How will emerging medical therapies change metabolic bariatric surgery practice– do we need more evidence?

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I have the following potential conflict(s) of interest to report:

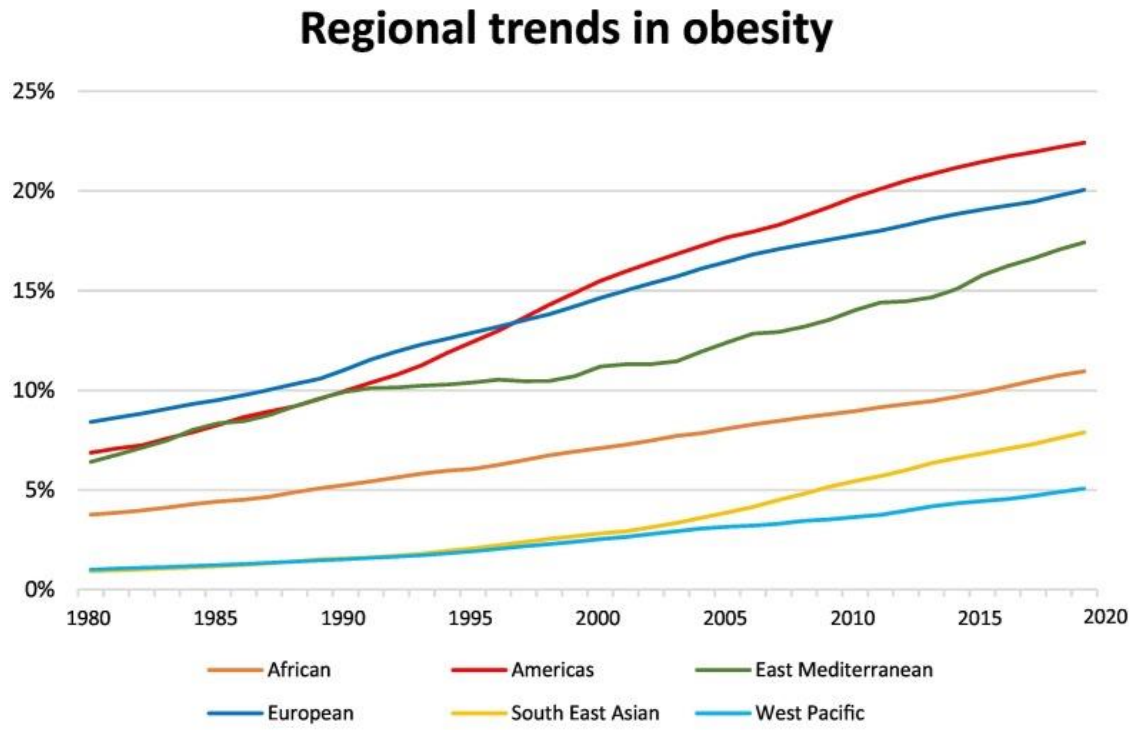
Research support	Nestle Healthcare Nutrition, Eli Lilly, Boehringer Ingelheim, Epitomee, Inc., UnitedHealth Group R&D, KVKTech, Weight Watchers, Regeneron
Consulting	Nestle Healthcare Nutrition, Eli Lilly, Optum Labs R&D, Novo Nordisk, Intuitive, Regeneron, Brightseed, Amgen, Almond Board
Advisory Board	Novo Nordisk, Nestle Healthcare Nutrition, Eli Lilly, Level2, Weight Watchers, Boehringer Ingelheim, Regeneron
Memberships	International Food Information Council- Assembly, The Obesity Society- president, American Diabetes Association, Society of Behavioral Medicine, Roundtable on Obesity Solutions, American Society for Nutrition, American Society for Nutrition Foundation- Board of Trustees Executive Committee

Objectives

- Will anti-obesity medications (AOM) replace metabolic bariatric surgery (MBS)?
- Will AOM be synergistic with MBS?
- What evidence is needed to support combination therapy?

Will AOM replace MBS?

- Factors for consideration: Medical
  - Increasing proportion of people with BMIs ≥ 40

