Evidence-Based Weight Loss & Management

OHSU

5 Nov 2021

PRESENTED BY: Jonathan Q. Purnell, MD
Professor, Knight Cardiovascular Institute
Oregon Health & Science University
Portland, Oregon

Disclosures

Novo Nordisk: Consulting Fee

Weight Regulation Physiology

The body weight **Set Point** is tightly regulated:

- **Sensing mechanisms** detect environmental changes in food intake (type, quantity) and activity level, as well as adipose tissue content.
- **Effector systems** respond (**adapt**) with changes in appetite and energy expenditure.
- Weight loss (or gain) is kept ± **5 lbs** of a set point (range)

Weight Regulation (Patho)Physiology

Overweight and **obesity** results when **leptin resistance** (deficiency) occurs, establishing **a higher body weight Set Point**.

Overweight and Obesity: Take Home Message

To achieve **sustained weight loss**, any therapy must ultimately **"interfere"** with the way that the brain senses and responds to feedback signals, **preventing counter-regulatory appetite and energy expenditure adaptions** from restoring baseline weight.

(and be continued **long-term**)

OHSU

Overweight and Obesity as a Chronic Disease

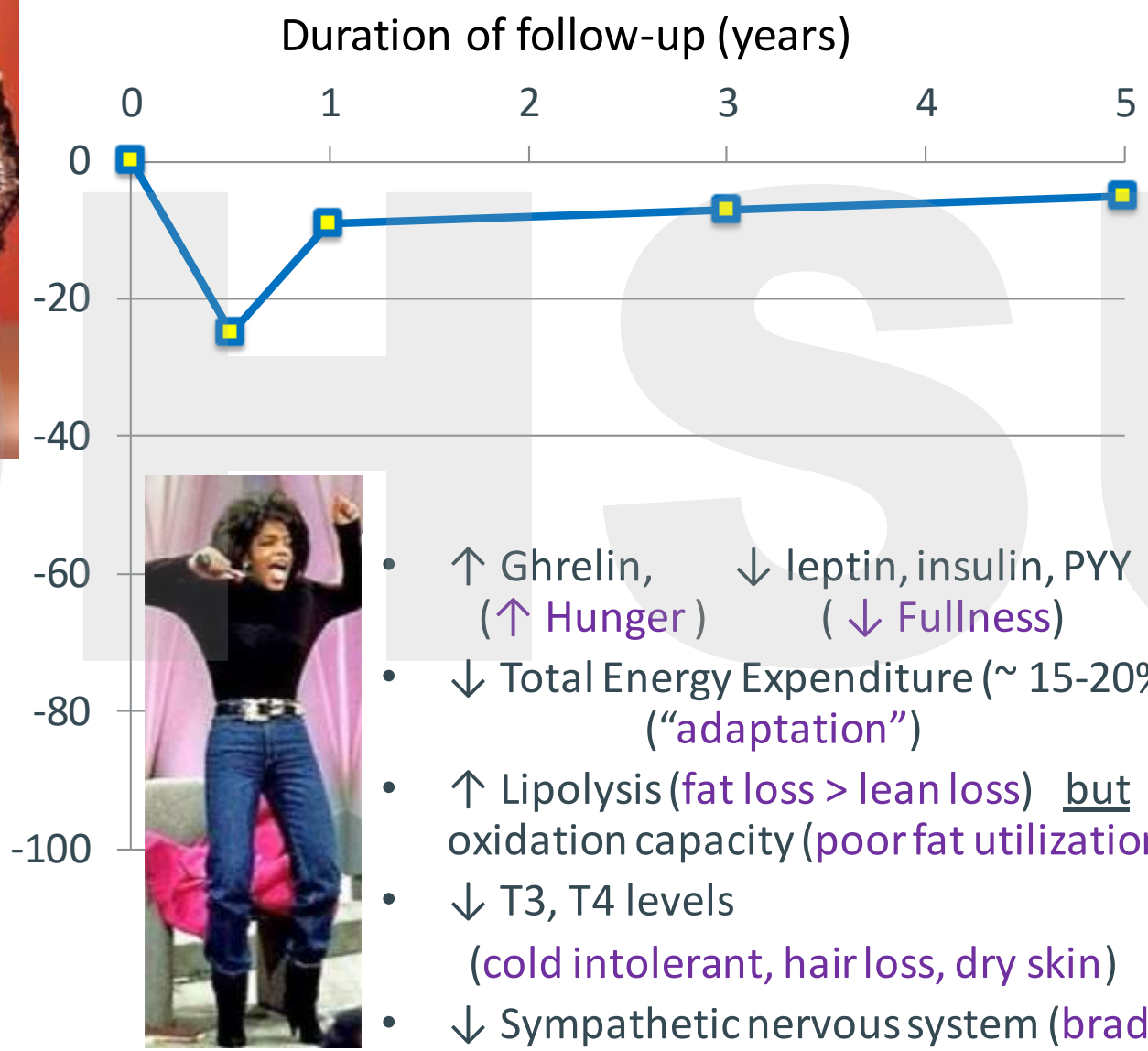
- Treatment of Overweight and Obesity
  - Lifestyle (diet and exercise)
  - Medications
  - Bariatric Surgery

Overweight and Obesity as a Chronic Disease

- Treatment of Overweight and Obesity
  - Lifestyle (diet and exercise)
  - Medications
  - Bariatric Surgery

Systematic Review of Commercial Weight Loss Programs

Tsai and Wadden. Ann Intern Med. 142:56-66, 2005



- ↑ Ghrelin, ↓ leptin, insulin, PYY
  (↑ Hunger) (↓ Fullness)
- ↓ Total Energy Expenditure (~ 15-20%)
  ("adaptation")
- ↑ Lipolysis (fat loss > lean loss) <u>but</u> NO ↑ in fat oxidation capacity (poor fat utilization)
- ↓ T3, T4 levels
  (cold intolerant, hair loss, dry skin)
- ↓ Sympathetic nervous system (bradycardia)

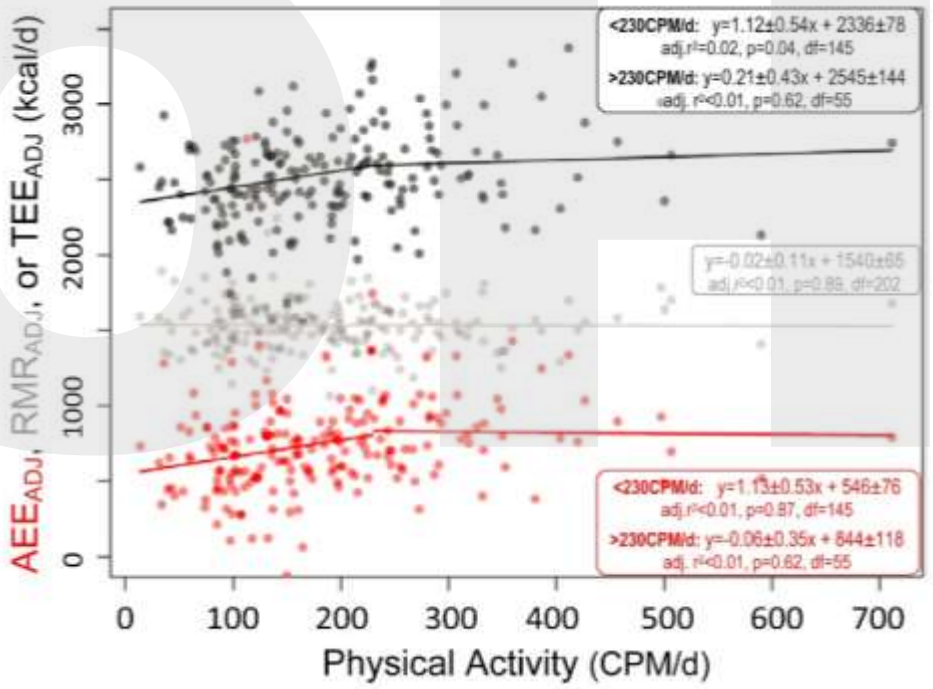
OHSU

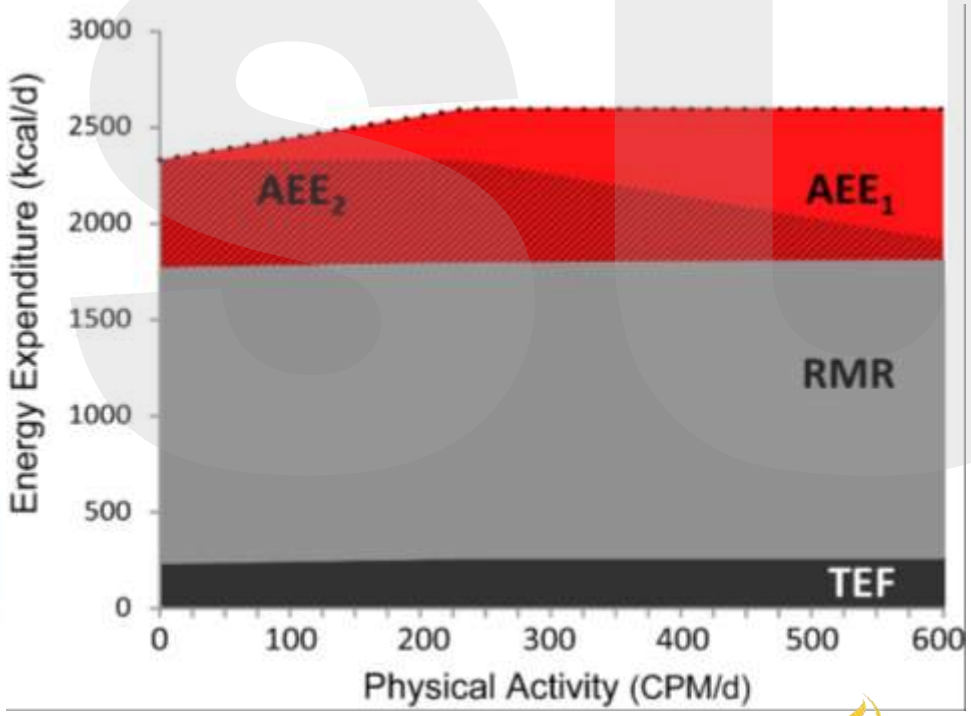
Approaches to Weight Loss

Yes, but, patients with obesity need to exercise more…

Constrained Total Energy Expenditure During Metabolic Adaptation to Physical Activity

Pontzer, et al. Current Biology. 2016:26, 410-417.

