DDC'24
Emerging Trends and Innovations in Gastroenterology and Hepatology
Sheraton Convention Center
February 8-11, 2024
Asociación Puertorriqueña de Gastroenterología

The Impact of Obesity on GI and Liver Disease

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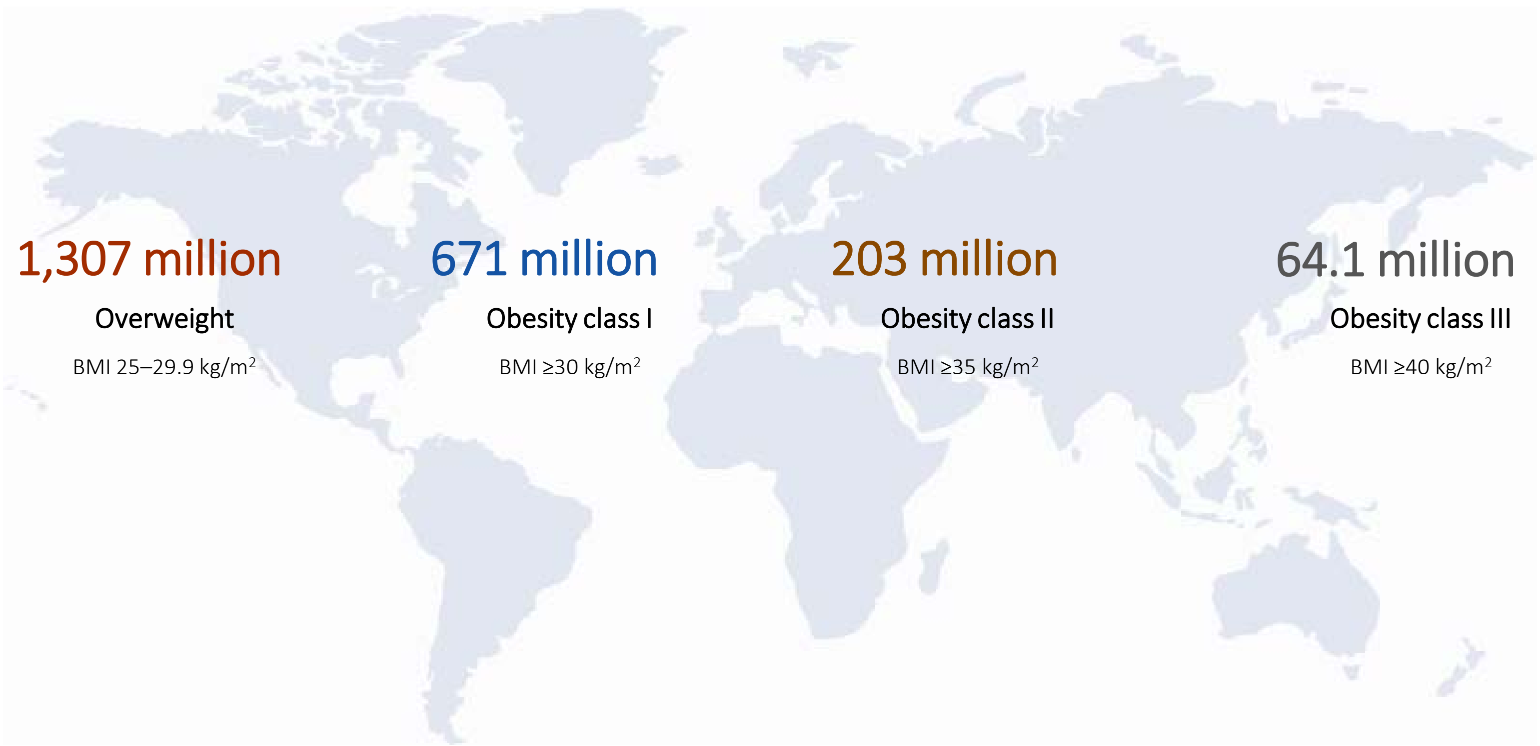
Disclosures

- Consultant: NovoNordisk, WebMD
- Investigator: VectivBio, ProventionBio


Impact of Weight loss on Disease
Obesity and GI/Liver Disease Outcomes
Obesity and GI/Liver Disease
The Gut and Obesity Pathogenesis
Obesity Epidemiology

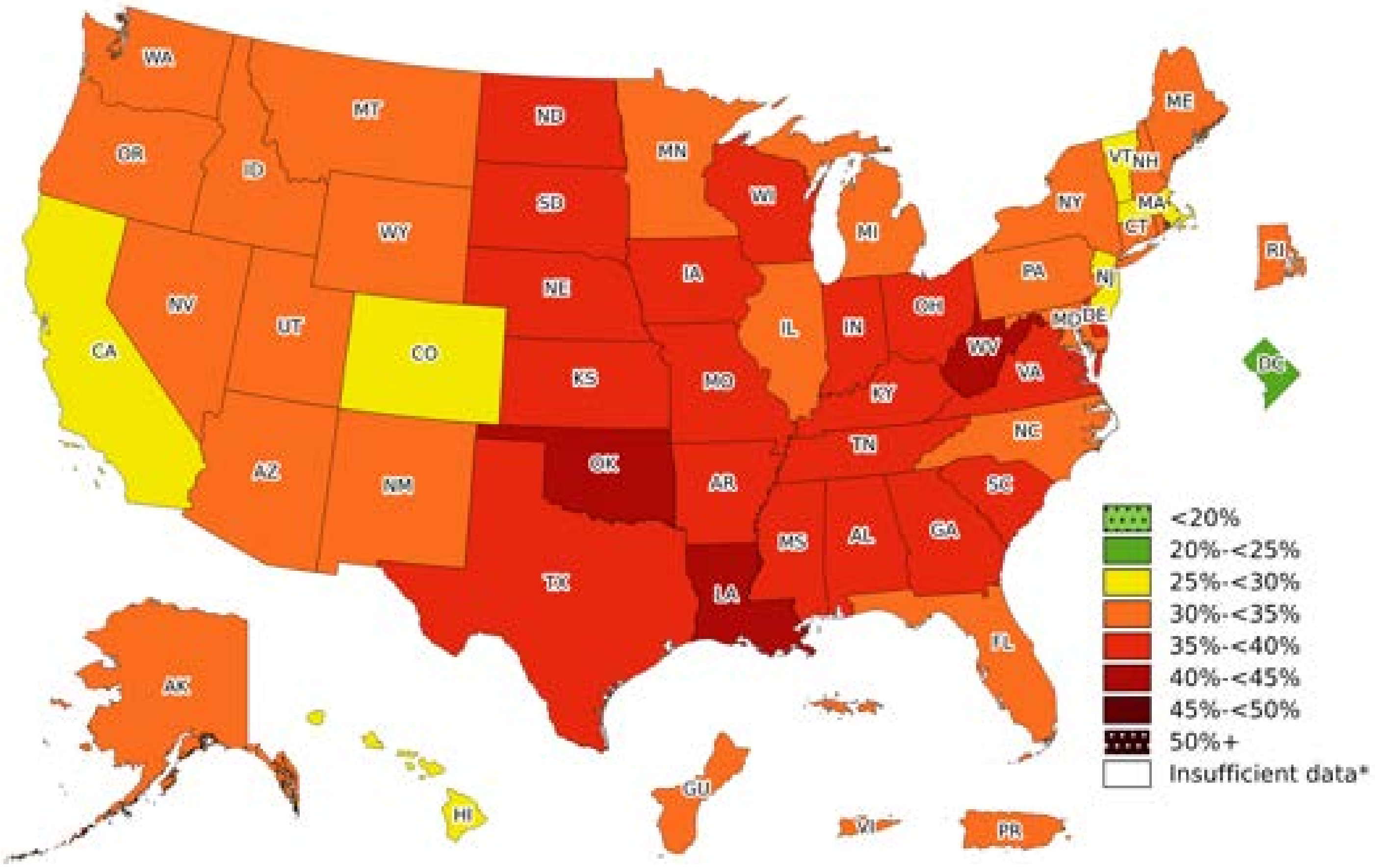
The Global Prevalence of Obesity



World Obesity Federation. Obesity: missing the 2025 global targets. 2020. Last accessed: September 2020. Available from: https://www.worldobesity.org/resources/resource-library/world-obesity-day-missing-the-targets-report

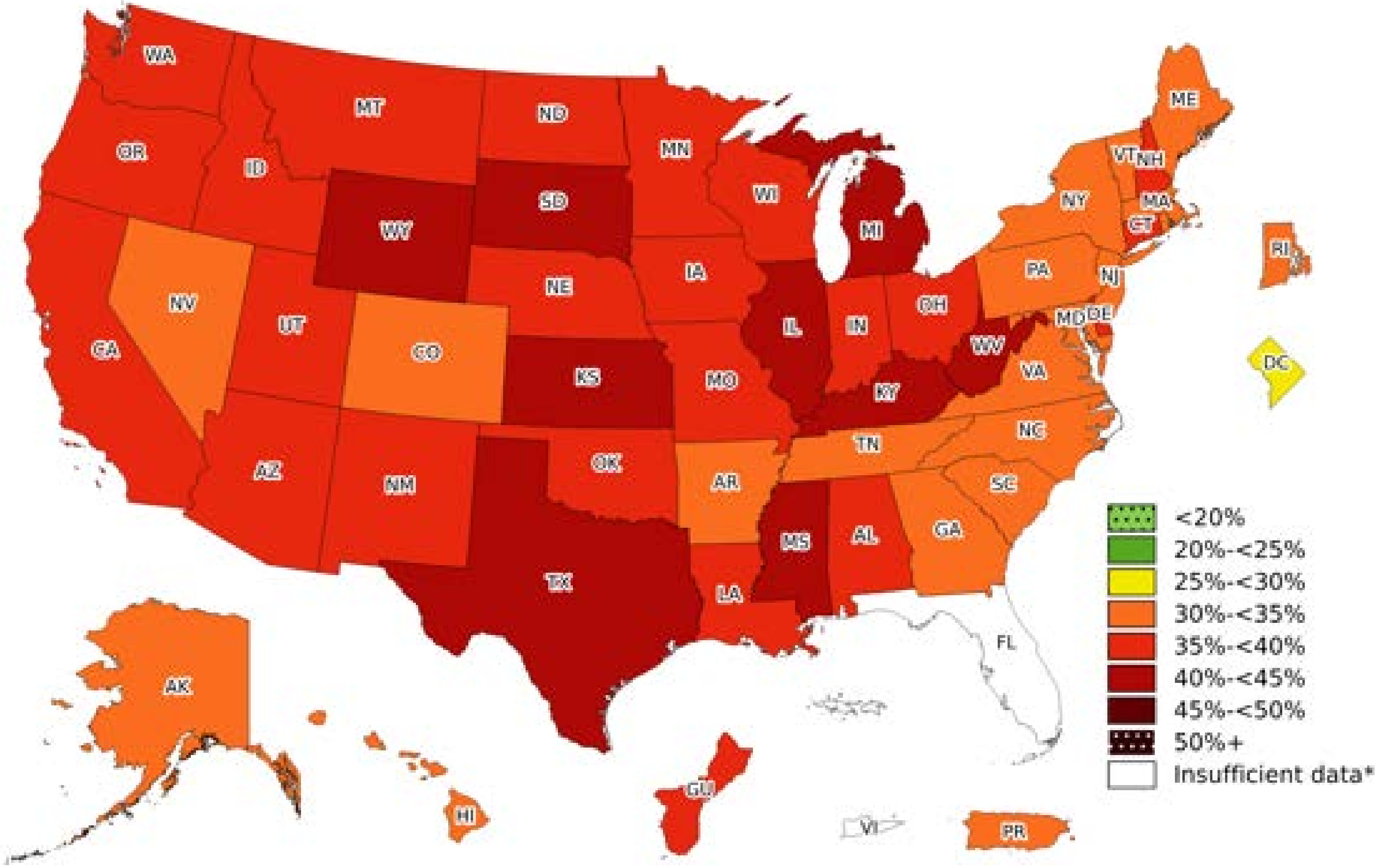
Prevalence† of Obesity Among U.S. Adults by State/Territory