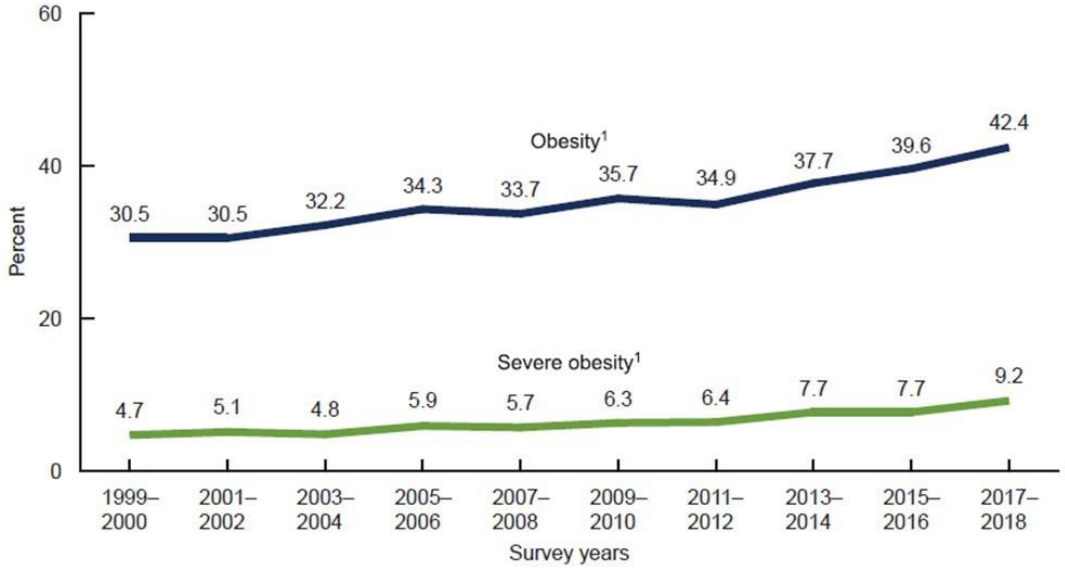


Metabolism. 2022 Aug; 133: 155217.

Will AOM replace MBS?

- Factors for consideration: Medical
  - Increasing proportion of people with BMIs ≥ 40
  - Tolerability of treatment
  - Heterogeneity of response

Trends in Obesity among Adults in the United States



https://www.niddk.nih.gov/health-information/health-statistics/overweight-obesity#trends

Will AOM replace MBS?

- Factors for consi
  Medical
  - Increasing prop
    with BMIs ≥ 40
  - Tolerability of t
  - Heterogeneity
  - Indications for MBS

Major Differences Between 1991 NIH Guidelines and ASMBS/IFSO Guidelines 2022

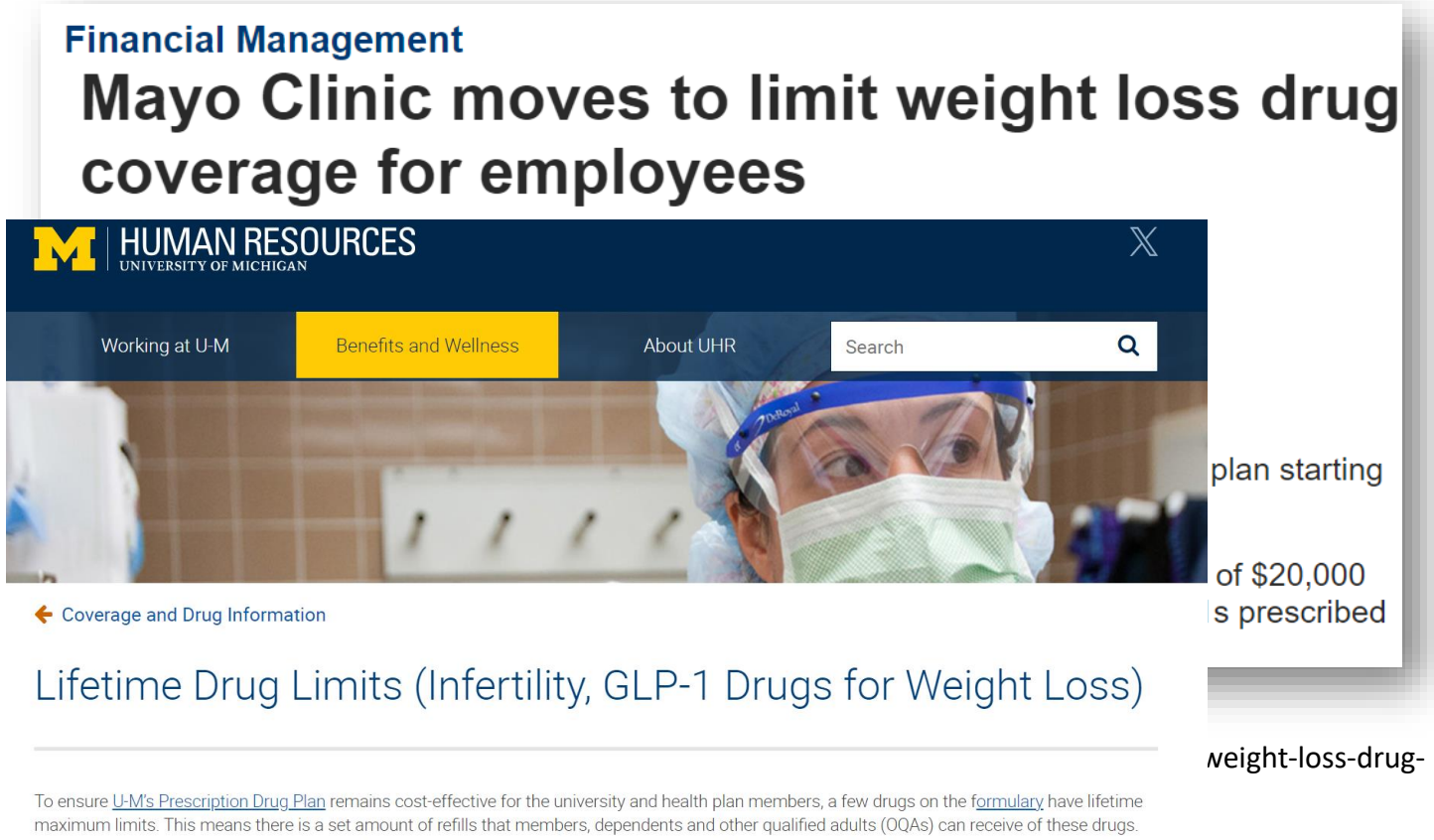
• Metabolic and Bariatric Surgery (MBS) recommended for individuals with BMI >35 kg/m2, regardless of presence or absence of comorbidities and should be considered for individuals with metabolic disease and BMI 30-34.9 kg/m2 who do not achieve substantial or durable weight loss or comorbidity improvement using nonsurgical methods.

