
2023
NCSCG
20TH ANNUAL
GI SYMPOSIUM

Medical Management of Obesity in Liver Disease

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Outline

- Obesity
  - Epidemiology
  - Timeline for treatment
  - Current therapies & review of data
- NAFLD
  - Epidemiology & risk factors for advanced disease
  - Effects of weight loss
  - Data from current obesity therapies

Sample Header

- Update on the Medical Management of Obesity
  - Epi of obesity, diabetes NAFLD & comorbid NAFLD
  - Timeline/mechanisms on med management of obesity
  - Focus on semaglutide and tirzepatide
- Attention to effects on NAFLD and NASH
  - What data we have, what we're telling patients & what we can expect to have for NASH and when…

A brief history of obesity medicine

- AMA Council on Science and Public Health lists 3 criteria for a ‘disease’ state:
  - An impairment of the normal functioning of some aspect of the body
  - Characteristic signs or symptoms
  - Harm or morbidity

AMA House of Delegates Resolution 420, 2013.

A brief history of obesity medicine

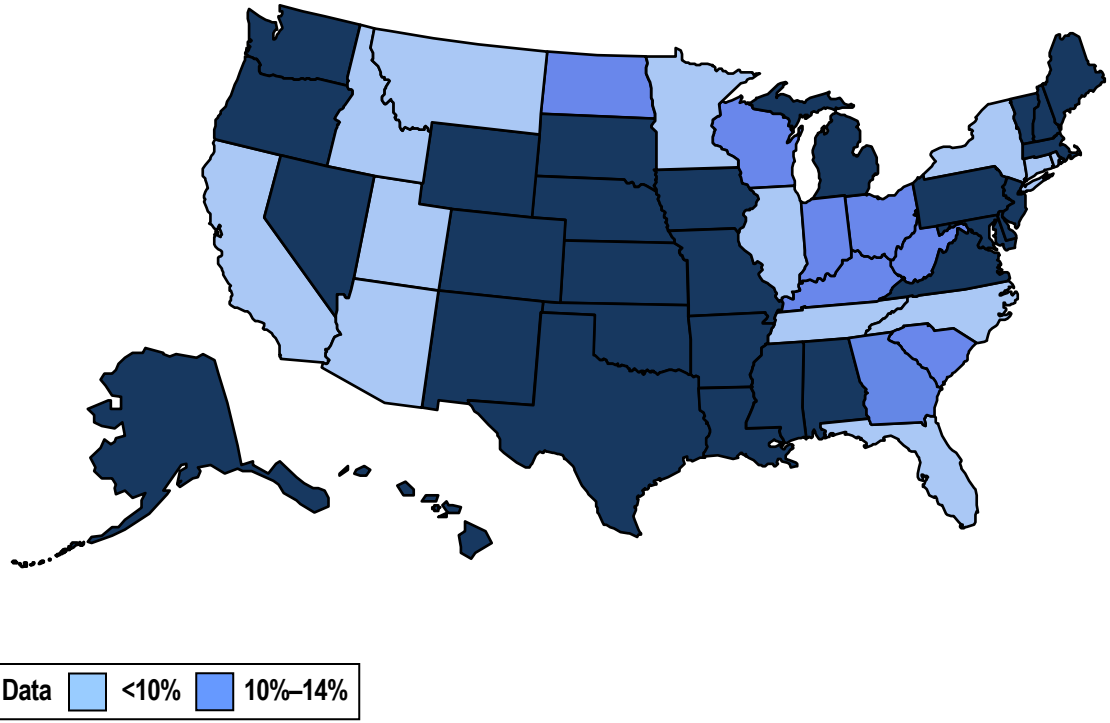
- 1948: WHO recognizes obesity as a disease[1]
- 1998: NIH declares obesity a disease[2]
- 2008: American Obesity Society declares obesity a disease[2]
- 2013: AMA recognizes obesity as a disease:

"Our AMA recognizes obesity as a disease state with multiple pathophysiological aspects requiring a range interventions to advance obesity treatment and prevention"

1. James WPT, Int J Obes 2008; 2. Rosen H, Mo Med 2014; 3. AMA House of Delegates Resolution 420, 2013.

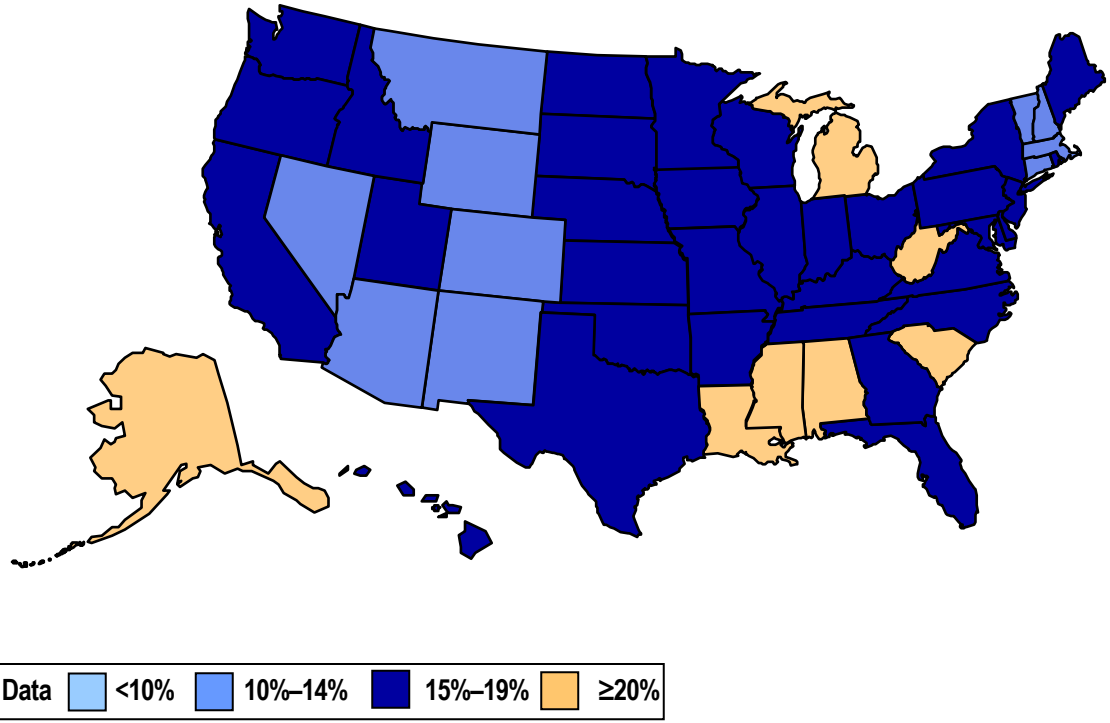
Obesity Trends* Among U.S. Adults: 1985

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)



