inflamm Bowel Dis. 2014 Jun;20(6):1085-90.

[WI] Wisconsin, a state in the USA:

Kugathasan et al, “Epidemiologic and clinical characteristics of children with newly diagnosed inflammatory bowel disease in Wisconsin : a state wide population-based study” , J Pediatr 143(4):525-531 (2003).

Item	[CR]	[MN]	[SA]	[WI]
Abbr for	**CEDATA-GPGE registry**	**Multi-National**	**Saudi Arabia**	**Wisconsin**
Region	Germany and Austria	16 countries in Europe, North America, and Australasia	Saudi Arabia	Wisconsin, USA
Years	2004-2014	unstated	2003-2007 , 2008-2012	Jan 2000 - Dec 2001
Participants	1257	29,838	340	199
Ages	< 18 years old	< 17 yrs, 17-40 yrs, > 40 yrs	0-14 years old	< 18 years old
Study type	Prospective	Retrospective	Retrospective	Prospective
Source	84 hospitals, clinics and practices	49 Registry Centers	20 Gastroenterology Centers	6 academic ,5 community centers
Study	Document diagnosis and treatment	Genetic, Immunochip genotype Illumina genotyping platform, 195,806 polymorphism	Population study	Population study

UC vs Crohn's, Macroscopic*

	Ulcerative Colitis	Crohn's Disease
• Rectum involved.	Yes	Variable
• Distribution	Diffuse	Segmental or diffuse
• Terminal Ileum	Backwash ileitis	Thickened-stenosed
• Serosa	Normal	Creeping fat
• Bowel wall	Normal thickness	Thickened
• Mucosa	Hemorrhagic	Cobblestone, Linear ulcers
• Pseudopolyps	Frequent	Less Common
• Strictures, Fistulas	No	Common
• Proximal to colon	No	Common

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UC vs Crohn's, Microscopic *

	Ulcerative Colitis	Crohn's Disease
• Inflammation	Mucosa, Superficial Submucosa	Transmural
• Lymphoid hyperplasia.	Infrequent	Common
• Crypt abscess	Extensive	Focal
• Mucus depletion	Frequent	Infrequent
• Deep sarcoid like granulomas	No	Yes
• Fissures, sinuses	No	Yes
• Villous surface transformation.	Common	Infrequent
• Submucosal fibrosis.	Rare	Common
• Neuromatous hyperplasia.	Rare	Common

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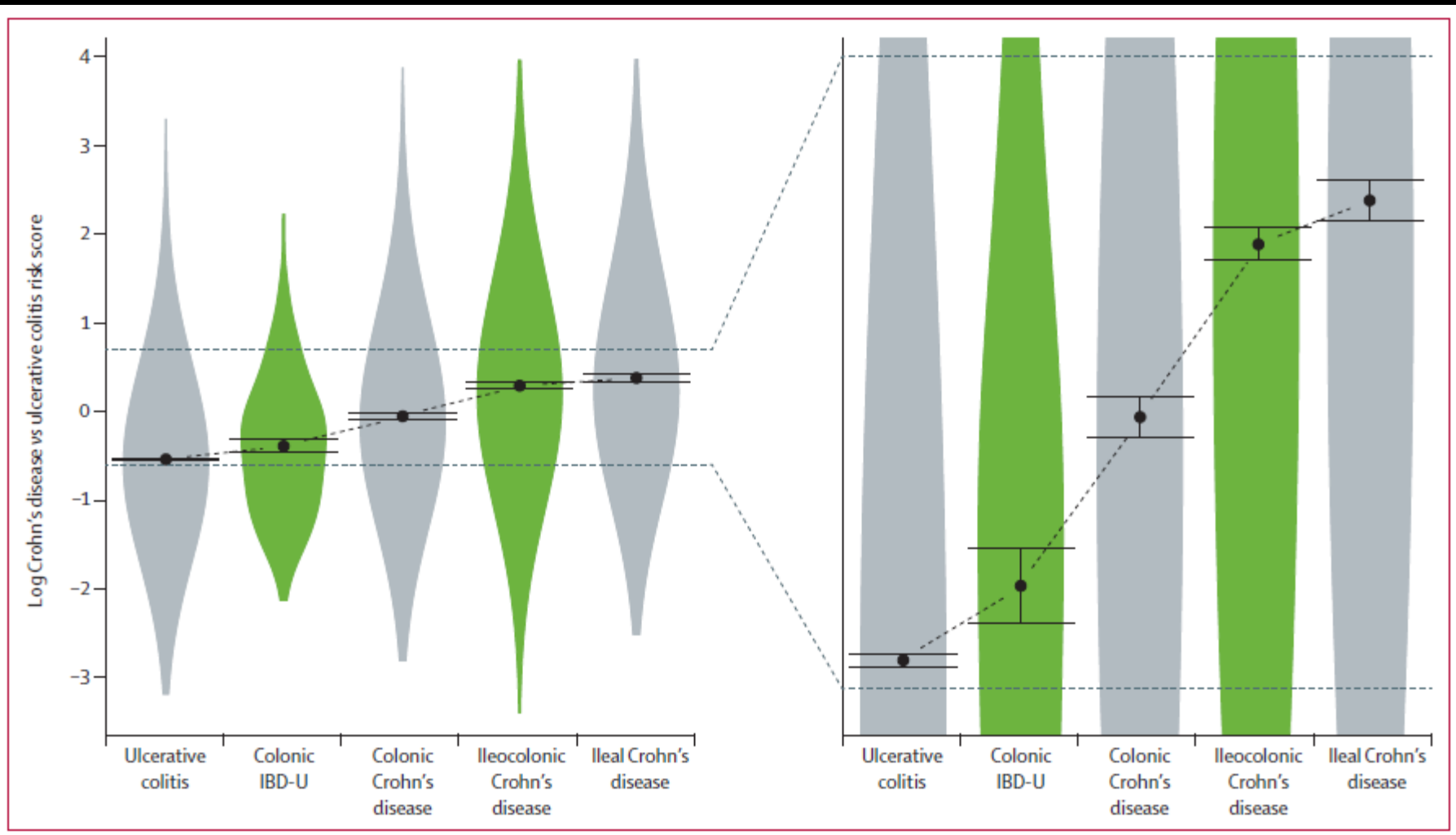
Subphenotypes of IBD – by Genetic Studies