• BMI thresholds should be adjusted in the Asian population such that BMI >25 kg/m2 suggests clinical obesity, and individuals with BMI >27.5 kg/m2 should be offered MBS

https://anzmoss.com.au/ifso-guidelines/

Will AOM replace MBS?

- Factors for consideration: Sociocultural
  - Cost
  - Coverage and access
  - Acceptance of long-term treatment



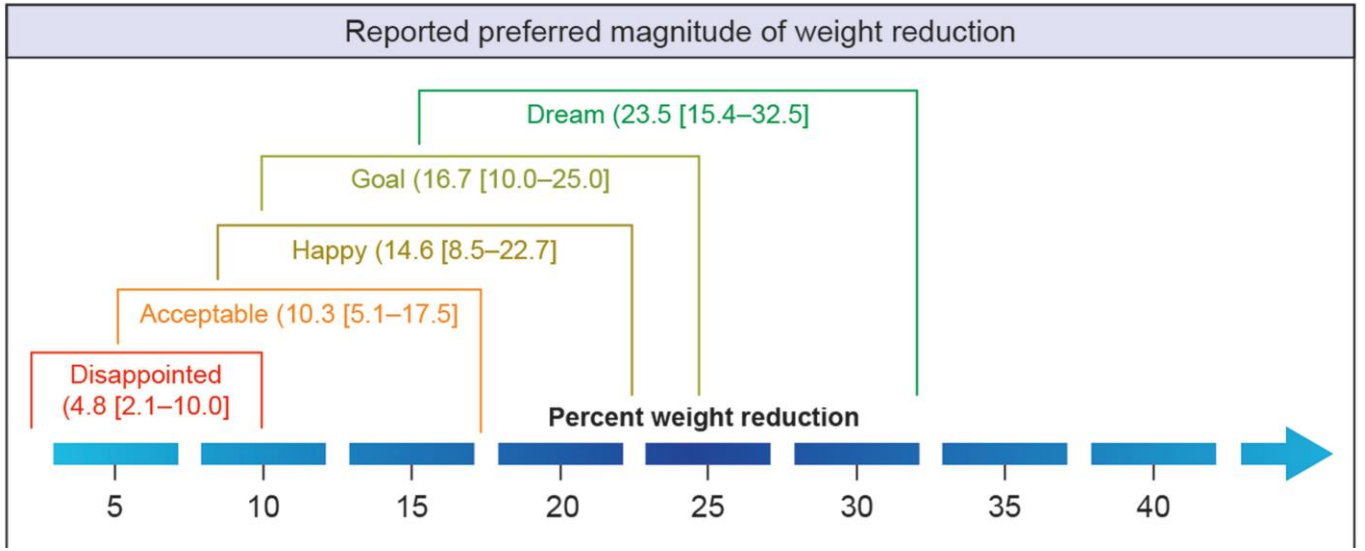
weight-loss-drug-

https://hr.umich.edu/benefits-wellness/health-well-being/prescription-drug-plan/coverage-drug-information/lifetime-drug-limits-infertility-glp-1-drugs-weight-loss

Will AOM replace MBS?