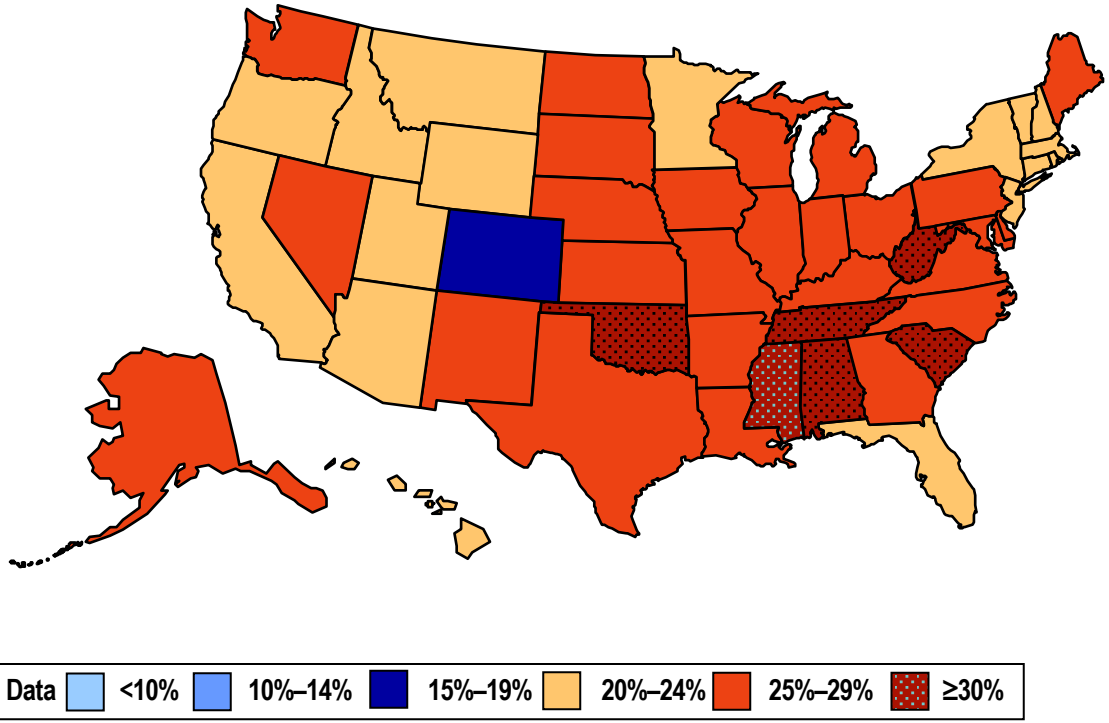
Obesity Trends* Among U.S. Adults: 1998

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)



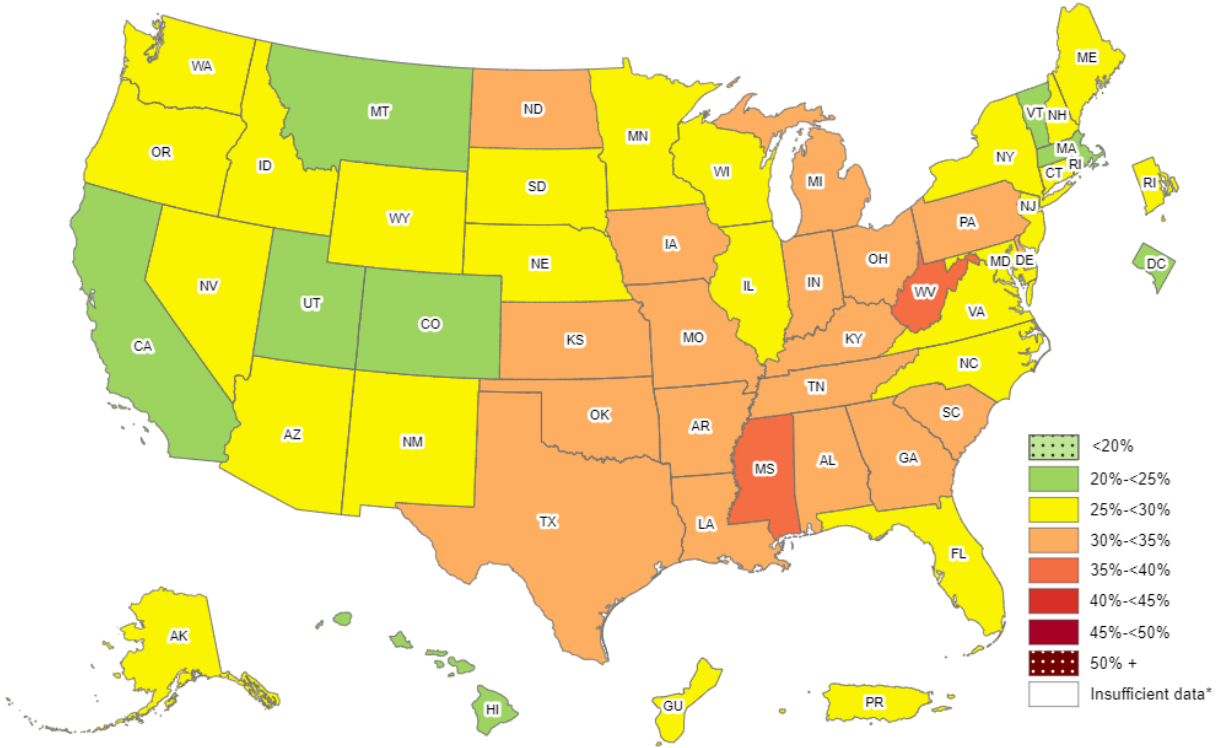
Obesity Trends* Among U.S. Adults: 2008

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)



Prevalence¶ of Self-Reported Obesity Among U.S. Adults by State and Territory, BRFSS, 2013

¶ Prevalence estimates reflect BRFSS methodological changes started in 2011. These estimates should not be compared to prevalence estimates before 2011.



*Sample size <50, the relative standard error (dividing the standard error by the prevalence) ≥30%, or no data in a specific year.

Prevalence¶ of Self-Reported Obesity Among U.S. Adults by State and Territory, BRFSS, 2021

