



Epidemiology of Inflammatory Bowel Disease

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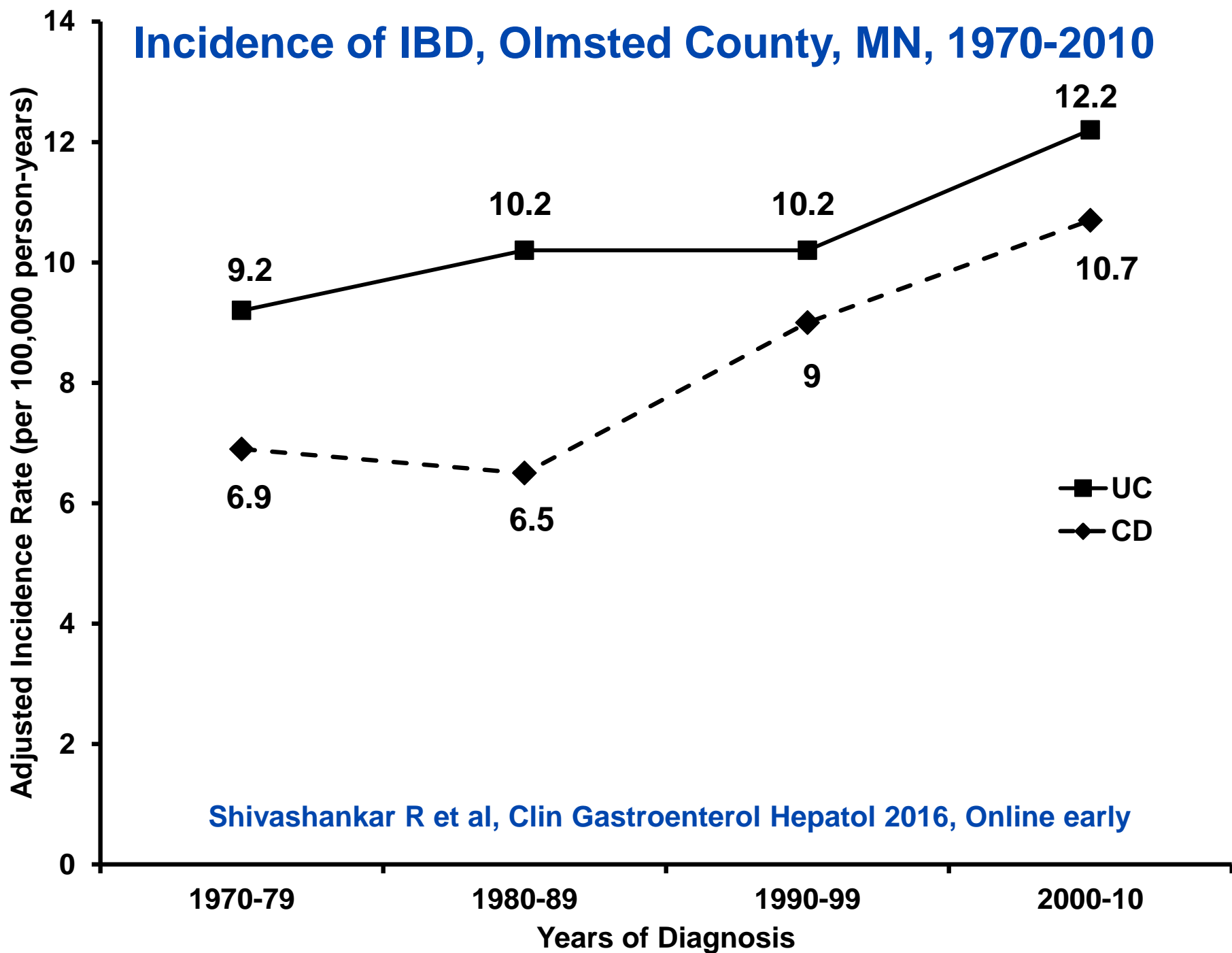
Loftus Disclosures (last 12 months)

- Research support
 - AbbVie
 - Janssen
 - Takeda
 - UCB
 - Genentech/Roche
 - Amgen
 - Pfizer
 - Robarts Clinical Trials
 - Gilead
 - Receptos
 - Seres Therapeutics
 - Celgene
- Consultant
 - AbbVie
 - UCB
 - Janssen
 - Takeda
 - Salix
 - Pfizer
 - Eli Lilly
 - Mesoblast
 - CVS Caremark

Overview

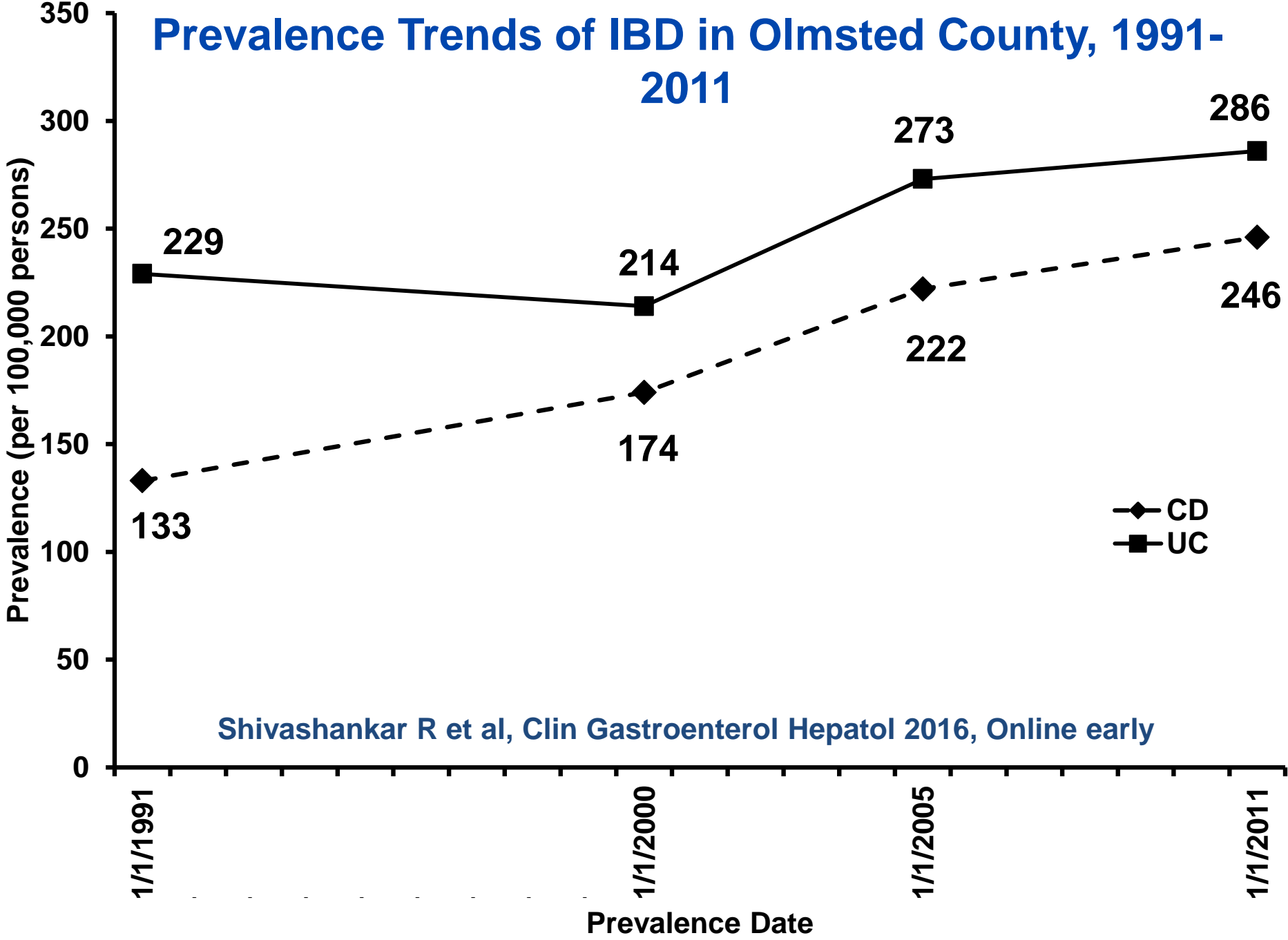
- Incidence and Prevalence
- New Regions
- Racial/Ethnic Differences
- Risk Factors
 - “Old”: smoking, appy, etc.
 - “New”: hygiene, antibiotics, diet, etc.