- Sleeve gastrectomy will likely decrease
  - Overlap with mean treatment effects of news AOMs
  - Weight regain concerns
- Interest in AOMs has clearly increased
  - Expectations for what would be considered “acceptable” weight outcome by patients is now being achieved with AOMs

What Patients Want for Weight Reduction Outcomes



Preferred percent weight reduction by weight class					
BMI categories*	**Dream**	**Goal**	**Happy**	**Acceptable**	**Disappointed**
Overweight	12.3 (8.1–17.5)	8.9 (5.3–14.4)	7.4 (3.6–11.3)	4.4 (1.9–8.4)	2.3 (0.7–4.2)
Class I obesity	20.0 (13.5–26.9)	13.3 (8.5–20.0)	12.5 (6.8–18.3)	8.7 (4.4–13.6)	3.9 (1.8–6.9)
Class II obesity	27.2 (20.4–34.8)	20.0 (14.2–27.3)	17.5 (12.4–24.3)	13.0 (8.9–19.7)	6.5 (3.5–12.5)
Class III obesity	36.9 (28.0–45.1)	27.0 (20.0–36.5)	24.0 (15.5–32.7)	17.5 (10.6–27.7)	9.1 (4.8–16.5)

Gudzune et al. Weight-Reduction Preferences Among OBSERVE Study Participants With Obesity or Overweight: Opportunities for Shared Decision-Making. Endocrine Practice 2024

Will AOM replace MBS? No

- Lower BMI indication
- Lower cost treatment than AOMs in some countries
- Disease severity + desired treatment effects + AOM access constraints
- Heterogeneity of treatment response
- Disease etiology

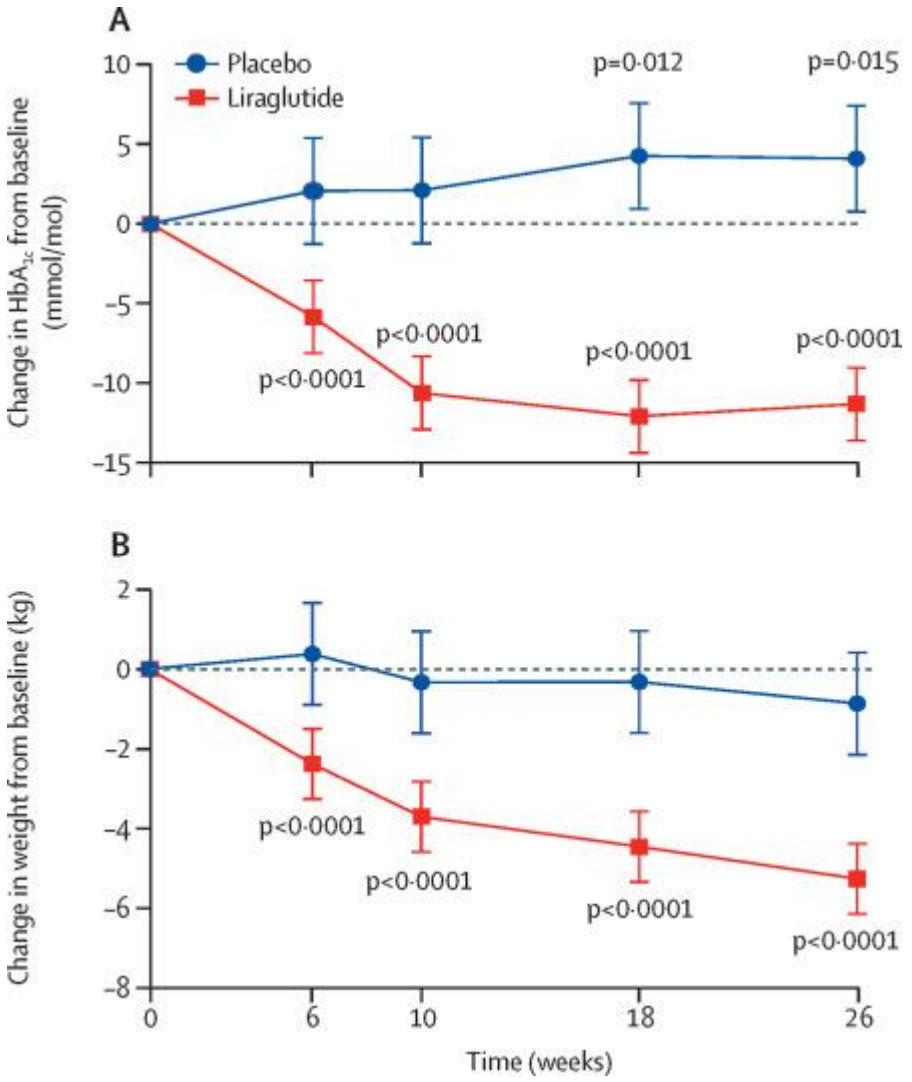
Will AOM be synergistic with MBS?

