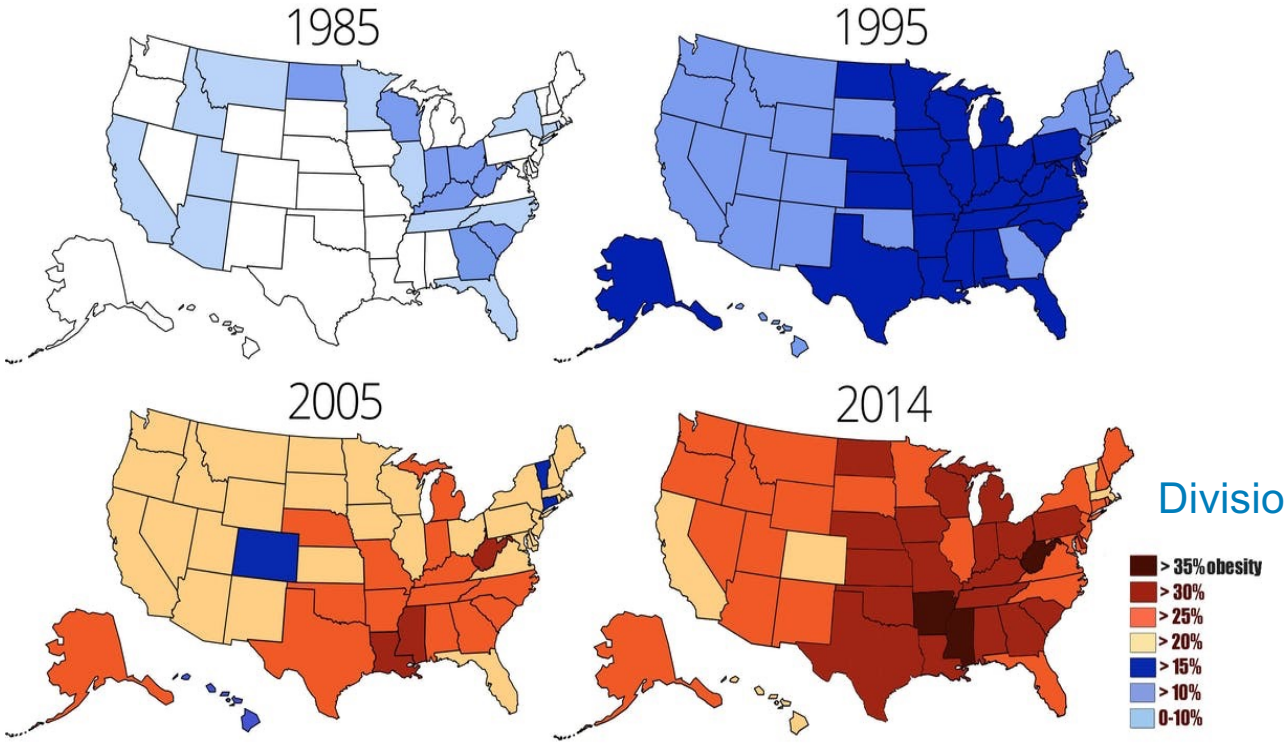


Obesity in IBD – Friend or Foe?

Siddharth Singh, MD, MS
Associate Professor of Medicine
Division of Gastroenterology and Division of Biomedical Informatics
Director, IBD Center
University of California San Diego

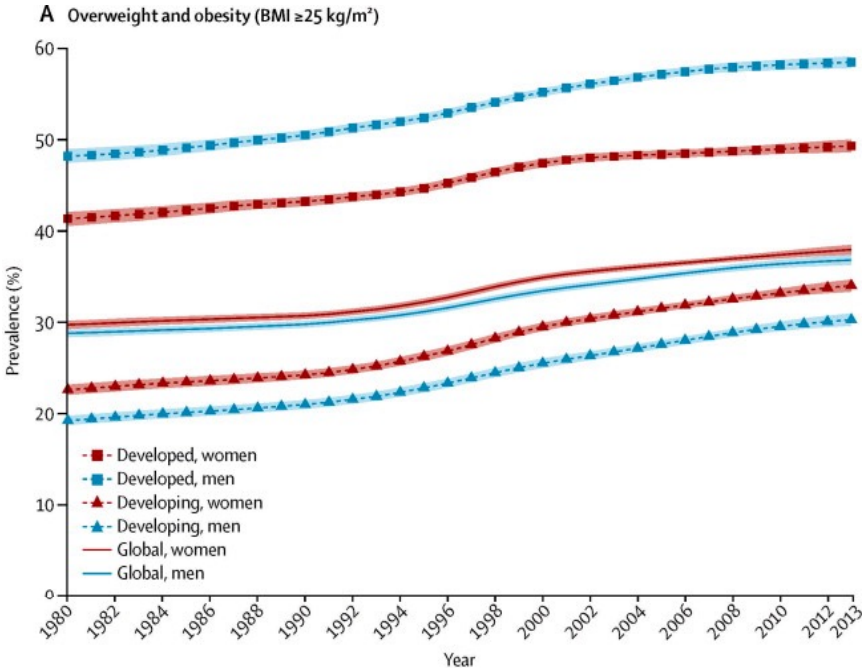
Mentoring in IBD XXIII
Toronto
November 4, 2022

UC San Diego Health

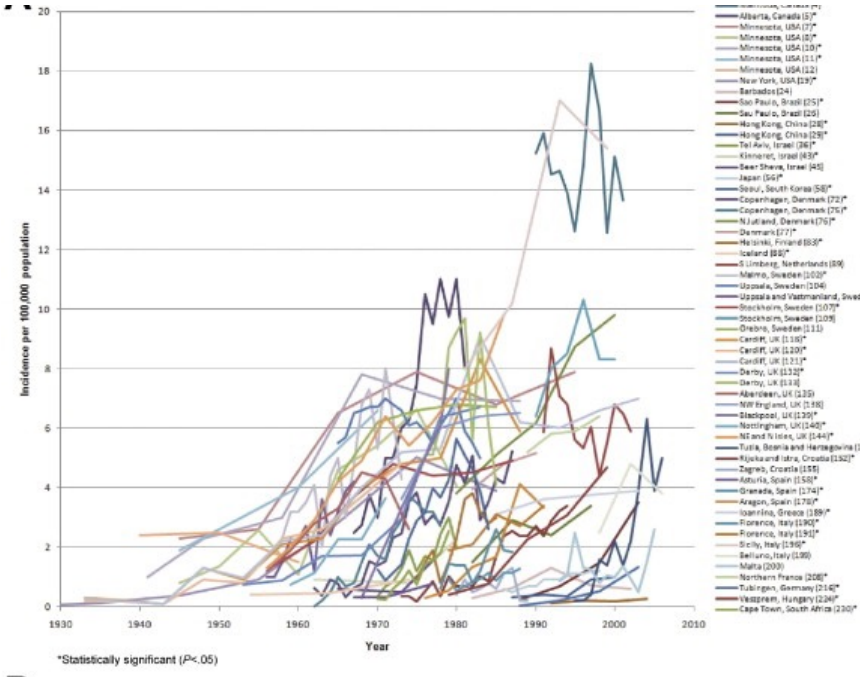
Overview

- Epidemiology and pathophysiology of obesity in IBD
- Impact of obesity on natural history of IBD
- Impact of obesity on treatment response in IBD
- Would treating obesity modify outcomes in patients with IBD?

A Tale of Two Epidemics



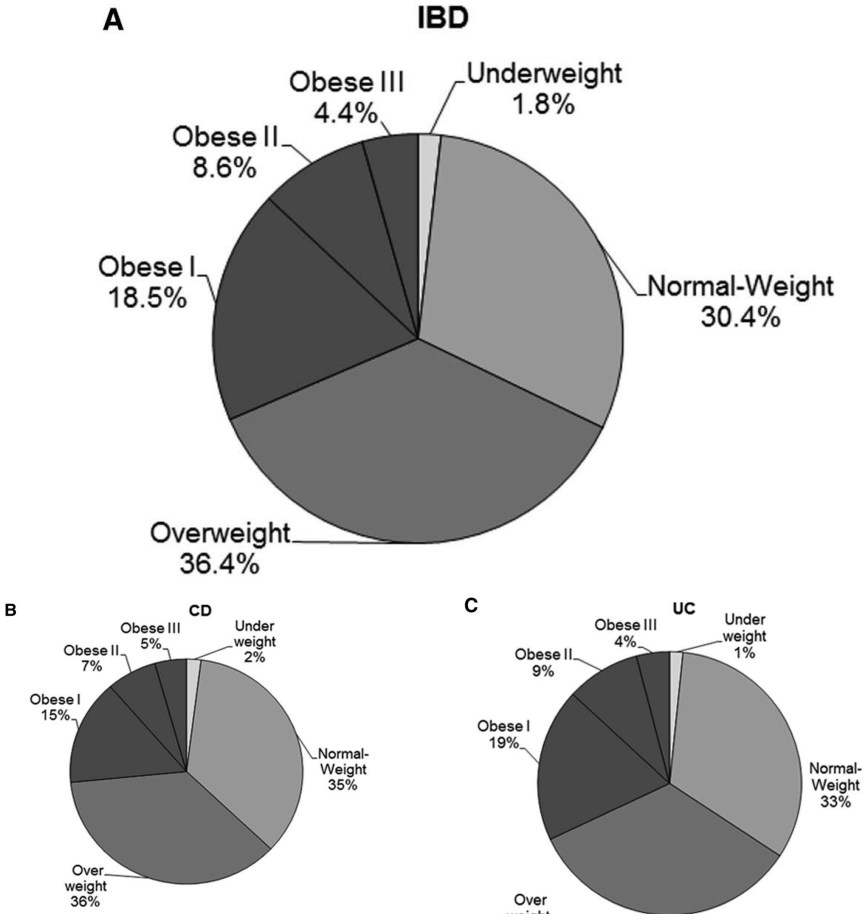
- Over 1/3rd of adults in the US are obese
- Proportion of overweight/obese – increased 28% in developed, 60% in developing countries over last 30y