- 49 centers in 16 countries in Europe, North America, and Australasia
- 29,838 patients (16,902 - Crohn's disease, 12,597 - ulcerative colitis).
- Genetic studies have identified 163 susceptibility loci for inflammatory bowel disease, mostly shared between Crohn's disease and ulcerative colitis.
- "Three loci (NOD2, MHC, and MST1 3p21) were associated with subphenotypes of inflammatory bowel disease, mainly disease location"
- "Our data support a continuum of disorders within inflammatory bowel disease, much better explained by three groups (ileal Crohn's disease, colonic Crohn's disease, and ulcerative colitis) than by Crohn's disease and ulcerative colitis as currently defined."

Isabelle Cleynen et al, "Inherited determinants of Crohn's disease and ulcerative colitis phenotypes: a genetic association", Lancet 2016; 387: 156–67.



- 163 susceptibility loci used to make a risk score (negative favors UC, positive favors CD)
- Scores predicted disease location along a continuum.

Isabelle Cleynen et al

Etiology not understood well - Inappropriate immune response (microbial or food) in genetically susceptible host.

- Proinflammatory cytokines TNF-α, IL-1β, Inf-γ, and IL-23 / IL17A pathway.
- Anti-Inflammatory cytokines, Dysfunction of IL-10 and its receptor.

More common in industrialized societies, possibly from a less educated gut immune system.

Incidence of IBD in first degree relatives:

- in patients < 5 yrs old = 56%
- in patients < 20 yrs old = 30%

25-35% of IBD patients have extraintestinal disease:

- arthritis (7-25%), transient, nondeforming synovitis, asymmetric, common in knees
- ankylosing spondylitis (2-6%), HLA-B27
- erythema nodosum (3% pediatric CD when active, anterior legs)
- pyoderma gangrenosum (< 1%, indolent chronic ulcer, can be in remission)

- Pathology of Pediatric Gastrointestinal and Liver Disease, 2nd Ed, ©2014. Edited by Pierre Russo, Eduardo D. Rucelli, and David A. Piccoli

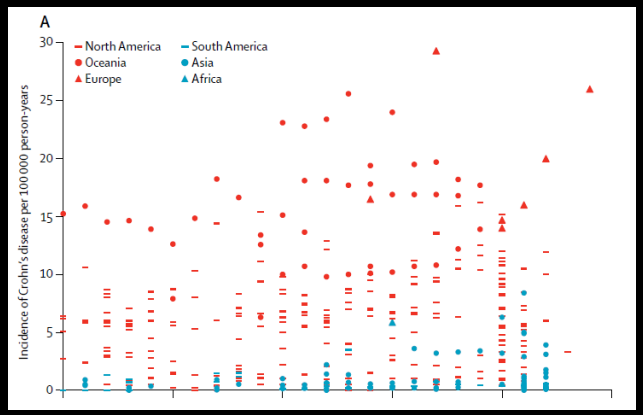
Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies

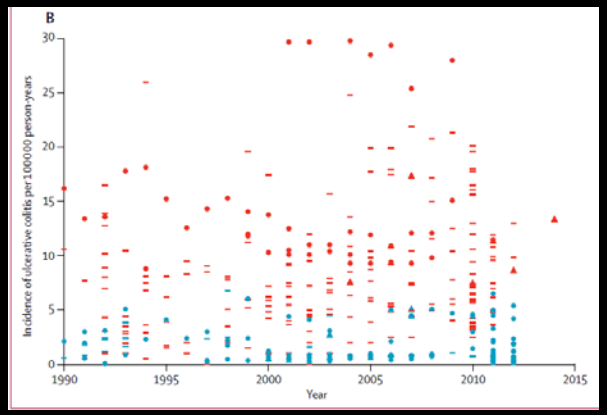
Siew C Ng, Hai Yun Shi, Nima Hamidi, Fox E Underwood, Whitney Tang, Eric I Benchimol, Remo Panaccione, Subrata Ghosh, Justin C Y Wu, Francis K L Chan, Joseph J Y Sung, Gilaad G Kaplan**