- Neo-adjuvant
  - Use of AOM before MBS, not continued thereafter
  - Primary intent: reduce weight to improve MBS operating time, decrease liver size, improve technical ease
  - Results:
    - Cunningham et al (2023)- neoadjuvant use of phentermine ± topiramate in patients with BMI ≥ 60 (n=8)
    - 1 year postop: neoadjuvant use = 31.3% weight loss vs 20.8% for no neoadjuvant use

Sher et al. Current Obesity Reports (2024) 13:377–402

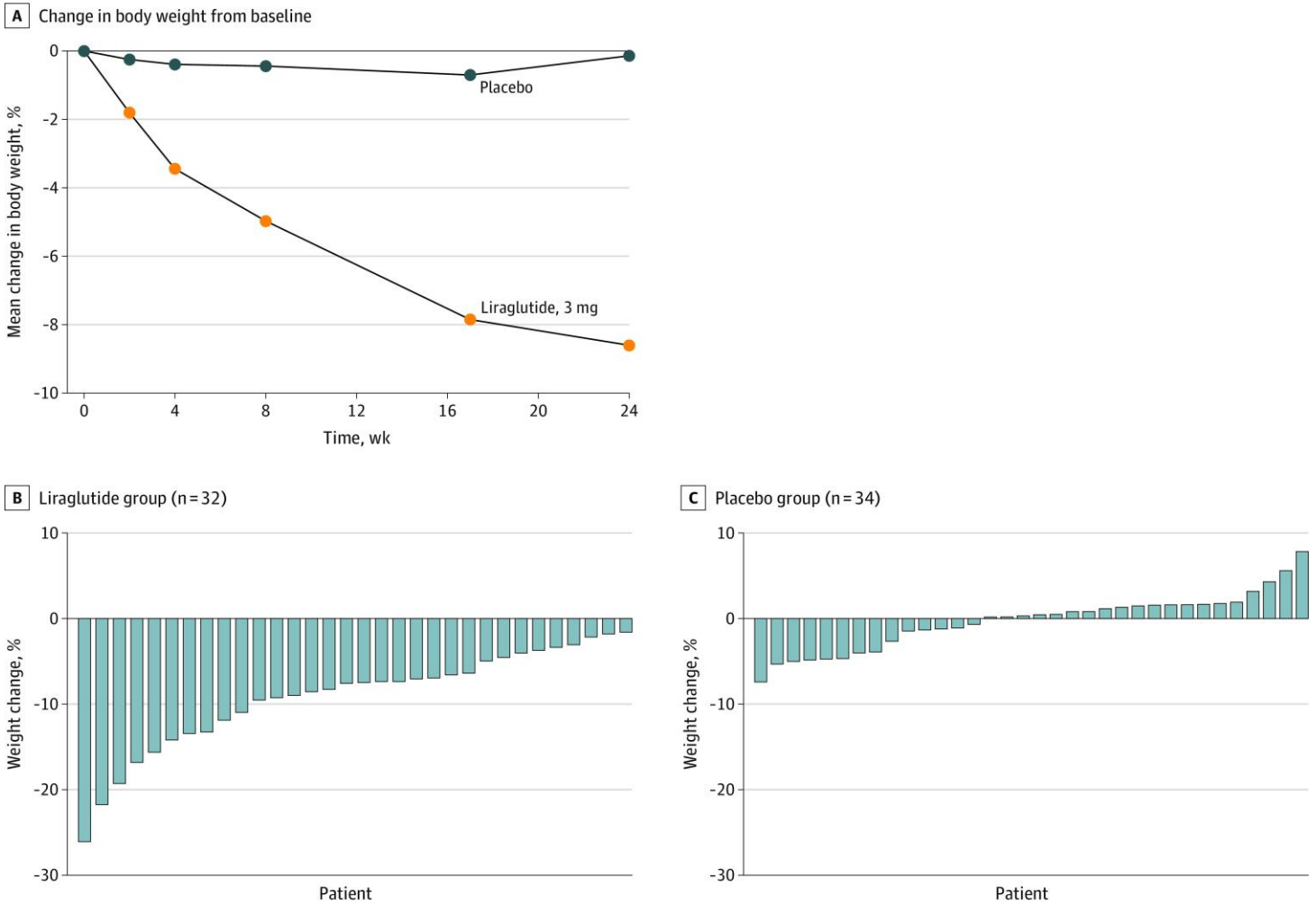
Will AOM be synergistic with MBS?

- Adjuvant
  - Use of AOM after MBS
  - Most often in case of inadequate treatment response or weight regain
  - Long-term treatment thereafter
  - Results:
    - GRAVITAS trial (Miras et al Lancet Diab 2019)
    - Liraglutide 1.8 mg daily for patients with HbA1c > 6.5% 1 year postop



Will AOM be synergistic with MBS?