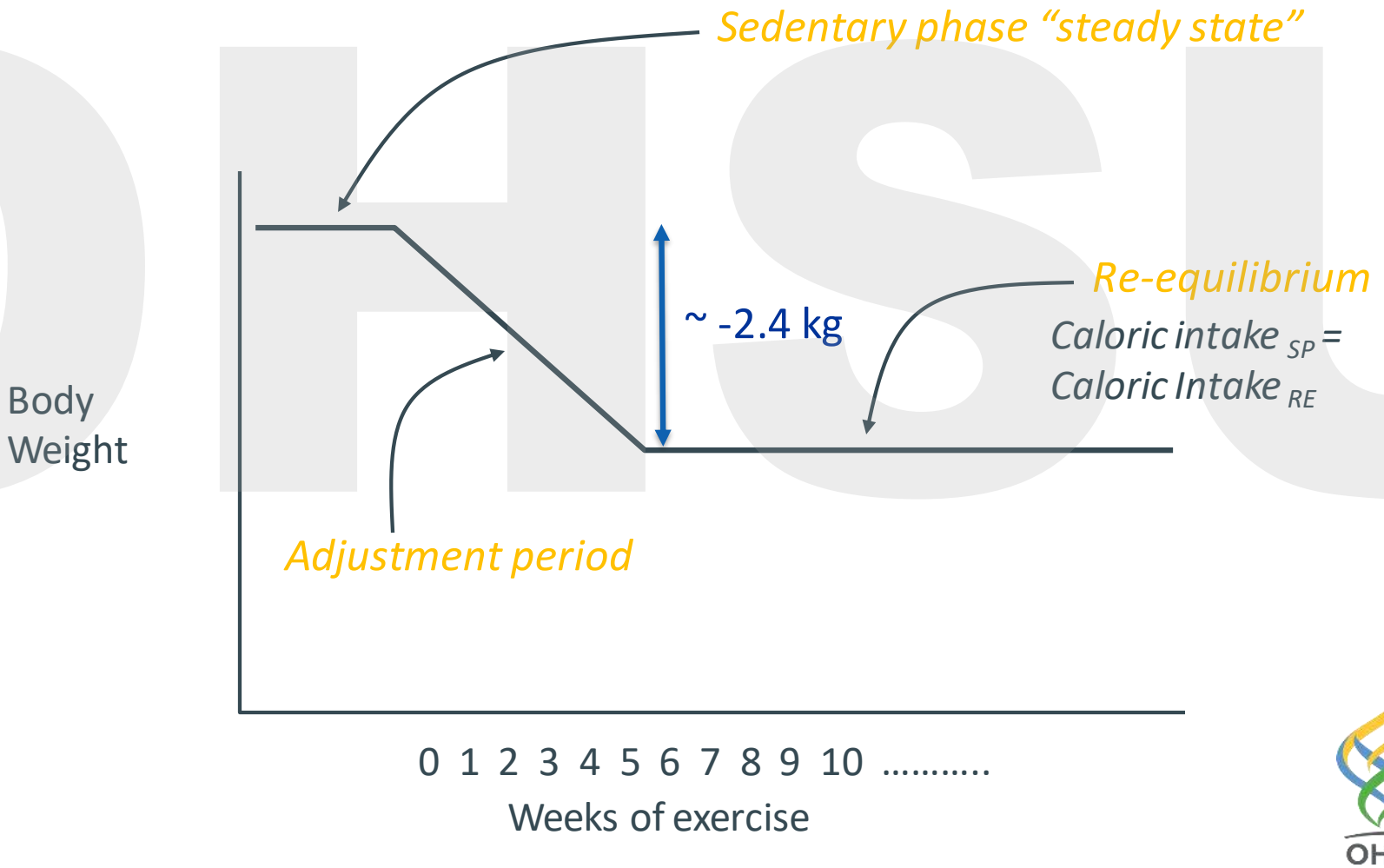




OHSU

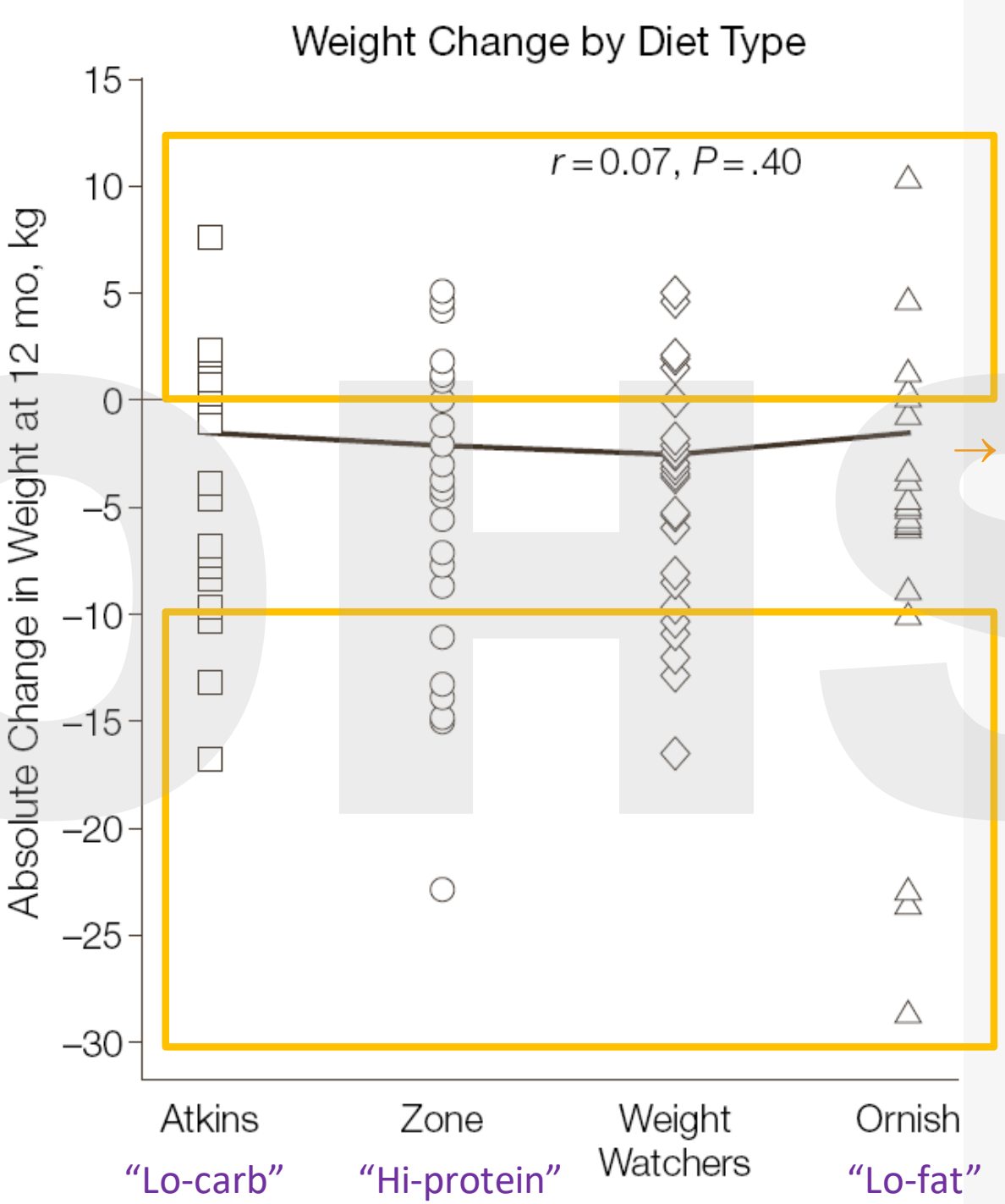
Exercise, Weight Loss, and Weight Regulation

Blundell and King. Nutrition. 7/8:519-22, 2000.



Weight Loss Comparison of "Named Diets."

Dansinger, et al. JAMA 2005;293:43-53.