- Global increase in incidence of IBD (10-30 per 100,000 in developed countries)
- New wave in newly developed nations

Ng. Lancet 2014;384:766
Molodecky. Gastroenterology 2012;142:46

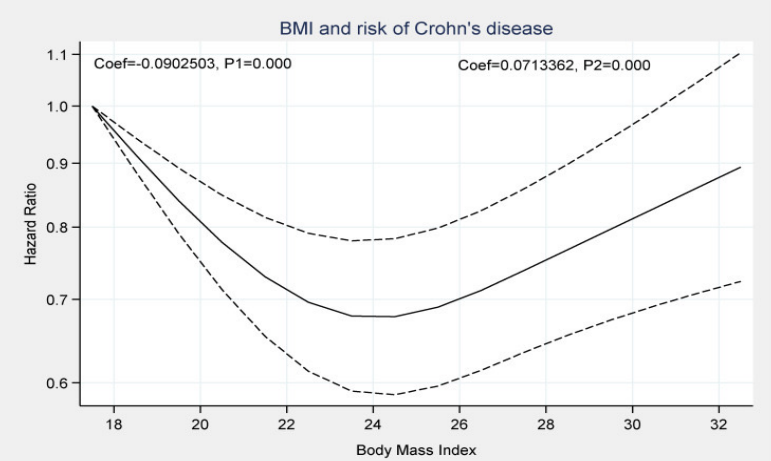
Prevalence of Obesity in IBD

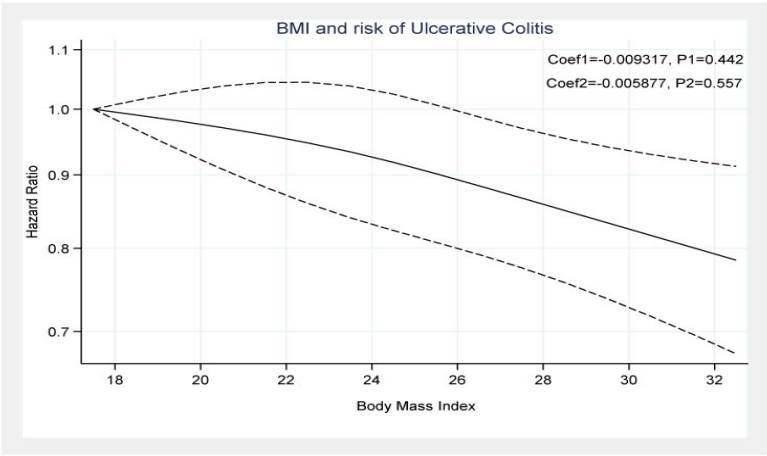


- **20-40%** of adult patients with IBD are OBESE!
  - In 2002 – 3% obese
- Similar patterns in pediatrics
  - 20-30% of pediatric patients with IBD are overweight or obese

Seminerio. Inflamm Bowel Dis 2015;21:2857
Long. Inflamm Bowel Dis 2011; 17:2162

Does Obesity Contribute to Development of IBD?





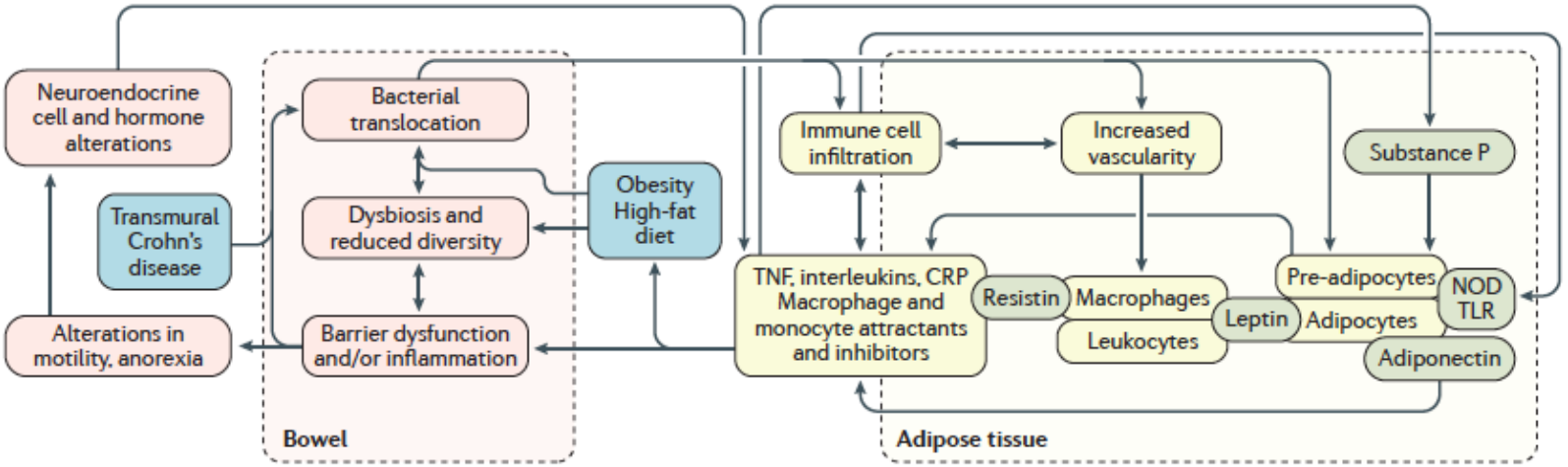
- Systematic review of 10 studies, 15.6 mi individuals, 23,371 cases of IBD
- Non-linear association between being underweight and obesity and risk of CD
- **25% higher risk of developing CD in obese adults**
- Weight gain during young-adulthood associated with increased risk of CD
- No association between BMI and risk of developing UC

Bhagavathula, et al. Healthcare 2021
Khalili, et al. Inflamm Bowel Dis 2015

How might obesity contribute to pathogenesis of IBD?