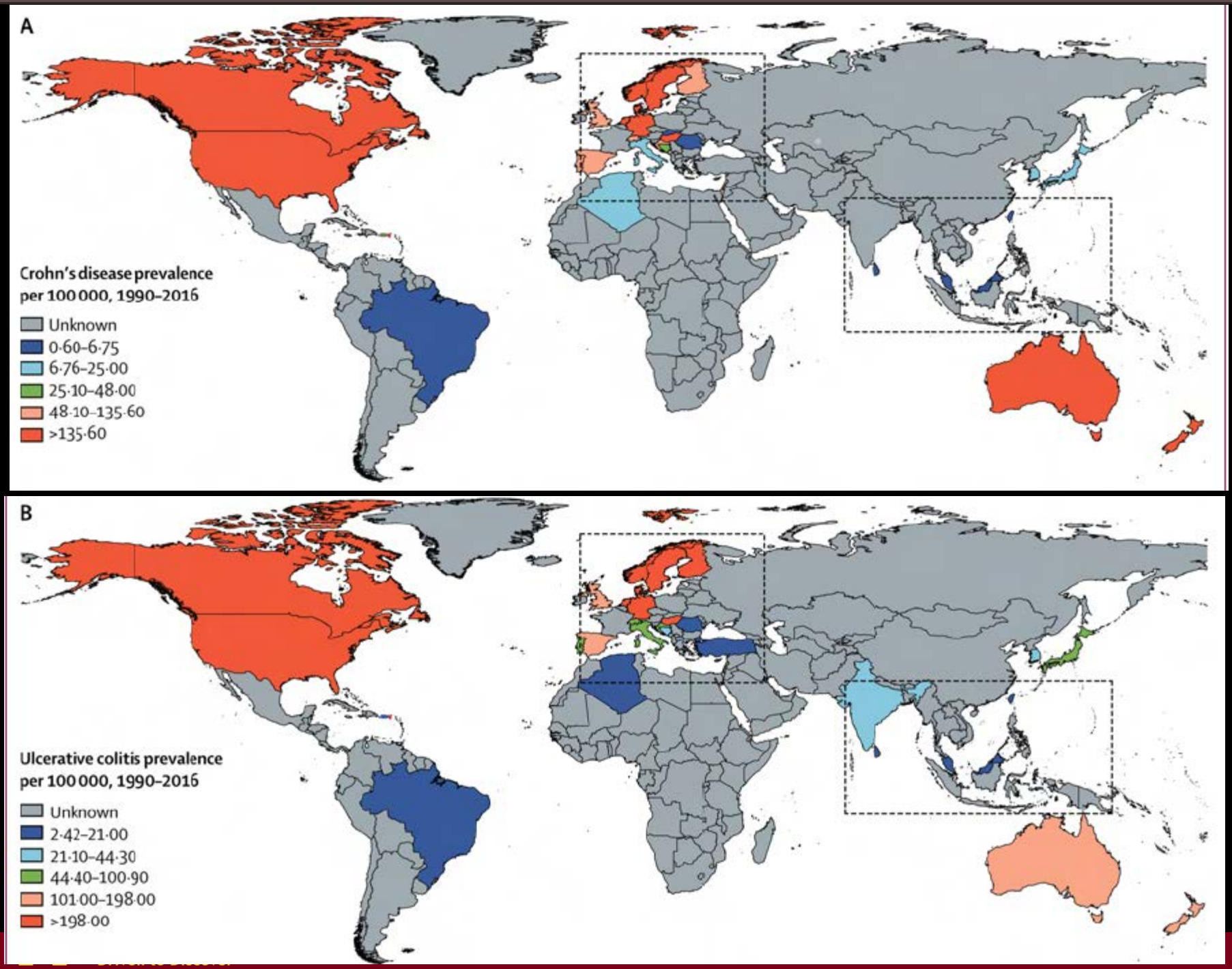
The Lancet, published online October 16, 2017

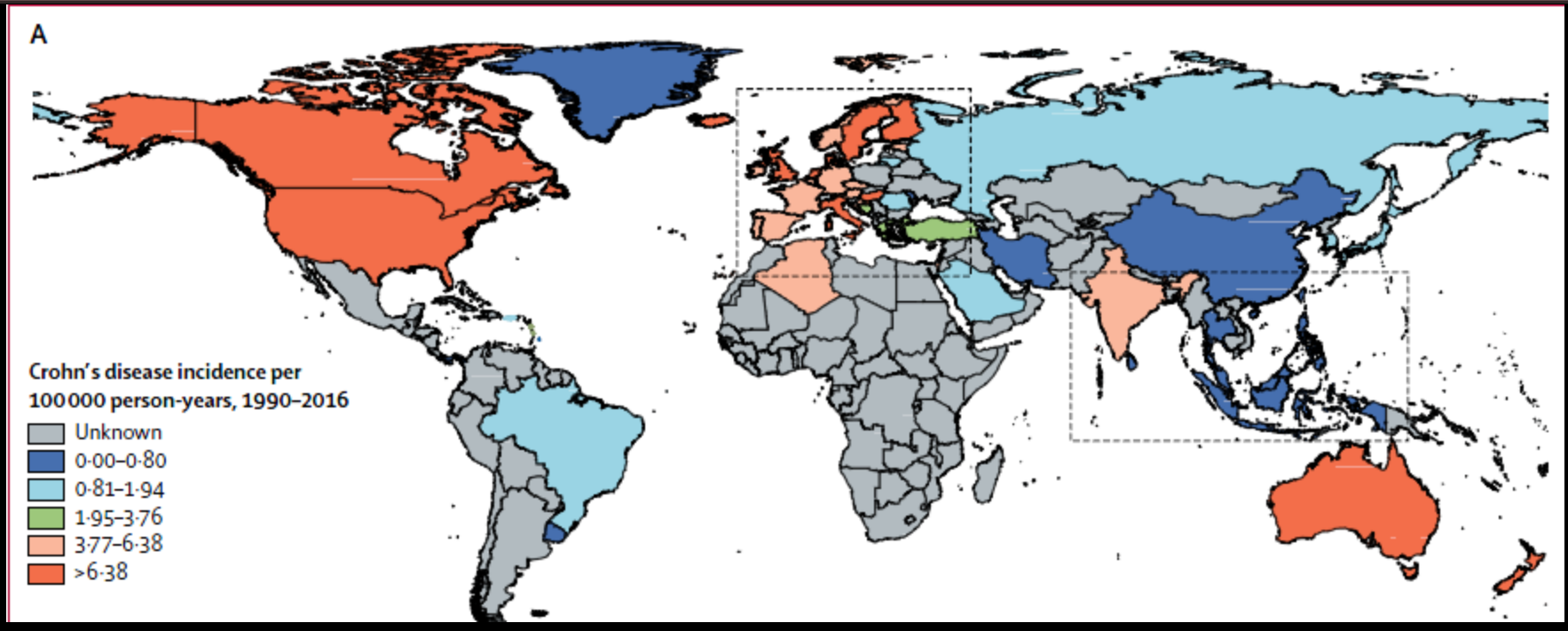
Findings We identified 147 studies that were eligible for final inclusion in the systematic review, including 119 studies of incidence and 69 studies of prevalence. The highest reported prevalence values were in Europe (ulcerative colitis 505 per