- Results:
  - BARI-OPTIMISE (Mok et al JAMA Surg 2023)
  - Liraglutide 3.0 mg once daily vs placebo for patients ≤ 20% weight loss 12 m after RYGB or SG



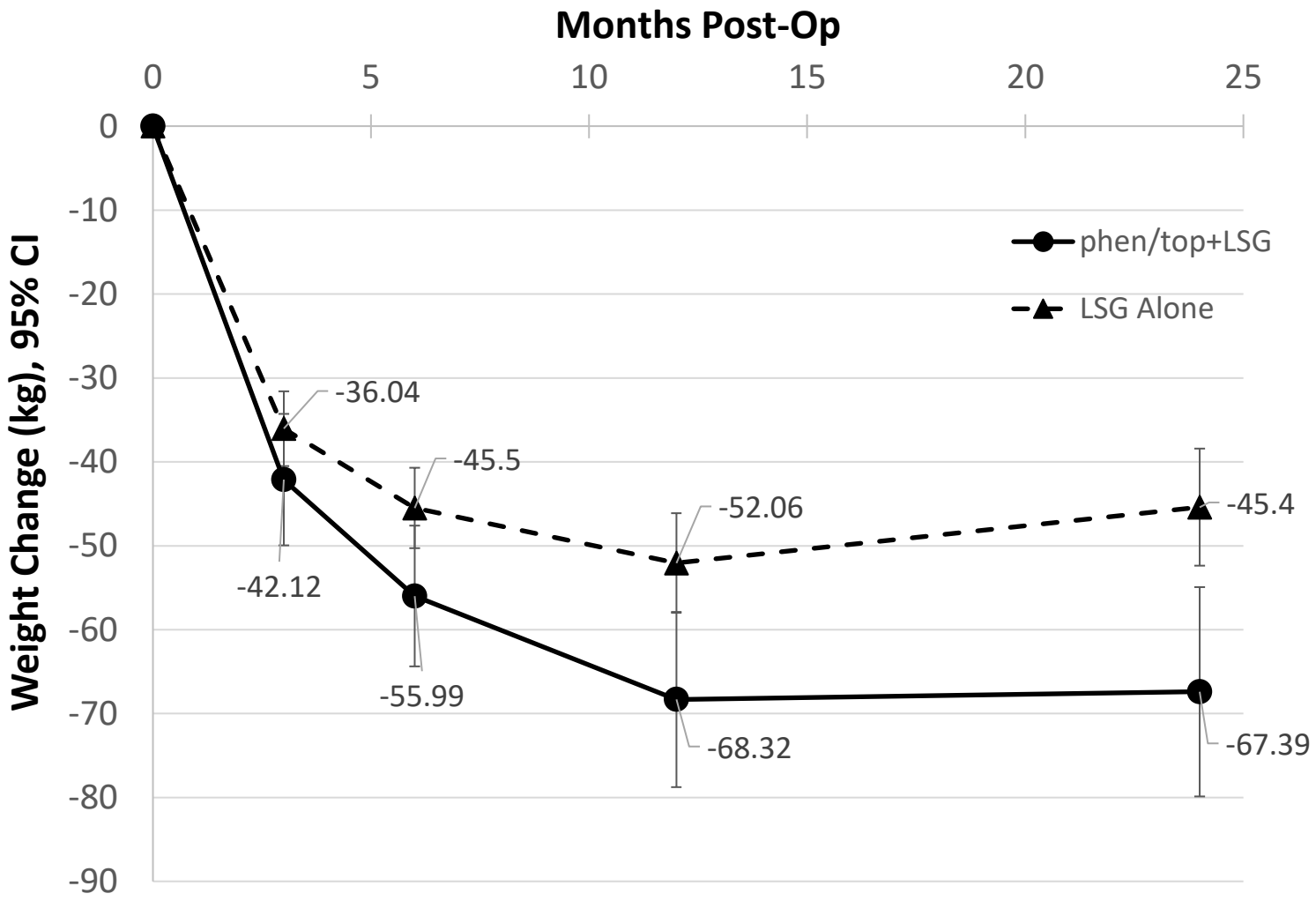
Will AOM be synergistic with MBS?

- Neo-adjuvant + adjuvant
  - Use prior to MBS followed by resumption after MBS for combination therapy thereafter

Preoperative Weight Loss

	SG only	SG + P/T
Initial Weight (kg)	159.5 ± 21.0	178.9 ± 31.1
Weight change initial to pre-op (kg)	-12.3 ± 12.5	-28.1 ± 12.8
Initial BMI (kg/m2)	57.0 ± 5.6	61.2 ± 7.1
Pre-op BMI (kg/m2)	52.7 ± 5.3	51.7 ± 6.2

JD Ard et al, Surgery for Obesity and Related Diseases, 2019



JD Ard et al, Surgery for Obesity and Related Diseases, 2019

Visit-specific estimates & comparisons from a mixed model approach adjusted for gender and initial body weight