Shared pathogenesis

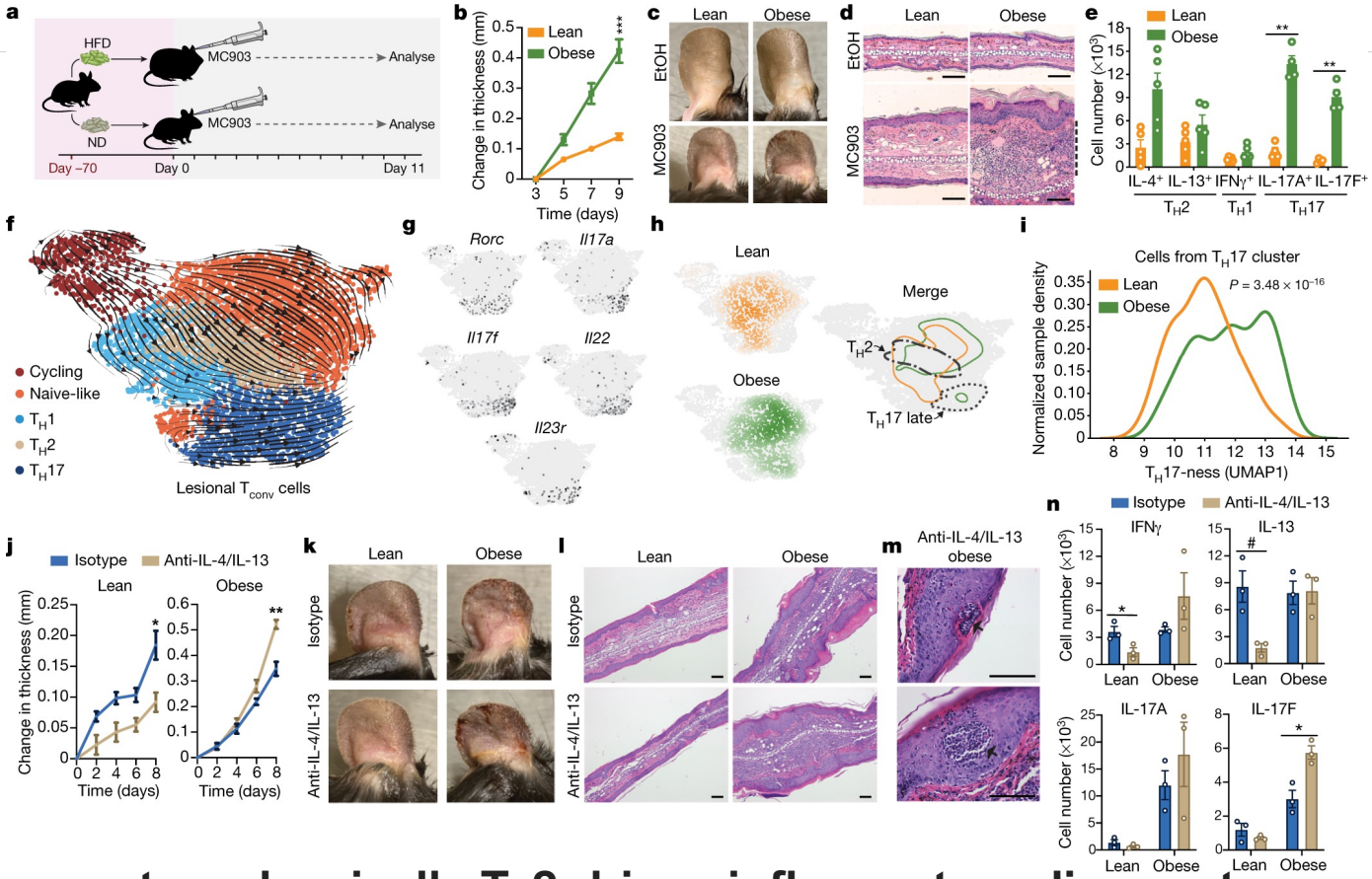
- Obesity-induced dysbiosis
- Impaired mucosal barrier dysfunction
- Increased leptin and decrease in adiponectin promotes inflammation
- Mesenteric fat in CD



Singh *et al. Nat Rev Gastroenterol Hepatol* 2016

Obesity alters pathology and treatment response in inflammatory disease

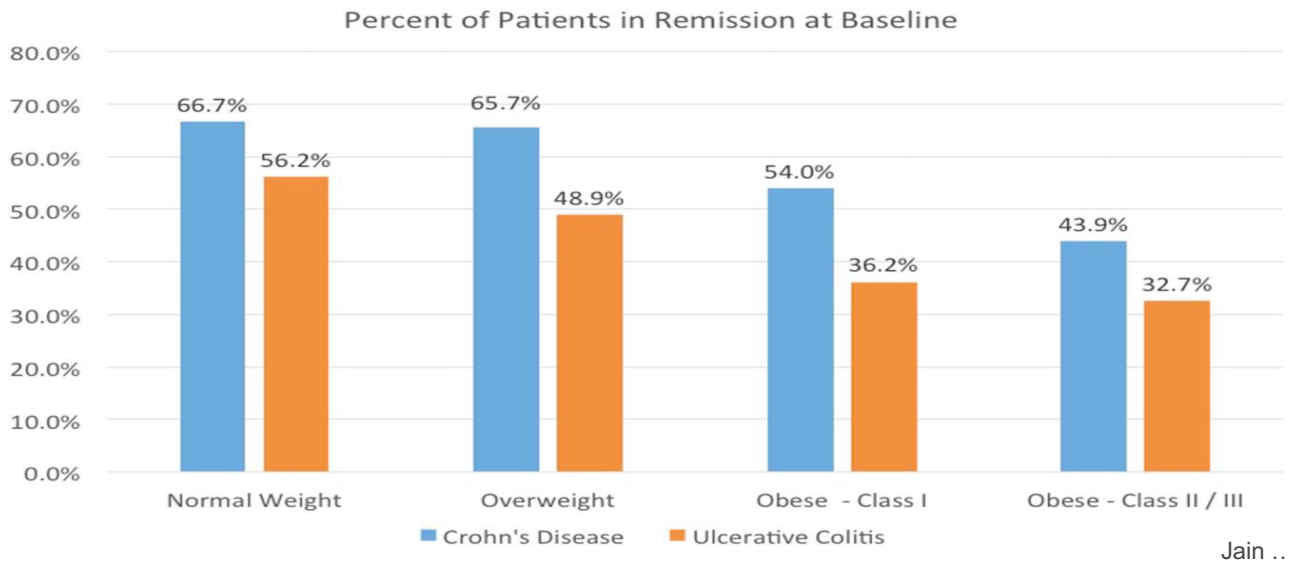
Nature | Vol 604 | 14 April 2022



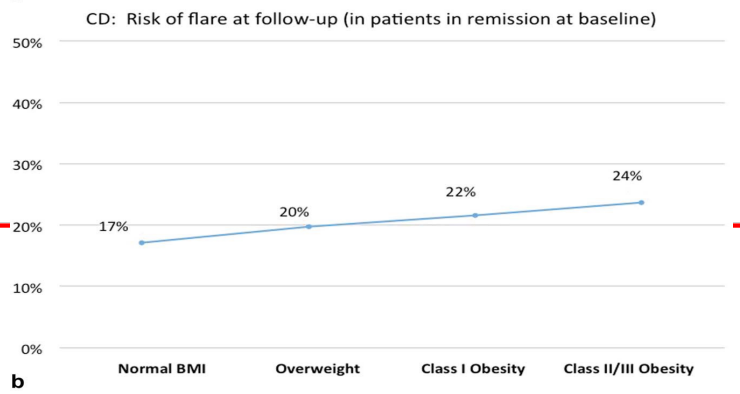
Obesity converts a classically T_H2-driven inflammatory disease to a more severe T_H17-driven disease that is worsened upon anti-T_H2 antibody treatment.

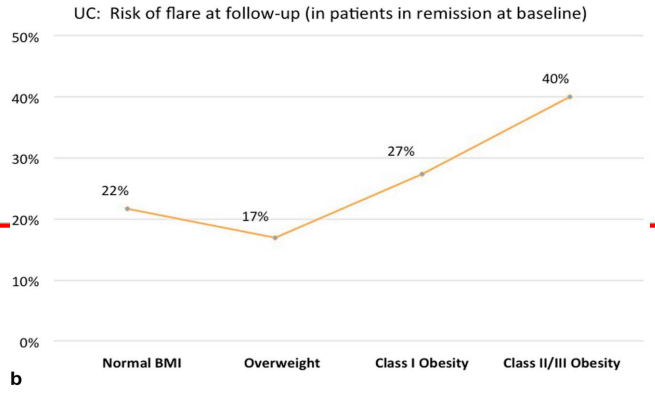
Impact of **Obesity** on **Clinical Course of IBD**

- Cross-sectional, and longitudinal cohort from IBD Partners
- 7296 adults with IBD with at least 1 follow-up of 6-12 months
- 65% with CD, 20% obese
- Higher anxiety, depression, fatigue, pain and inferior social function scores in CD and UC