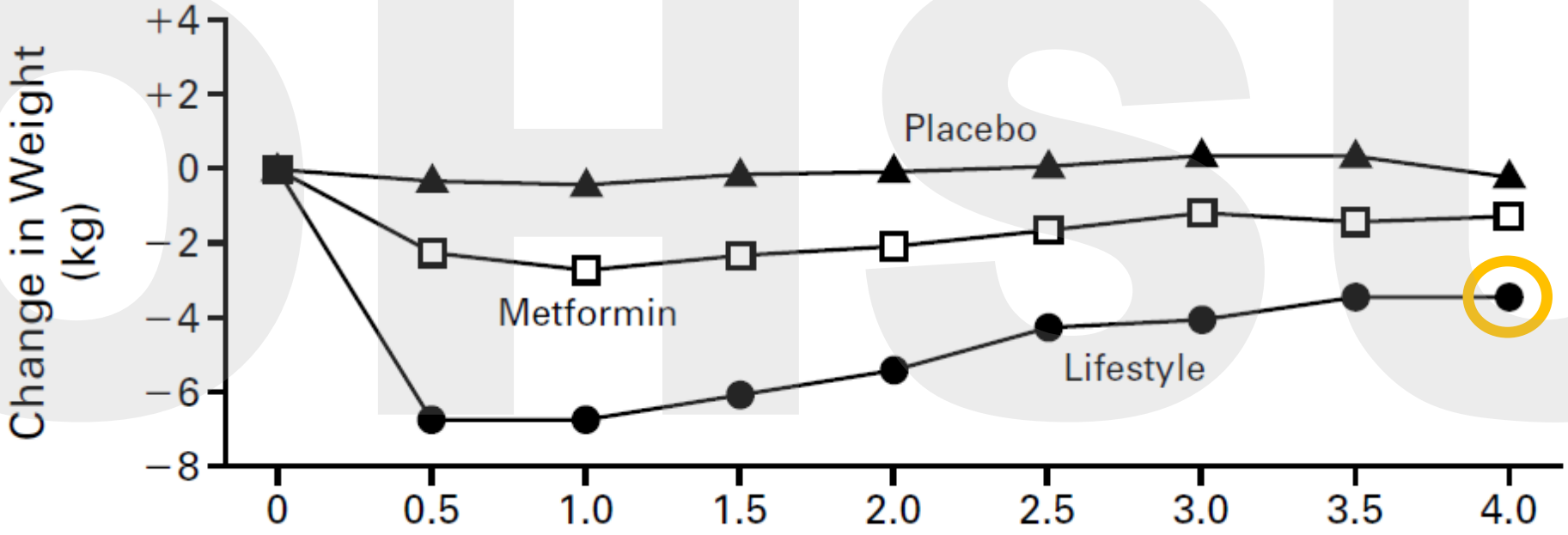


→ Average weight loss: 2 - 3 kg

Diabetes Prevention Program: Modest Effect on Weight (Low-fat Diet + Exercise)

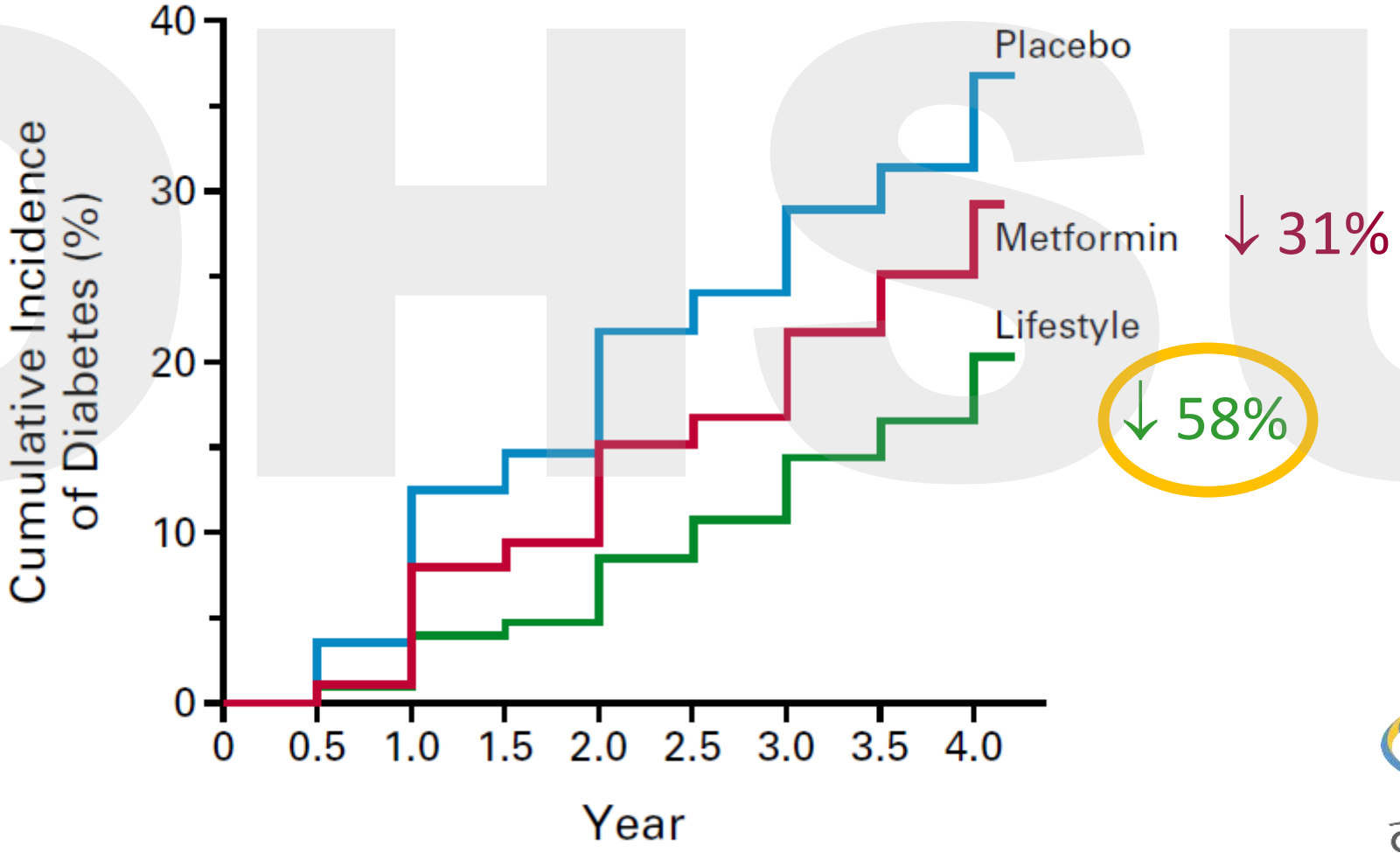
N Engl J Med 346:393–403, 2002.

Four years: - 4%



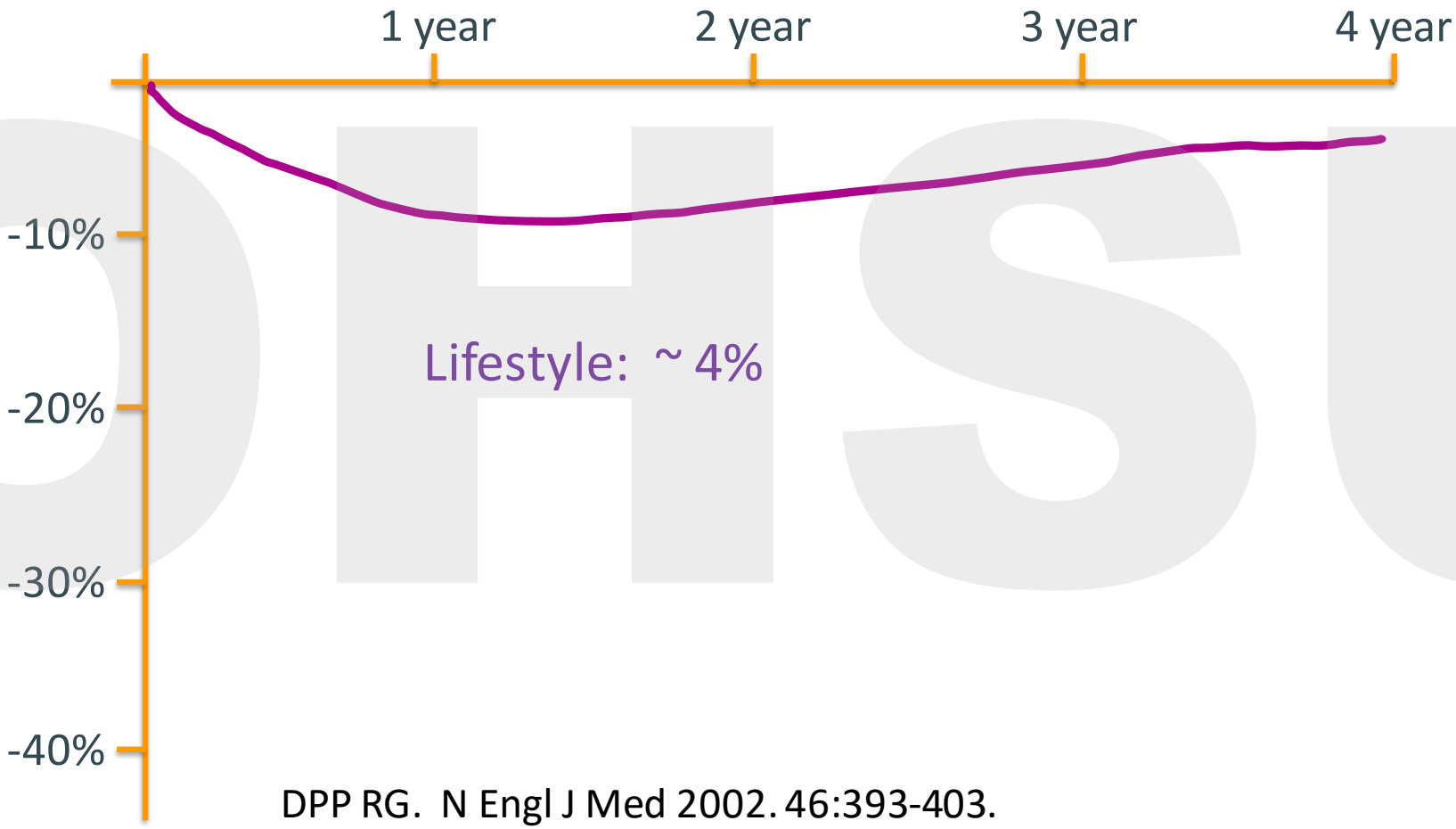
Diabetes Incidence Best Lowered by Lifestyle (Low-fat Diet + Exercise)