Incidence of IBD, Olmsted County, MN, 1970-2010



Shivashankar R et al, Clin Gastroenterol Hepatol 2016, Online early

Prevalence Trends of IBD in Olmsted County, 1991-2011



Shivashankar R et al, Clin Gastroenterol Hepatol 2016, Online early

Prevalence of IBD in Olmsted County, Minnesota, 2011

	Prevalence (per 100,000)
Ulcerative Colitis	286
<u>Crohn's Disease</u>	<u>246</u>
Total IBD	532

(or 0.53% or about 1 in 200)

If extrapolated to estimated U.S. population of 324 million today, there are approximately 1.6-1.7 million persons with IBD in the U.S. currently

Estimates of IBD Prevalence – North America

Location	Prevalence Date	UC Prevalence	Crohn's Prevalence
Olmsted County, MN	Jan 1, 2005	273	222
Manitoba	1998 – 2000	248	271
Canada, 5-province	1998 – 2000	194	234
9 HMO (CCFA/CDC)	1999 – 2001	191	129
PharMetrics	2003 – 04	238	201

Ingle SB, et al. Gastroenterology 2007;132(Suppl):A19.

Bernstein CN, et al. Am J Gastroenterol 2006;101:1559.

Herrinton LJ, et al. Inflamm Bowel Dis 2007;13:451.

Kappelman MD, et al. Clin Gastroenterol Hepatol 2007;5:1424.

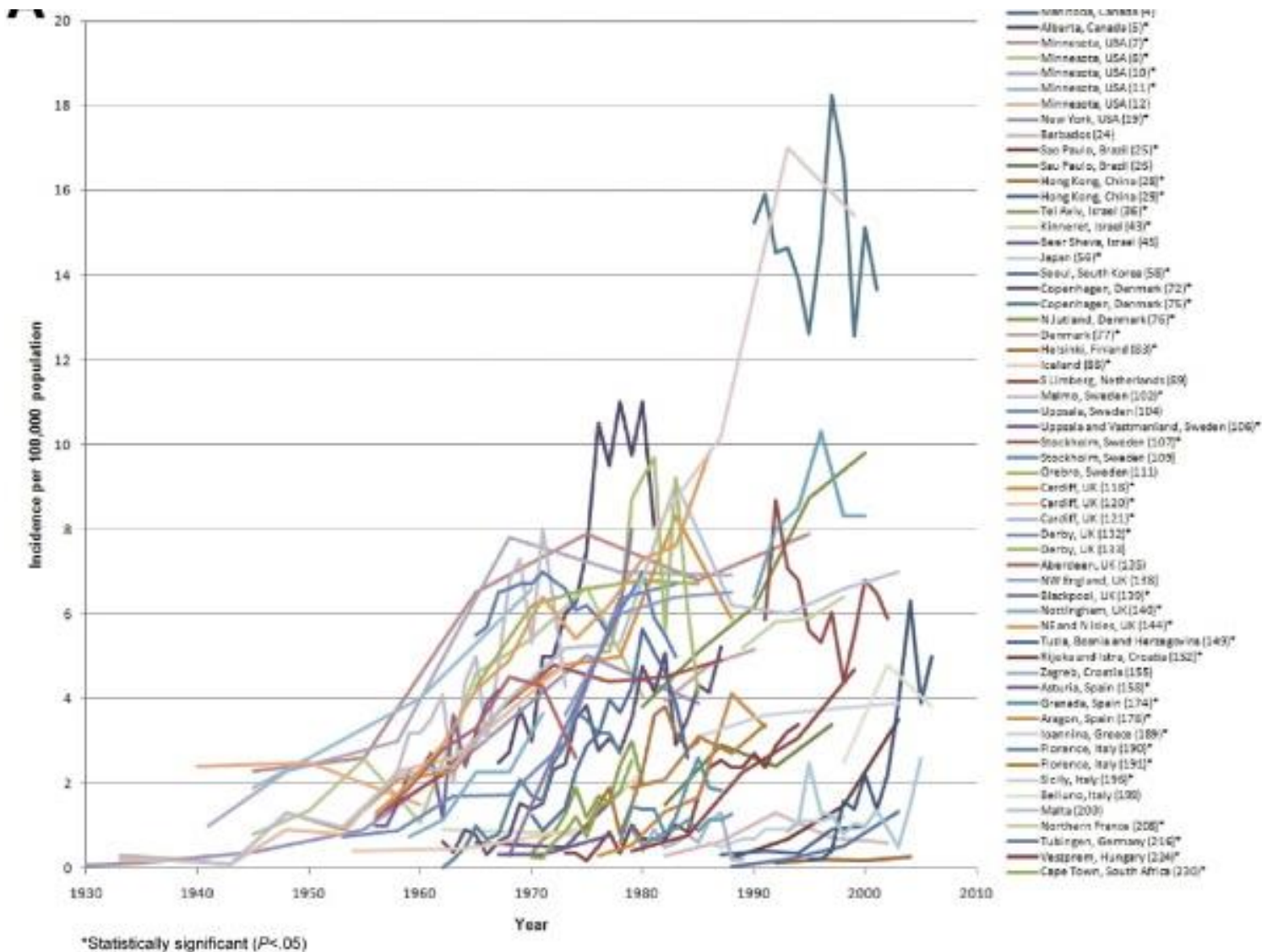
Recent Estimate of US Prevalence of IBD Using National Health Interview Survey

- 1999 NHIS estimate = 1.8 million persons with IBD (0.9% of population)¹
- 2015 NHIS²
 - 33,672 respondents across US; response rate had been approximately 55%
 - Estimated that 3.0 million persons in US had ever received IBD diagnosis (1.3%)
 - Limitations
 - Self-reported; answered yes to “Have you ever been told by a doctor or other healthcare professional that you had Crohn’s disease or ulcerative colitis?”--no medical record validation
 - Excludes those in long-term care, military, prison
 - Concerns about non-response bias

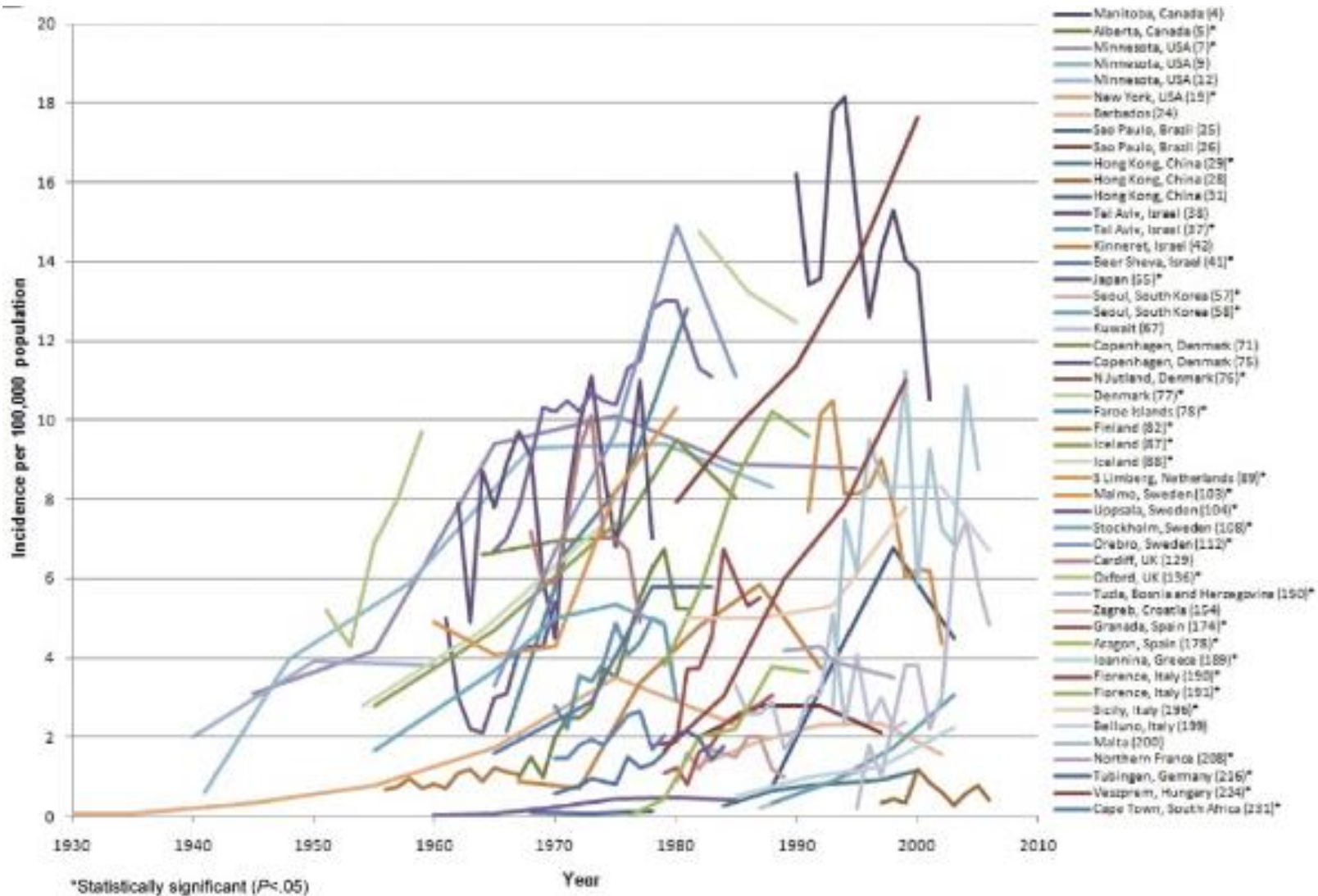
¹Nguyen GC et al, J Crohns Colitis 2014;8:288-95