Jain … Singh. Am J Gastroenterol 2019;114:630

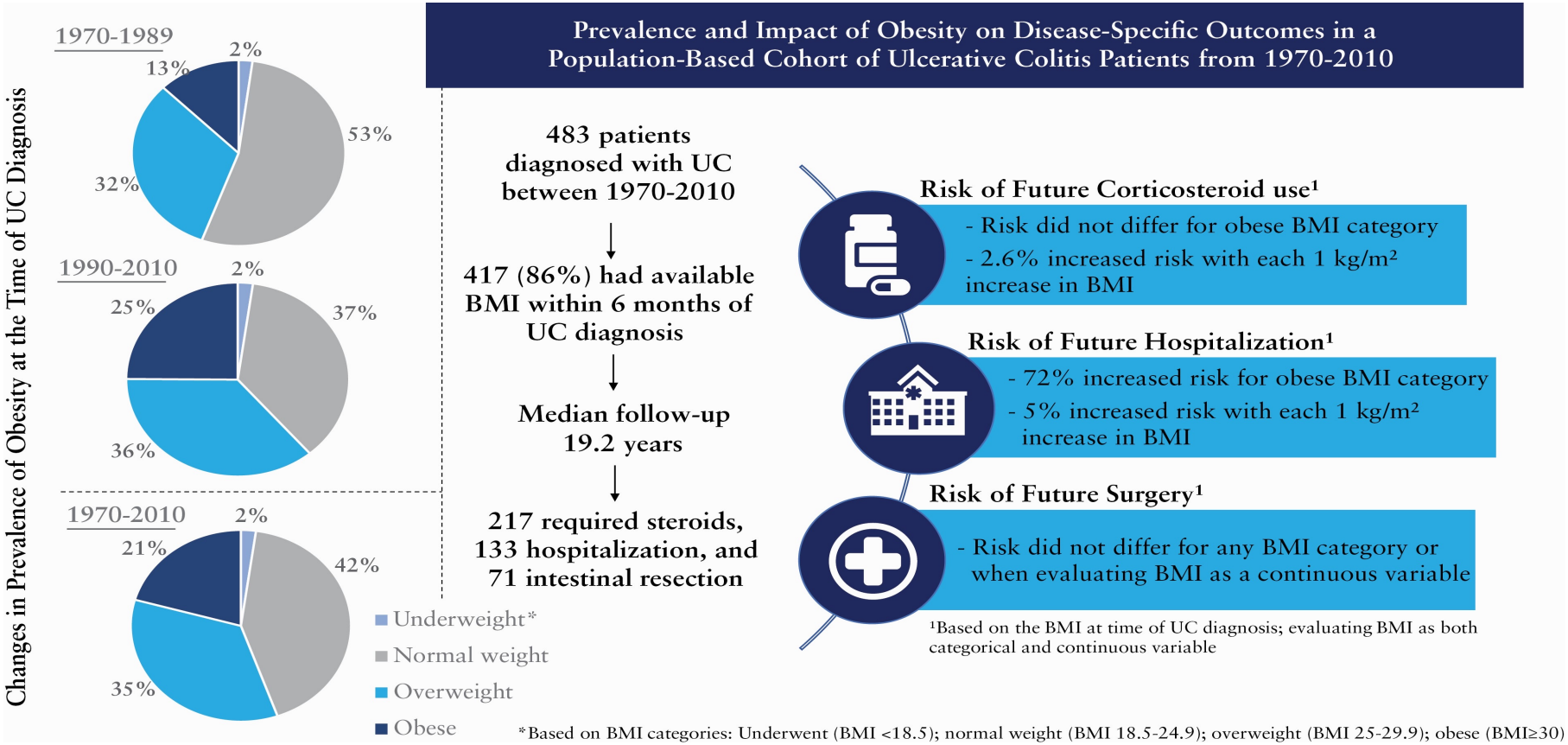




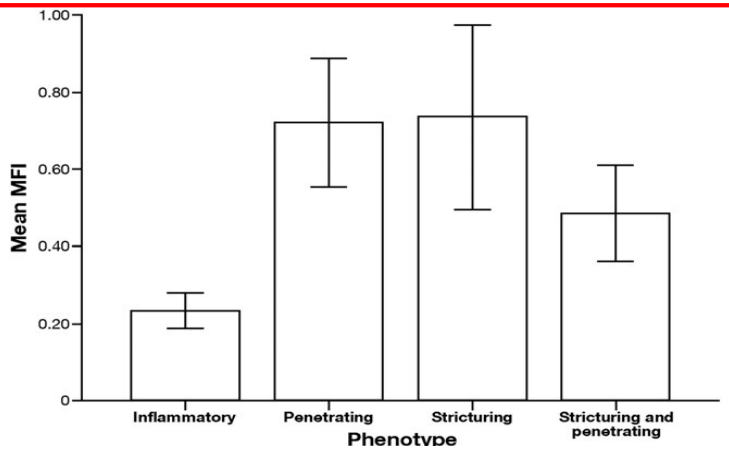
Risk of active disease at follow-up	Crohn's disease	Ulcerative colitis
Normal BMI (18.0-24.9 kg/m^2)	1.0	1.0
Overweight (BMI, 25-29.9 kg/m^2)	**1.39 (1.08-.78)**	1.03 (0.75-1.42)
Class I obesity (30-34.9 kg/m^2)	**1.50 (1.07-2.09)**	**1.67 (1.05-2.61)**
Class II or III obesity (≥35 kg/m^2)	**1.86 (1.30-2.68)**	**2.97 (1.75-5.17)**

Prevalence and Impact of Obesity on Disease-specific Outcomes in a Population-based Cohort of Patients with Ulcerative Colitis

Amanda M. Johnson,[a,e] W. Scott Harmsen,[b] Satimai Aniwan,[a,c]
William J. Tremaine,[a] Barham K. Abu Dayyeh,[a] Edward V. Loftus Jr[a]

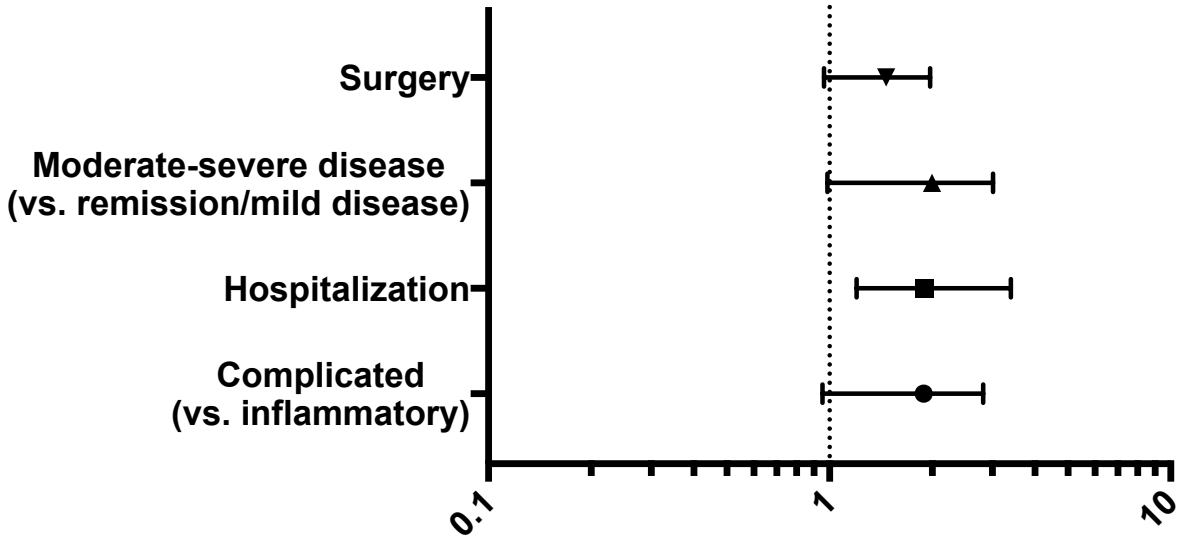


Impact of **Visceral Adiposity** in Crohn's Disease



	Complicated	Inflammatory	*P* value
All patients (n = 50)			
MFI	0.67 ± 0.29	0.23 ± 0.1	.01
Visceral fat area (cm^2)	125.3 ± 89.7	53.1 ± 35.9	.01
Subcutaneous fat area (cm^2)	192.0 ± 102.7	245.4 ± 153.9	.18

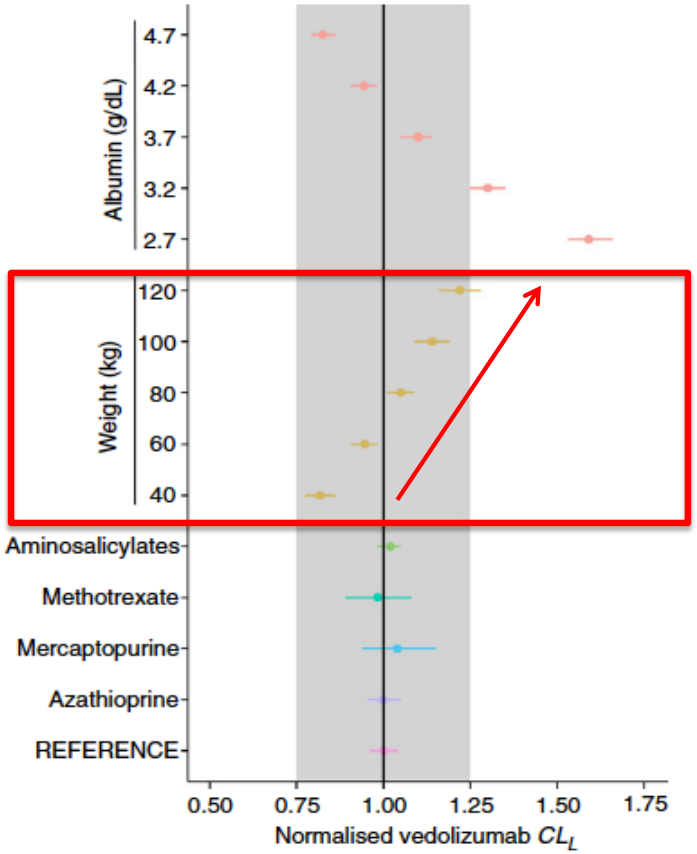
CD outcomes, with increasing VAT



Visceral adiposity (> overall obesity) may be associated with high-risk phenotype and adverse outcomes in CD