BRFSS, 2022



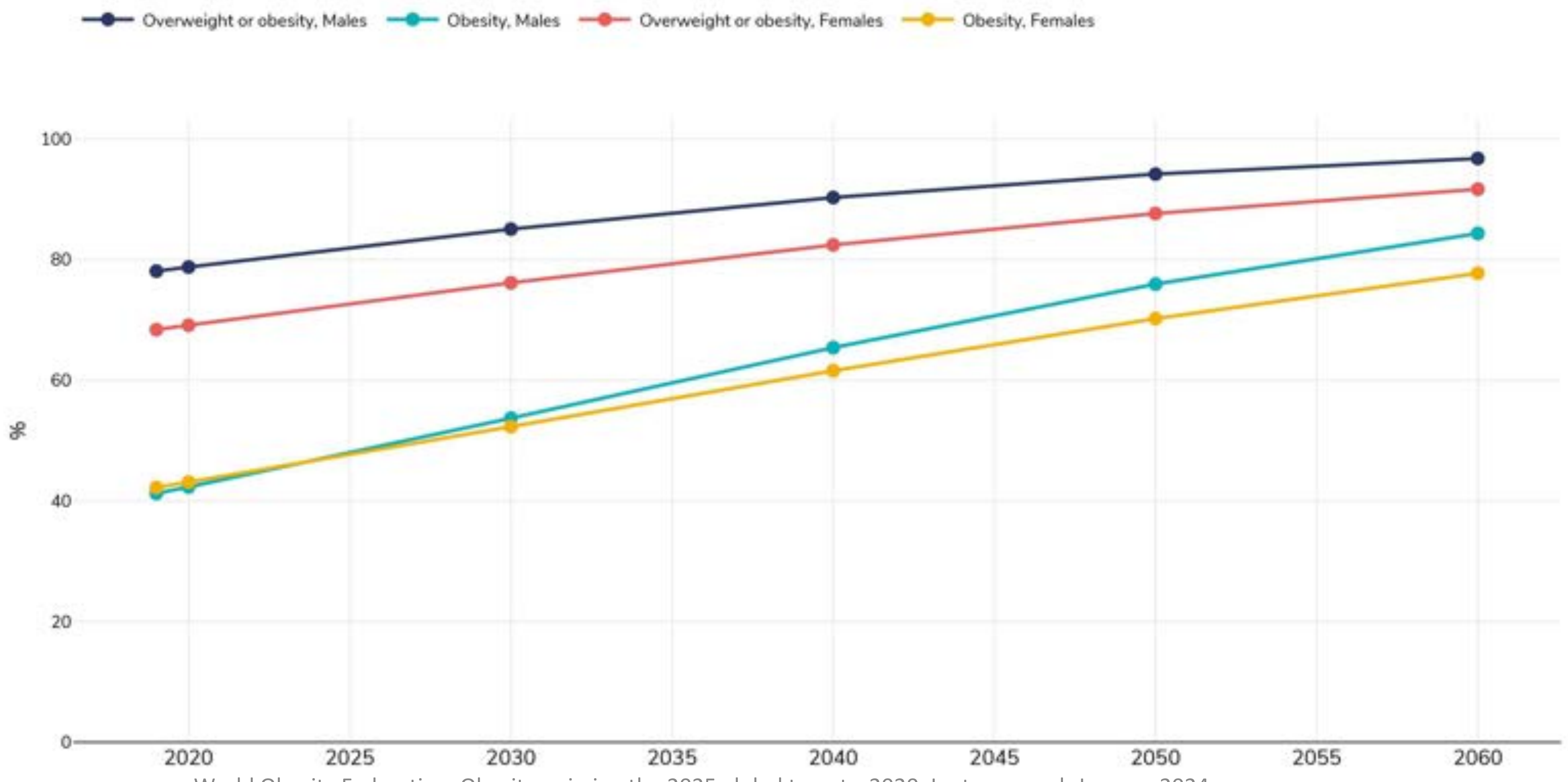
Adult Obesity Prevalence Maps | Overweight & Obesity | CDC; accessed January 2024.

Prevalence† of Obesity Among Hispanic Adults BRFSS, 2022



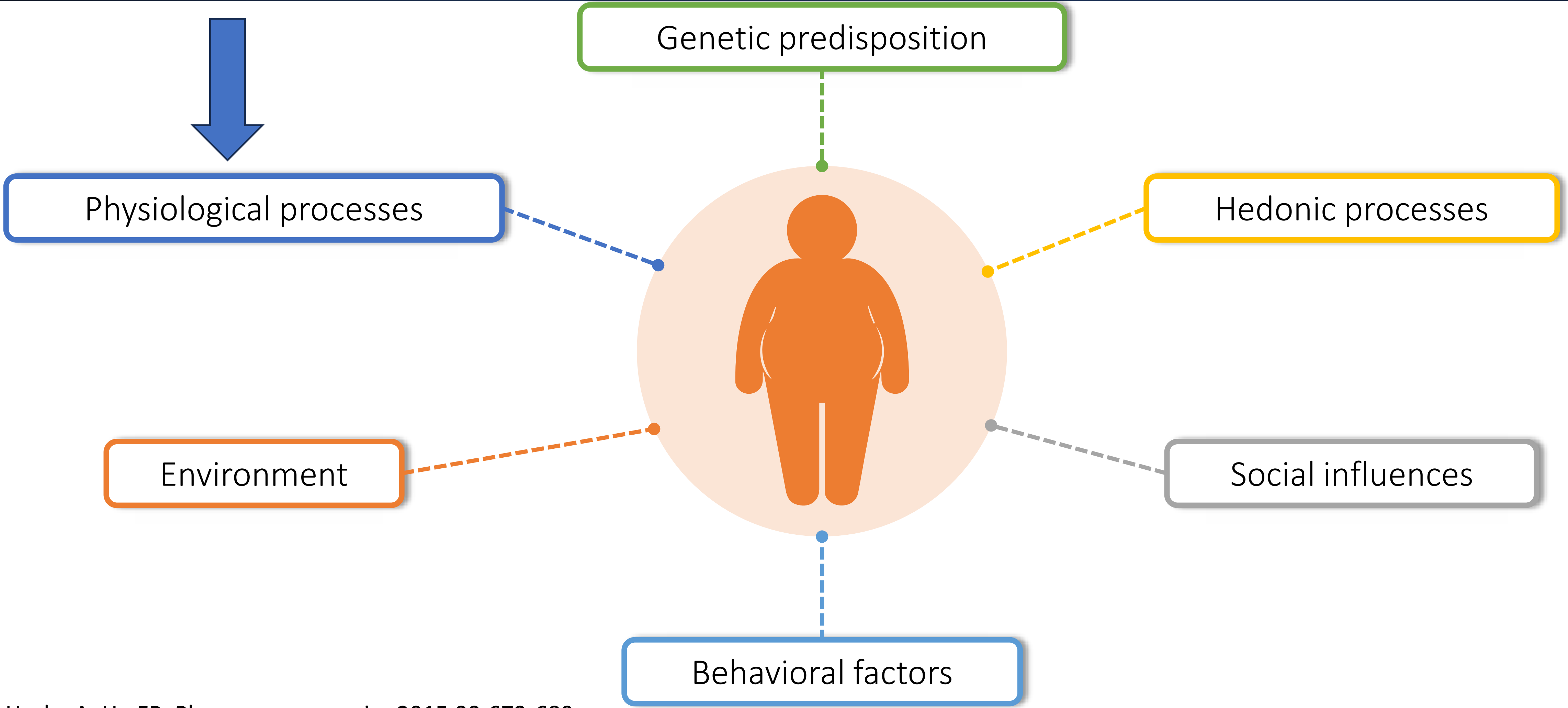
Projected % of individuals (aged >20 years) living with overweight or obesity (BMI>25kg/m²), 2020-2060

United States



World Obesity Federation. Obesity: missing the 2025 global targets. 2020. Last accessed: January 2024.
Available from: https://www.worldobesity.org/resources/resource-library/world-obesity-day-missing-the-targets-report

Drivers of obesity



Hruby A, Hu FB. Pharmacoeconomics 2015;33:673-689;
Mishra AK, et al. Metabolism 2016;65:48-65