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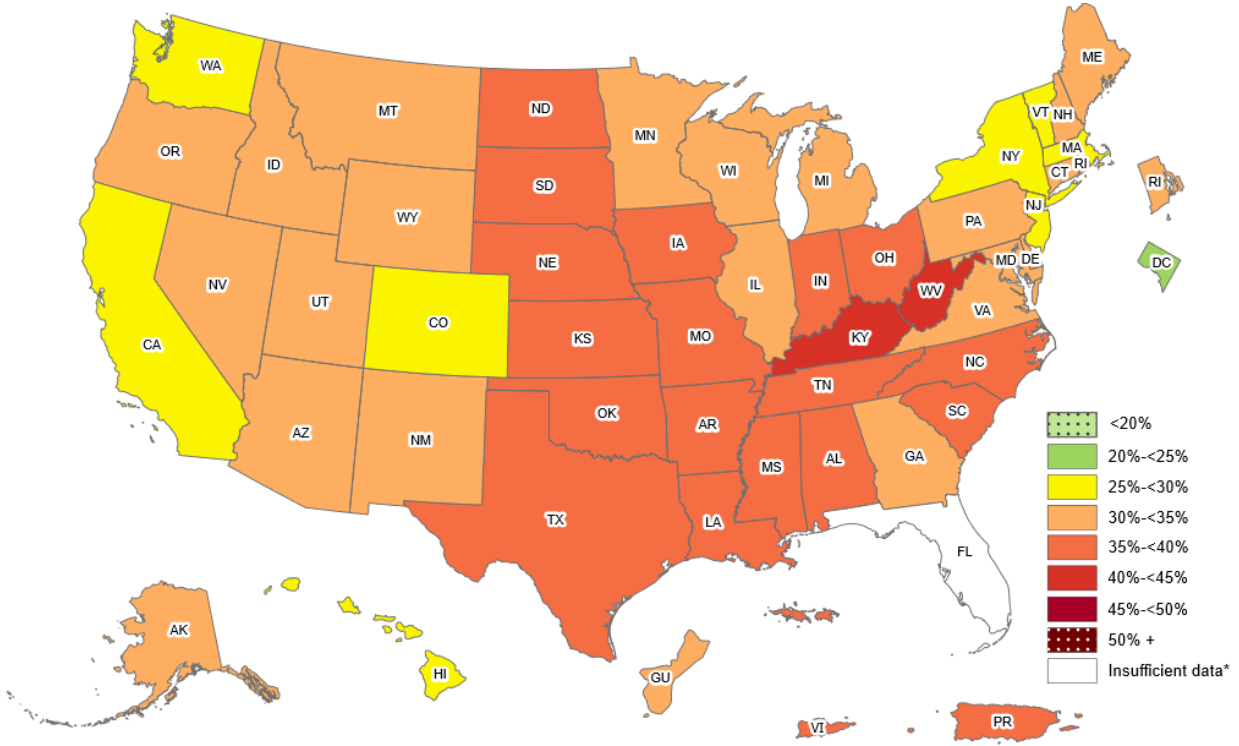
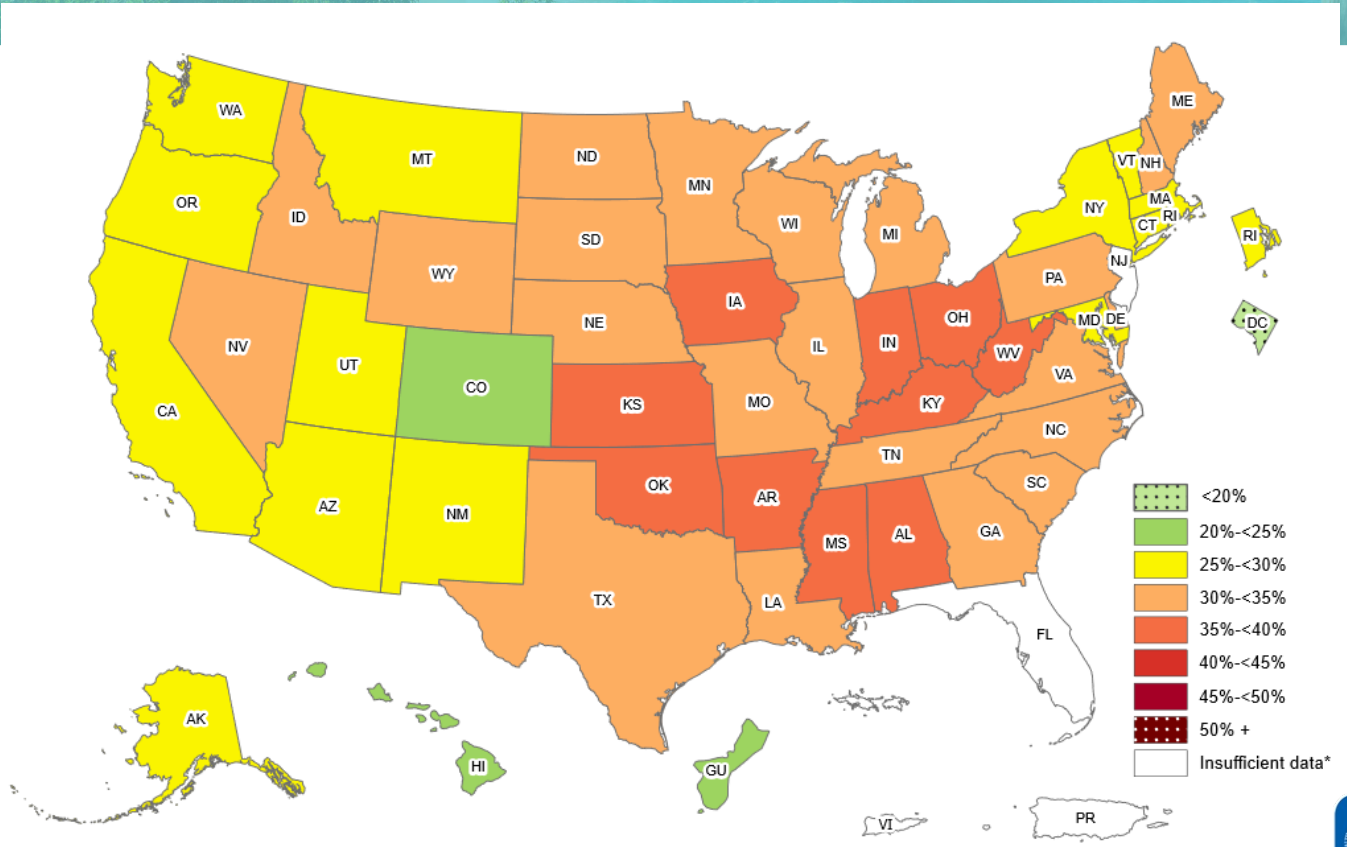


*Sample size <50, the relative standard error (dividing the standard error by the prevalence) ≥30%, or no data in a specific year.

Prevalence of Self-Reported Obesity Among Non-Hispanic White Adults, by State and Territory, BRFSS, 2019–2021



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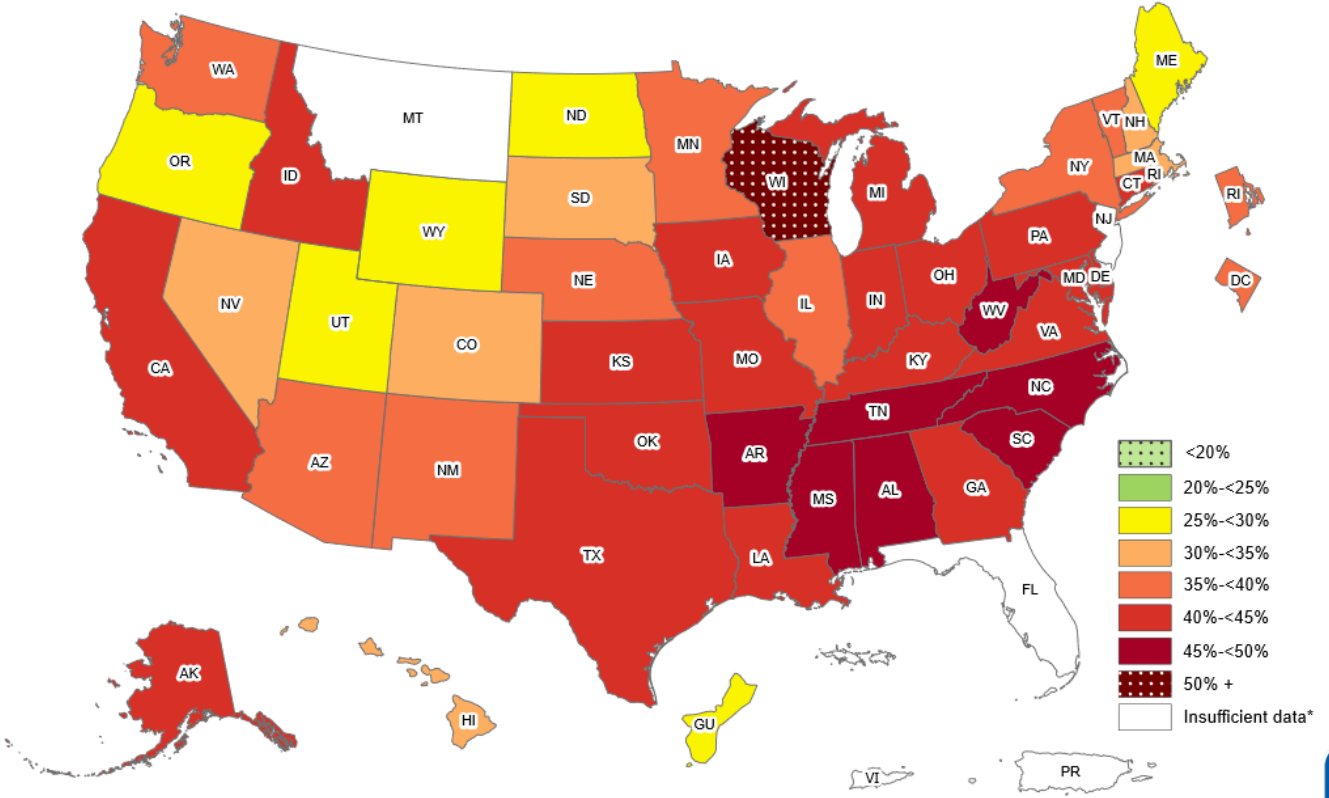
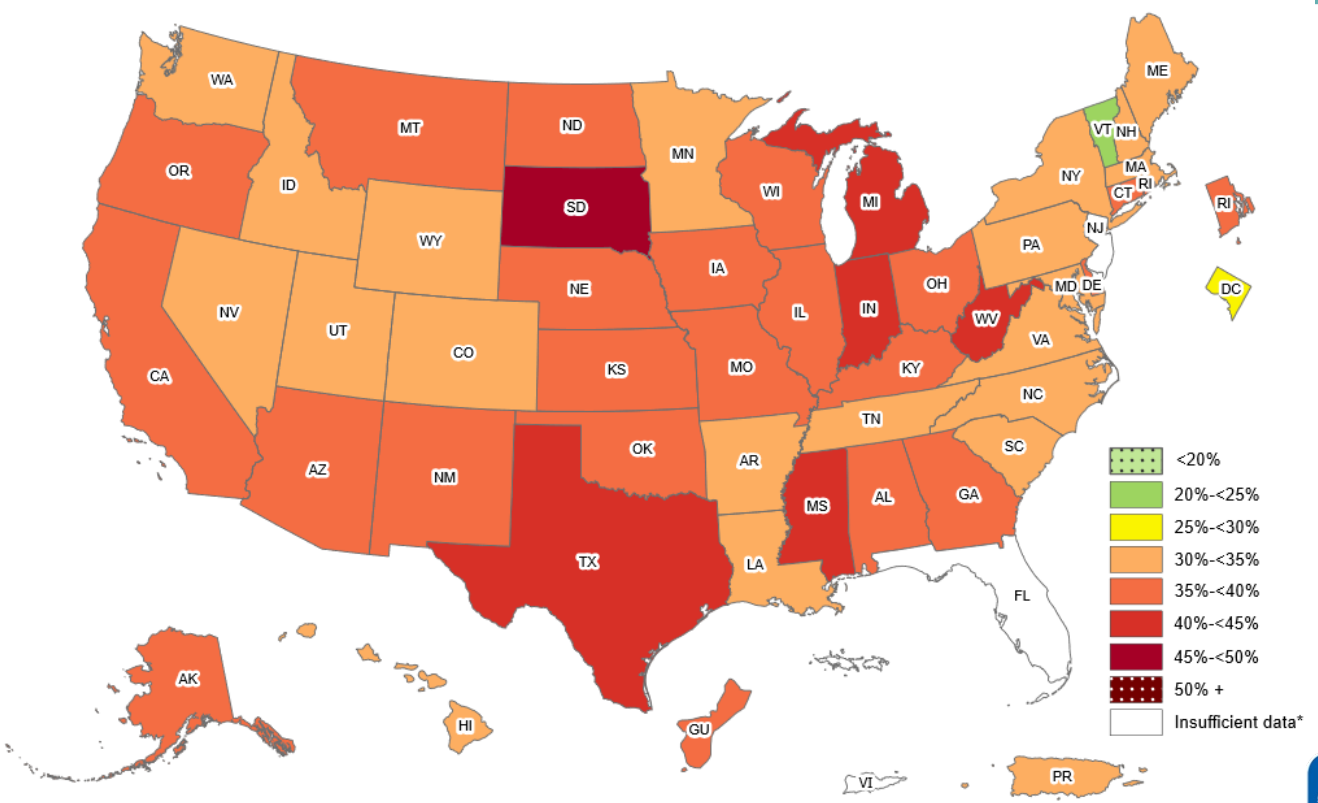
Prevalence of Self-Reported Obesity Among Non-Hispanic Black Adults, by State and Territory, BRFSS, 2019–2021