Eryahiem. Clin Gastroenterol Hepatol 2011;9:684
Uko. Inflamm Bowel Dis 2014;20:2286

Obesity impacts pharmacokinetics of biologic agents



- Obesity modifies systemic drug exposure and absorption
  - Weight-based dosing vs. fixed dose
  - Intravenous vs. subcutaneous
- High body weight is independently associated with increased drug clearance (non-linear association), for all biologic agents

Rosario. Aliment Pharmacol Ther 2015;42:188

Impact of **Obesity** on **Response to Biologic Agents** in UC

- Single-center, retrospective cohort study, 2011-16
- 160 patients with UC, 55% on weight-based therapy (infliximab), 45% on fixed-dose therapy (adalimumab, golimumab, vedolizumab)
- **1kg/m^2** increase in BMI associated with **4% higher risk of treatment failure** (HR, 1.04; 95% CI, 1.00-1.08) (adjusting for age, sex, disease duration, hospitalization, prior anti-TNF therapy, steroid use, albumin)
- 1kg/m^2 increase in BMI associated with **6% lower risk of achieving endoscopic remission** (aOR, 0.94; 95% CI, 0.87-1.00)

1kg/m^2 increase in BMI	Weight-based dosing	Fixed-dosing regimens
Treatment Failure	1.05 (1.00-1.10)	1.05 (0.99-1.12)
Surgery/hospitalization	1.10 (1.03-1.19)	1.09 (0.99-1.20)
Endoscopic remission	0.98 (0.96-0.99)	0.96 (0.85-1.10)

Kurnool, …, Singh. Aliment Pharmacol Ther 2018

Obesity and response to anti-tumor necrosis factor-α agents in patients with select immune-mediated inflammatory diseases: A systematic review and meta-analysis

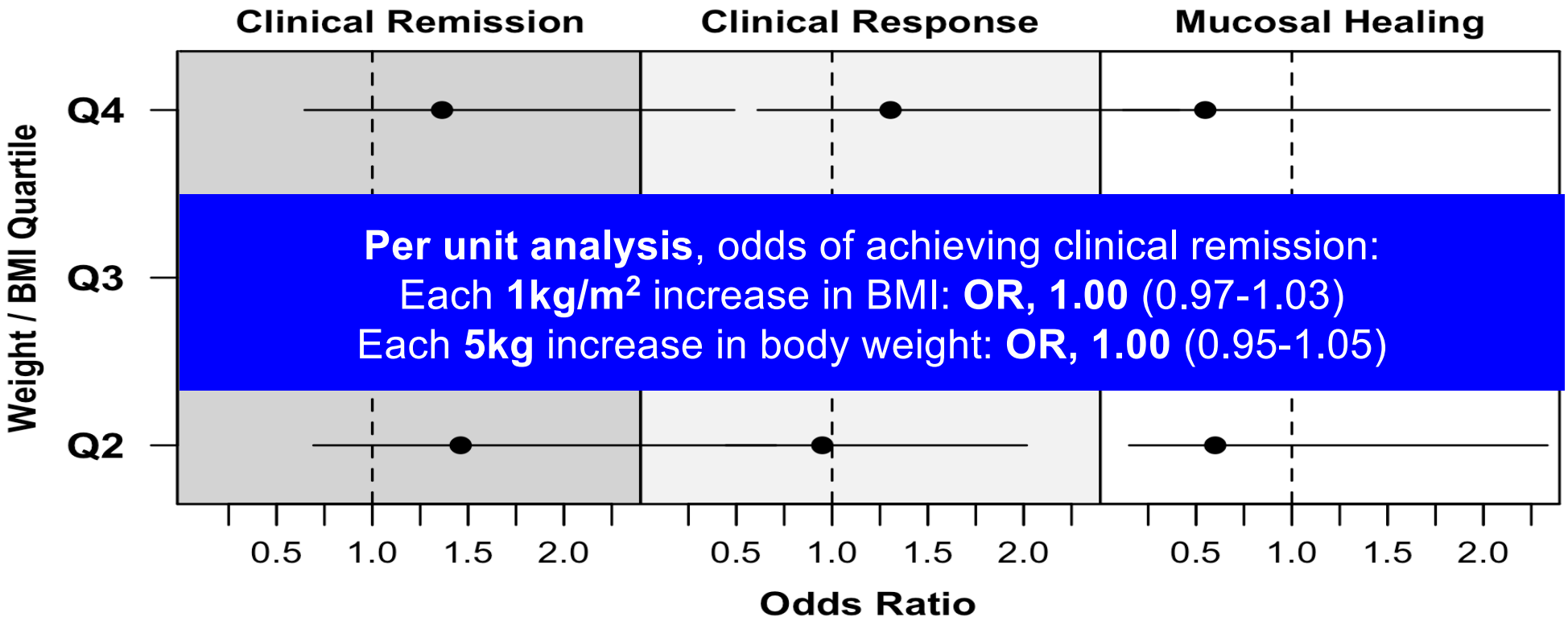
- 54 cohorts, 19,372 patients (23% obese)
- Only 8.3% RCTs reported outcomes stratified by weight
- Obese patients have **60% higher odds of failing** anti-TNF therapy – OR, 1.60 (95% CI, 1.39-1.83)
- Dose-response relationship
  - Overweight (vs. normal BMI): OR, 1.38 (1.11-1.74)
  - Obese (vs. normal BMI): OR, 1.87 (1.39-2.52)
  - Per 1kg/m^2 increase in BMI: OR, 1.07 (1.04-1.09)

Singh et al. PLOS One 2018

Obesity and Response to Infliximab in Patients with Inflammatory Bowel Diseases: Pooled Analysis of Individual Participant Data from Clinical Trials

AJG The American Journal of GASTROENTEROLOGY

Siddharth Singh, MD, MS[1,2], James Proudfoot, MS[3], Ronghui Xu, PhD[4] and William J. Sandborn, MD[1]



Per unit analysis, odds of achieving clinical remission:
Each **1kg/m²** increase in BMI: **OR, 1.00** (0.97-1.03)
Each **5kg** increase in body weight: **OR, 1.00** (0.95-1.05)

After adjusting for sex, smoking, baseline disease activity, and concomitant immunomodulators and/or prednisone use

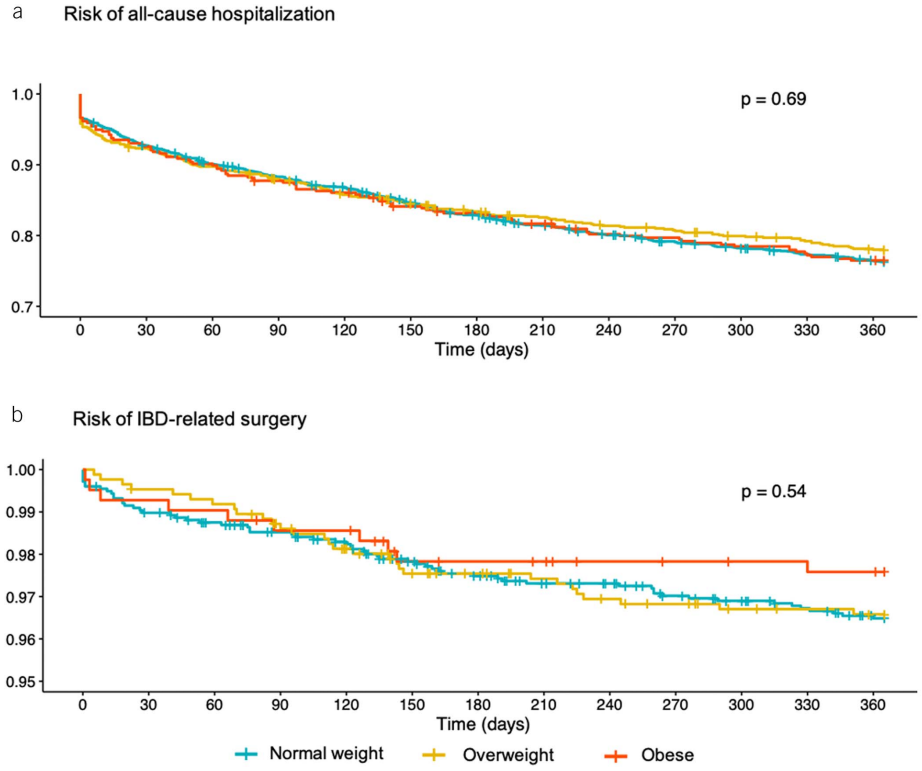
Singh et al. Am J Gastroenterol 2018;113:883

Effect of Obesity on Risk of Hospitalization, Surgery, and Serious Infection in Biologic-Treated Patients With Inflammatory Bowel Diseases: A CA-IBD Cohort Study