N Engl J Med 346:393–403, 2002.



OHSU

Weight Loss Averages by Approach



DPP RG. N Engl J Med 2002. 46:393-403.
LOOK AHEAD. N Engl J Med 2013. 369:145-54.

Overweight and Obesity as a Chronic Disease

- Treatment of Overweight and Obesity
  - Lifestyle (diet and exercise)
  - Medications
  - Bariatric Surgery

Recommendation For Consideration of Pharmacological Weight Management

- BMI 27 - 30 kg/m^2 and a weight-related comorbidity:
  - HTN
  - Dyslipidemia
  - Diabetes
  - Other

OR

- BMI $\geq$ 30 kg/m^2

https://www.nhlbi.nih.gov/files/docs/guidelines/prctgd_c.pdf

Anti-Obesity Medicines (AOMs)

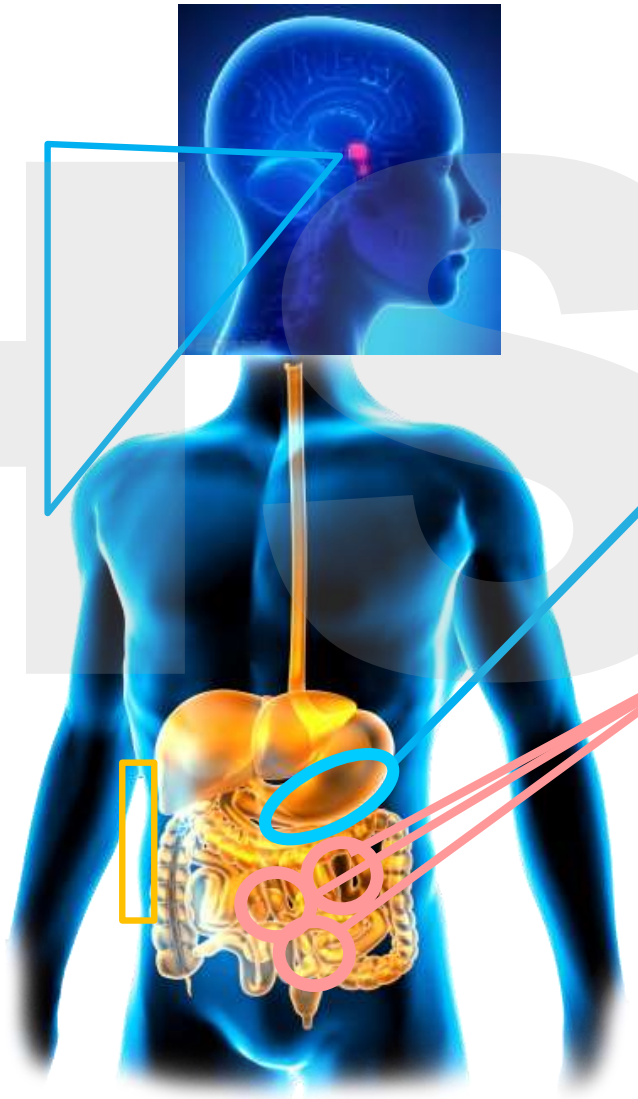
<u>Currently FDA Approved</u>

- tetrahydrolipstatin (Orlistat) $$$
  - (now over the counter as “alli”-60 mg dose)

- phentermine (Fastin, Ionamin, Adipex) $
- phentermine + topiramate (Qsymia) $$
- bupropion + naltrexone (Contrave) $$
- liraglutide 3.0 (Saxenda)
- Semaglutide 2.4 mg (Wegovy)

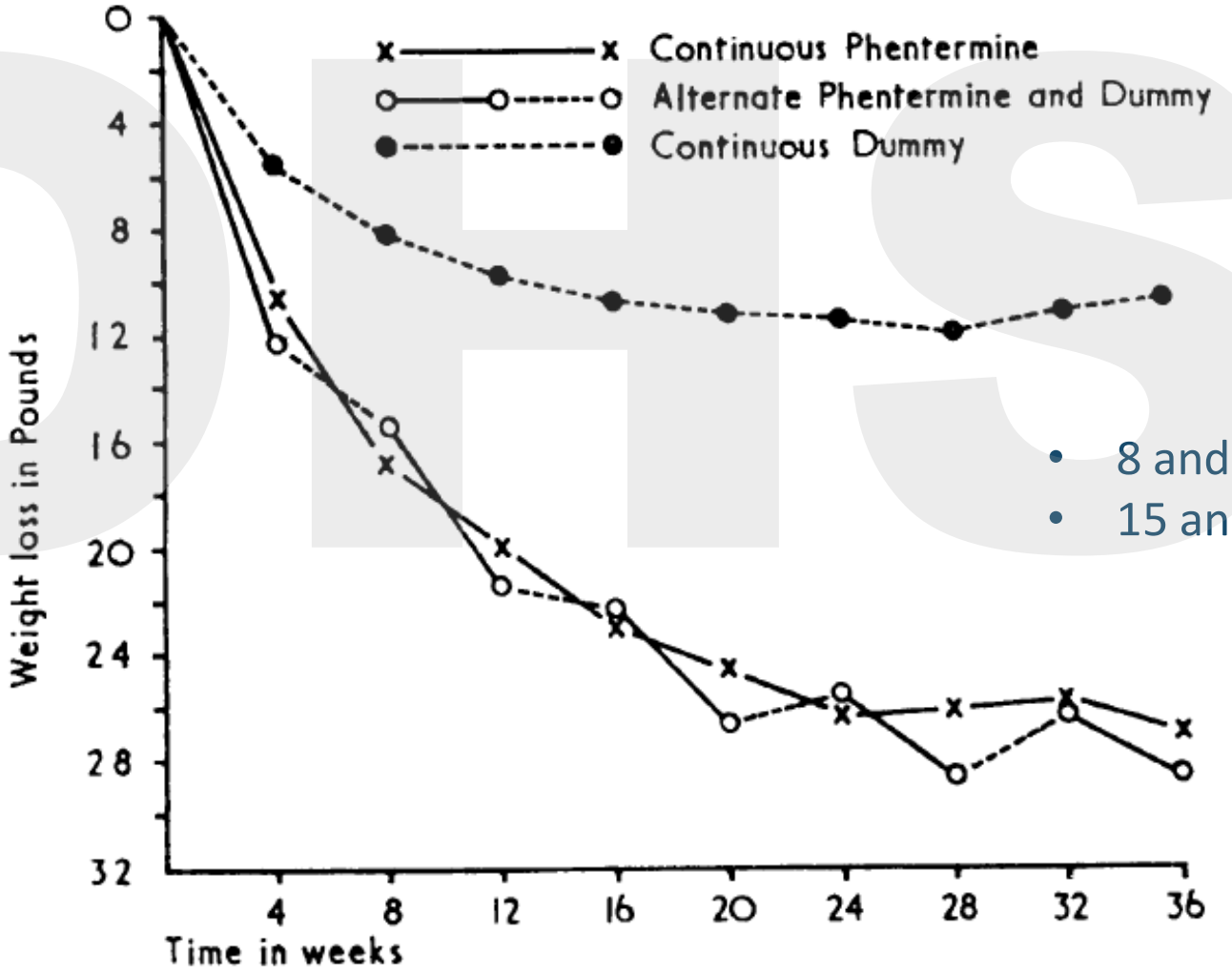
Weight Loss Medications Enhance CNS Signaling to Meal-related Signals

- phentermine
- phentermine + topiramate
- bupropion + naltrexone
- liraglutide
- semaglutide



Weight Loss With Phentermine

Monroe, et al. BMJ. 1:352-54. 1968.