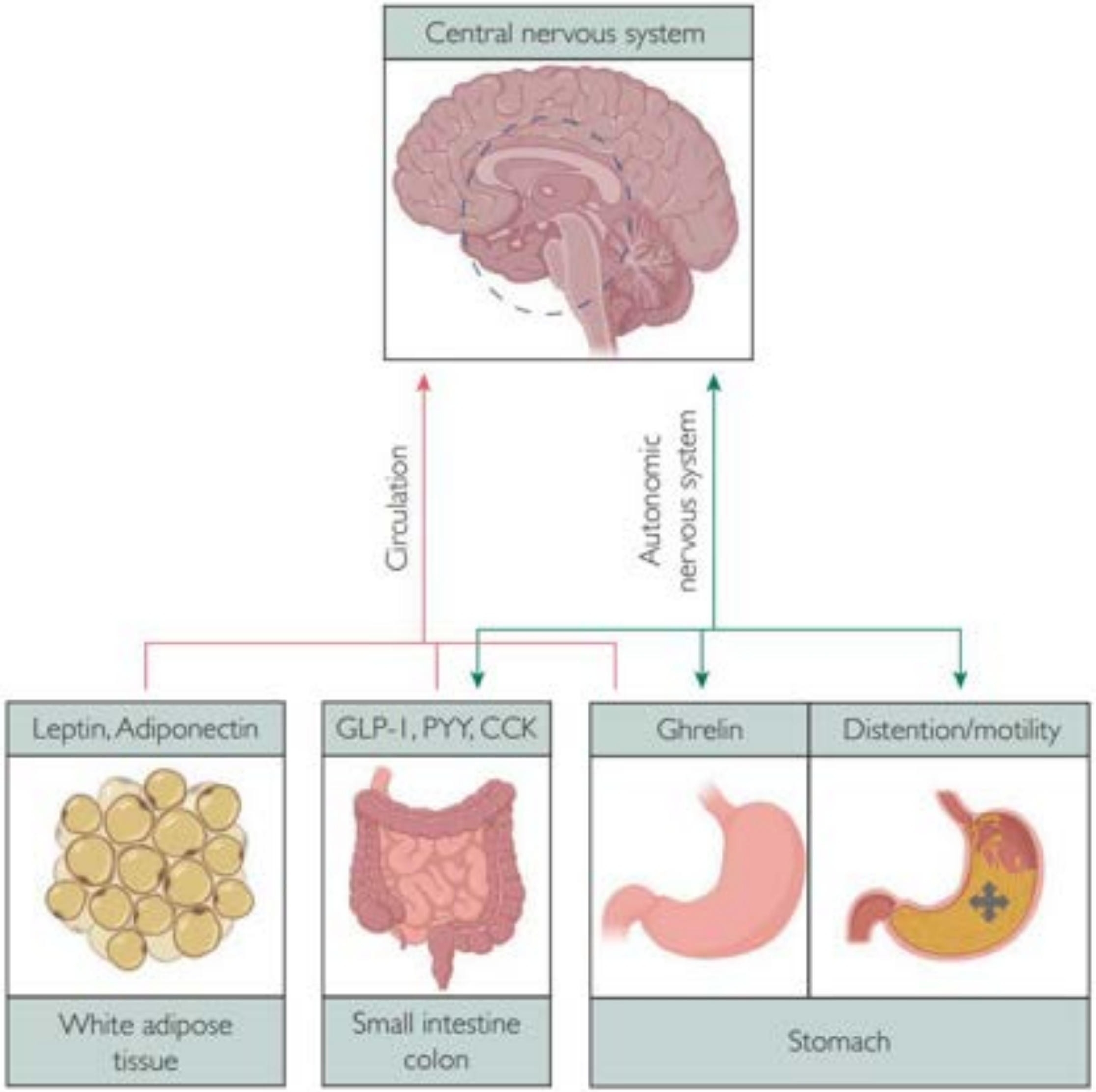
The GI tract and obesity pathogenesis

Energy IN

Energy OUT

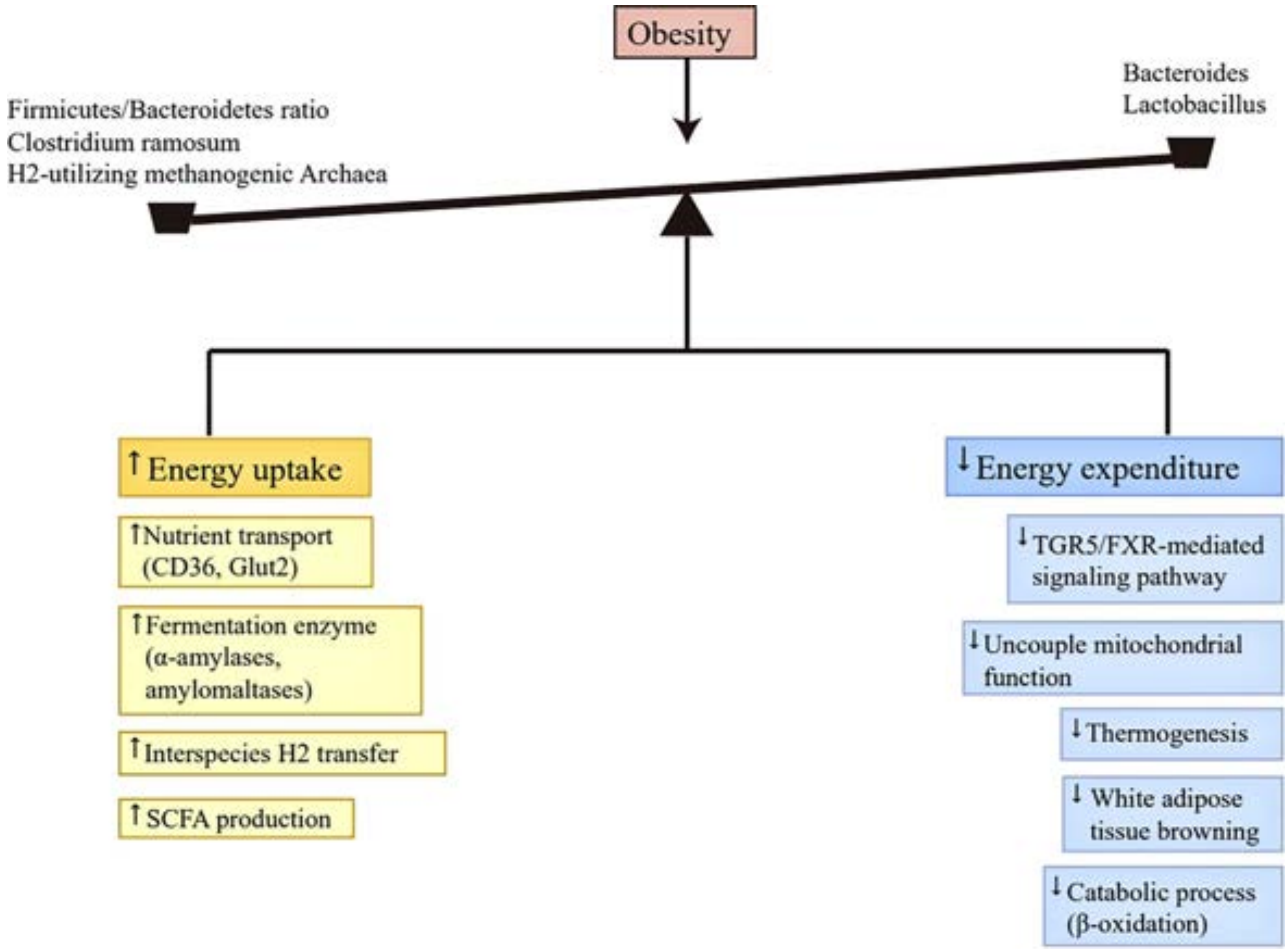
- basal metabolic rate
- thermic effect of food
- energy of activity

Gut Hormones



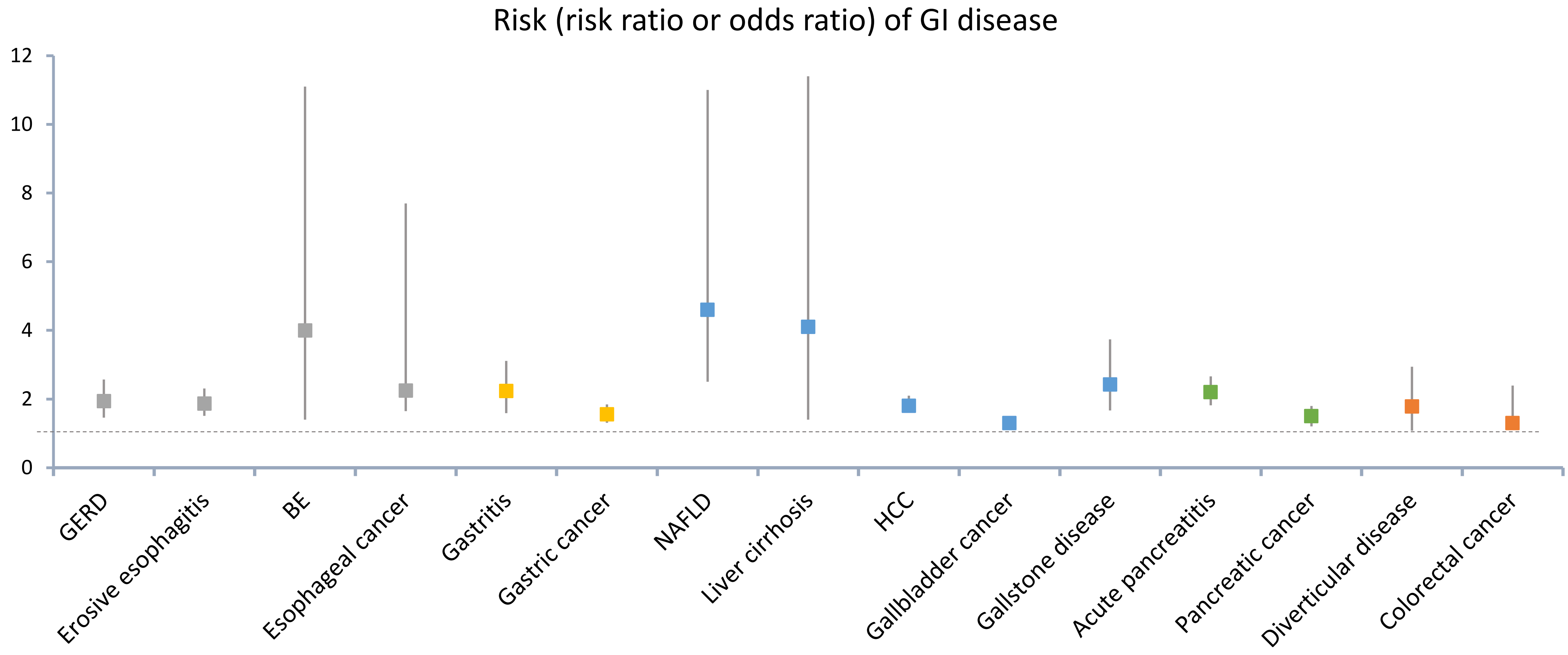
Busebee B et al. Mayo Clin Proc. 2023 Dec;98(12):1842-1857.

Gut Microbiota



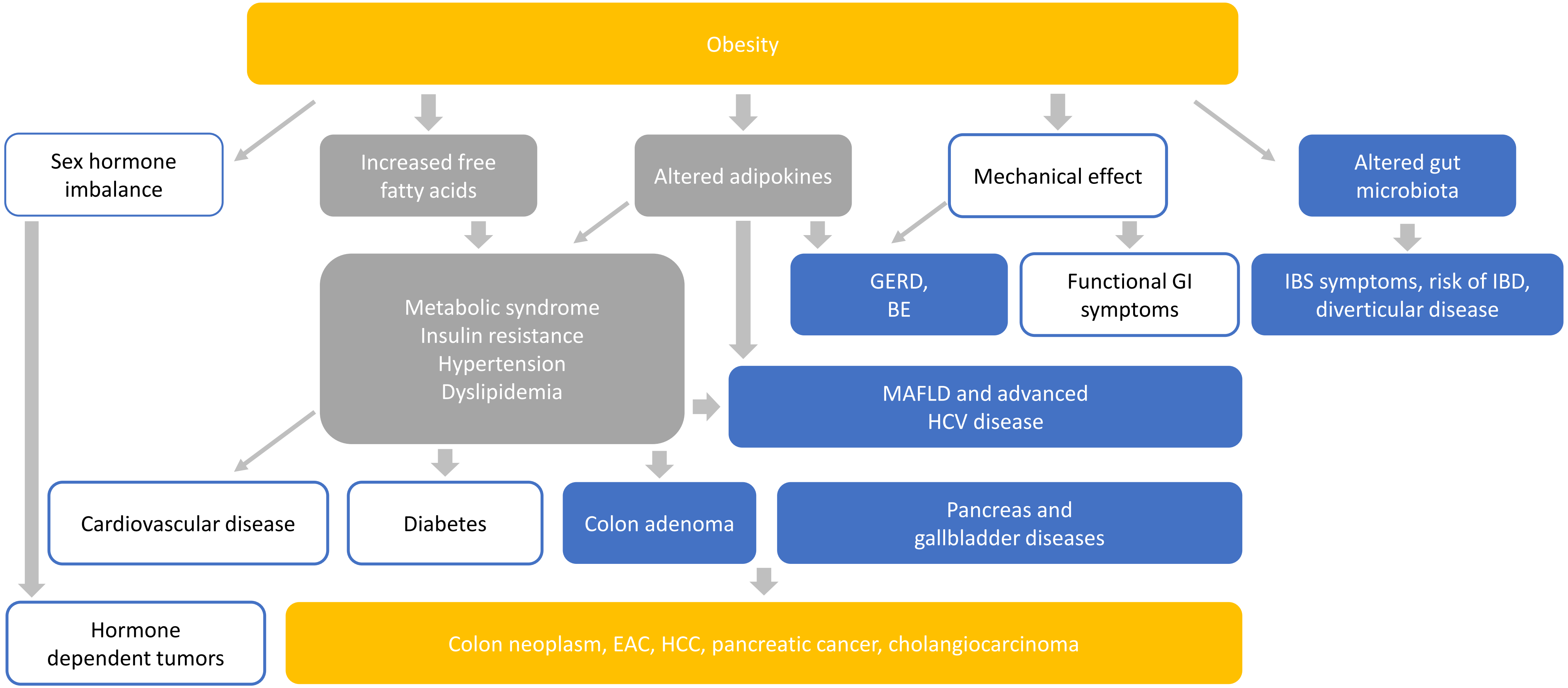
Cheng Z et al. Front Endocrinol (Lausanne). 2022 Oct 20;13:1025706.