AJG The American Journal of GASTROENTEROLOGY

Phillip Gu, MD[1], Jiyu Luo, MS[2], Jihoon Kim, MS[3], Paulina Paul, MS[3], Berkeley Limketkai, MD, PhD[4], Jenny S. Sauk, MD[4], Sunhee Park, MD[5], Nimisha Parekh, MD[5], Kai Zheng, MD[6], Vivek Rudrapatna, MD, PhD[7], Gaurav Syal, MD, MHDS[1], Christina Ha, MD[1], Dermot P. McGovern, MD, PhD[1], Gil Y. Melmed, MD, MS[1], Phillip Fleshner, MD[8], Samuel Eisenstein, MD[9], Sonia Ramamoorthy, MD[9], Parambir S. Dulai, MD[10], Brigid S. Boland, MD[10], Eduardo Grunvald, MD[11], Uma Mahadevan, MD[7], Lucila Ohno-Machado, MD, PhD[3], William J. Sandborn, MD[10] and Siddharth Singh, MD, MS[3,10]

- Multi-center EHR-based cohort study of biologic-treated patients with IBD
  - 3038 patients treated with biologics, between 2010-17
  - 14% obese + 28% overweight
  - 76% treated with infliximab, 12% each on vedolizumab and ustekinumab
  - Outcomes within 1 year of biologic initiation
    - Hospitalization = 23%
    - IBD-related surgery = 3.3%
    - Serious infections = 5.8%



Gu, …, Singh. Am J Gastroenterol 2022;117:1639

Summary

- Barrier dysfunction
- Bacterial translocation
- Dysbiosis
- Adipokines

Obesity

?

IBD
(CD > UC)

Disease phenotype and behavior

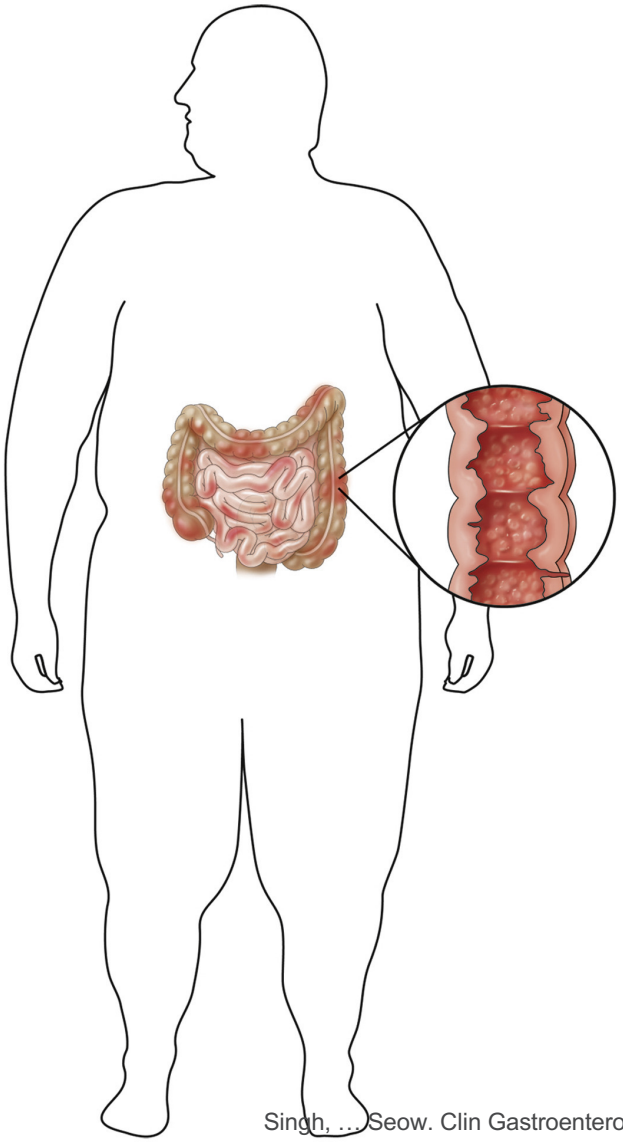
- Milder disease phenotype
- Lower prevalence of clinical remission
- Higher anxiety, depression, fatigue, pain

Natural history and treatment response

- More difficult to achieve remission
- Higher risk of disease relapse (UC > CD)
- Higher burden and costs of hospitalization
- Higher likelihood of failing biologic therapy

Surgical management

- Technical challenges during surgery (stoma-related, and creation of J-pouch)
- Higher risk of post-surgical complications

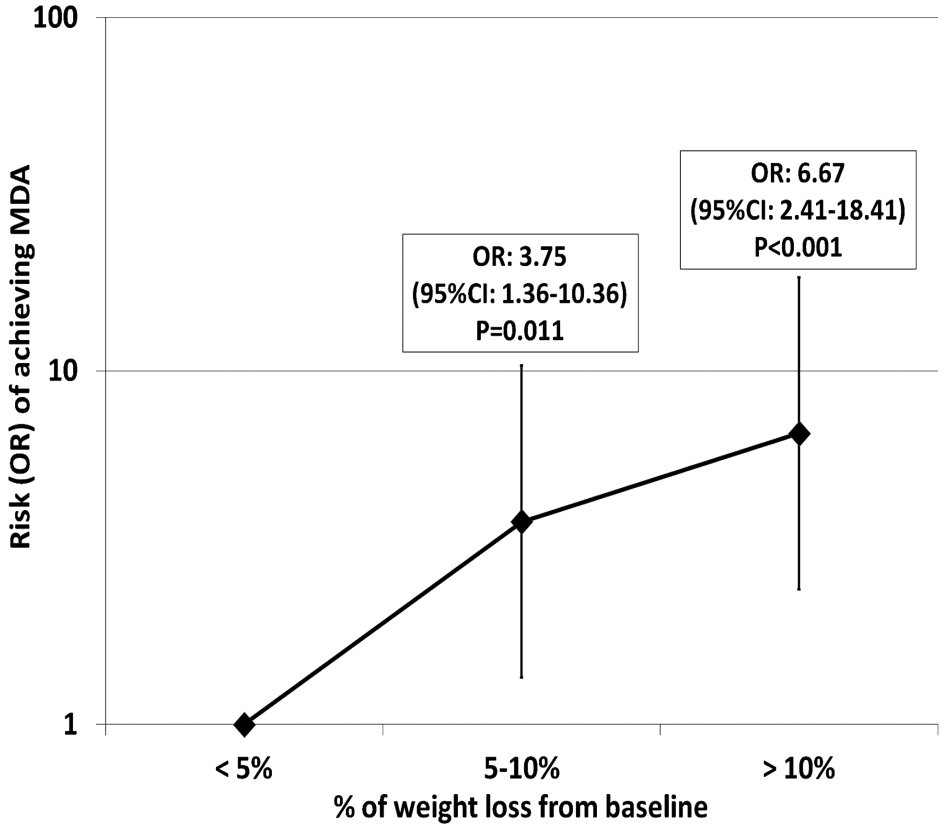


Singh, … Seow. Clin Gastroenterol Hepatol 2020

Would treating obesity improve IBD outcomes?

Weight loss and achievement of minimal disease activity in patients with psoriatic arthritis starting treatment with tumour necrosis factor α blockers

Di Minno MND, *et al. Ann Rheum Dis* 2014;**73**:1157–1162.