²Dahlhamer JM et al, MMWR 2016;65:1166-9

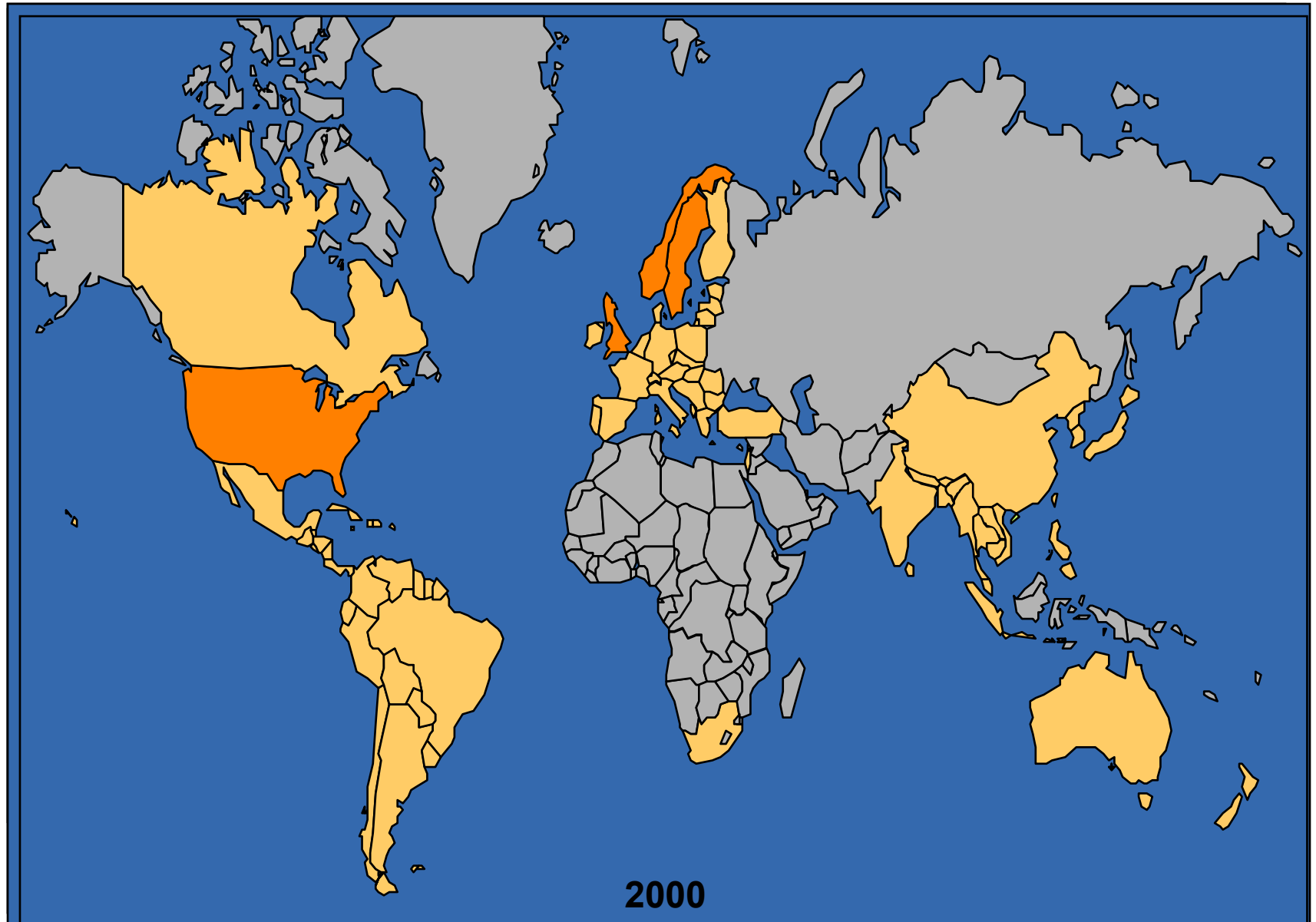
Temporal Trends in Crohn's Incidence



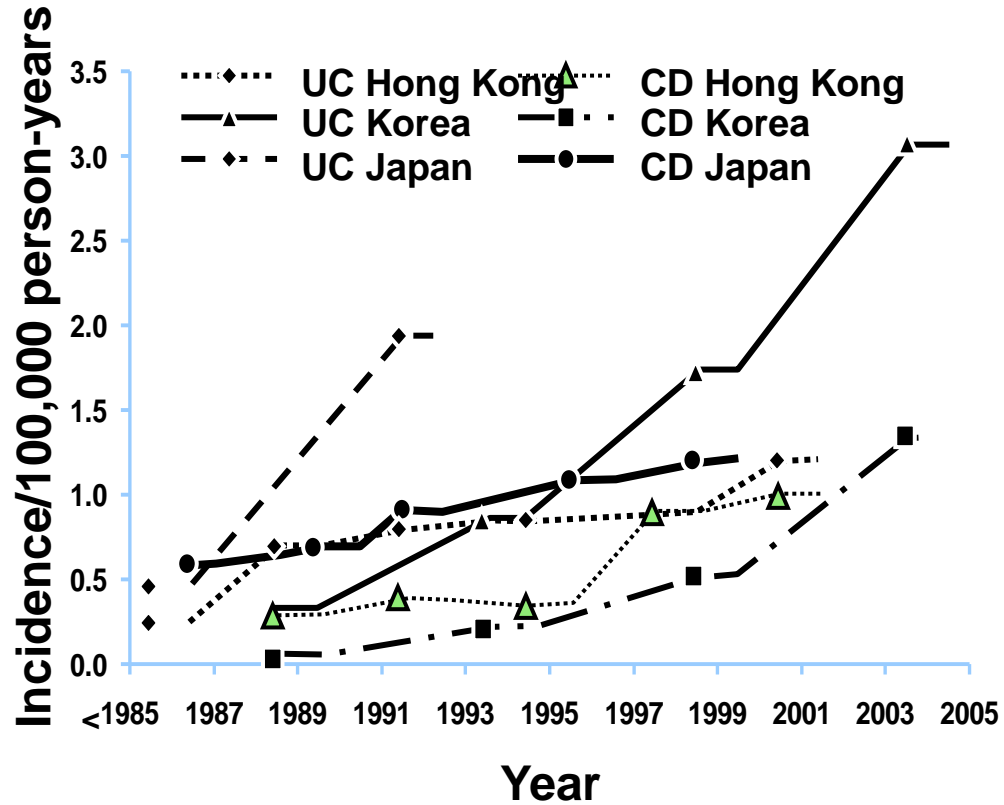
Temporal Trends in UC Incidence



Changing Geographic Distribution of IBD

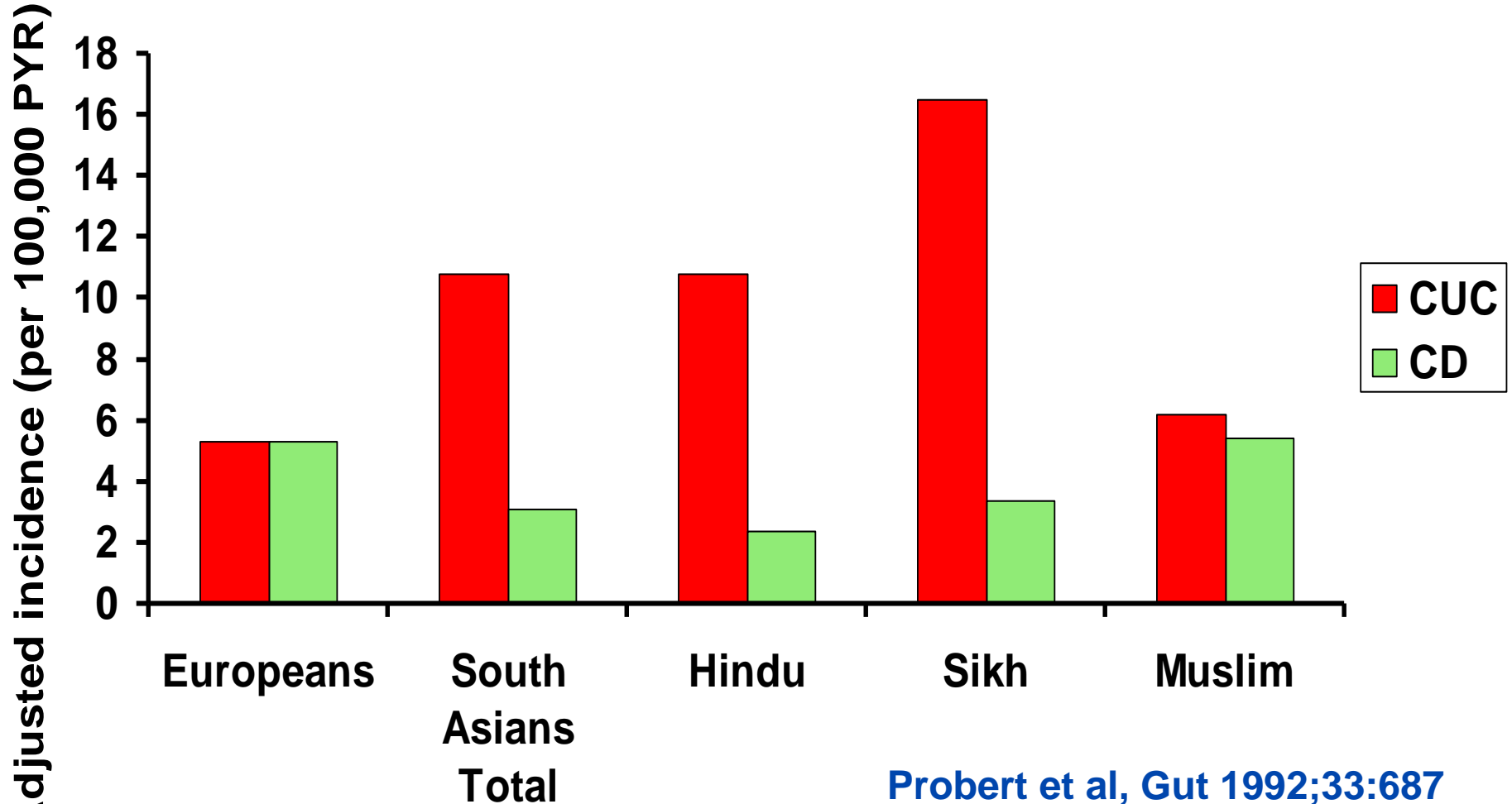


Rise of IBD in Asia



Thia KT et al, Am J Gastroenterol 2008;103:3167-82.

Incidence of IBD Among South Asians and Native Britons in Leicestershire, 1981-89



Probert et al, Gut 1992;33:687
Jayanthi et al, QJMed 1992;82:125

Incidence and Prevalence of IBD in US Among Racial/Ethnic Groups

Group	UC Prev Per 10⁵	CD Prev Per 10⁵	IBD Inc Per 10⁵ PY	IBD Prev Per 10⁵
African American	25-130	29.8-89	24.9	239-324
Hispanic	35-100	15-47	9.9	147-383
Asian American	40-100	5.6-62	n/a	162

Kurata JH et al, Gastroenterology 1992;102:1940-8.

Betteridge JD et al, Inflamm Bowel Dis 2013;19:1421-7.

Wang YR et al, Digestion 2013;88:20-5.

Nguyen GC et al, J Crohns Colitis 2014;8:288-95.