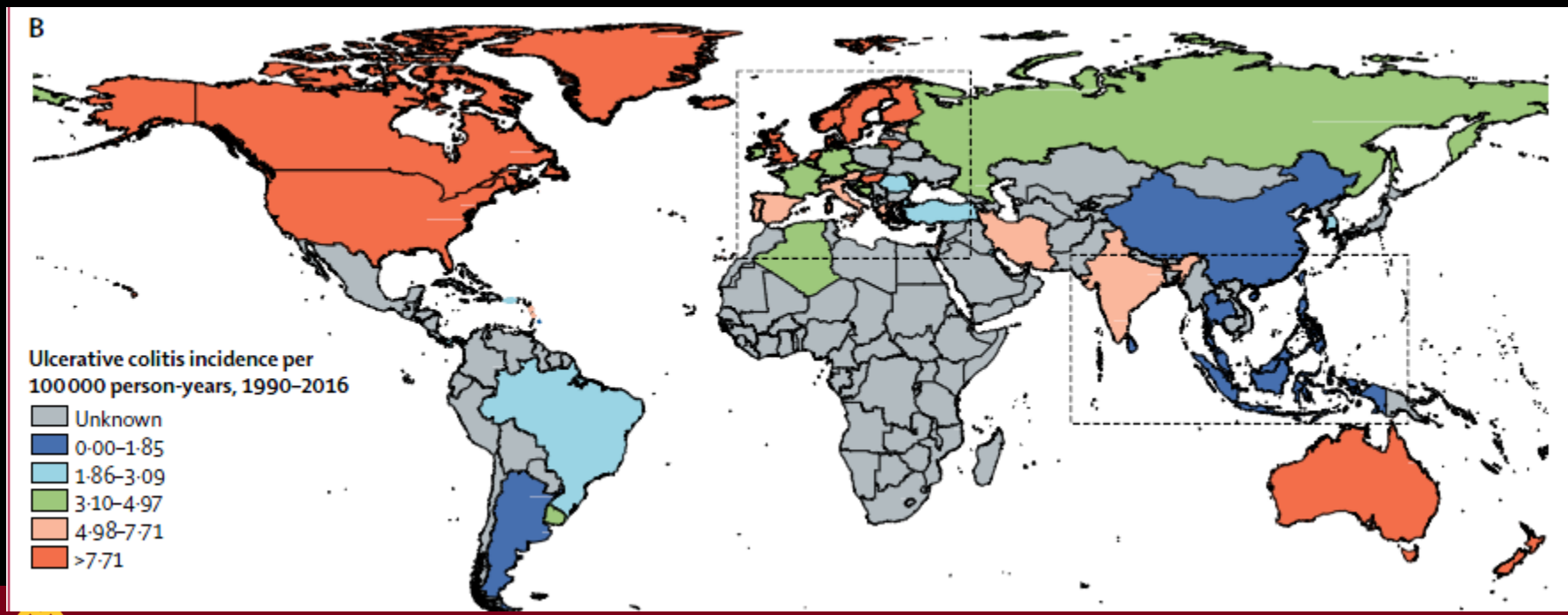
Incidence of IBD rose in North America and Europe latter half of 20th century until 1990 when plateaued or decreased. At the same time, since 1990, the incidence is on the rise in newly industrialized countries.






A
Crohn's disease prevalence per 100 000, 1990–2016
Unknown
0·60–6·75
6·76–25·00
25·10–48·00
48·10–135·60
>135·60
B
Ulcerative colitis prevalence per 100 000, 1990–2016
Unknown
2·42–21·00
21·10–44·30
44·40–100·90
101·00–198·00
>198·00