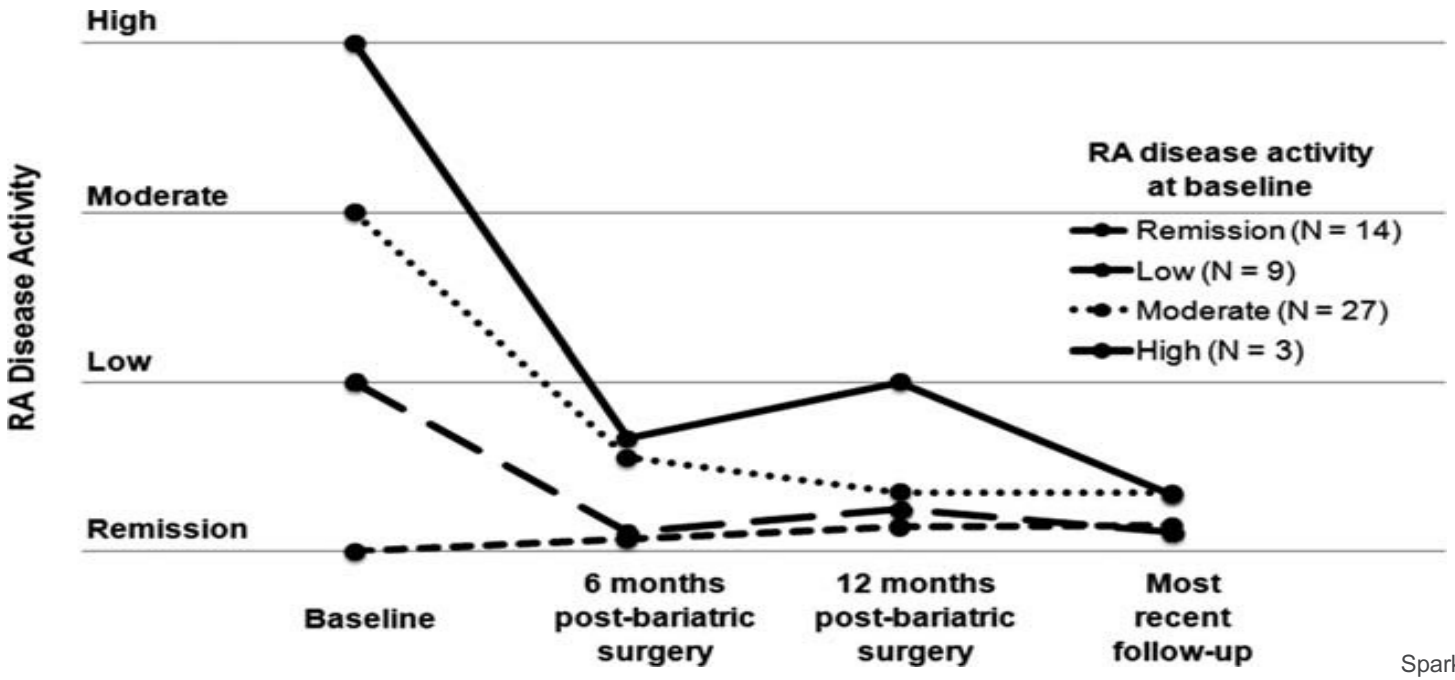


- 126 overweight-obese patients with psoriatic arthritis, starting anti-TNF therapy
- Low-fat diet vs. free-managed diet
- ≥5% weight loss, 58.7%, and ≥10% weight loss, 20.6%
- **Regardless of intervention, magnitude of intentional weight loss associated with better outcomes**

Di Minno. Ann Rheum Dis 2014;73:1157

Bariatric surgery improves outcomes in rheumatoid arthritis

- Single-center, 53 RA patients undergoing bariatric surgery
- Decrease in proportion with moderate-severe disease (52% vs. 6%)
- Lower ESR, CRP, RA-related medication use



Sparks. Arthritis Care Res 2015;67:1619

Bariatric surgery in patients with IBD

- Systematic review with 10 studies, 168 patients with IBD, 58% CD
- Sleeve gastrectomy (58%) vs. Roux-en-Y gastric bypass (30%)
- 52% not on any specific IBD-related therapy; 28% on biologic agents
- Early surgery-related adverse events – 16%
  - Higher with REYGB > sleeve gastrectomy
- **Change in IBD-related outcomes**
  - **De-escalation of IBD therapy = 46%**
  - **Escalation of IBD therapy = 11%** (higher risk with REYGB vs. sleeve gastrectomy = 18% vs. 7%)

Garg, et al. Obes Surg 2020

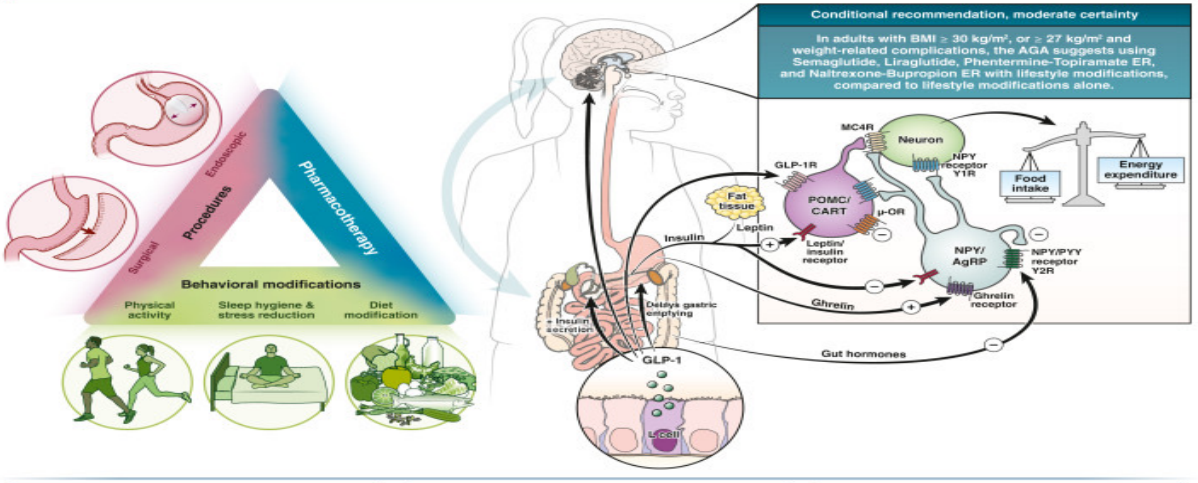
So, ho ents?

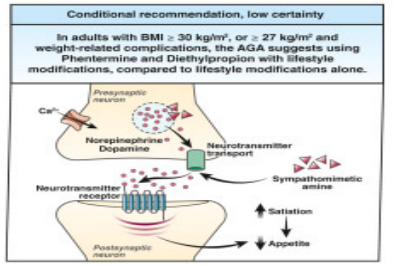
aga American Gastroenterological Association
Gastroenterology Spotlight

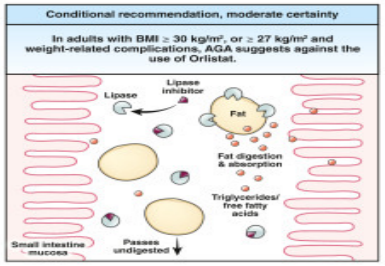
Spotlight: Pharmacological Interventions in the Management of Obesity in Adults

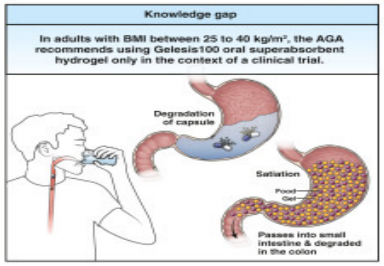
Octavia Pickett-Blakely, MD, MHS[1], Perica Davitkov, MD[2,3], Eduardo Grunvald, MD[4], Siddharth Singh, MD[5], Raj Shah, MD[6], Ruben Hernaez, MD, MPH, PhD[7-9], Apoorva Krishna Chandar, MD[2], Levi M. Teigen, PhD, RD[10], Tasma Harindhanavudhi, MD[11], Shahnaz Sultan, MD[12]

In adults with BMI ≥ 30 kg/m², or ≥ 27 kg/m² and weight-related complications, who have had an inadequate response to lifestyle interventions, the AGA recommends adding pharmacological agents to lifestyle interventions over continuing lifestyle interventions alone.
(strong recommendation, moderate certainty)









[1]Division of Gastroenterology and Hepatology, Department of Medicine, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania; [2]Department of Medicine, Case Western Reserve University, Cleveland, Ohio; [3]Division of Gastroenterology, Louis Stokes Cleveland VA Medical Center, Cleveland, Ohio; [4]Department of Medicine, University of California San Diego, La Jolla, California; [5]Division of Gastroenterology and Hepatology, Department of Medicine, University of California San Diego, La Jolla, California; [6]Division of Gastroenterology, Hepatology, and Endoscopy, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; [7]Division of Gastroenterology and Hepatology, Department of Medicine, Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas; [8]Center for Innovations in Quality, Effectiveness and Safety, Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas; [9]Division of Gastroenterology and Hepatology, Department of Medicine, Baylor College of Medicine, Houston, Texas; [10]Division of Gastroenterology, Hepatology and Nutrition, Department of Medicine, University of Minnesota, Minneapolis, Minnesota; [11]Division of Endocrinology, Department of Medicine, University of Minnesota, Minneapolis, Minnesota; [12]Division of Gastroenterology, Hepatology, and Nutrition, Department of Medicine, University of Minnesota, Minneapolis Veterans Affairs Healthcare System, Minneapolis, Minnesota

Clinical Decision Support Tool

Pharmacological Interventions for Adults With Obesity

In adults with overweight (BMI ≥ 27 kg/m² and weight-related complications) or obesity (BMI ≥ 30 kg/m²), with inadequate response to lifestyle interventions, add pharmacological therapy*

(strong recommendation, moderate certainty)

Anti-obesity medications

	Semaglutide	Liraglutide	Phentermine-topiramate ER	Naltrexone-bupropion ER	Orlistat	Gelesis100 superabsorbent hydrogel	Diethylpropion	Phentermine
AGA recommendation	**Suggest using**				**Suggest against using**	**No recommendation**	**Suggest using**	
Mean difference % total body weight loss achieved (drug vs placebo)	**10.8%**	**4.8%**	**8.5%**	**3.0%**	**2.8%**	**2.0%**	**5.4%**	**3.6%**