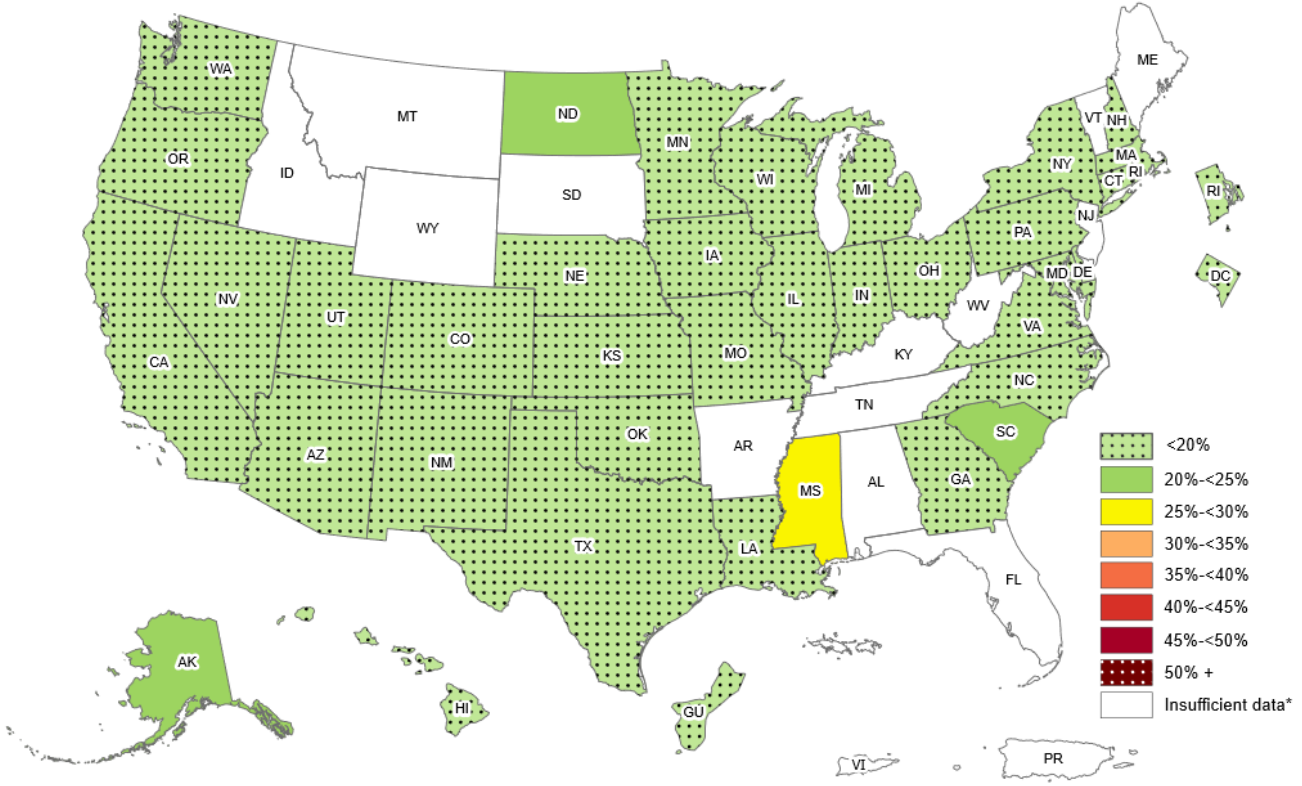
*Sample size <50, the relative standard error (dividing the standard error by the prevalence) ≥30%, or no data in a specific year.