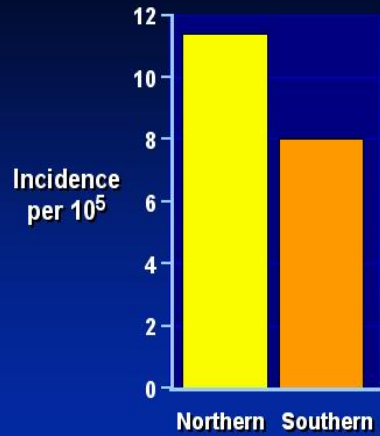
Adapted from Afzali A & Cross RK. Inflamm Bowel Dis 2016;22:2023-40.

Are There Differences in Phenotype of IBD Among Racial/Ethnic Groups?

- African-Americans more likely to have Crohn's than UC; also may be a slight female predominance
 - Less influence of NOD2 in Crohn's?
- For UC, Asians and Hispanics more likely to have extensive involvement
- Hispanics seem to be diagnosed with IBD at older age than whites and African-Americans
- No consistent trends noted related to extent and behavior of Crohn's and to prevalence of EIM

Afzali & Cross, Inflamm Bowel Dis 2016;22:2023-40

IBD - North / South Gradient



Shivananda et al., *Gut* 1996; 39:690



“North-South Gradient”

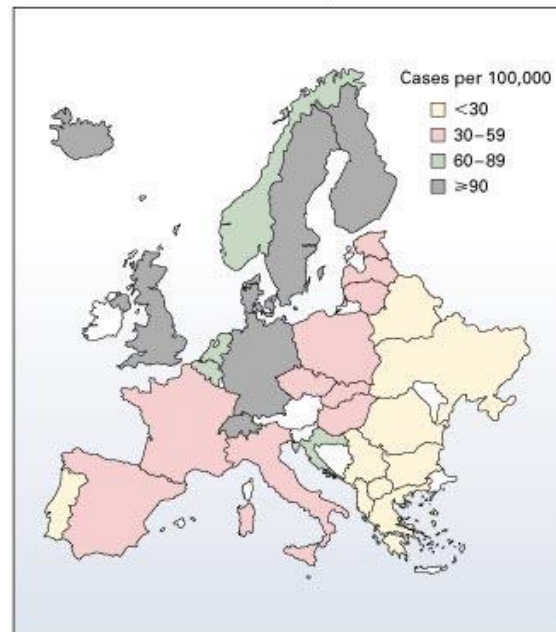
Not just IBD...

Shivananda S, et al. *Gut* 1996; 39: 690-7.

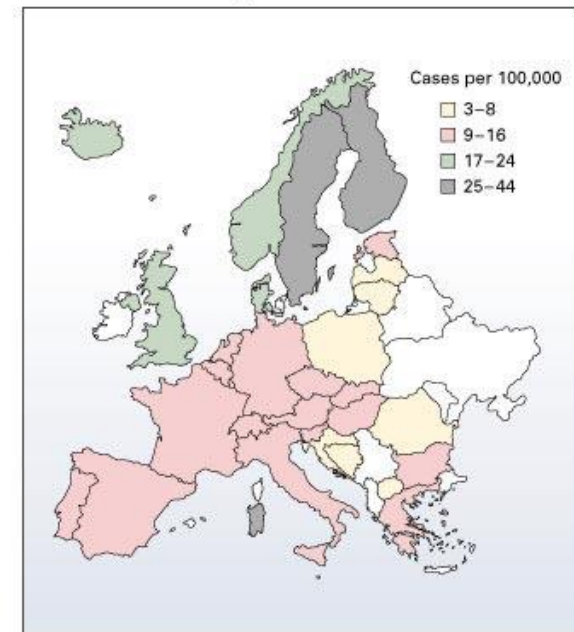
...but also in other immune-mediated diseases.

Bach JF. *N Engl J Med* 2002.