If failure to achieve adequate weight loss (e.g., 5% reduction in total body weight) and/or unable to control weight-related complications, consider change in therapy based on patient's preference (switching drugs, endoscopic bariatric procedures, and/or bariatric surgery)*

Given the chronic nature of weight management, many practitioners use these medications longer than 12 weeks in an off-label fashion

*Selection of the medication or intervention should be based on the clinical profile and needs of the patient including but not limited to complications, patients' preferences, costs, and access to the therapy

Association of Pharmacological Treatments for Obesity With Weight Loss and Adverse Events A Systematic Review and Meta-analysis

Rohan Khera, MD; Mohammad Hassan Murad, MD, MPH; Apoorva K. Chandar, MBBS, MPH; Parambir S. Dulai, MD; Zhen Wang, PhD; Larry J. Prokop, MLS; Rohit Loomba, MD, MHSc; Michael Camilleri, MD; Siddharth Singh, MD, MS

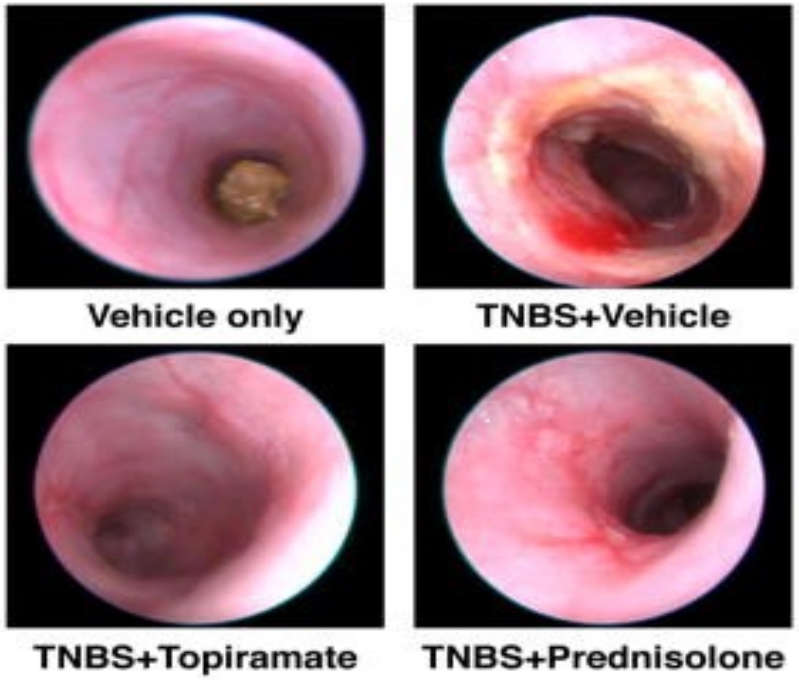
JAMA

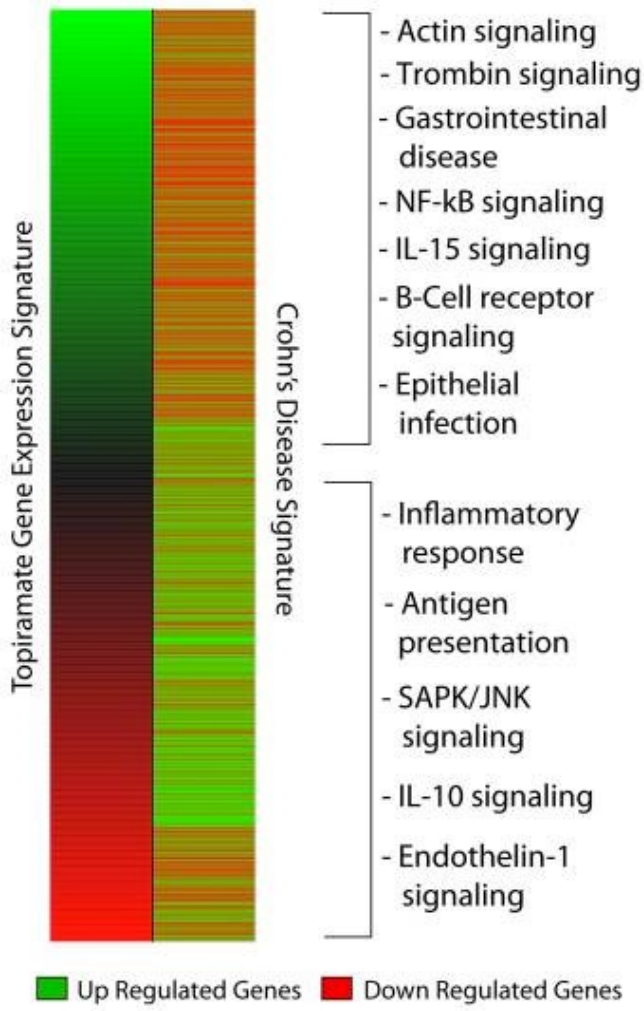
Agent	≥ 5% weight loss	≥ 10% weight loss	Excess weight loss over placebo
Placebo	23%	9%	N/A
Phentermine-topiramate (Qsymia)	**75%**	**54%**	8.8 kg (7.4-10.2)
Liraglutide (Saxenda)	63%	34%	5.3 kg (4.5-6.1)
Naltrexone-bupropion (Contrave)	**55%**	**30%**	5.0 kg (4.0-5.9)
Lorcaserin (Belviq)	49%	25%	3.2 kg (2.5-4.0)
Orlistat (Alli)	44%	20%	2.6 kg (2.2-3.0)

Khera, …, Singh. JAMA 2016;315:2424

Phentermine-Topiramate in IBD

- Computational analysis comparing gene expression profile of topiramate, with gene expression signature of IBD





Dudley. Sci Transl Med 2011;3:96

GLP-1 based therapies and disease course of inflammatory bowel disease

Marie Villumsen[a,#,*], Astrid Blicher Schelde[b,#], Espen Jimenez-Solem[b,c], Tine Jess[d], Kristine Højgaard Allin[d]

- Danish population-based cohort
- 3,751 patients with IBD AND diabetes mellitus - 982 patients in GLP-1 receptor agonists/DPP-4 inhibitors vs. 2769 patients treated with other anti-diabetics
- Composite outcome – need for corticosteroids, TNFa antagonists, IBD-related surgery, IBD-related hospitalization
- GLP-1 receptor agonists/DPP-4 inhibitors – **48% lower risk of adverse outcomes**

IRRs of composite and specific outcomes comparing treatment with GLP-1 receptor agonists/DPP-4 inhibitors with other antidiabetic therapies.

	New users of GLP-1-receptor agonists and/or DPP-4 inhibitors			Non-users of GLP-1-receptor agonists and/or DPP-4 inhibitors			Crude estimate	Adjusted estimate
Composite outcome	Events	PY	IR per 1000 PY	Events	PY	IR per 1000 PY	IRR (95% CI)	IRR (95% CI)
Total	199	1861	106·9	2333	9652	241·7	0·44 (0·38–0·51)	0·52 (0·42–0·65)
Sex								
Female	50	344	145·1	1079	4325	249·5	0·44 (0·35–0·54)	0·49 (0·35–0·69)
Male	149	1517	98·2	1235	5202	237·4	0·45 (0·37–0·55)	0·55 (0·41–0·73)
IBD subtype								
CD	90	836	107·6	640	2144	298·5	0·49 (0·36–0·65)	0·62 (0·41–0·92)
UC	109	1025	106·3	1674	7382	226·8	0·43 (0·37–0·51)	0·50 (0·39–0·65)
Separate outcomes								
Hospitalisation	178	2889	61·6	1445	14,024	103·0	0·60 (0·51–0·70)	0·73 (0·58–0·91)
Surgery	97	3675	26·4	593	17,456	34·0	0·78 (0·63–0·96)	0·79 (0·57–1·09)
Steroid initiation	133	2813	47·3	1238	13,104	94·5	0·50 (0·42–0·60)	0·54 (0·41–0·70)
TNF-α-inhibitor initiation	29	4183	6·9	213	18,737	11·4	0·61 (0·41–0·90)	0·56 (0·32–1·00)

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Summary

1. **Obesity is common in patients with IBD**, and may contribute to increased risk of developing Crohn's disease
2. Effects of obesity are mediated by dysbiosis, pro-inflammatory adipocytokines, intestinal barrier disruption (and activation of adipocytes in mesentery, in CD), and altered pharmacokinetics of biologic agents
3. Obesity **adversely impact disease course** and outcomes in patients with IBD
4. Obesity results in **inferior response to biologic therapy**, potentially by promoting rapid drug clearance regardless of dose
5. **Treating obesity may augment treatment response to biologics in IBD**

Thank You!

sis040@ucsd.edu

UC San Diego
Health Sciences