Prevalence of Self-Reported Obesity Among Hispanic Adults, by State and Territory, BRFSS, 2019–2021



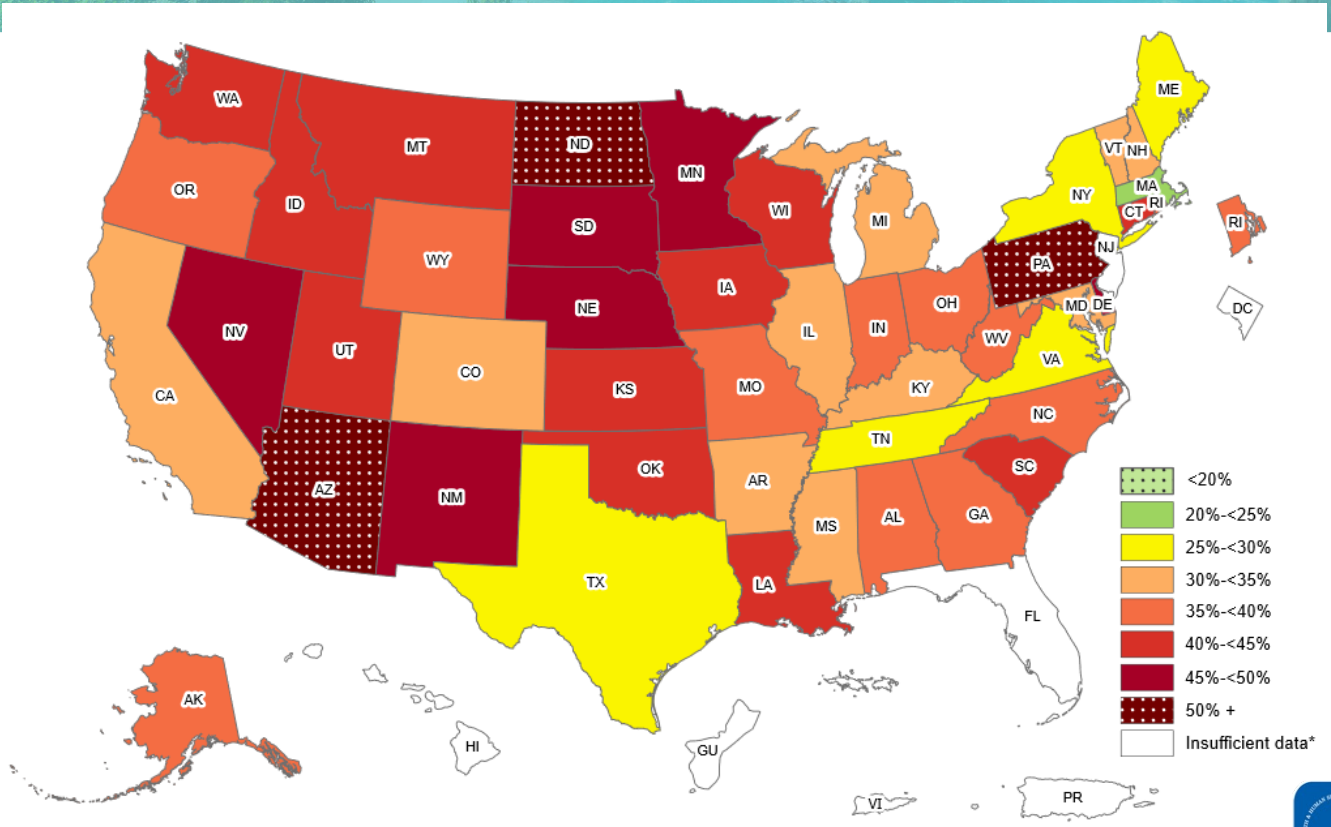
*Sample size <50, the relative standard error (dividing the standard error by the prevalence) ≥30%, or no data in a specific year.

Prevalence of Self-Reported Obesity Among Non-Hispanic Asian Adults, by State and Territory, BRFSS, 2019–2021



*Sample size <50, the relative standard error (dividing the standard error by the prevalence) ≥30%,
or no data in a specific year.

Prevalence of Self-Reported Obesity Among Non-Hispanic American Indian or Alaska Native Adults, by State and Territory, BRFSS, 2019–2021



*Sample size <50, the relative standard error (dividing the standard error by the prevalence) ≥30%,
or no data in a specific year.

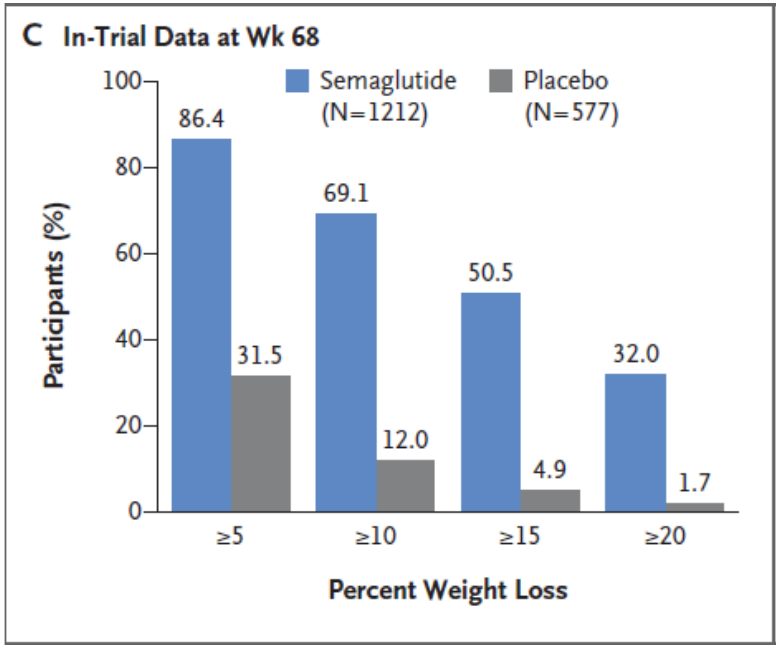
Timeline of obesity treatment

Year	Generic	Brand	Mechanism	% Wt. Loss
1959	phendimetrazine	Bontril	sympathomimetic	*no data*
1959	phentermine	Lomaira, Adipex	sympathomimetic	7.4%
1999	orlistat	Xenical	pancreatic lipase inhibitor	10.2%
2012	phentermine/topiramate	Qsymia	sympathom./anticonvulsant	9.3%
2014	naltrexone/buproprion	Contrave	Opioid RA/DRI/NERI	6.1%
2014	liraglutide	Saxenda	GLP-1 agonist	8%
2021	semaglutide	Wegovy	GLP-1 agonist	14.9%
2023?	terzepatide	Mounjaro	GLP-1/GIP agonist	20.9%

Muller TD, Nat Rev Drug Discov 2022; Jastreboff AM, N Engl J Med 2022

Semaglutide for the treatment of obesity

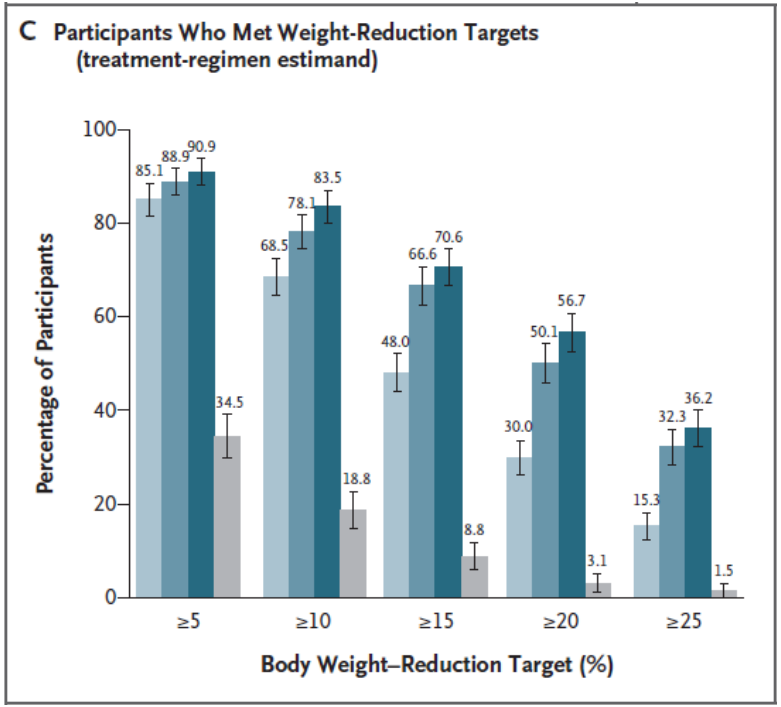
- RCT of 1961 nondiabetic adults
  - BMI >30 kg/m^2 or BMI >27 kg/m^2 with at least 1 of: HTN, dyslipidemia, OSA, CVD
  - 68 weeks of 2.4 mg weekly subQ injection vs placebo
  - Both groups had monthly lifestyle counseling sessions