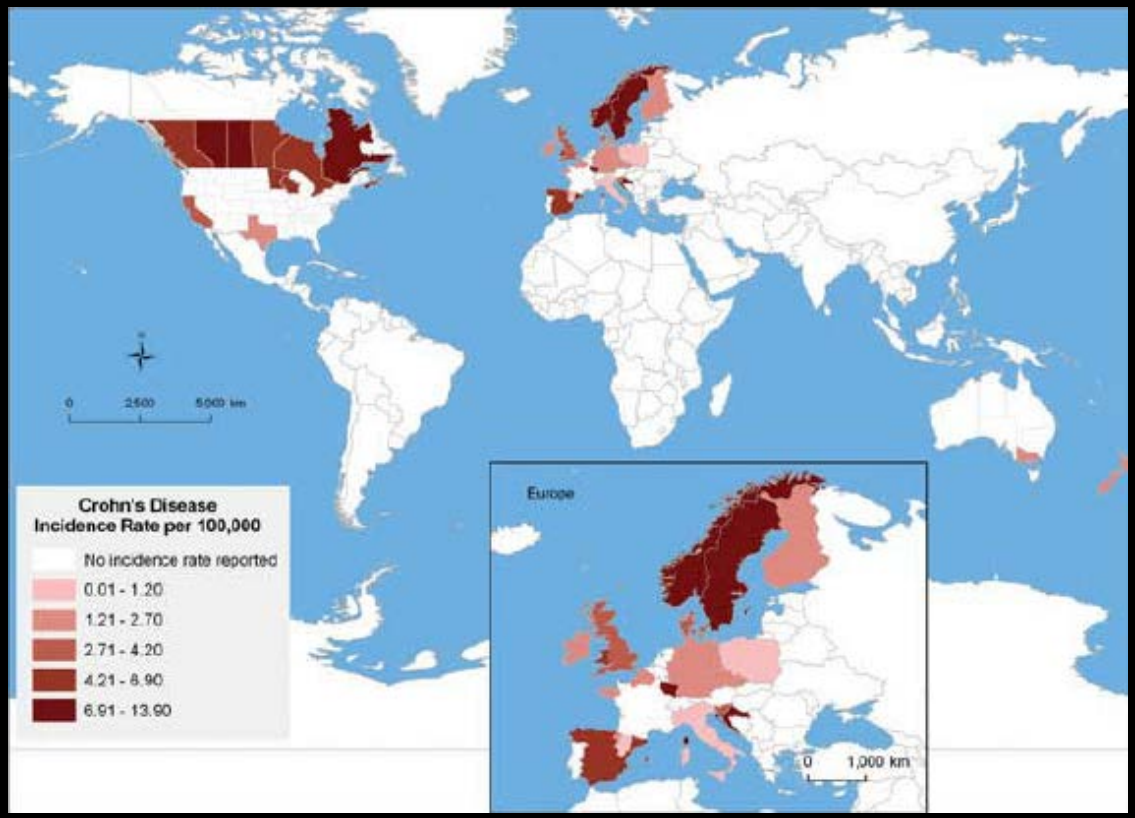


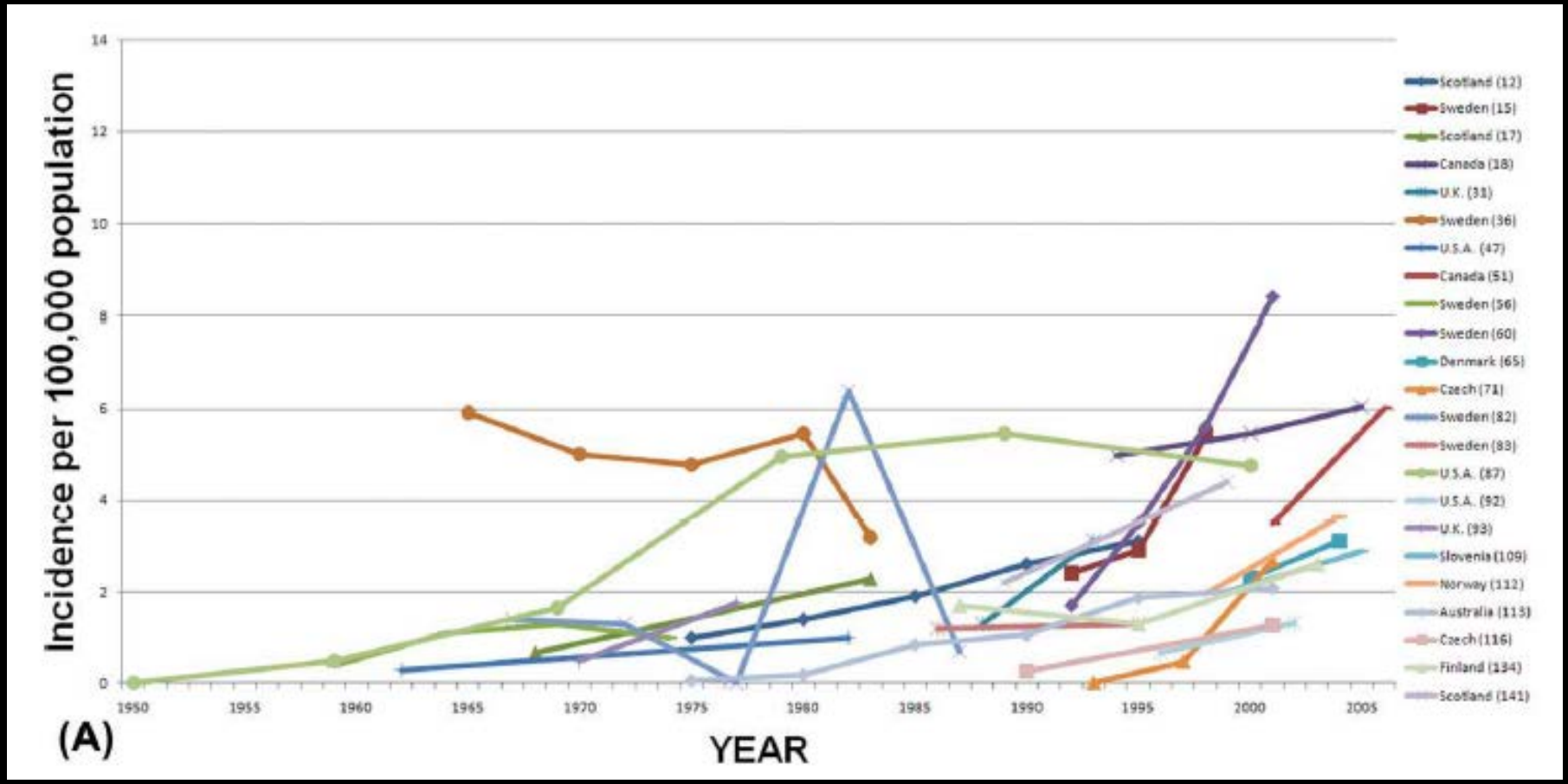


Epidemiology of Pediatric Inflammatory Bowel Disease: A Systematic Review of International Trends