GI/Liver Complications of Obesity



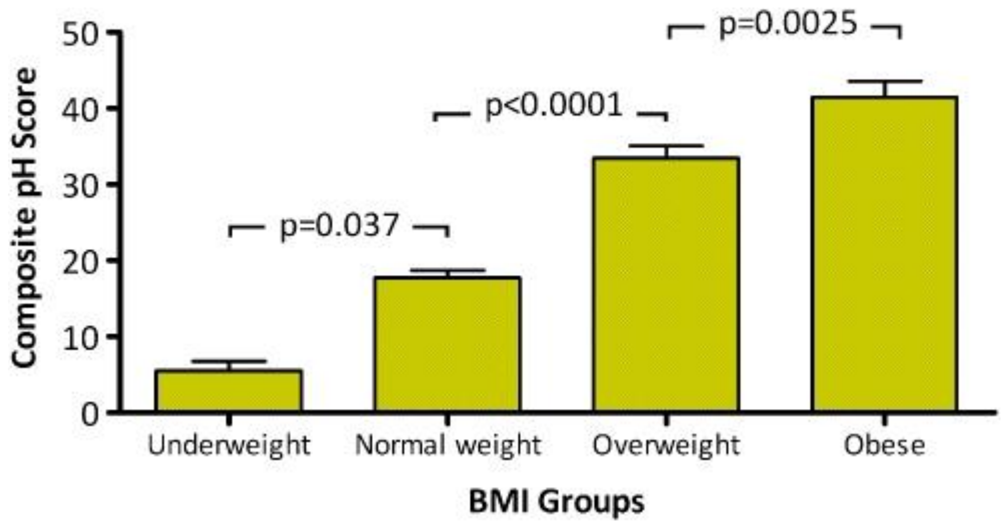
Ansari S, et al. Frontline Gastroenterol. 2020;12:235-45.

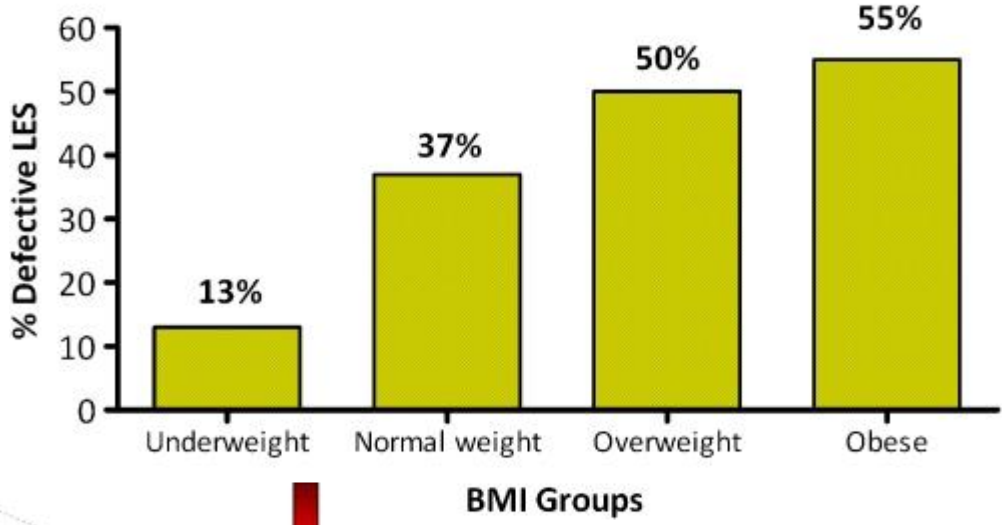
Pathophysiologic links between Obesity and gastrointestinal/liver disease

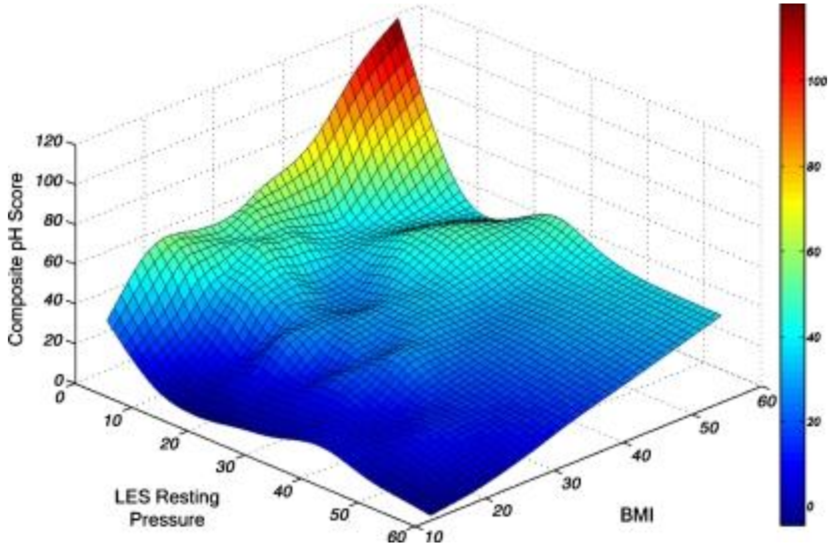


1. Emerenziani S, et al. Nutrients. 2020;12:111.
2. Nam SY. Gut Liver. 2017;11:323-34.

GERD is linked to BMI



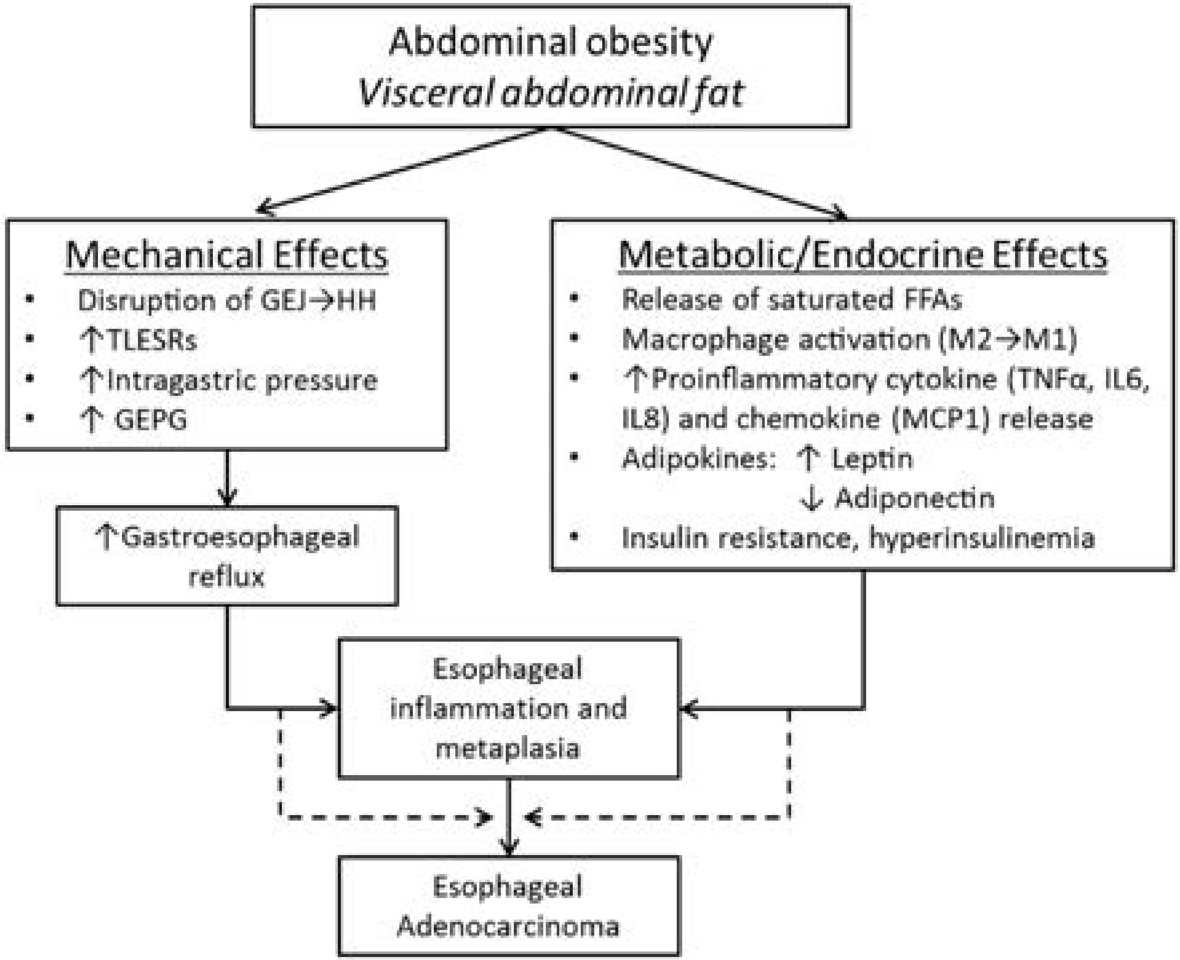




*additive effect of LES pressure and BMI on composite pH score

Ayazi S. J Gastrointest Surg. 2009;13:1440-1447.

Pathophysiologic mechanisms linking obesity to GER, Barrett’s esophagus and EAC



Chandar et al. GI Clinics NA 2015.

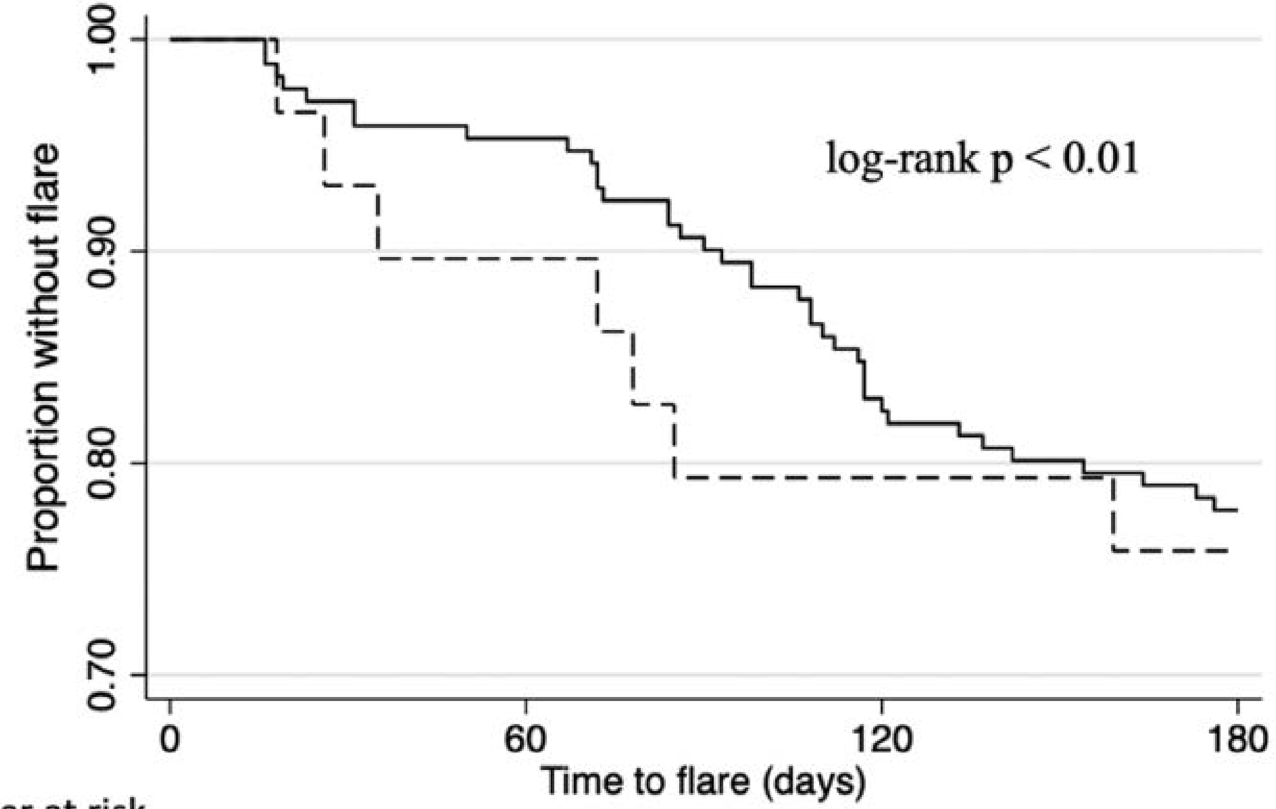
IBD

- Incident disease/risk of disease development→ conflicting data[1]
- IBD –related complications
  - surgery, steroid use, time to anti-TNF
  - conflicting data in UC and CD
  - *some studies show protective effect of obesity in CD
- Response to therapy
  - accelerated drug clearance, higher volumes of distribution → lower trough levels
  - some studies→ reduced response or increased loss of response to anti-TNF agents

1. Johnson AM, Loftus EV. Saudi J Gastroenterol. 2021 Jul-Aug;27(4):183-190.
2.Michalak et al. Nutrients. 2022 Sep 25;14(19):3983.