Wilding JPH, New Engl J Med 2021

Tirzepatide for the treatment of obesity

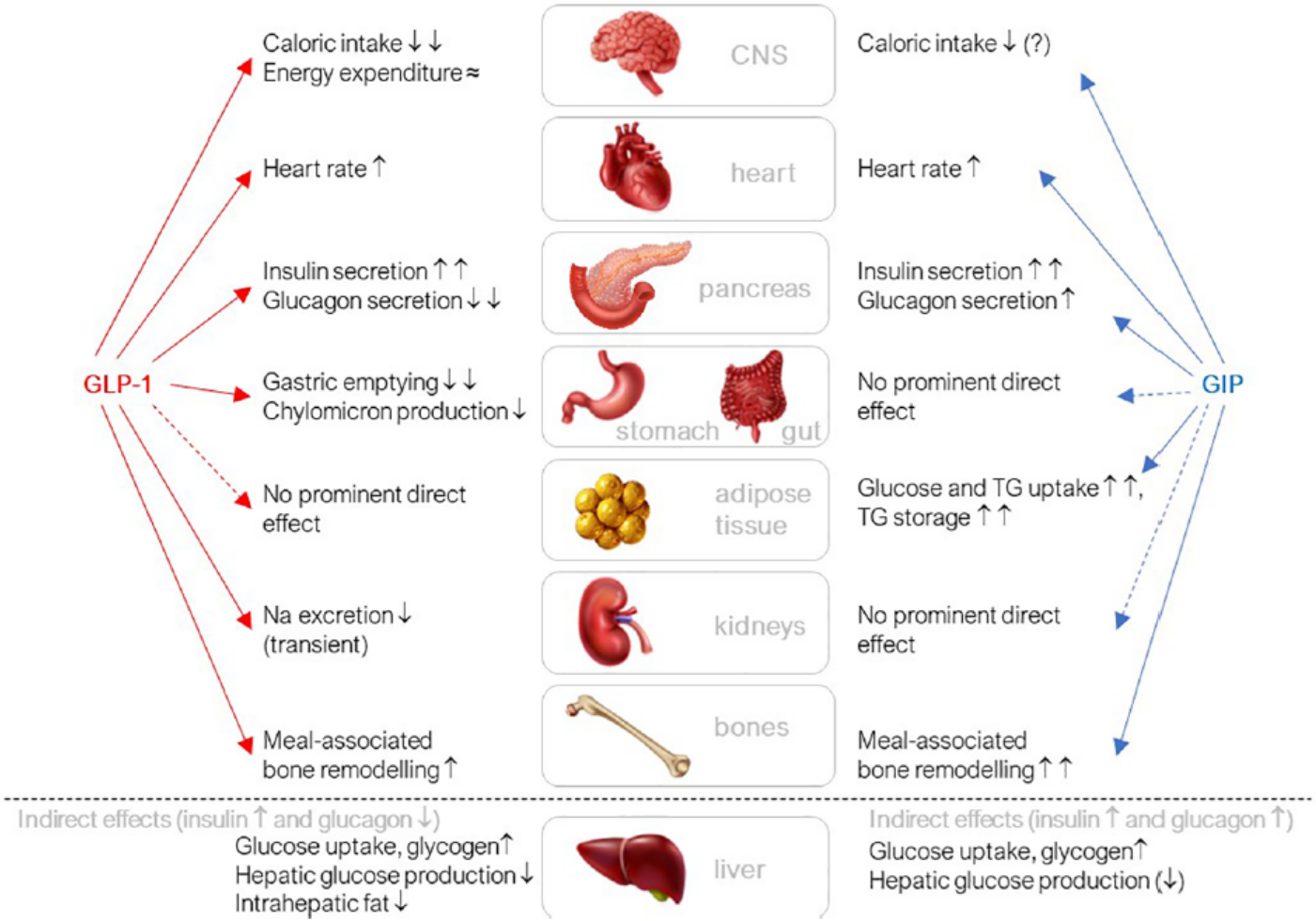
- RCT of 2539 nondiabetic adults
  - BMI >30 kg/m^2 or BMI >27 kg/m^2 with at least 1 of: HTN, dyslipidemia, OSA, CVD
  - 72 weeks of placebo vs 5/10/15 mg weekly subQ injection
  - All groups had ‘regular’ lifestyle counseling sessions



Jastreboff AM, New Engl J Med 2022

GLP-1 and GIP agonist mechanism of action

- Glucagon-like peptide 1 receptor agonists
  - GLP-1 produced in the L cells in the small intestine in response to meal ingestion & absorption of glucose, protein and fat.
  - Enhanced insulin secretion, delayed gastric emptying, suppression of postprandial glucagon, reduction in food intake
- Glucose-dependent insulinotropic polypeptide receptor agonists
  - GIP produced in K cells in the small intestine
  - Co-secreted with GLP-1, has similar/additive effects but does not directly influence gastric emptying and does not suppress glucagon secretion



Nauck MA, Diabetes Obes Metab 2021

Patients in the GLP-1 and GIP agonist trials

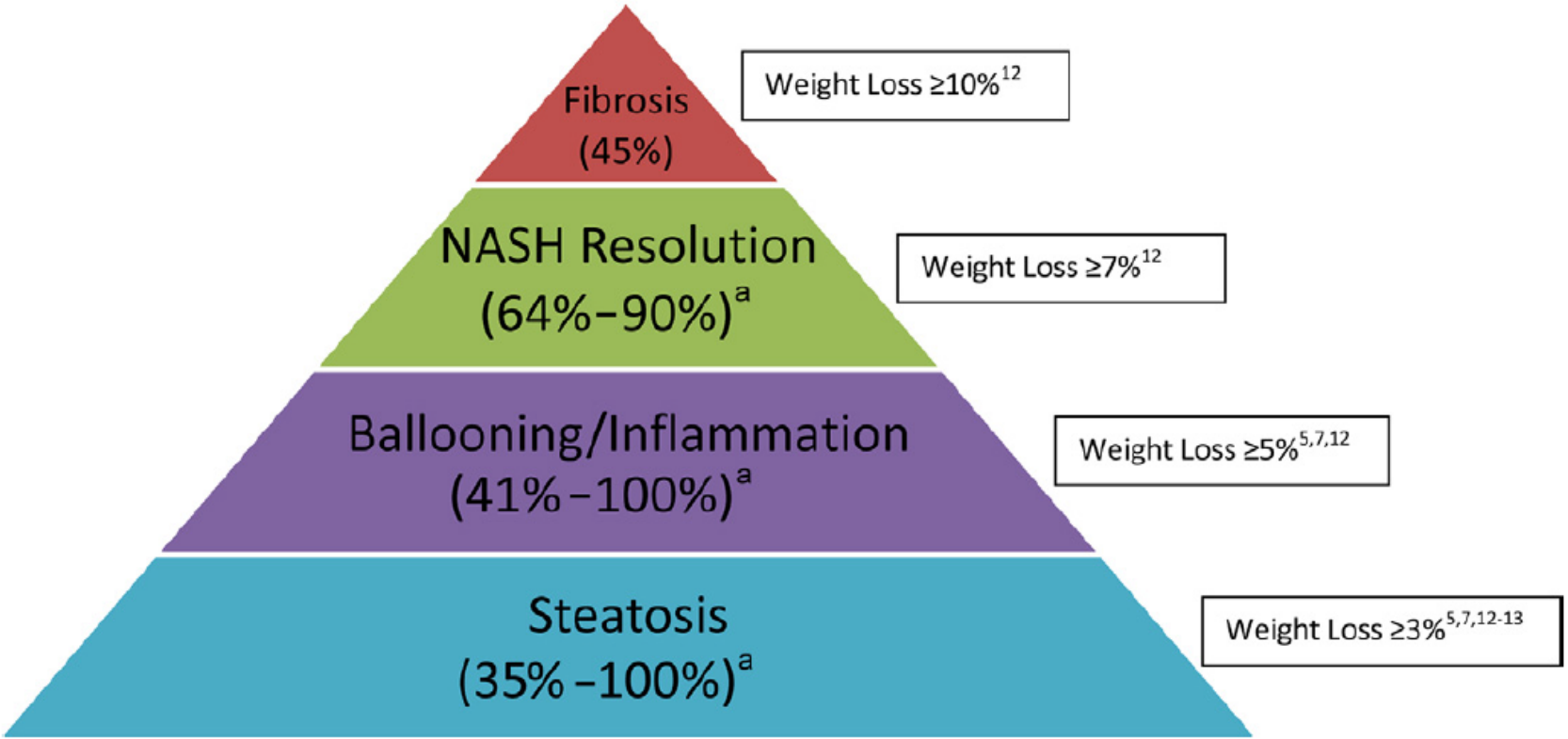
	Semaglutide[1] (Treatment arm)	Tirzepatide[2] (All 4 arms)
Age	46 years	44.9 years
Female sex	73.1%	67.5%
BMI	37.8 kg/m^2	38 kg/m^2
BMI >40 kg/m^2	29.3%	31.6%
Prediabetes	45.4%	40.6%
White race	74.5%	70.6%
Asian race	13.9%	10.9%
Black race	5.5%	7.9%