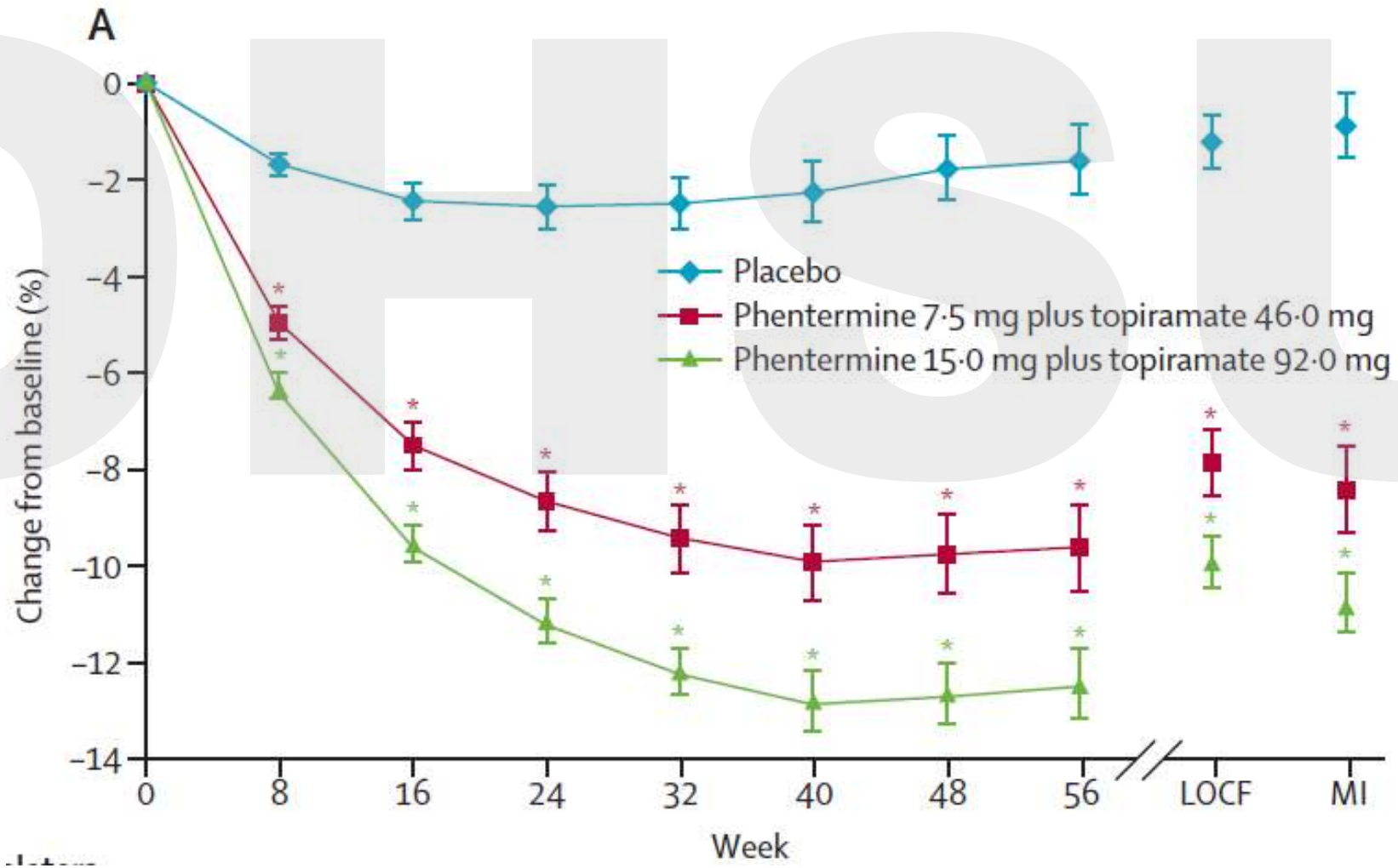
- 8 and 37.5 mg tablets
- 15 and 30 mg capsules

~ 9-10% wt loss

OHSU

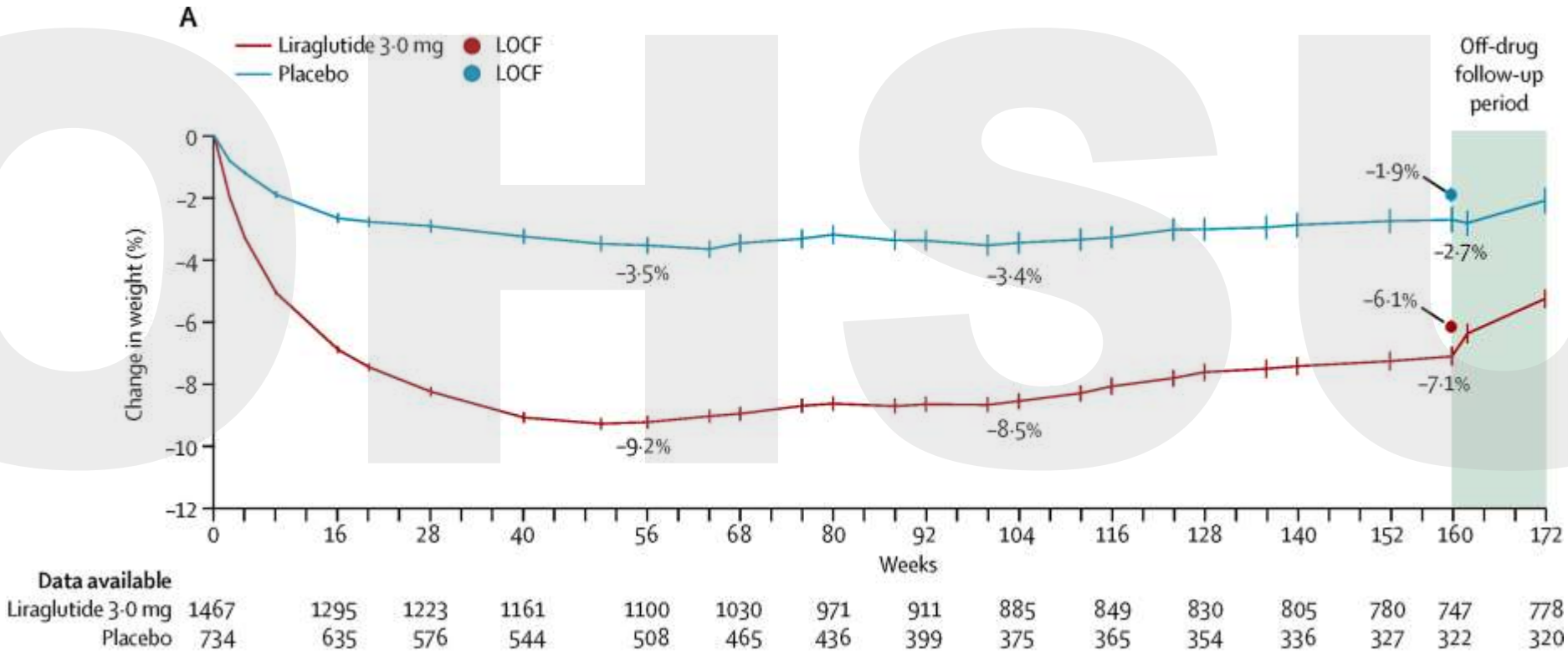
Phentermine + Topiramate (Qsymia)

Gadde, et al. Lancet 2011; 377: 1341–52



Liraglutide 3.0 for Weight Management and Type 2 Diabetes Risk Reduction in Pre-diabetes

le Roux, et al. Lancet 2017; 389: 1399–409

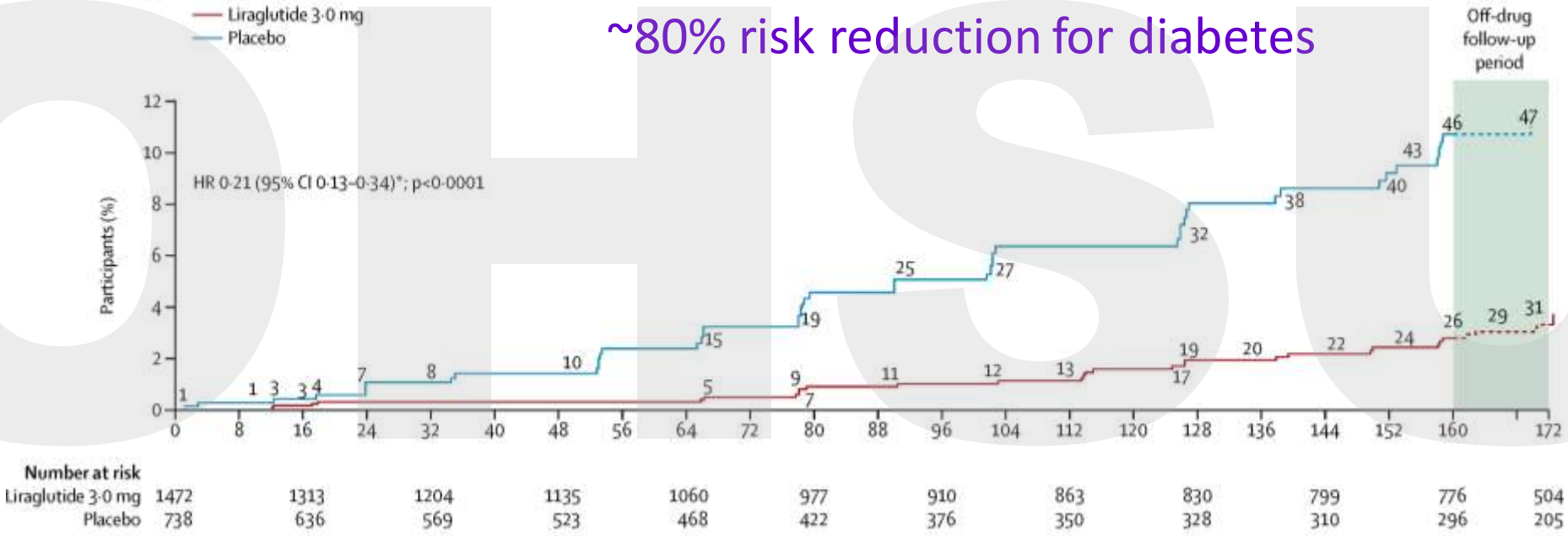


OHSU

Liraglutide 3.0 for Weight Management and Type 2 Diabetes Risk Reduction in Pre-diabetes