A Prevalence of Multiple Sclerosis



B Incidence of Type 1 Diabetes in Children

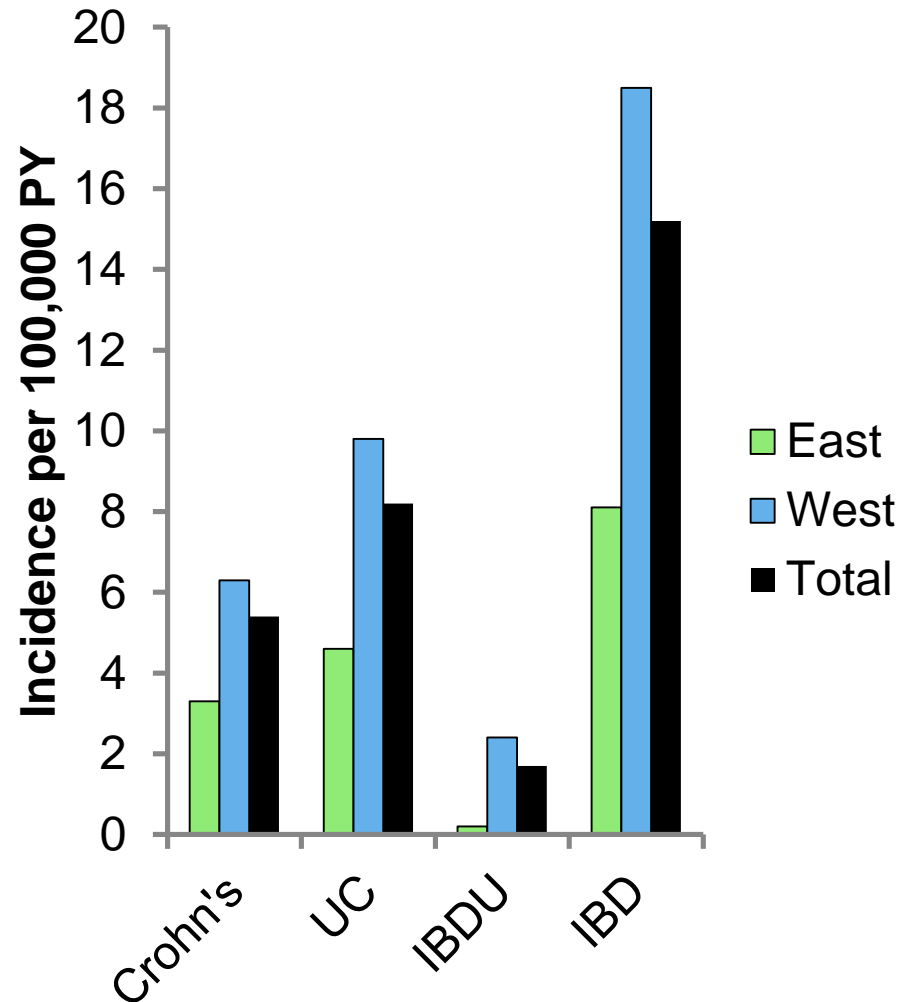


North-South Gradient in US?

- Nurses' Health Studies
- Geographic residence at birth, and ages 15 years and 30 years recorded
- Stratified incidence by northern, middle, and southern latitudes
- Effect was strongest for residence at age 30
- Incidence of UC was 36% lower in southern latitudes relative to northern
- Incidence of Crohn's was 53% lower in southern relative to northern

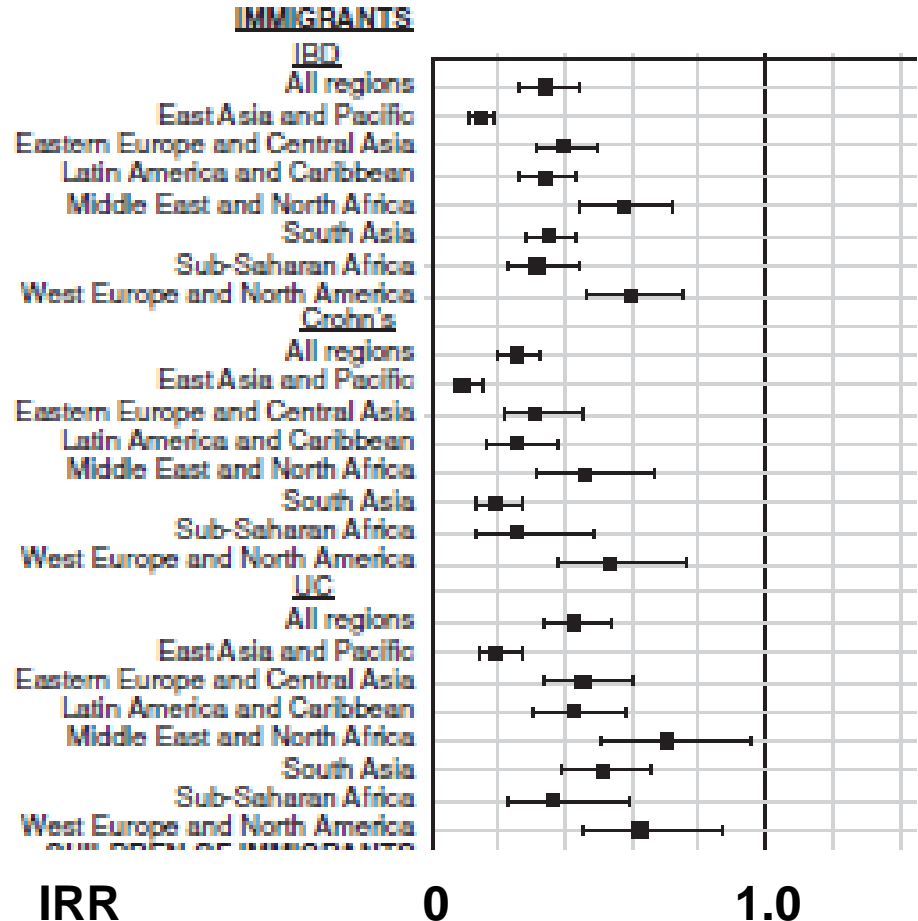
West-East Gradient in Europe, 2010

- ECCO EpiCom cohort (n=1515)
- Prospective inception cohort from 31 centres in 14 Western and 8 Eastern European countries
- Excludes those under 15 years of age
- IBD more than twice as common in Western Europe



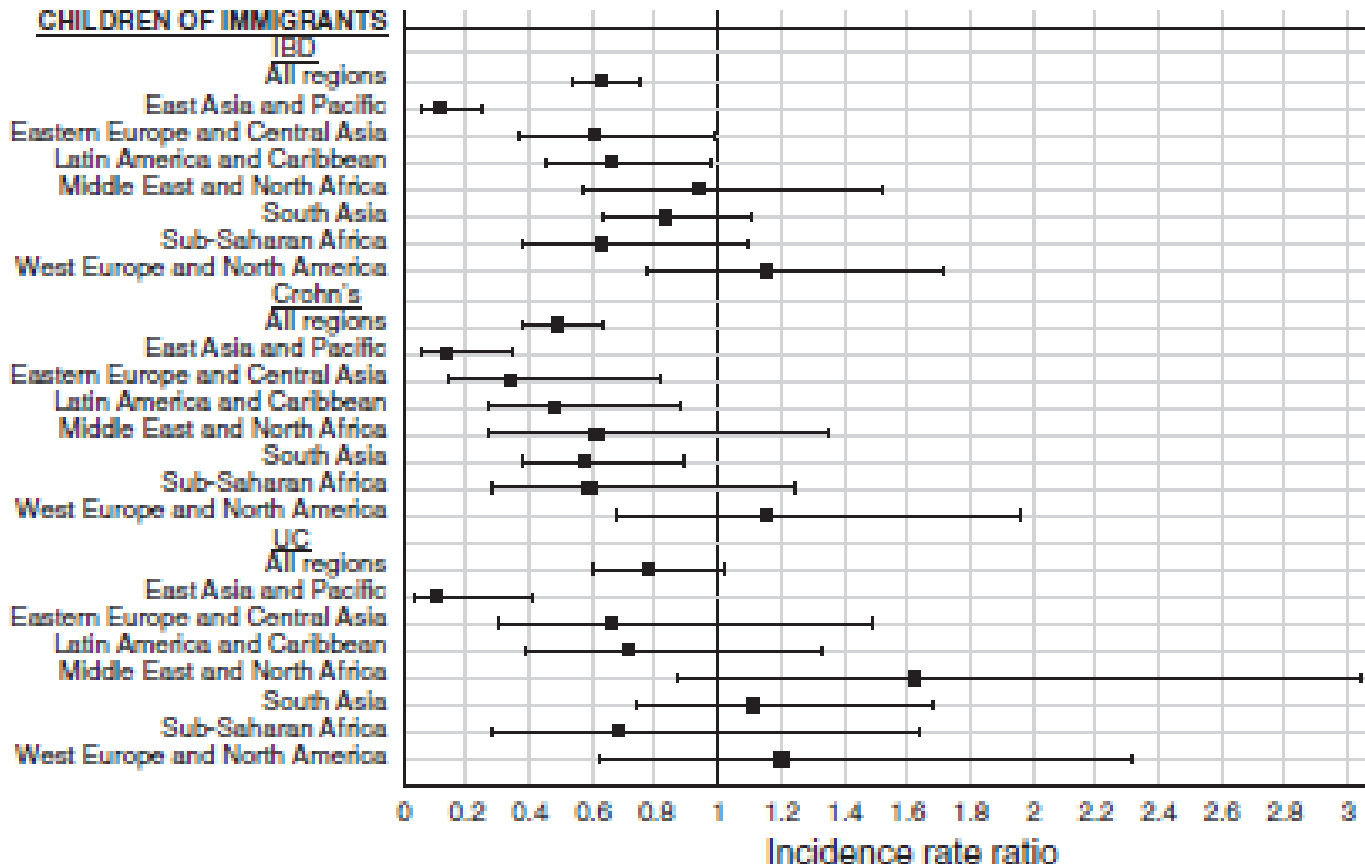
IBD Incidence, Ontario, 1994-2010

- Administrative database
- Incidence compared to that of non-immigrants to derive incidence rate ratio (IRR)
- Risk of IBD among immigrants was 1.2% less for each year older at immigration
 - Those who immigrated before the age of 30 were about 3 times more likely to get IBD than those who immigrated at >60 yrs