NAFLD present in 75.27% of obese individuals.[3]

NAFLD present in 85% of persons with BMI >40 kg/m^2.[4]

1. Wilding JPH, New Engl J Med 2021; 2. Jastreboff AM, New Engl J Med 2022
3. Quek J, Lancet Gastroenterol Hepatol 2023; 4. Fabbrini E, Hepatology 2010

Weight loss as treatment for NAFLD



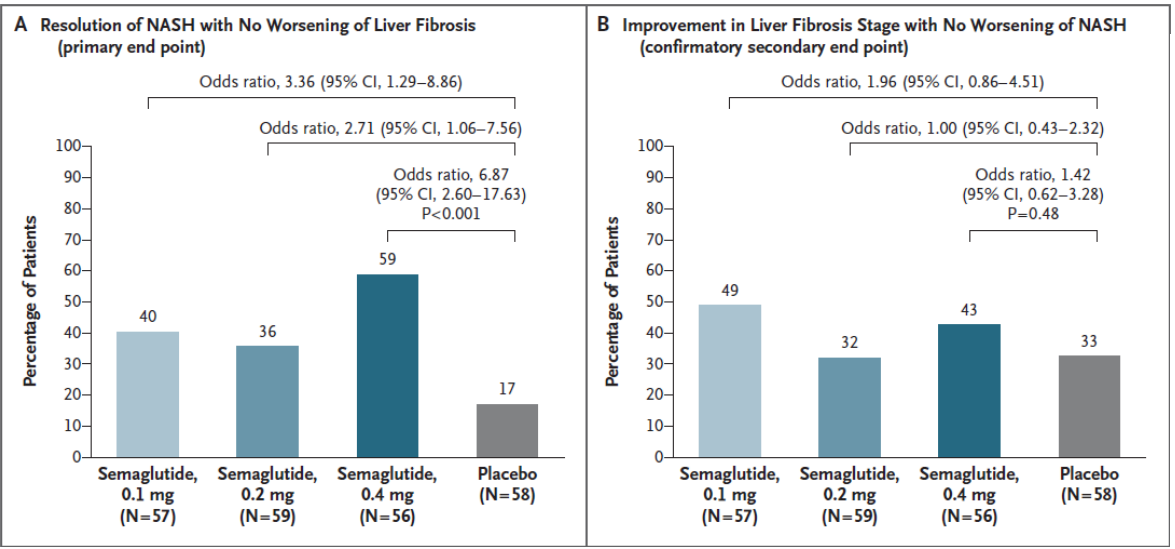
Hannah WN, Clin Liver Dis 2016 (all references)

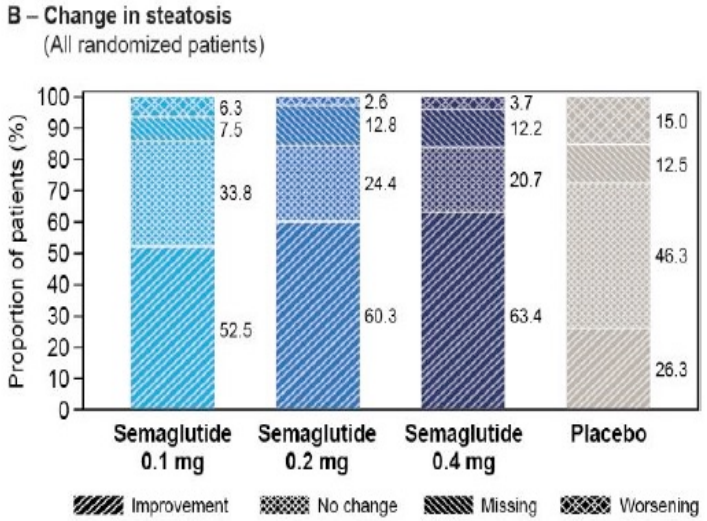
GLP-1 and GIP agonists and NAFLD

- Semaglutide phase 2 LEAN trial
  - 320 adults (230 F2 or F3, no F4) randomized to 48 weeks of *daily* semaglutide 0.1 mg, 0.2 mg, 0.4 mg or placebo.
  - For semaglutide 0.4 mg daily vs placebo:
    - Significant improvement in NASH with no worsening of fibrosis in 59% vs 17% ($p<0.001$)
    - Nonsignificant improvement in Fibrosis with no worsening of NASH in 43% vs 33% ($p=0.48$)
    - Improvement in Steatosis in 63.4% vs 26.3%

GLP-1 and GIP agonists and NAFLD

- Semaglutide





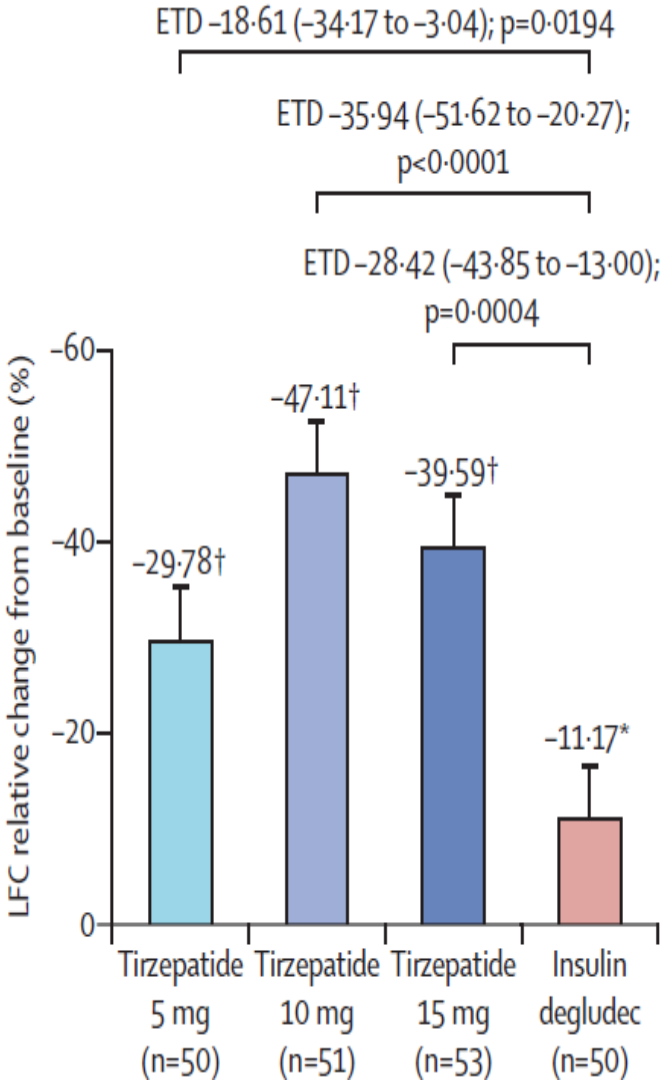
Newsome PN, New Engl J Med 2020

GLP-1 and GIP agonists and NAFLD

- Tirzepatide phase 3 substudy of SURPASS-3
  - 296 adults randomized to 52 weeks of daily titrated ultralong-acting insulin or daily tirzepatide 5 mg, 10 mg or 15 mg injections
  - Liver fat content (LFC) was reduced by 8.09% in the pooled tirzepatide 10 mg and 15 mg groups, vs. 3.38% in the insulin group
  - In a separate study, NASH biomarkers improved with tirzepatide: AST, ALT, K18, Pro-C3