Visceral Adiposity Independently Predicts Time to Flare in Inflammatory Bowel Disease but Body Mass Index Does Not

Priya Sehgal, MD, MPH,[*] Steven Su, MD, PhD,[†], John Zech, MD[‡], Yael Nobel, MD, MS,[*],
Lyndon Luk, MD, [‡] Ioannis Economou, MD,[§], Bo Shen, MD,[§], James D. Lewis, MD,[¶], and
Daniel E. Freedberg, MD, MS[*]



Number at risk

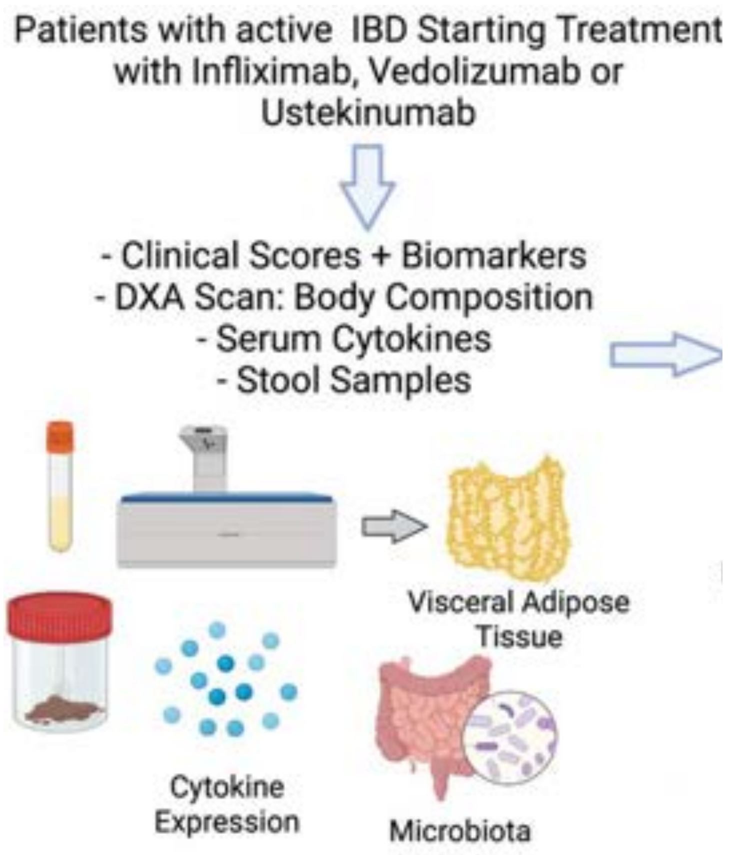
VAT:SAT < 1.0	163	142	133
VAT:SAT ≥ 1.0	26	23	22

——— VAT:SAT < 1.0 ----------- VAT:SAT ≥ 1.0

Sehgal P et al. Inflamm Bowel Dis. 2023 Jun 12:izad111.

Higher Intra-Abdominal Visceral Adipose Tissue Mass Is Associated With Lower Rates of Clinical and Endoscopic Remission in Patients With Inflammatory Bowel Diseases Initiating Biologic Therapy: Results of the Constellation Study

Andres J. Yarur,[1,2] Alexandra Bruss,[2] Andrea Moosreiner,[2] Poonam Beniwal-Patel,[2] Lizbeth Nunez,[2] Brandon Berens,[2] Jean F. Colombel,[3] Stephan R. Targan,[1] Caroline Fox,[2] Gil Y. Melmed,[1] Maria T. Abreu,[4] and Parakkal Deepak[5]

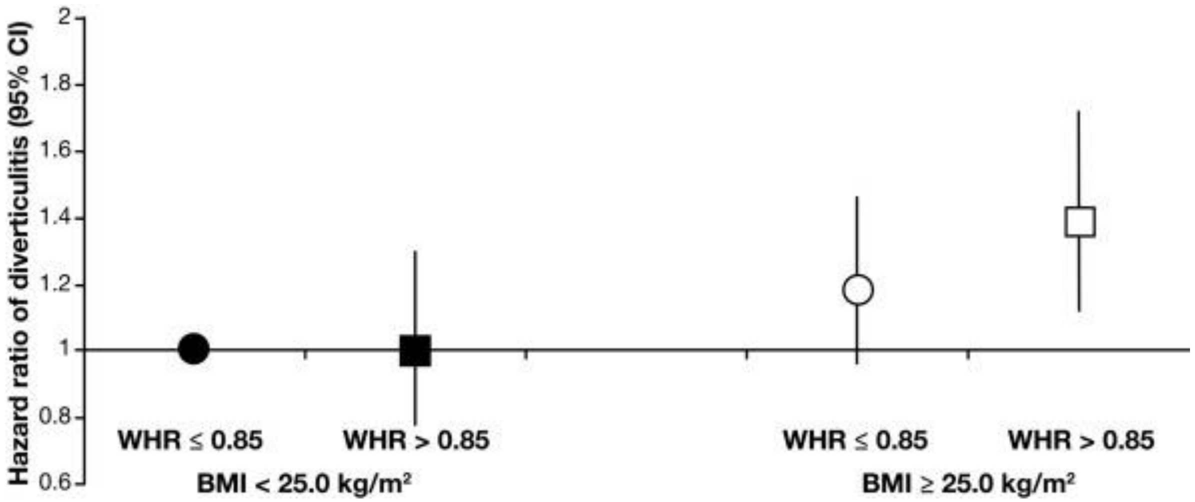


Gastroenterology

Gastroenterology. 2023 Oct;165(4):963-975.e5.

Diverticular disease

- Associations with diverticulitis
  - Diet
    - risk is higher in meat eaters > pescatarian >vegetarian > vegan[1]
    - Risk higher with low dietary fiber intake[1]
  - Low exercise[1]
  - Body weight/obesity, **weight gain**, waist-hip ratio[2]



1. *Crowe et al. BMJ* 2011;343:d4131
2. Ma et al. Gastroenterology 2018;155:58–66

Pancreatitis

Fig. 2 Body mass index and acute pancreatitis, linear dose-response analysis per 5 kg/m² (a) and nonlinear dose-response analysis (b)

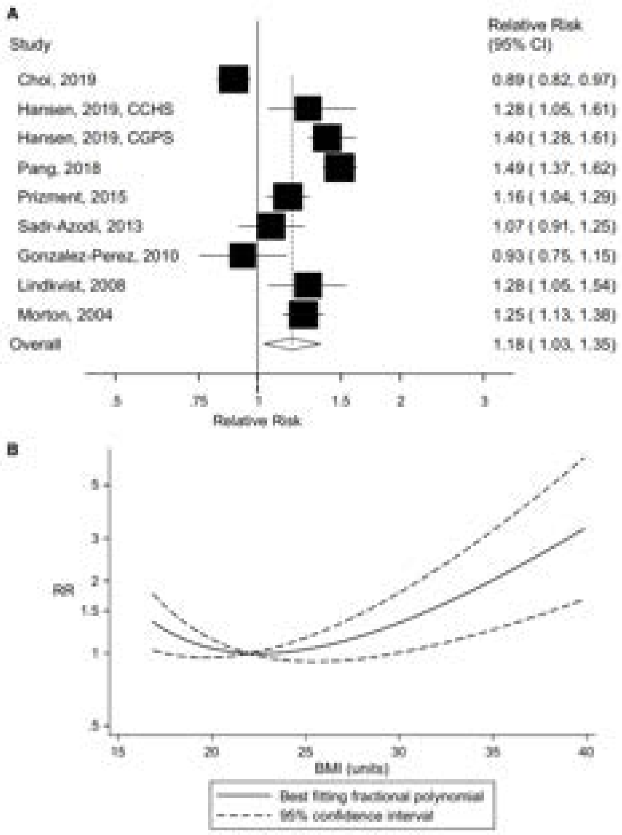
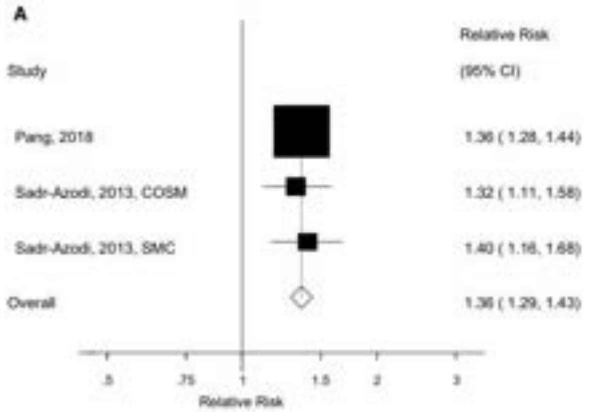


Fig. 3 Waist circumference and acute pancreatitis, linear dose-response analysis per 10 cm (a) and nonlinear dose-response analysis (b)

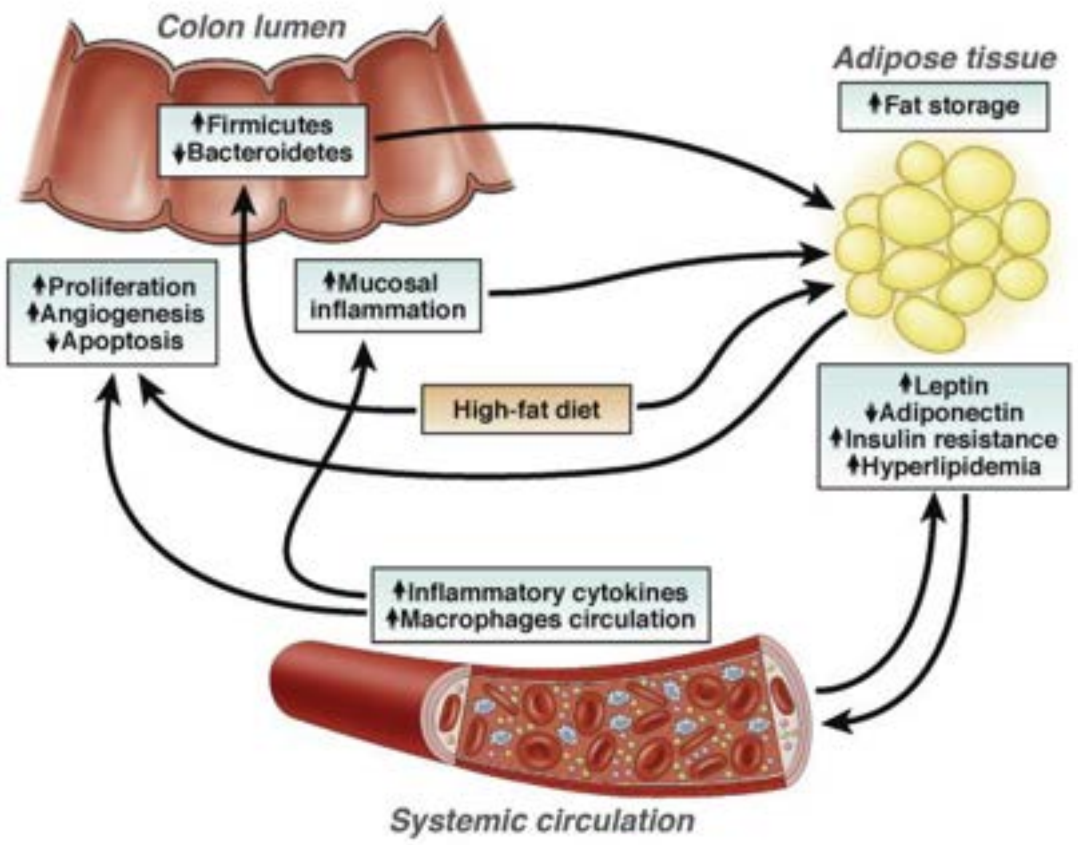


- In acute alcoholic pancreatitis[2]
  - longer LOS
  - higher hospital costs
  - greater risk of complications and mortality

1. Aune et al. Digestive Diseases and Sciences (2021) 66:1249–1267
2. Pellegrini J et al. Cureus)2024) 16(1): e51653.

Colorectal Cancer

- Obesity/visceral adipose tissue strong risk factor[1]
- Effect differs with respect to sex (M>F)[1]
- Complex biology[2,3]
- Obesity and weight gain from early adulthood linked to early onset CRC[4]



1. Nam SY. Gut Liver 2017;11:323-34.
2. Appunni, et al. Front Nutr 2021;8:718389.
3. Gastroenterology 2014;146:357–373
4. Liu PH et al. JAMA Oncol. 2019 Jan 1;5(1):37-44.