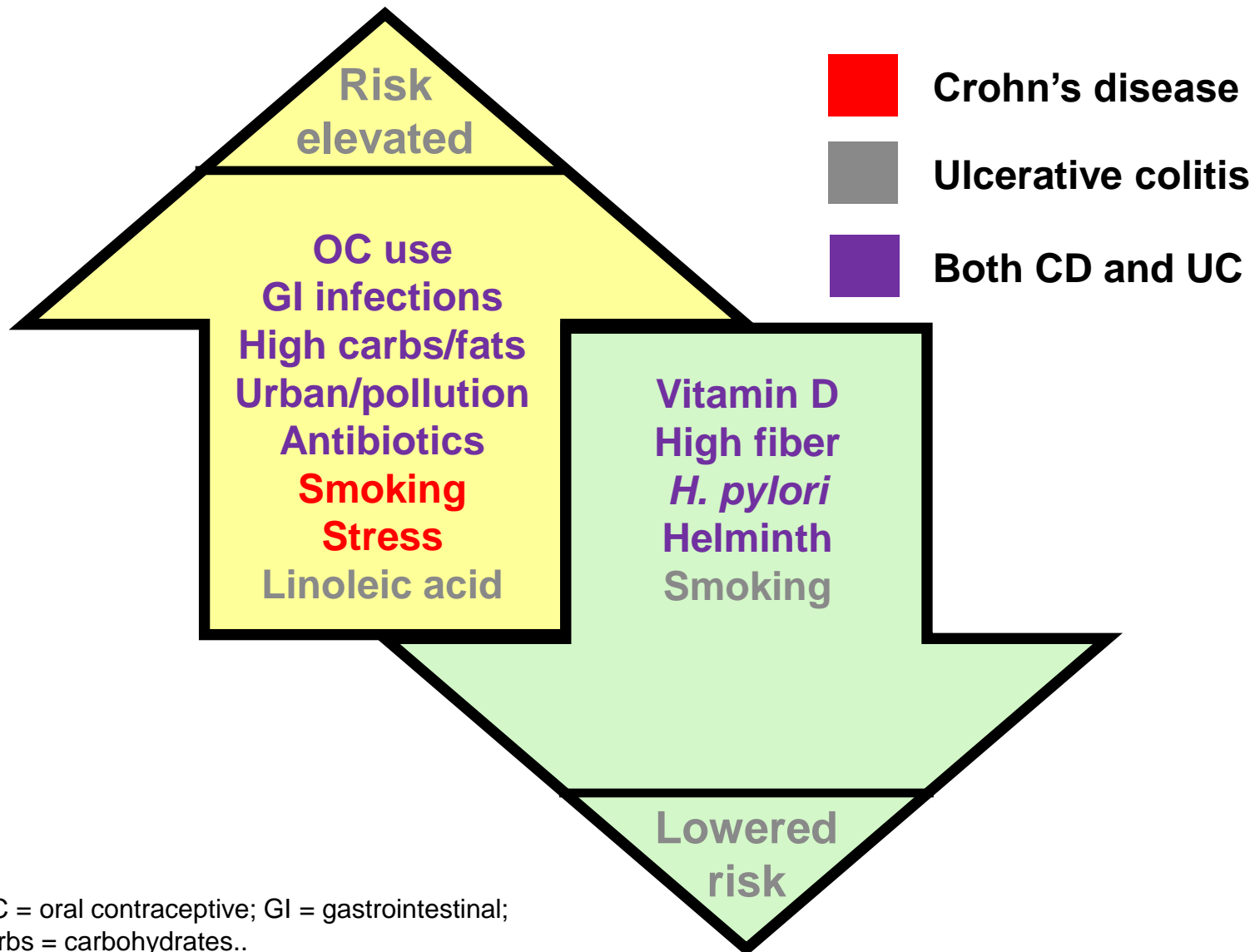
IBD Incidence, Ontario, 1994-2010

- For children of immigrants, differences in IBD incidence between non-immigrants much less clear
 - Especially among those from Middle East, Africa, Western Europe, North America



Benchimol El et al, Am J Gastroenterol 2015;110:553-63

Relationship Between Environmental Factors and Development of CD and UC



OC = oral contraceptive; GI = gastrointestinal;
carbs = carbohydrates..

Ponder A, Long MD. Clin Epidemiol. 2013;5:237-247.

Cigarette Smoking and IBD: Updated Meta-Analysis

Ulcerative Colitis

- 13 studies, >11,000 patients for UC
- Current smoking is protective of development of UC: RR, 0.58 (95% CI, 0.45 - 0.75)
- Quitting smoking is associated with UC: RR, 1.79 (1.37 - 2.34)

Crohn's Disease

- 9 studies, >10,000 patients for Crohn's
- Current smoking is associated with Crohn's: RR, 1.76 (1.40 – 2.22)
- Former smoking is weakly associated with Crohn's: RR, 1.30 (0.97 – 1.76)

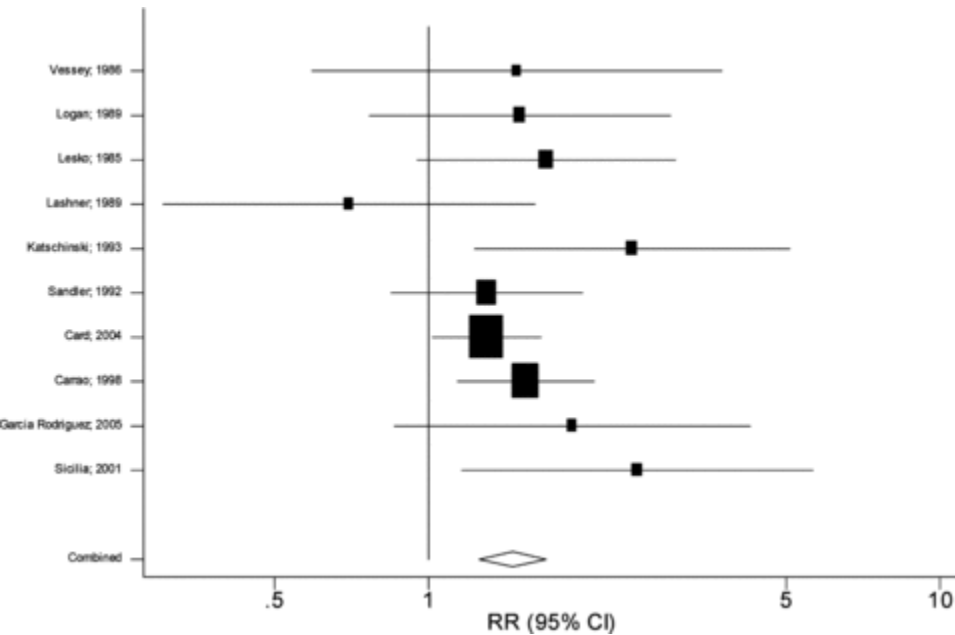
Appendectomy Is Protective Against the Risk of Ulcerative Colitis

- Multiple studies show that risk of UC is decreased by almost 70% among those who underwent appendectomy
- But only among those undergoing appendectomy for appendicitis under the age of 20 years
- Slight increased risk of Crohn's?
 - But may be confounded by fact that some patients with Crohn's present with RLQ abdominal pain and are mistakenly diagnosed with appendicitis

Koutroubakis et al, Inflamm Bowel Dis 2002;8:277
Andersson et al, N Engl J Med 2001;344:808

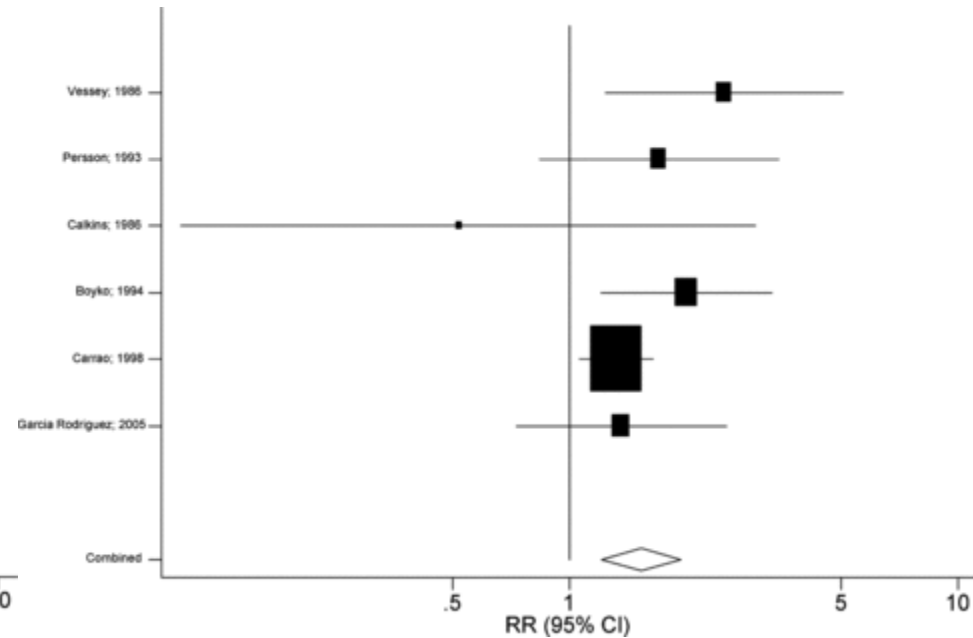
Oral Contraceptive Meta-Analysis

Crohn's Disease



Adjusted RR, 1.46 (1.26-1.70)

Ulcerative Colitis



Adjusted RR, 1.28 (1.06-1.54)

•Former OCP use not associated with increased RR

Cornish JA et al, Am J Gastroenterol 2008; 103: 2394-2400.