le Roux, et al. Lancet 2017; 389: 1399–409

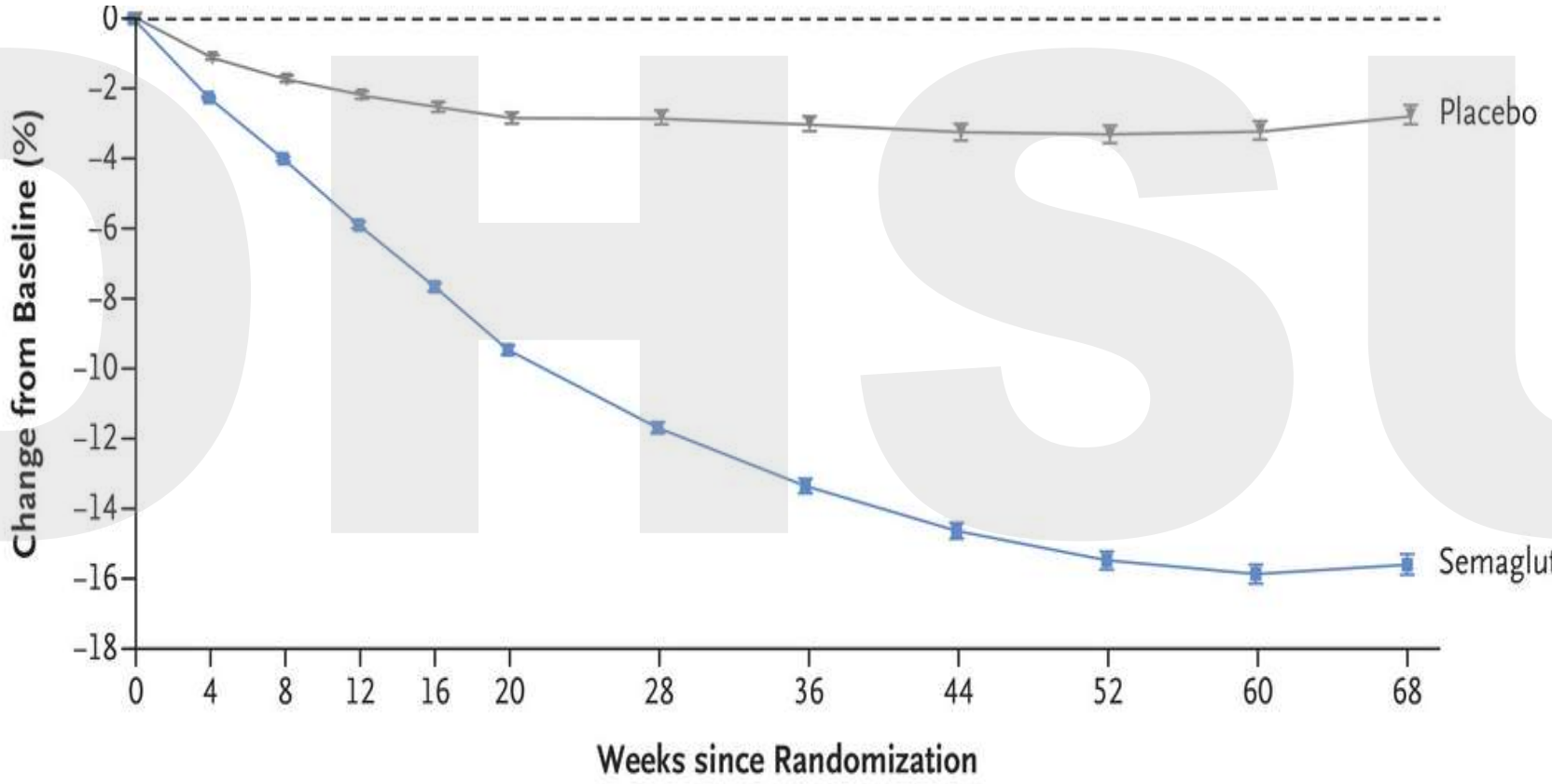
~80% risk reduction for diabetes



OHSU

Semaglutide 2.4 for Weight Management in Overweight and Obesity

le Roux, et al. Lancet 2017; 389: 1399–409

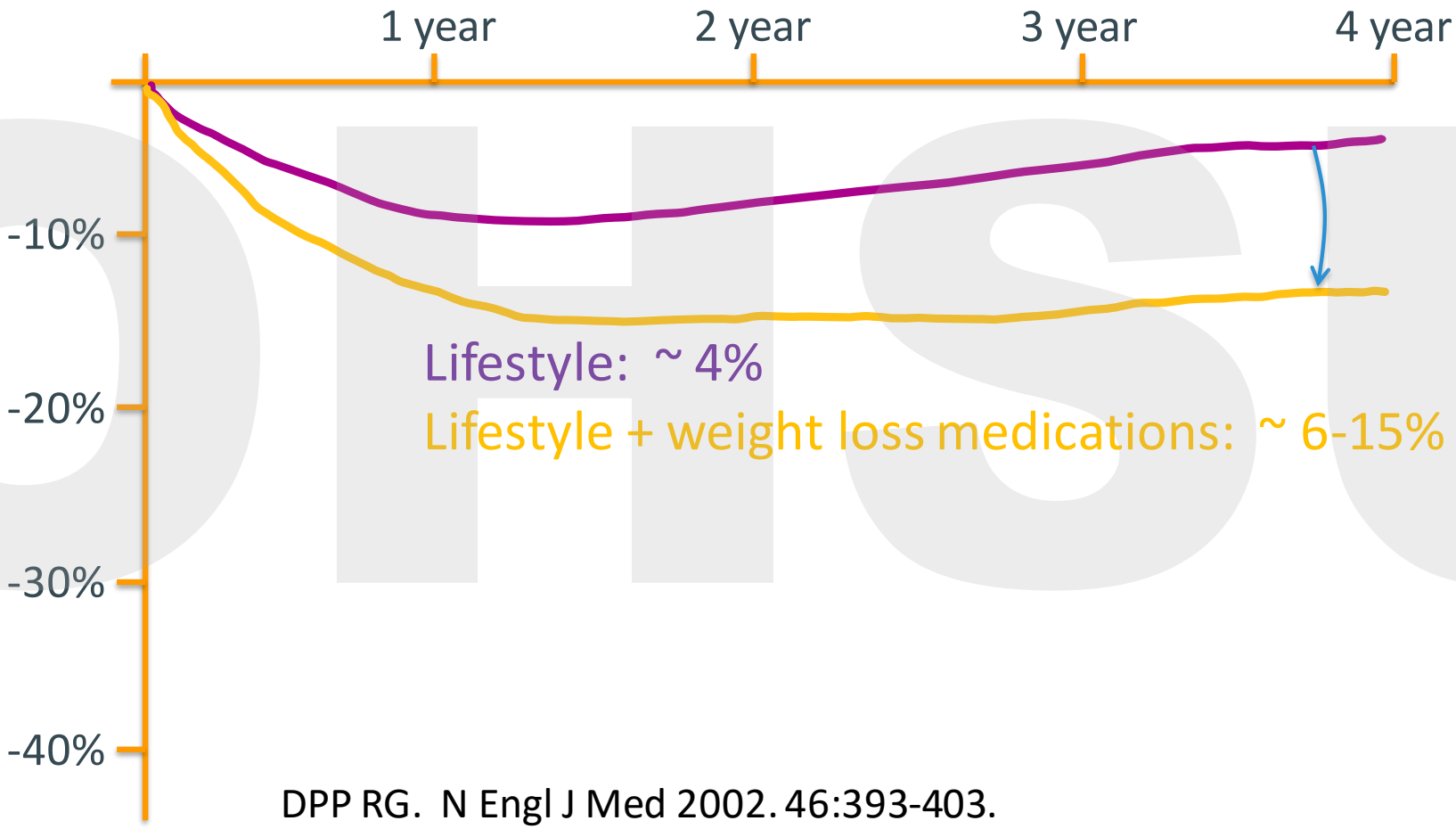


~14.9%

No. at Risk

Placebo	655	649	641	619	615	603	592	571	554	549	540	577
Semaglutide	1306	1290	1281	1262	1252	1248	1232	1228	1207	1203	1190	1212

Weight Loss Averages by Approach



DPP RG. N Engl J Med 2002. 46:393-403.
LOOK AHEAD. N Engl J Med 2013. 369:145-54.
Wilding JPH, et al. N Engl J Med 2021; 384:989-1002.