Obesity and early onset colorectal cancer

Current BMI and Risk of Early-Onset Colorectal Cancer

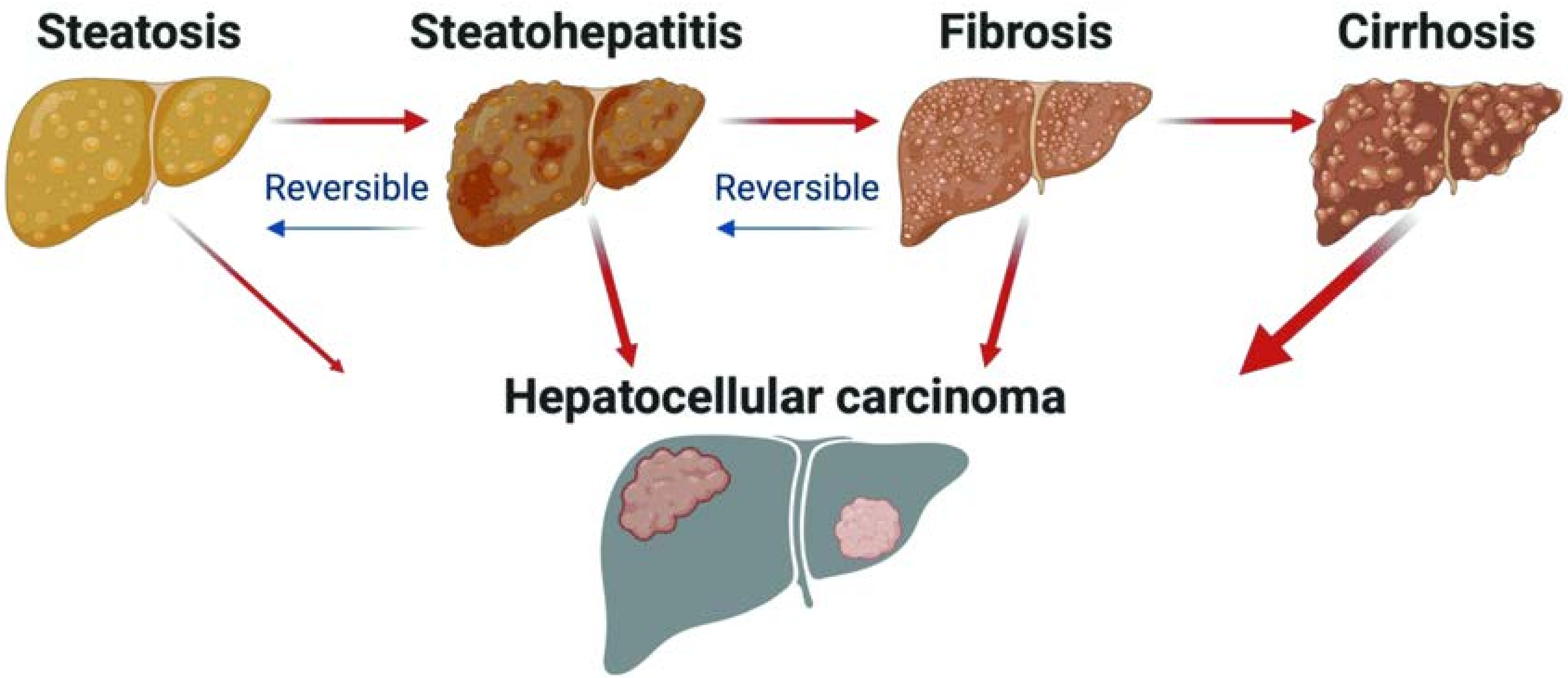
Variable	No. of Cases	No. of Person-Years	Age-Adjusted RR (95% CI)	Multivariable-Adjusted RR (95% CI)[a]
All Participants				
Current BMI				
18.5-22.9	29	455 250	1 [Reference]	1 [Reference]
23.0-24.9	20	217 271	1.27 (0.71-2.24)	1.33 (0.75-2.36)
25.0-29.9	30	296 763	1.32 (0.79-2.22)	1.37 (0.81-2.30)
≥30	35	230 169	1.86 (1.13-3.06)	1.93 (1.15-3.25)
Each 5-unit increase	NA	NA	1.18 (1.04-1.35)	1.20 (1.05-1.38)
P for trend[b]	NA	NA	.01	.01

Weight Change Since 18 Years of Age[d]

Loss or gain <5.0 kg[e]	27	373 061	1 [Reference]	1 [Reference]	1 [Reference]
Gain of 5.0-19.9 kg	42	561 417	0.86 (0.53-1.41)	0.86 (0.52-1.42)	0.86 (0.52-1.43)
Gain of 20.0-39.9 kg	34	214 633	1.66 (0.99-2.77)	1.64 (0.96-2.81)	1.65 (0.96-2.81)
Gain ≥40.0 kg	11	47 342	2.25 (1.11-4.59)	2.15 (1.02-4.54)	2.15 (1.01-4.55)
Each 5-kg increase	NA	NA	1.09 (1.03-1.16)	1.09 (1.03-1.16)	1.09 (1.02-1.16)
P for trend[c]	NA	NA	.002	.006	.007

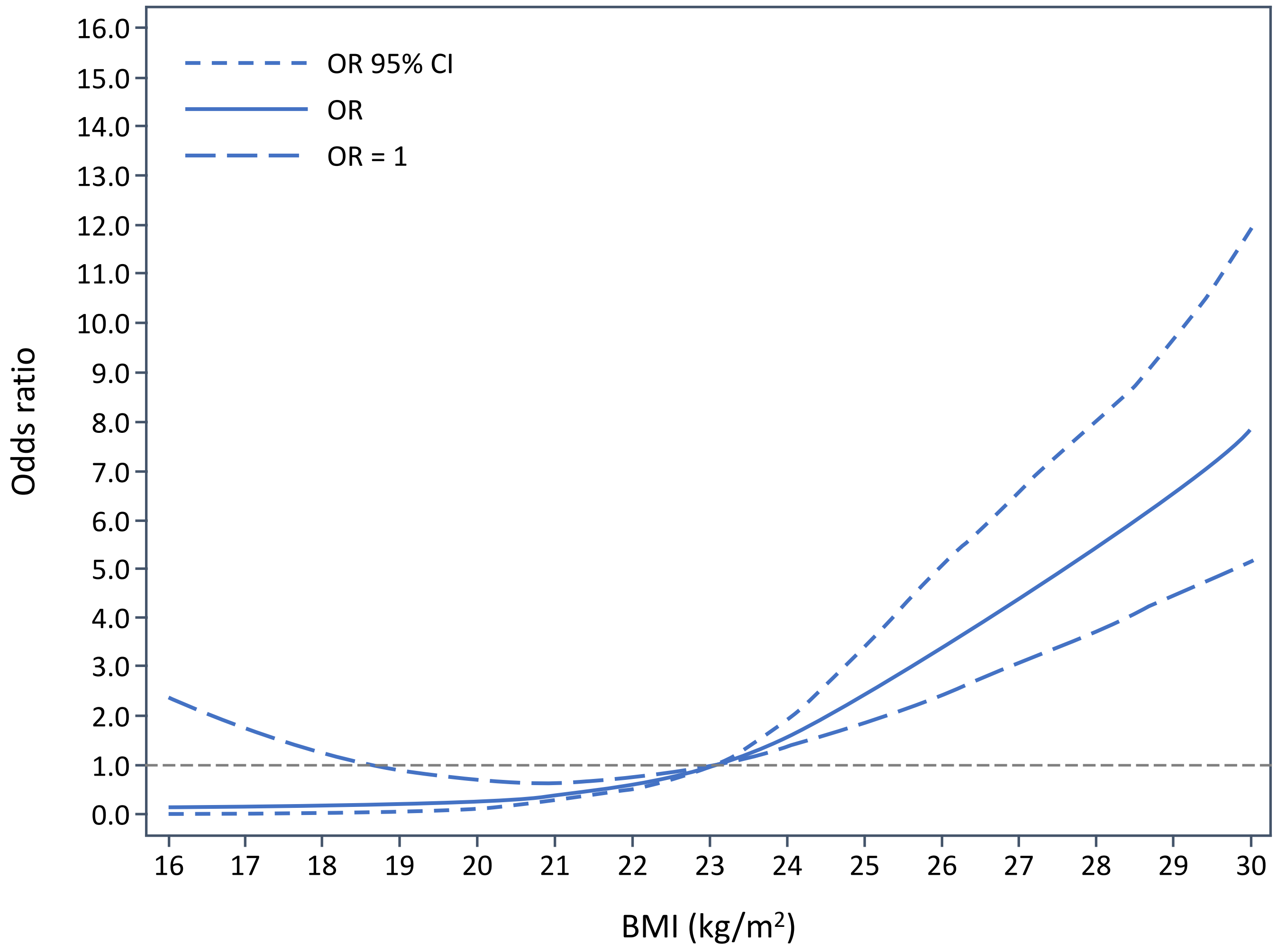
1. Liu PH et al. JAMA Oncol. 2019 Jan 1;5(1):37-44.

MAFLD Continuum



Adapted from: Zunica et al. (2022). Cancers. 14. 4051. 10.3390/cancers14164051.