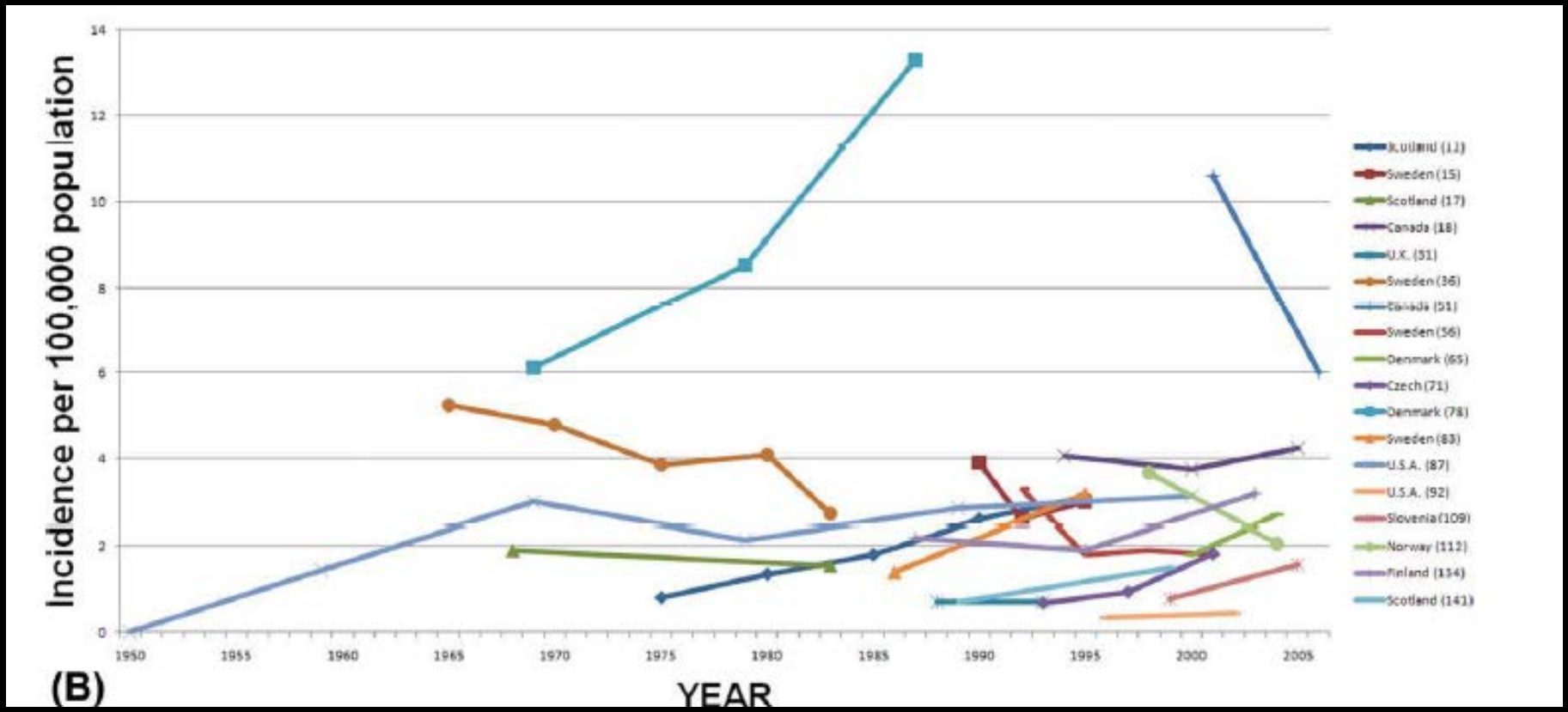
Eric I. Benchimol, MD, PhD,[,†,‡,§,‖] Kyle J. Fortinsky, BSc,[*,†] Peter Gozdyra, MA,[‖] Meta Van den Heuvel, MD,[§] Johan Van Limbergen, MD, PhD,[‡,§] and Anne M. Griffiths, MD[‡,§]*