Nurses' Health Studies

- Nearly 250,000 women enrolled
- Millions of person-years of follow-up
- Prospectively collected data
- Incident cases of IBD identified over time – approximately 400 each
- Advantage:
 - Allows for high-quality risk factor analysis since data are collected prospectively
- Disadvantage:
 - Does it only apply to women who are diagnosed with IBD in their 30's or later?

Summary of Nurses' Health Study Findings

• Risk Factor

- Ex-smoking, UC
- Smoking, CD
- Hormone replacement, UC
- Oral contraceptives, CD
- NSAID use >15 days/month for both
- Vitamin D deficiency, CD>UC
- Depressive symptoms, CD
- Trans-unsaturated fats, UC

• Protective Factor

- Long-chain n-3 polyunsaturated fatty acids, UC
- Dietary fiber intake, CD
 - Fruits>vegetables>cereal/grains/legume

Higuchi L et al, *Am J Gastroenterol* 2012;107:1399-1406

Khalili H et al, *Gastroenterology* 2012;143:1199-1206

Khalili H et al, *Gut* 2013;62:1153-9.

Ananthakrishnan A et al, *Ann Intern Med* 2012;156:350-9

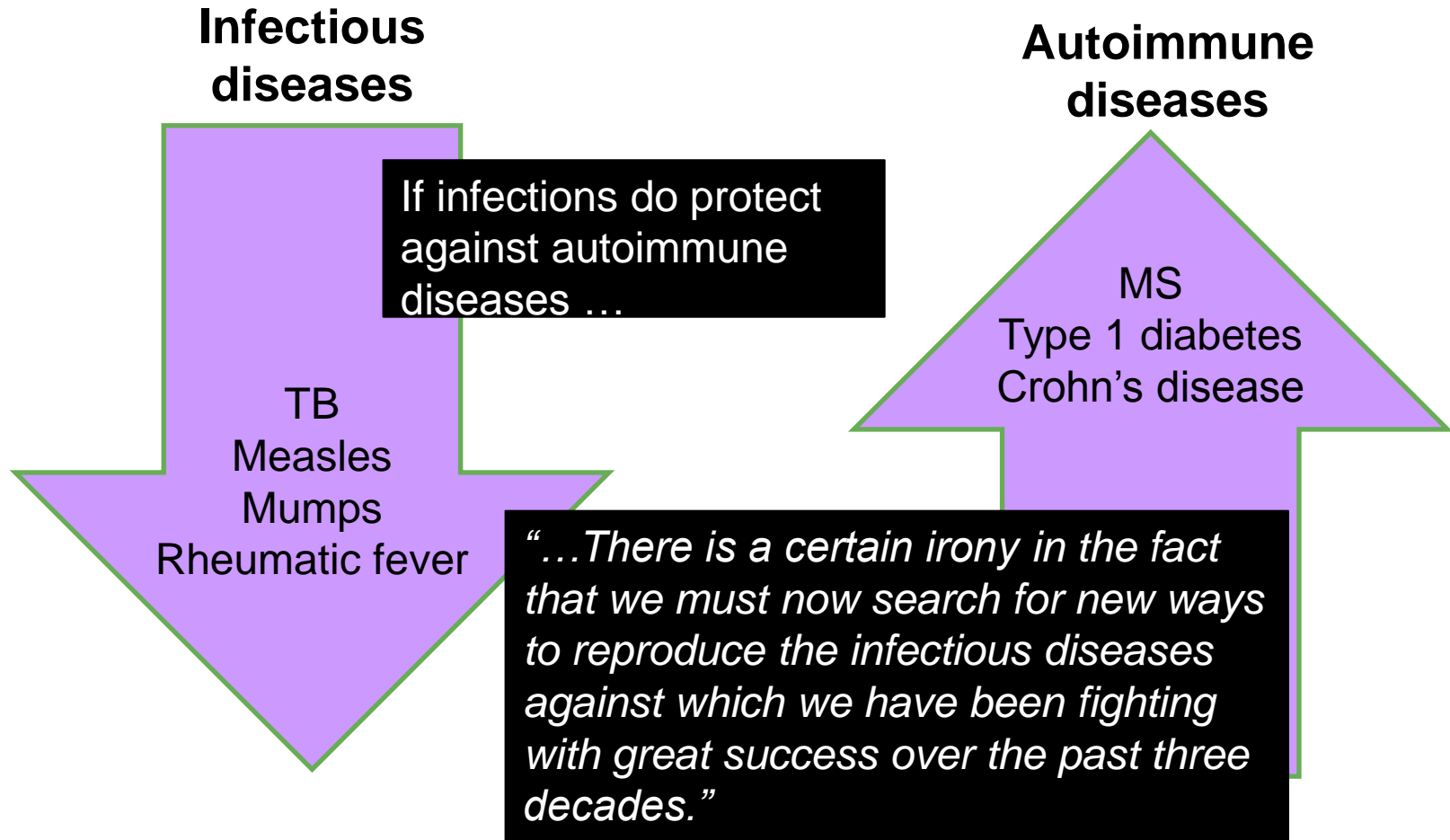
Ananthakrishnan AN et al, *Gut* 2013 (online early). Doi: 10.1136/gutjnl-2013-305304.

Ananthakrishnan AN et al, *Gastroenterology* 2013 (online early). Doi: 10.1053/j.gastro.2013.07.050.

Ananthakrishnan AN et al, *Gastroenterology* 2012;142:482-9.

Ananthakrishnan AN et al, *Clin Gastroenterol Hepatol* 2013;11:57-62.

Incidence of Infection and Autoimmunity: Inverse Relationship?



TB = tuberculosis; MS = multiple sclerosis.

Bach JF. N Engl J Med. 2002;347(12):911-920.

'Hygiene Hypothesis'

- Incidence of immune-mediated diseases rising in developed countries
 - Related to modern hygiene, lack of exposure to bacteria?
- Conflicting data in IBD
 - Manitoba case-control: early childhood exposure to pets, being from larger families protective
 - Montreal case-control: owning a pet was risk factor; less crowding, owning personal towel were protective



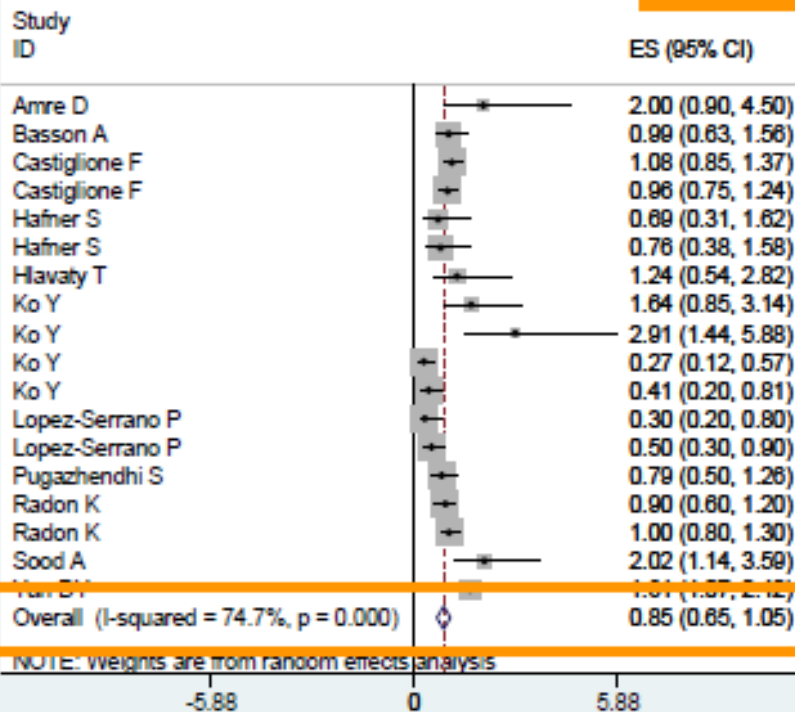
Bernstein CN et al, Am J Gastroenterol 2006;101:993-1002
Amre DK et al, Am J Gastroenterol 2006;101:1005-11.