BMI, an independent, dose-dependent risk factor for steatotic liver disease and progression



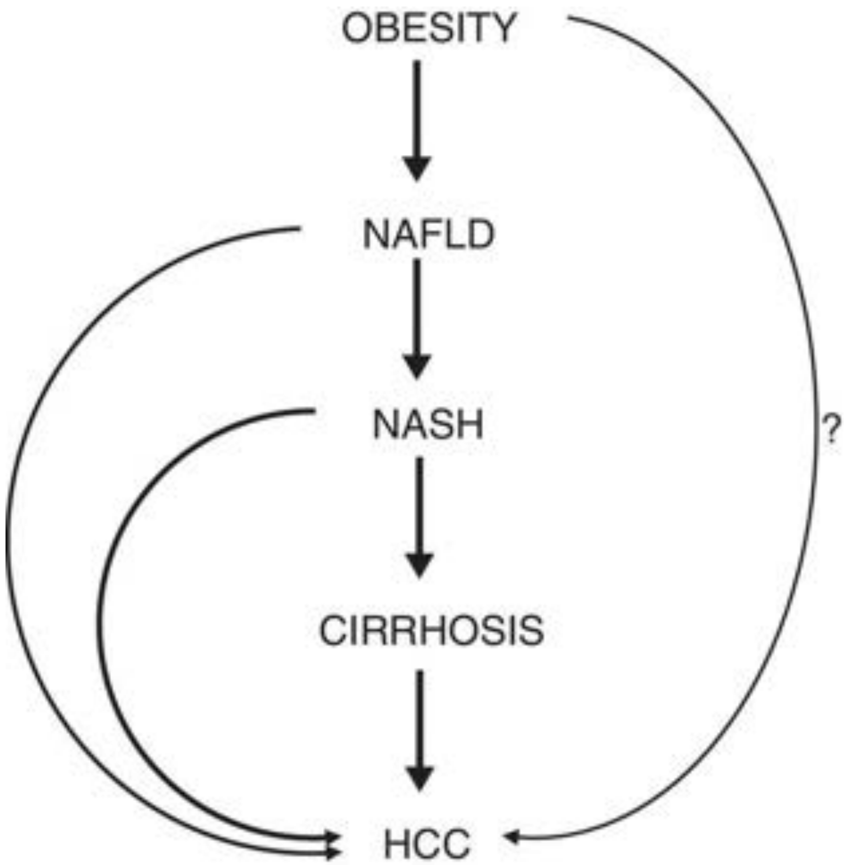
Fan R et al. Sci Rep. 2018;8:15273.
Cotter T, Rinella M. Gastroenterology. 2020;158(7):1851-1864.

Other chronic liver diseases

- Alcoholic liver disease[1]
  - shared pathogenesis →synergistic affect on disease
  - obesity is an independent risk factor for acute alcoholic hepatitis and cirrhosis
  - greater risk of hepatocellular carcinoma (HCC)
- Hepatitis B[2,3]
  - carriers in the highest BMI quartile (>25kg/m2)→greater HCC risk and liver-related mortality
  - impaired HBV vaccine response
- Hepatitis C[4]
  - obesity/insulin resistance adversely affects treatment response (*INF-based therapy)
  - greater risk of HCC

1. Chiang DJ McCullough AJ. Clin Liver Dis. 2014 Feb;18(1):157-63.
2. Journal of Clinical Oncology 26, no. 34 (December 01, 2008) 5576-5582.
3. Liu F et al. Hum Vaccin Immunother. 2017 May 4;13(5):1014-1017.
4. Charlton MR et al. Hepatology. 2006 Jun;43(6):1177-86.

Hepatocellular carcinoma



- Obesity = independent risk factor for HCC

  ⬆ liver cancer risk by ~ 25% per 5 kg/m2 BMI increase

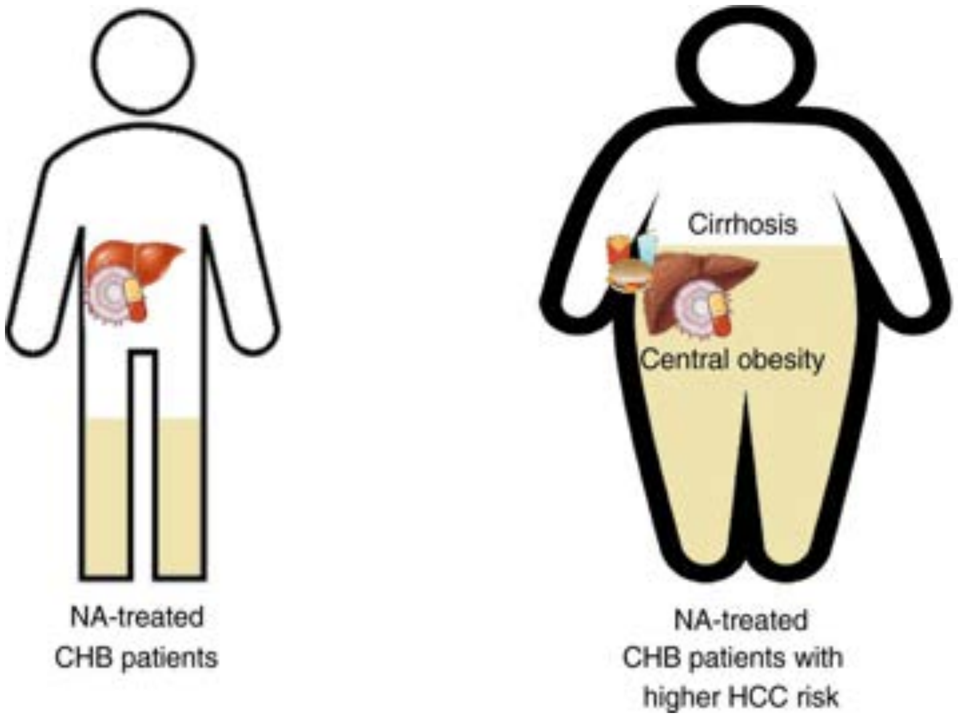
  - higher BMI in childhood increases the risk of primary liver cancer in adults (HR 1.36/unit increase in BMI)
- Greater HCC-related mortality amongst patients with obesity
- MASLD-associated HCC

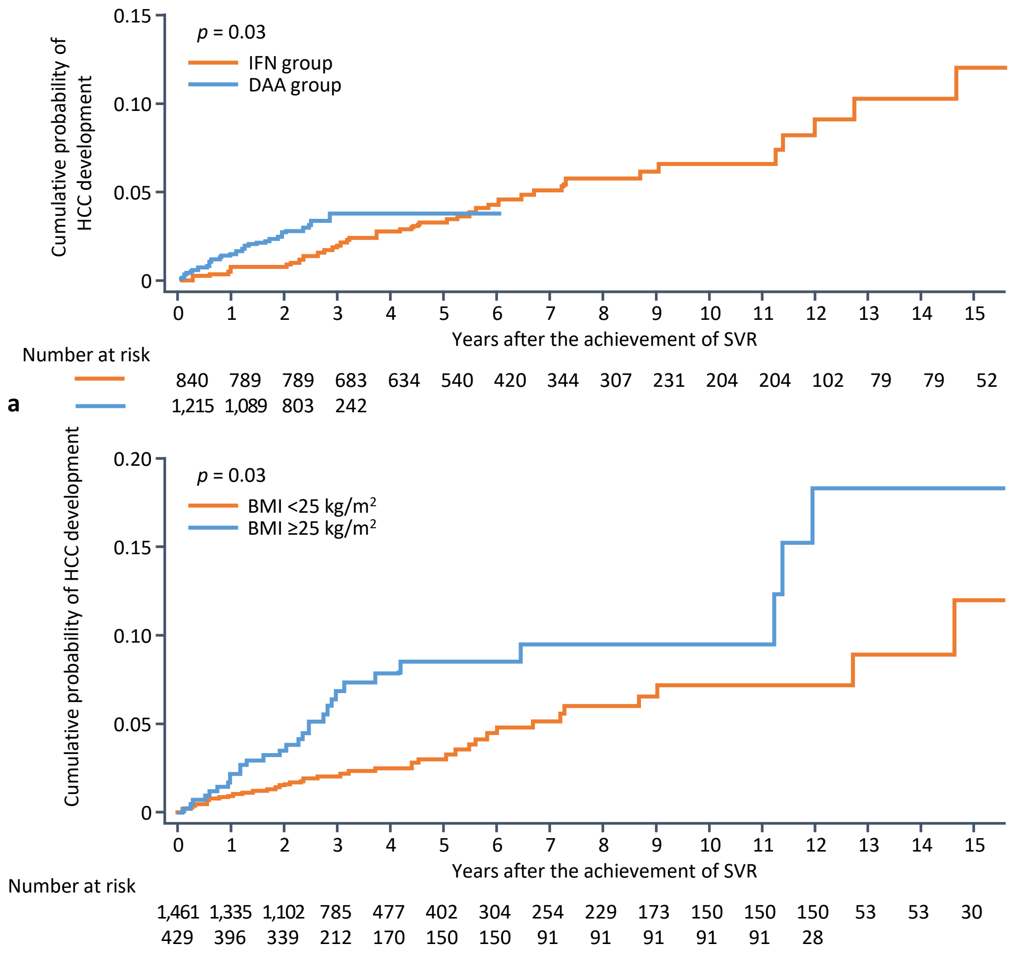
  - growing indication for liver transplant

  - can occur in the absence of cirrhosis

Saitta C, Pollicino T, Raimondo G. Ann Hepatol. 2019;18(6):810-815.

Obesity and HCC risk in treated HBV and HCV



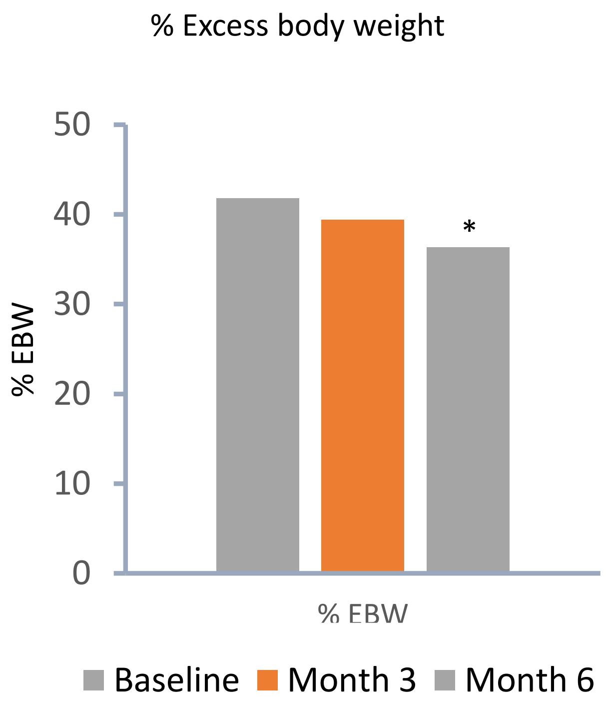


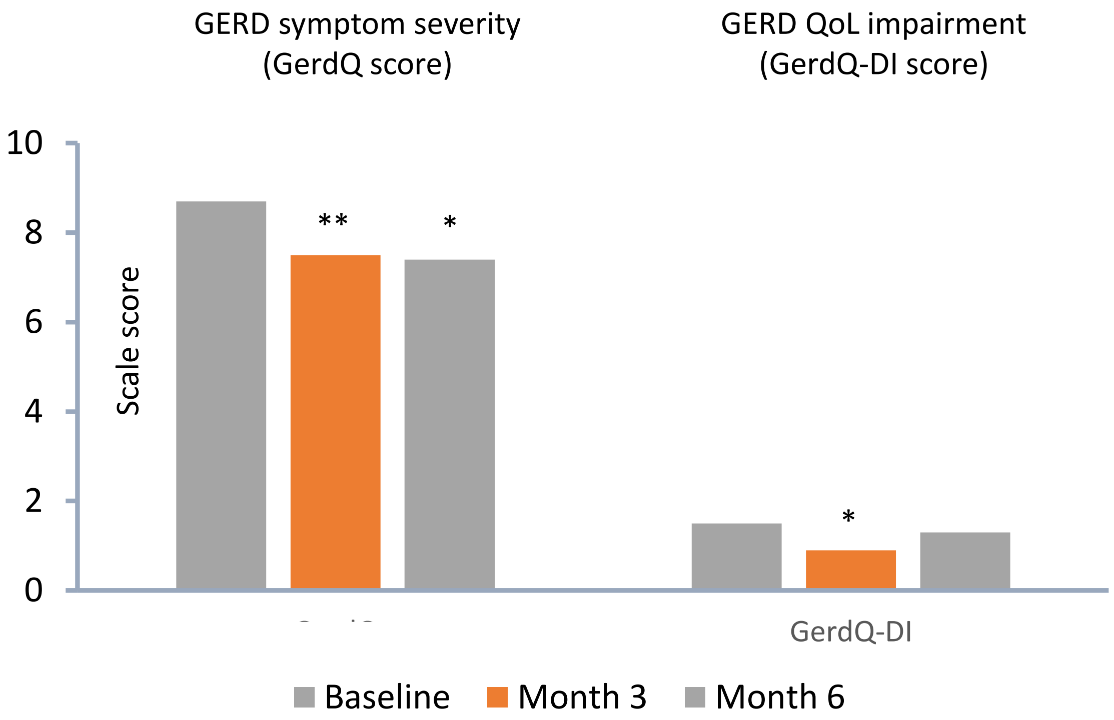
Yip TCF & Wong VWS. Aliment Pharmacol Ther. 2021;(54):722-723.