Visit	SG Alone (95% CI) N= 40	SG + P/T (95% CI) N=13	Difference (95% CI)	P-value
3 months	-21.46 (-23.96, -18.97)	-25.24 (-29.63, -20.84)	-3.77 (-8.27, 0.72)	0.098
6 months	-27.25 (-29.97, -24.53)	-32.79 (-37.56, -28.02)	-5.54 (-10.52, -0.56)	0.030
12 months	-31.43 (-34.86, -28.01)	-39.34 (-45.36, -33.32)	-7.91 (-14.43, -1.39)	0.018
24 months	-27.00 (-31.02, -22.99)	-38.16 (-45.39, -30.94)	-11.16 (-19.07, -3.24)	0.007

Will AOM be synergistic with MBS?

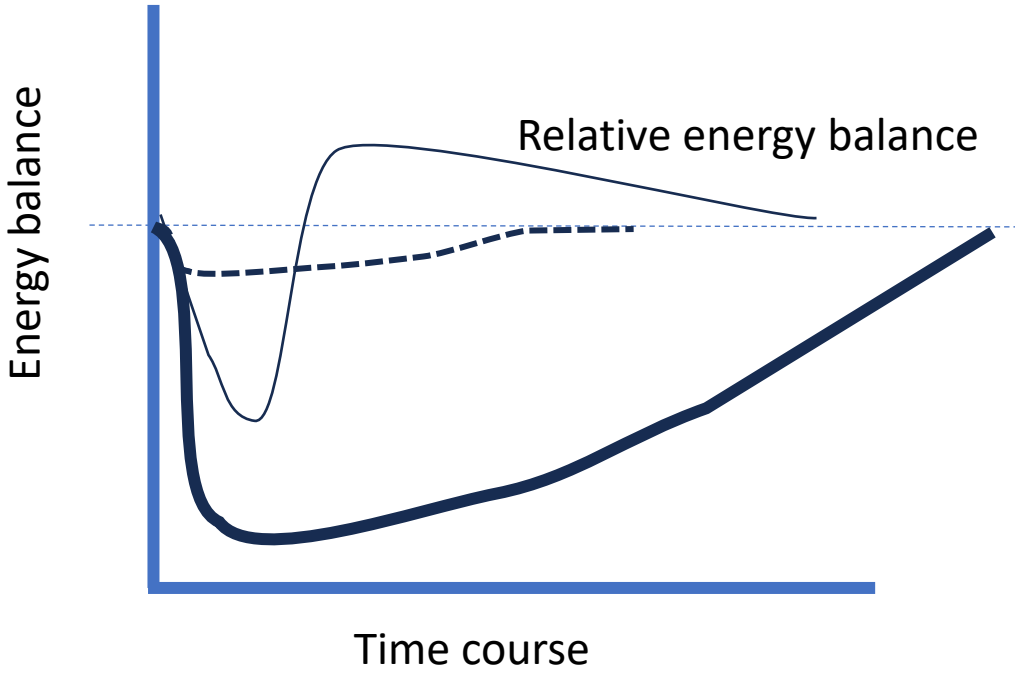
- New category of AOM therapy
  - Lean mass augmentation with anti-myostatin/Activin A treatments
    - Bimagrumab
    - Trevogrumab / Garetosmab
  - Enhancing retention of lean mass and reduction of fat mass
  - Could be highly synergistic with MBS

Will AOM be synergistic with MBS?

- Why don’t we already know the answer?
  - Need better systems of care
  - Continuum of care that considers treatment effects as continuous (e.g., achieved x% of expected mean or target treatment effect)
  - Rather than binary and reductive to success or failure

Will AOM be synergistic with MBS?