Early life factors

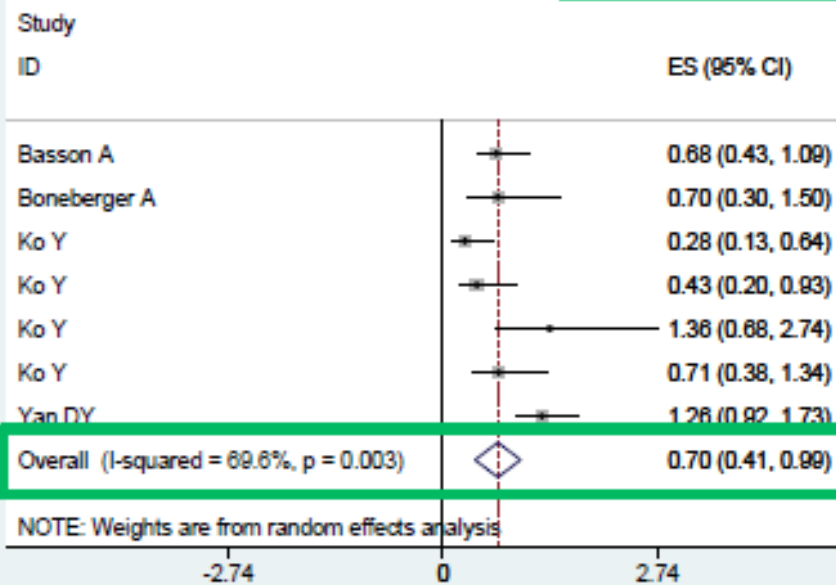
Hygiene Hypothesis

Exposure to pets, particularly during childhood, is inversely associated with risk of IBD

Adult



Childhood



H. Pylori Infection and IBD Risk: Meta-Analysis

- 23 articles
- Pooled risk of IBD in H. pylori infected individuals: 0.64 (0.54-0.75)
 - 0.60 in Crohn's, 0.75 in UC
 - Significant heterogeneity
 - Subgroups analyses by methods of diagnosis, region, age couldn't explain

Is Helminth Exposure Protective?

- Can have profound effects on mucosal immune system
- South African case-control study: childhood exposure to helminths, OR of Crohn's, 0.2 (0.1-0.4) and OR of UC, 0.2 (0.1-0.6)
- Small trials of *Trichuris suis* ova (pig whipworm eggs) in IBD showed beneficial effect, larger studies underway

Chu KM et al, *Inflamm Bowel Dis* 2013;19:614-20. Summers RW et al, *Gut* 2005;54:87-90. Summers RW et al, *Gastroenterology* 2005;128:825-32.

Antibiotic Use and Risk of IBD

- Case-control study of pediatric onset IBD in Manitoba
 - 58% of cases had antibiotics prescribed in 1st yr of life, vs. 39% of controls (OR, 2.9; 1.2-7.0)
- Case-control study of adult onset IBD in Manitoba
 - 12% of cases had at least 3 antibiotic courses 2-5 yrs before dx vs 7% of controls
 - OR, 1.5 (1.3-1.8)

Shaw SY et al, Am J Gastroenterol 2010;105:2687-92. Shaw SY et al, Am J Gastroenterol 2011;106:2133-42.

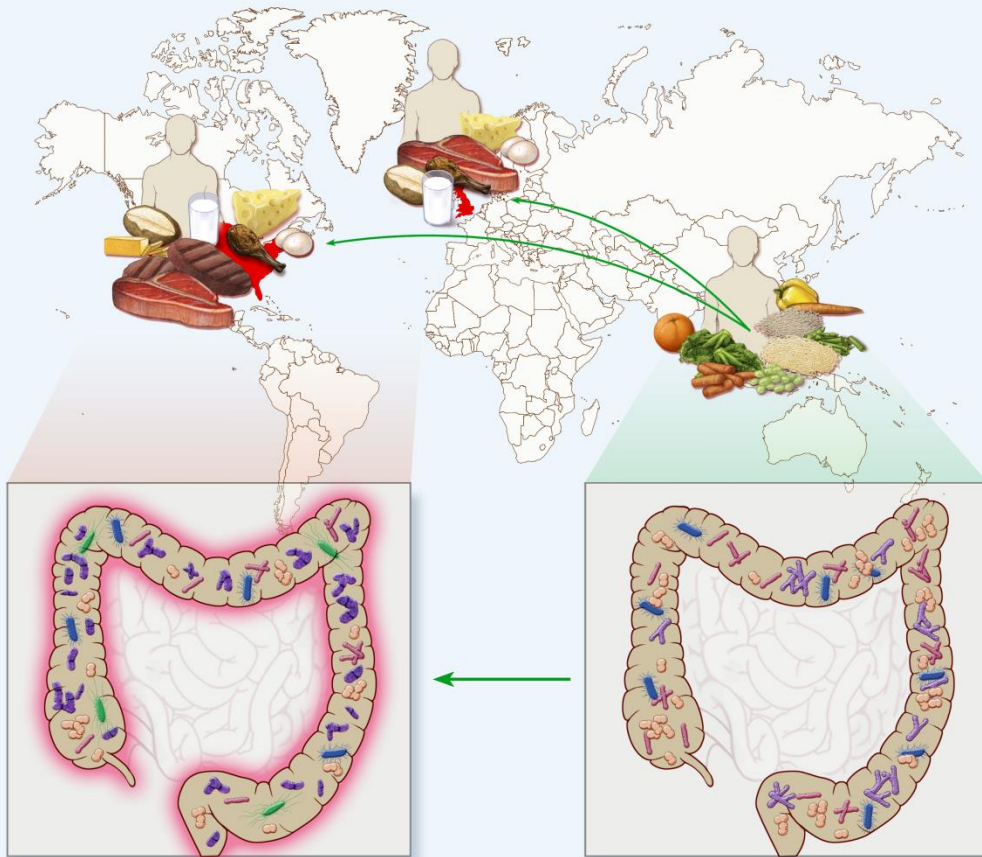
Gastroenteritis and Risk of IBD

- U.S. military database: infectious gastroenteritis increased risk of IBD by 40%
 - Previous IBS diagnosis along with gastroenteritis increased risk of IBD 5-fold
- Large GPRD study in U.K. showed 2- to 3-fold increased risk of IBD among those with gastroenteritis

Porter CK et al, *Gastroenterology* 2008;135:781-6.

Garcia-Rodriguez LA et al, *Gastroenterology* 2006;130:1588-94.

Diet and Microbiome and IBD?



- Large differences in microbiome between regions and between rural/urban
- High fat diets increase Proteobacteria and Firmicutes and decrease Bacteroidetes

Kashyap PC et al, J Allergy Clin Immunol 2013;152:250-250.e5
Wu GD et al, Anaerobe 2013 (online early)

The Return of Diet as a Risk Factor?

- Difficult to study
- May exert effect indirectly via microflora
- Increased sugar intake
- Increased fat intake
- Increased protein intake
- Future studies may need to focus on dietary patterns rather than individual foods

Chapman-Kiddell CA et al, Inflamm Bowel Dis 2010

Summary of Diet Studies

Direction	Crohn's disease	Ulcerative colitis
Reduced Risk	Fiber	Long-chain n-3 PUFA
	Fruits and Vegetables	
	N-3 PUFA (pediatric)	
	Zinc	
	Vitamin D	
Increased risk	Sugar	Animal protein
		N-6 PUFA
		Total carbohydrates
		Sulfur, Iron

Courtesy of Dr. Ashwin Ananthakrishnan

Psychological Stress and IBD

- Recent systematic review of 18 prospective studies examining stress as a risk factor for disease exacerbations
- 13 studies showed significant association
- Coping behaviors appear to modulate effect of stress

Camara RJA et al, *Digestion* 2009

How Modern Lifestyle Might Alter Enteric Microflora

- Improved sanitation
- Decline in endemic parasitism
- Decreased exposure to soil microbes
- Decline in *Helicobacter*
- Increased antibiotic usage
- Less crowded living conditions
- Refrigeration
- Sedentary lifestyle / obesity
- Increased consumption refined sugars, saturated fats

**“Life on
concrete”**

Adapted from Bernstein C & Shanahan F. Gut 2008; 57: 1185-91.

Conclusions

- Incidence and prevalence of IBD still rising in many areas
- Studies of migrant populations suggest environmental factors
- Hygiene hypothesis is promising
 - *H. pylori* infection and helminth exposure protective
- Changes in fecal microbiome?
- Vitamin D deficiency may explain north-south gradient
- In summary, IBD epidemiology rapidly evolving