Minami T, et al. Liver Cancer. 2021;10(4):309-319.

Does weight loss change disease risk and/or outcomes?

Weight reduction improves GERD symptoms





**p<0.01, *p<0.05 vs. baseline.

Yadlapati R, et al. Am J Gastroenterol. 2018;113:23-30.

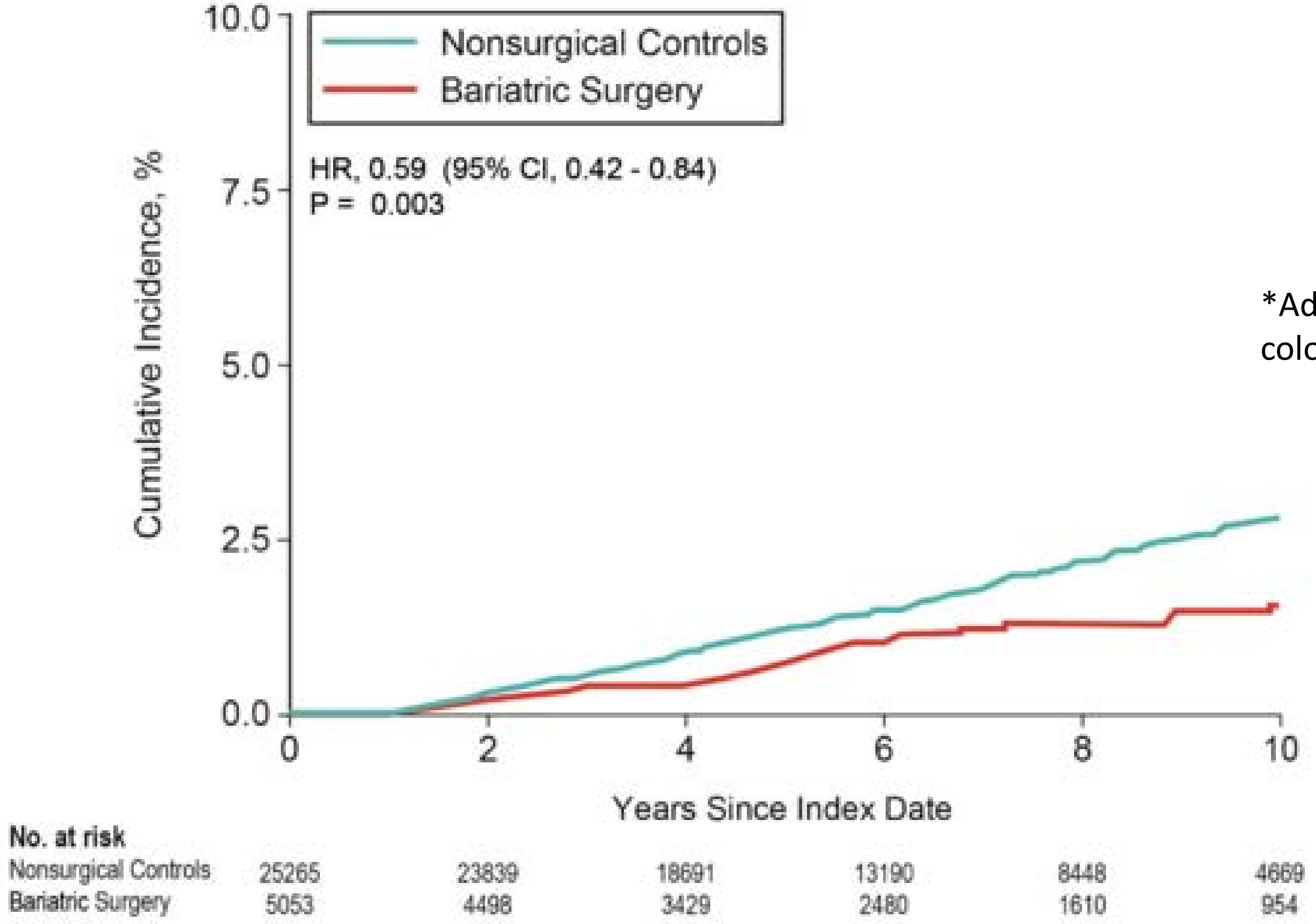
GERD, Barrett's and EAC after weight loss surgery

- Improved GER symptoms after weight loss surgery[1]
- Regression of Barrett's esophagus after weight loss with bariatric surgery[2]
- Lower risk of esophageal adenocarcinoma after bariatric surgery[3]

	Control (n=4978)	Gastric bypass (n=4978)	Odds ratio (95% CI)
Esophageal cancer			
Overall	7 (0.1)	2 (0.0)	0.29 (0.06–1.38)
Men	4 (0.4)	2 (0.2)	0.50 (0.09–2.73)
Women	3 (0.1)	0 (0)	7.01 (0.36–135.67)

1. Colquitt JL, et al. Cochrane Database Syst Rev 2014;8:CD003641.
2. Andrew B, et al. Surg Endosc 2018;32:930–936.
3. Mackenzie H, et al. Br J Surg 2018;105:1650-1657.

Weight loss surgery and obesity-related cancer



*AdenoCA of the esophagus, colon, rectum, and pancreas

Aminian A et al. Association of Bariatric Surgery With Cancer Risk and Mortality in Adults With Obesity. *JAMA.* 2022;327(24):2423–2433.

Weight loss improves MAFLD disease activity

Meta-analysis of weight loss interventions
Behavioral, pharmacotherapy, or surgery
(22 studies, N=2588)

↓ ALT
–9.81 U/L (95% CI: –13.12 to –6.50)

↓ Liver steatosis
Histologically or radiologically measured; mean difference: –1.48 (95% CI: –2.27 to –0.70)

↓ MASLD activity score
Histologic; mean difference: –0.92 (95% CI: –1.75 to –0.09)

↓ MASH presence
Odds ratio: 0.14 (95% CI: 0.04-0.49)

Koutoukidis DA, et al. JAMA Intern Med. 2019;179:1262-71.

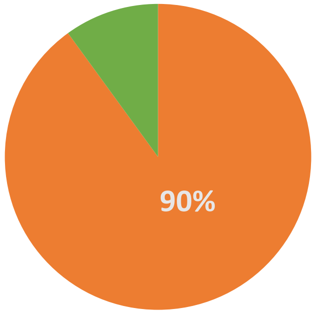
Anti-obesity medications and MASLD/MASH

	Vitamin E	**Pioglitazone** (thiazolidinedione)	**Liraglutide** (GLP-1 RA)	**Semaglutide** (GLP-1 RA)	**Tirzepatide** (GIP/GLP-1 RA)	**Empaglifozin Dapaglifozin** (SGLT2i)
FDA indication		T2D	T2D, obesity	T2D, obesity	T2D, obesity	T2D
MASLD population with proven benefit	MASH without cirrhosis or T2D	MASH with/without T2D	MASH without cirrhosis	MASH without cirrhosis	T2D or obesity with MASLD	T2D and MASLD
Steatosis improvement	✓	✓	✓	✓	✓	✓
Fibrosis benefit		?		?		
MASH resolution	?	✓	✓	✓		

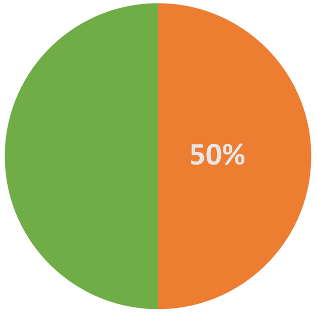
Bariatric endoscopy-induced weight loss and MASLD outcomes

Intragastric Balloon[1]

- N= 21 with obesity and early hepatic fibrosis
- 6-month follow-up after procedure



MASH Activity Score improvement
(median decrease 3 points)



Improvement in MRE-detected fibrosis of ≥ 1.5 stages

Endoscopic sleeve gastroplasty[2]

- N= 118 with obesity and MASLD
- 2-year follow-up after procedure

Measure	Annual decrease	*P* (trend)
Hepatic steatosis index score	4 points	< .001
Fibrosis score	0.3 points	.034

Meta-analysis[3]

- 4 studies on endobariatric interventions (N = 162)
- Significant reduction in liver fibrosis following intervention; SMD = 0.7 (*P* = .02)

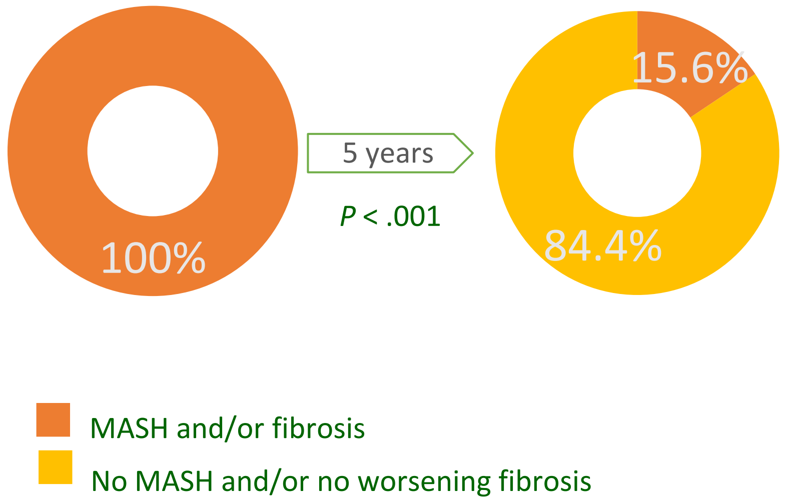
1. Bazerbachi F, et al. *Clin Gastroenterol Hepatol*. 2021;19(1):146-154. 2.
2. Hajifathalian K, et al. *Gastrointest Endosc*. 2021;93(5):1110-1118.
3. Jirapinyo P, et al. *Clin Gastroenterol Hepatol*. 2022;20(3):511-524.

Bariatric surgical weight loss and MASH outcomes

Long-term observational study[1]

Bariatric-metabolic surgery with paired liver biopsies

(N =180 ; 5-year follow-up)



BRAVES trial[2]

Bariatric-metabolic surgery vs. lifestyle intervention plus best medical care

(N = 288; 1-year follow-up)

Study group	MASH resolution without worsening fibrosis (proportion)
Roux-en-Y gastric bypass	56.3%[a]
Sleeve gastrectomy	57.3%[a]
Lifestyle intervention	15.6%

[a] *P* < .0001 vs lifestyle intervention

1. Lassailly G, et al. *Gastroenterology*. 2020;159(4):1290-1301.
2. Verrastro, O, et al. *Lancet*. 2023; doi:10.1016/S0140-6736(23)00634-7.

Final points

- Obesity is chronic medical condition with a pathogenesis that overlaps with gut and liver physiology
- Obesity has a substantial negative impact on gut and liver health
- Weight loss can reduce the risk of and improve symptoms related to GER and GER-related complications, MASLD and GI cancers.

- Our charge: **Recognize obesity (link obesity to GI/liver health with patients), offer Rx for obesity, and refer appropriate patients to obesity specialists**

Thank you!

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