Topline information for today's family physician

Diagnosis and Management of Obesity

Key Practice Recommendations

Recommendations	Comments
Screen all adults for obesity. Offer or refer patients with a body mass index (BMI) of 30 kg/m^2 or greater to intensive, multicomponent behavioral interventions.[1]	This recommendation applies to all adults, not just those with known cardiovascular risk factors.
Screen children 6 years and older for obesity, and offer or refer them to comprehensive, intensive behavioral interventions to promote improvement in weight status.[2]	
A 5% to 10% weight loss can reduce risk of heart disease and diabetes and should be encouraged for all patients who are overweight and obese.[3,4]	
Consider pharmacotherapy in adults who have not been able to lose weight through diet and physical activity alone and who have: BMI of 30 kg/m^2 or greater BMI of 27 kg/m^2 or greater, and obesity-related comorbidity[3,4]	
Consider bariatric surgery in adults who have not been able to lose weight through diet and physical activity alone and who have: BMI of 40 kg/m^2 or greater BMI of 35 kg/m^2 or greater, and obesity-related comorbidity[3]	
Regardless of body weight or weight loss, all patients should be encouraged to be physically active for improved health and weight maintenance.[3]	Regular physical activity is strongly related to maintaining normal weight. Exercise also mitigates health-damaging effects of obesity, even without weight loss.

1. *U.S. Preventive Services Task Force. Screening for and management of obesity in adults.* Ann Intern Med. *2012;157(5):373-378.*

2. *U.S. Preventive Services Task Force. Screening for and management of obesity in children and adolescents. www.uspreventiveservicestaskforce.org/uspstf/uspschobes.htm. Accessed April 18, 2013.*

3. *National Heart, Lung and Blood Institute. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults. www.nhlbi.nih.gow/guidelines/obesity/ob_gdlns.pdf. Accessed April 18, 2013.*

4. *Institute for Clinical Systems Improvement. Obesity, prevention and management of (Mature Adolescents and Adults). www.icsi.org/guidelines__more/catalog_guidelines_and_more/catalog_guidelines/catalog_endocrine_guidelines/obesity/*

AAFP

Low Adoption of Weight Loss Medications

Of the **829,962** active physicians in the United States IMS Health Xponent database:

n=129,414 (**16%**) prescribed phentermine

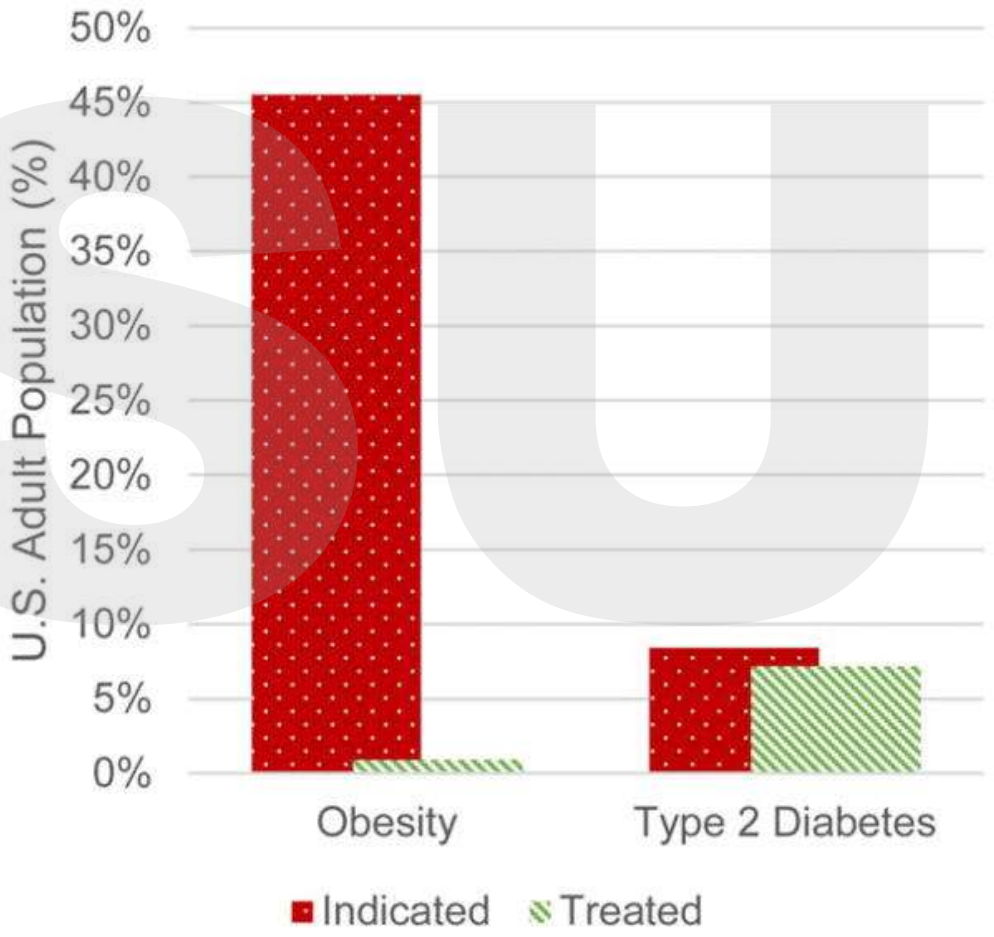
n=79,624 (**10%**) prescribed a new antiobesity medication

34%-42% Family Practice

19%-27% Internal Medicine

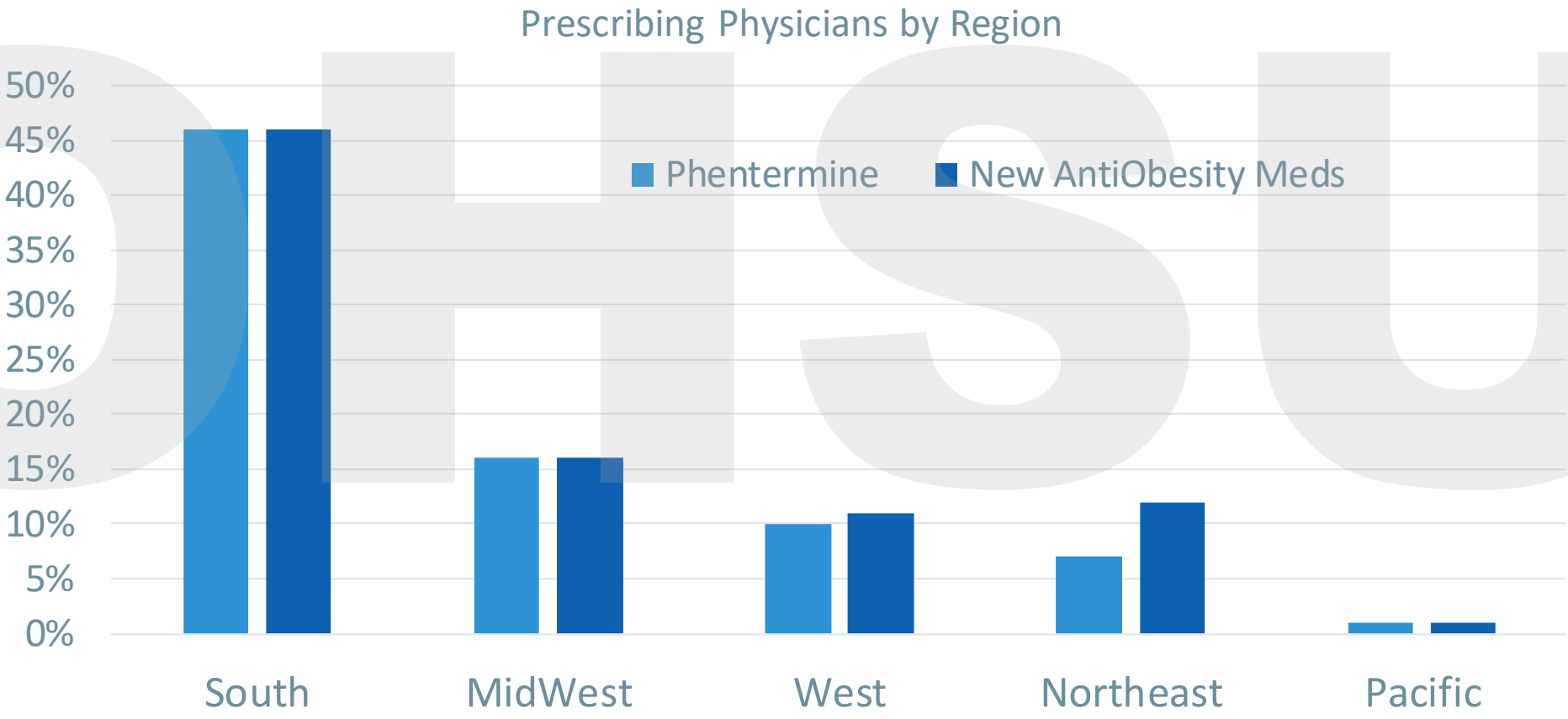
7%-13% OB/Gyn

2%-13% Endocrinology



Thomas CE, et al. Obesity (Silver Spring). 2016 Sep;24(9):1955-61.