Inflamm Bowel Dis 2011;17:423-439 Literature: 139 studies from 32 countries



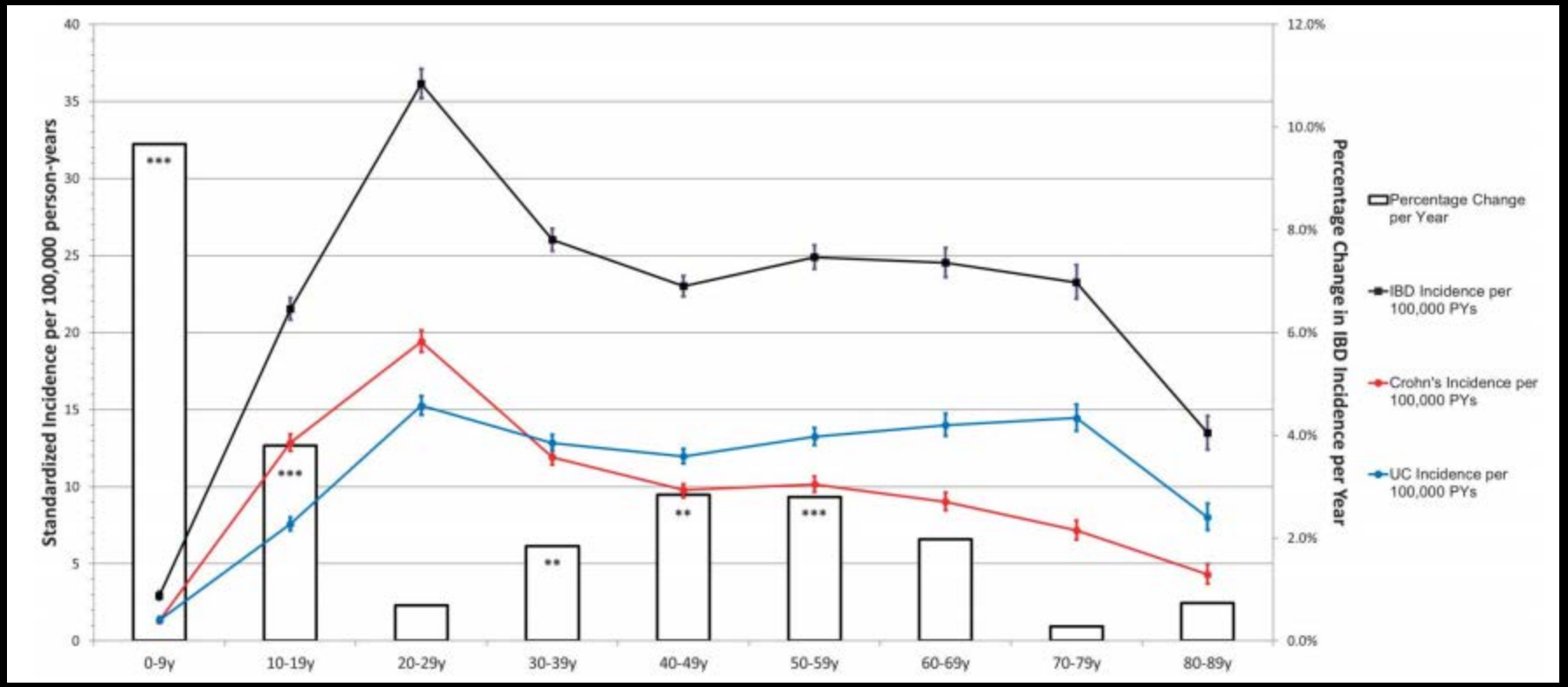


Crohn's Disease Incidence from 1990 to 2010



Ulcerative Colitis Incidence from 1990 to 2010

15 Benchimol EI, Manuel DG, Guttmann A, et al. Changing age demographics of inflammatory bowel disease in Ontario, Canada: a population-based cohort study of epidemiology trends. *Inflamm Bowel Dis* 2014; 20: 1761–69.



Differences in Children vs Adults

Adults

- Cryptitis and crypt abscesses most likely IBD.
- Crohn's more commonly ileal and proximal colon.
- Ulcerative colitis usually distal colon.

Children

- Present with growth failure.
- Cryptitis and crypt abscesses might be self limited colitis.
- Genetic factors in early onset IBD.
- Family history in 40% of affected children.
- Crohn's colitis more prevalent in children.
- Ulcerative colitis is pan colitis.
- Isolated ileal disease less in younger.
- More strictures and fistulas.
- Shorter time from diagnosis to colectomy.
- More frequently progress from limited to extensive disease.

Rectal Sparing (RS) in Children

- In adults, UC tends to start in rectum and proceed proximally in a confluent fashion.
- Absolute RS – no inflammation or chronicity
- Relative RS – inflammation but no chronicity
- In various studies up to 25% of children with ulcerative colitis have relative rectal sparing, many fewer absolute.

IBD vs Acute Self Limited Colitis (ASLC)

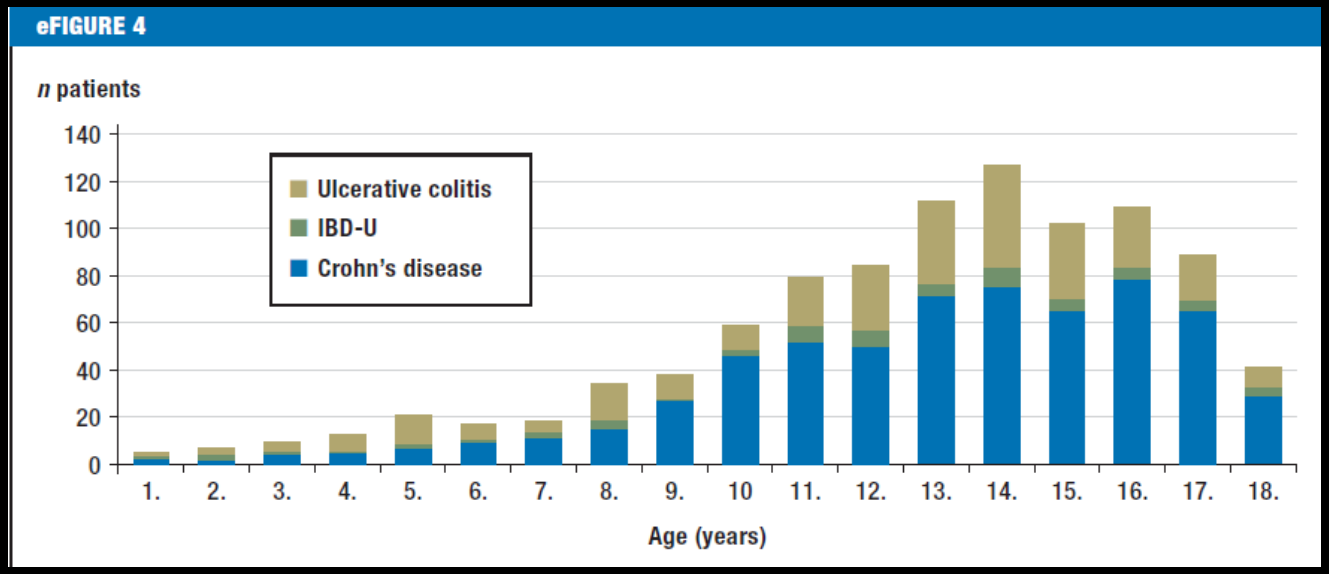
Diarrhea lasting for more than a few weeks without identification of a pathogen more likely to have IBD. Salmonella, Campylobacter, Yersinia may be found in upto 15% of patients with IBD. (G Schumacher, "First attack of inflammatory bowel disease and infectious colitis. A clinical, histological and microbiological study with special reference to early diagnosis", Scand J Gastroenterol Suppl. 1993;198:1-24.)

ASLC
- no signs of chronicity
- neutrophils in superficial mucosa, sometimes with small ulcers
- cryptitis and crypt abscesses may occur
- numerous crypt abscess may be UC, CD, or C. difficile.

New onset IBD
- in adults will show chronicity (branching, shortening, dropout, basal plasmacytosis)
- in pediatric patients 10-34% show no signs of chronicity (especially <10 years old)
- in pediatric patients, Paneth cells in 11/13 UC and 14/15 CD and none in controls*
- in pediatric patients Paneth cell metaplasia anywhere in colon only seen in IBD, and not necessarily with inflammation – not associated with chronicity. (more than 10 Paneth cells per 10 crypts)*

Naomi Simmonds, et al, "Paneth cell metaplasia in newly diagnosed inflammatory bowel disease in children", Gastroenterology 2014, 14:93.