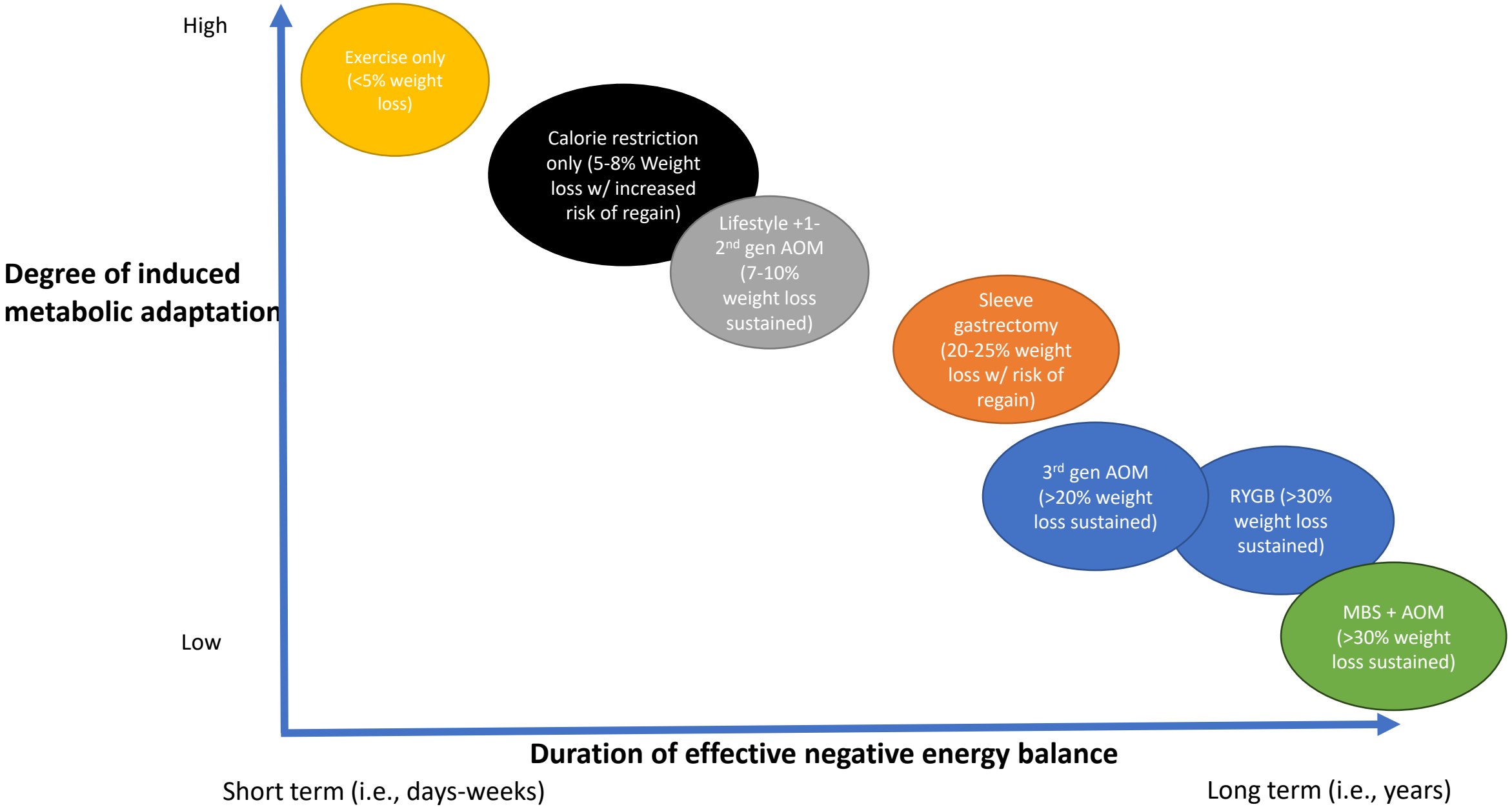
- What if we consider the efficacy of a given weight reduction intervention as a function of
  - Degree and duration of effective negative energy balance
  - Counterbalanced by the degree of metabolic adaptation



Will AOM be synergistic with MBS?

The goal is therefore to employ treatment strategies that achieve sustained negative energy balance while minimizing metabolic adaptation

- Longer weight loss phase
- Easier weight maintenance


High
Low
Degree of induced metabolic adaptation
Exercise only (<5% weight loss)
Calorie restriction only (5-8% Weight loss w/ increased risk of regain)
Lifestyle +1-2nd gen AOM (7-10% weight loss sustained)
Sleeve gastrectomy (20-25% weight loss w/ risk of regain)
3rd gen AOM (>20% weight loss sustained)
RYGB (>30% weight loss sustained)
MBS + AOM (>30% weight loss sustained)
Duration of effective negative energy balance
Short term (i.e., days-weeks)
Long term (i.e., years)

What evidence is needed to support combination therapy?

- What is the optimal timing / sequencing of combination therapy?
  - Is synergy a function of achieving the appropriate timing of therapy?

What evidence is needed to support combination therapy?

- Are there mechanistic pathways that can be better covered by complimentary treatments?
  - How do we match treatment to the patient?

What evidence is needed to support combination therapy?

- We need a biomarker that can provide direct feedback on the effectiveness of combination treatment to drive energy homeostasis

What evidence is needed to support combination therapy?

- Randomized, controlled trials of combination strategies
  - Neo-adjuvant → adjuvant
  - Low dose vs Approved dose
  - Continuous vs Intermittent use
  - MBS for weight loss maintenance, post AOM
  - Early use of AOM (e.g., begin 1 month post op) vs Late use of AOM (e.g., weight plateau)

What evidence is needed to support combination therapy?

- Who is likely to benefit from this approach?
  - Prospective phenotyping (clinically feasible & discovery)
  - Retrospective assessments (AI, machine learning)