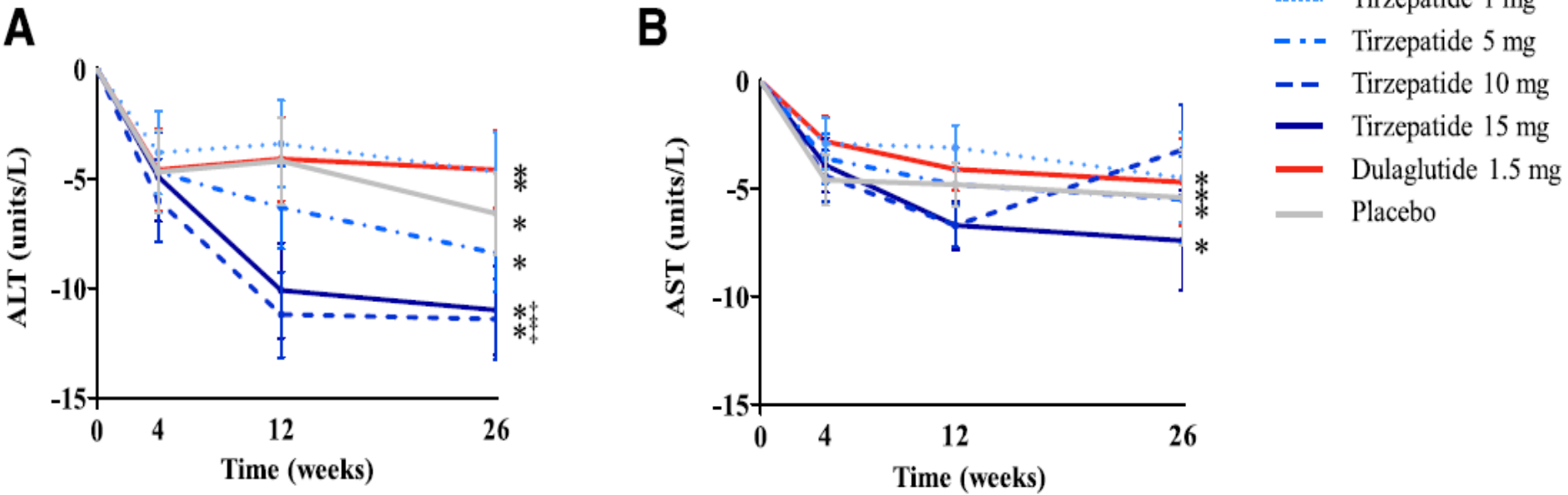
Gastaldelli A, Lancet Diabetes Endocrinol 2022; Hartman ML, Diabetes Care 2020

Tirzepatide and liver fat



Gastaldelli A, Lancet Diabetes Endocrinol 2022

Tirzepatide and NASH biomarkers



Hartman ML, Diabetes Care 2020

Mechanism of benefit with GLP-1 and GIP

- Most anti-obesity drugs improve fatty liver indirectly, though weight loss – orlistat, phentermine, topiramate, naltrexone, buproprion
- GLP-1 and GIP agonists also yield direct benefit:
  - Direct effect on lipid metabolism in hepatocytes
  - Hepatic inflammation

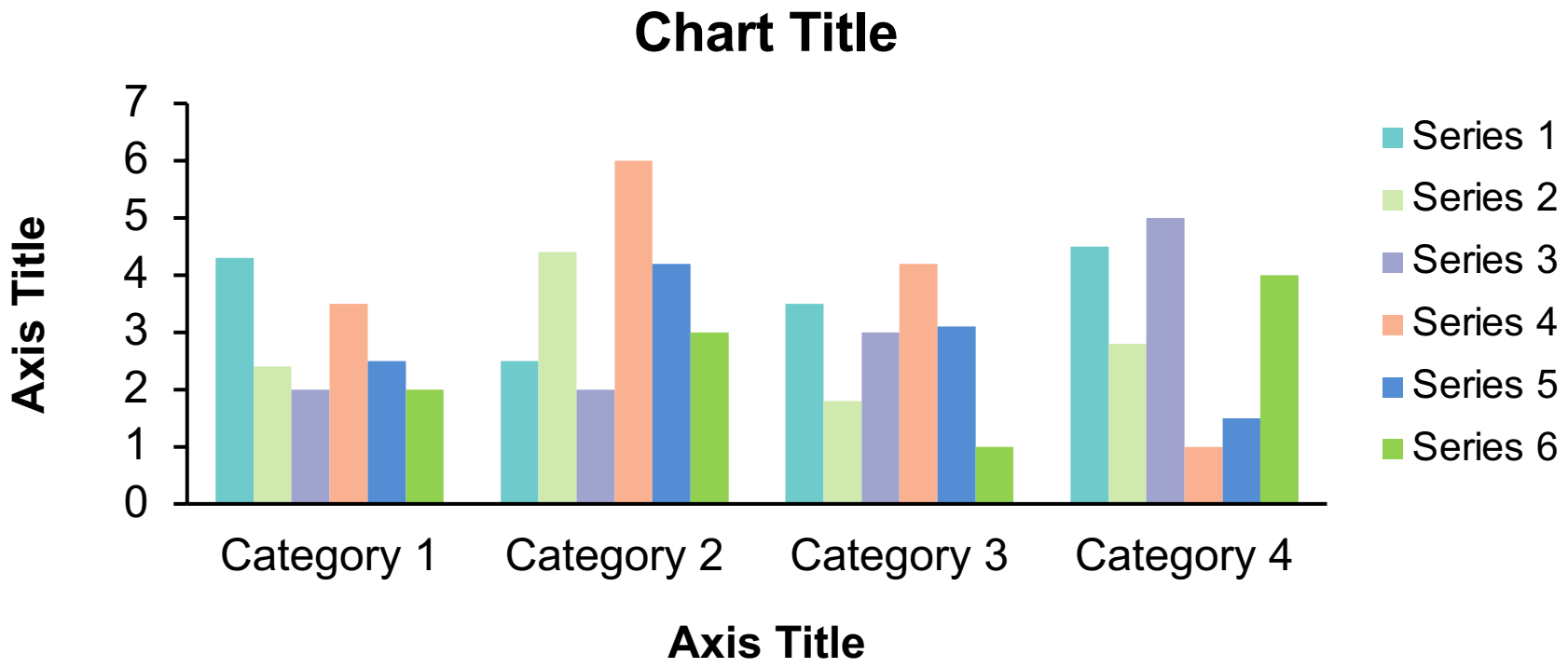
Proposed alorithm

- Identify those with obesity at highest risk of NASH with fibrosis
- Outline a comprehensive, multifaceted approach to NAFLD treatment including diet, exercise and weight loss
- Use GLP-1 and GIP agonists in appropriate patients (knowing that indications overlap with risk factors for NASH with fibrosis)

- Sample Text

- Sample Text

Sample Chart



Sample Table

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