[CR]



[MN] - X

[SA]

0-4 yr	15.9%
5-9 yr	31.5%
10-14 yr	52.6%

[WI]

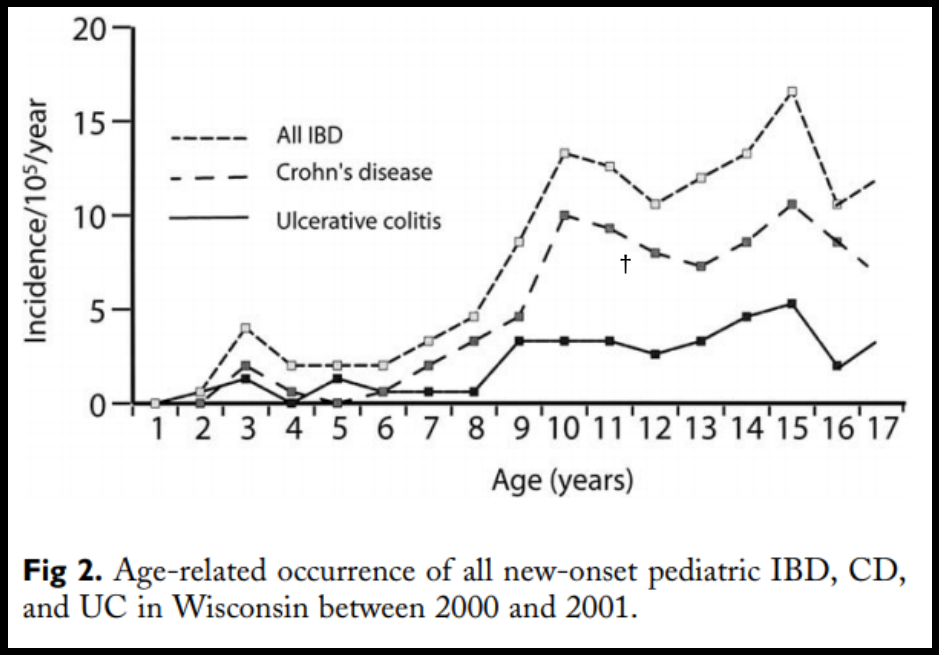


Fig 2. Age-related occurrence of all new-onset pediatric IBD, CD, and UC in Wisconsin between 2000 and 2001.

Equal distribution among all racial and ethnic groups

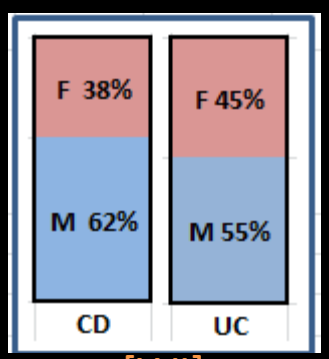
No modulatory effect of urbanization

Possibly environmental factors

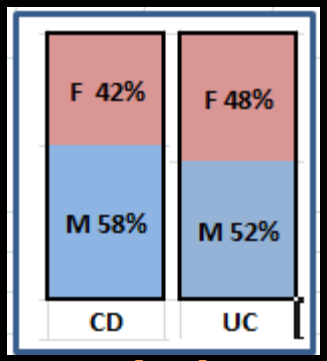
Percent of IBD – CD, UC, IC

↓Data Study→	[CR]	[MN]	[SA]	[WI]
CD	64	57	57	65
UC	29	43	43	30
IC	7	-	-	5
CD/UC =	2.2	1.3	1.3	2.2
USA Census 2000 reported 42.7% of population claimed German ancestory, 2005 - 39.6% German, 0.5% Austrian				

Distribution by Gender



[WI]



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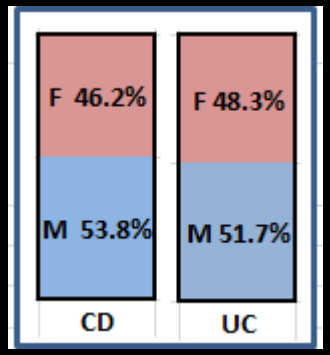
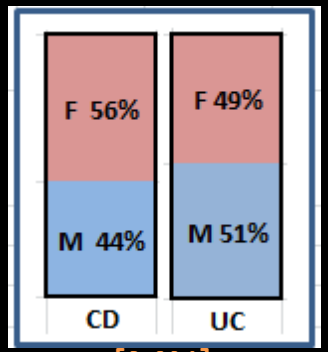


[SA]



[MN]

- Ileal inflammation can be backwash ileitis (<10 cm involved, no thickening, no stenosis of ICV, no granulomas).

- Upper GI involvement in up to 30% of CD.

- Upper GI findings (granulomas in stomach) may compel a diagnosis change from a previous lower GI study.

- Reflux and H pylori do happen in context of IBD.

- "Focal Enhanced Gastritis" (perifoveolar or periglandular mononuclear or neutrophilic infiltrates) favor CD over UC: CD (52%)/UC (8%) *; CD (43%)/UC (12%)/Cntrl (19%)†; CD (65.1%)/ UC (20.8%)/ Ctrl (2.3%)/ HP(2.6%) ‡.

* P. S. Kundhal, "Gastral Antral Biopsy in the Differentiation of Pediatric Colitides", Am J Gastroenterol 2003;98:557–561. © 2003

† Fabrizio Parente, M.D., "Focal Gastric Inflammatory Infiltrates in Inflammatory Bowel Diseases: Prevalence, Immunohistochemical Characteristics, and Diagnostic Role", Am J Gastroenterol 2000;95:705–711. © 2000

‡F. Sharif, "Focally Enhanced Gastritis in Children With Crohn's Disease and Ulcerative Colitis", Am J Gastroenterol 2002;97:1415–1420. © 2002

- Superficial inflammation in the appendix (cryptitis and crypt abscesses) and no transmural inflammation, sometimes in UC.

- Do not overcall loose or mucin granulomas as CD.

- Tuberculous granulomas tend to be multiple, large, caseous.

- Yersina, Schistosomes, CGD other considerations.

- Marked reduction in plasma cells – possible immune deficiency.

- Absence of goblet or Paneth cells – autoimmune.

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Lectures at: IBDregistry.net

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