Low Adoption of Weight Loss Medications: A Regional Thing



Thomas CE, et al. Obesity (Silver Spring). 2016 Sep;24(9):1955-61.

Reasons for Underutilization of Weight Management Medications

- Previous weight loss drugs had poor safety record (fenfluramine, sibutramine, rimonabant)
- Perceived need for frequent follow-ups needed for AE monitoring
- Some are controlled substances:
  - Phentermine is a DEA schedule IV (low potential for abuse and low risk of dependence)
  - Compared to Adderall, Concerta, and Vyvanse (all schedule II)
- Lack of understanding of current guideline recommendations
- Misperception that meds are only used "short-term," leading to weight regain
- Variable response among patients, including many "non-responders"
- Poor and inconsistent insurance coverage

Slide credit: clinicaloptions.com

Overweight and Obesity as a Chronic Disease

- Treatment of Overweight and Obesity
  - Lifestyle (diet and exercise)
  - Medications
  - Bariatric Surgery

Recommendation For Consideration of Bariatric Surgery

- BMI 35- 40 kg/m^2 and a weight-related comorbidity:
  - HTN
  - Dyslipidemia
  - Diabetes
  - Other (sleep apnea, GERD, OA, etc)

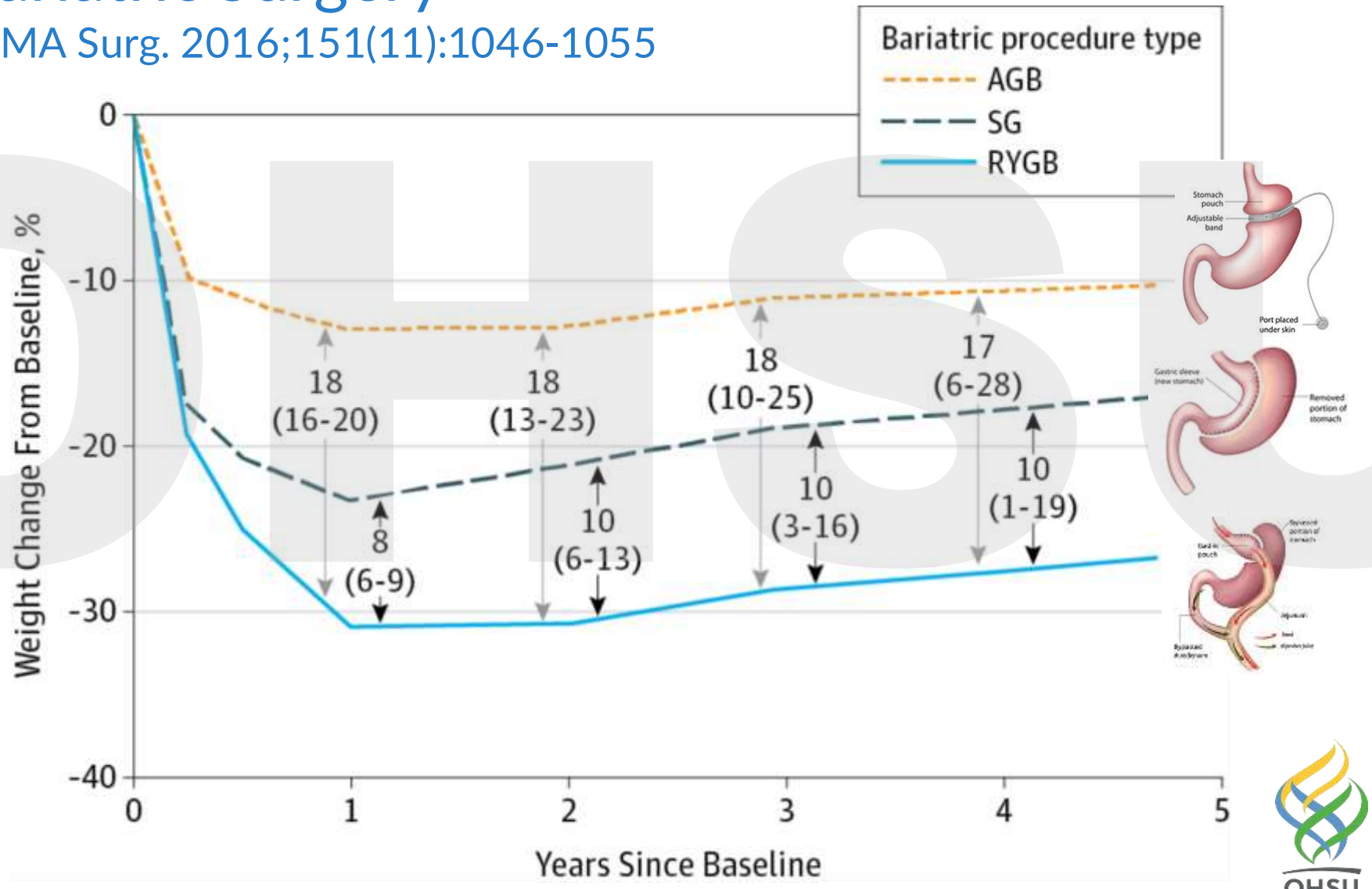
OR

- BMI $\geq$ 40 kg/m^2

https://www.nhlbi.nih.gov/files/docs/guidelines/prctgd_c.pdf

Long-Term Weight Loss Durability After Bariatric Surgery

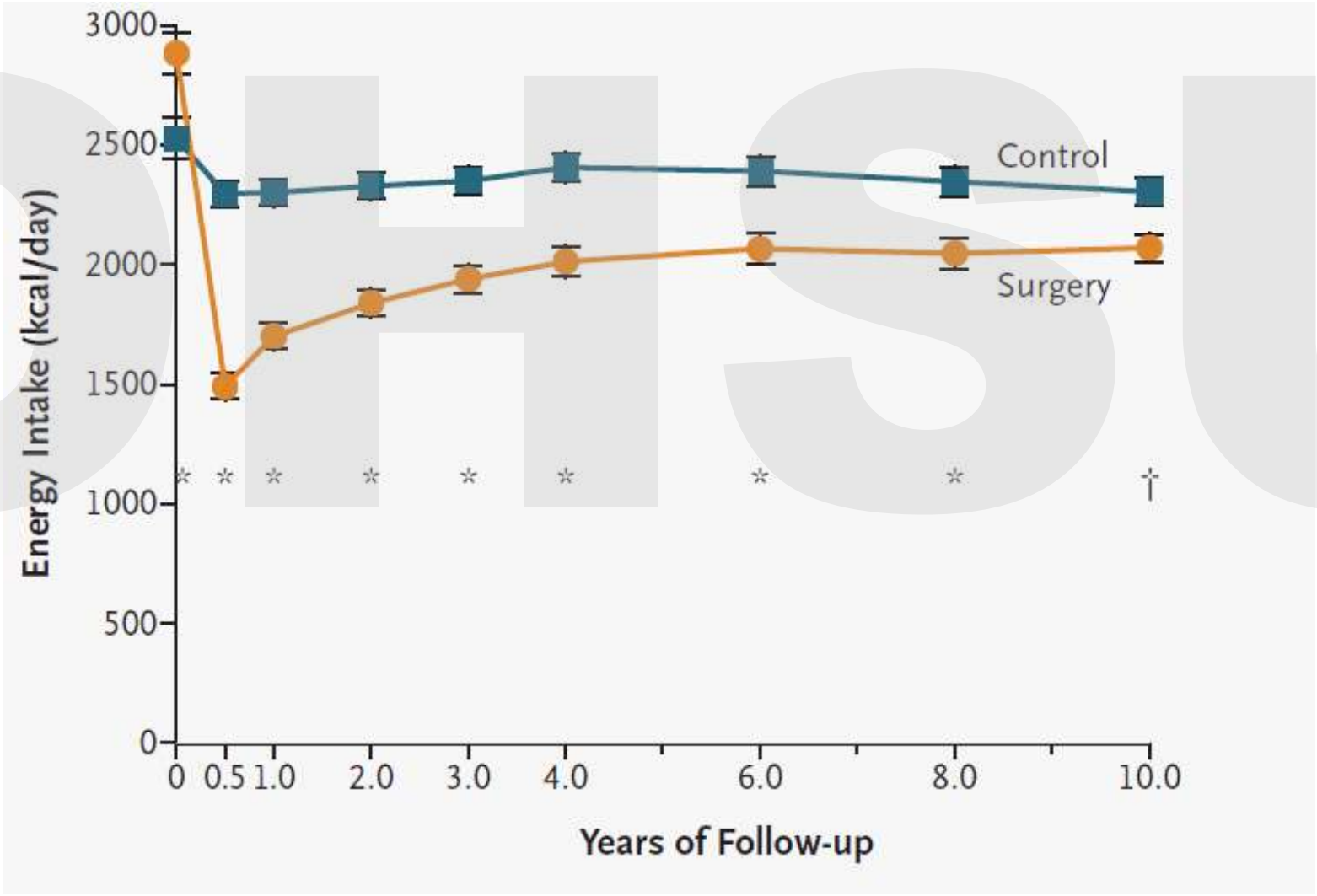
JAMA Surg. 2016;151(11):1046-1055



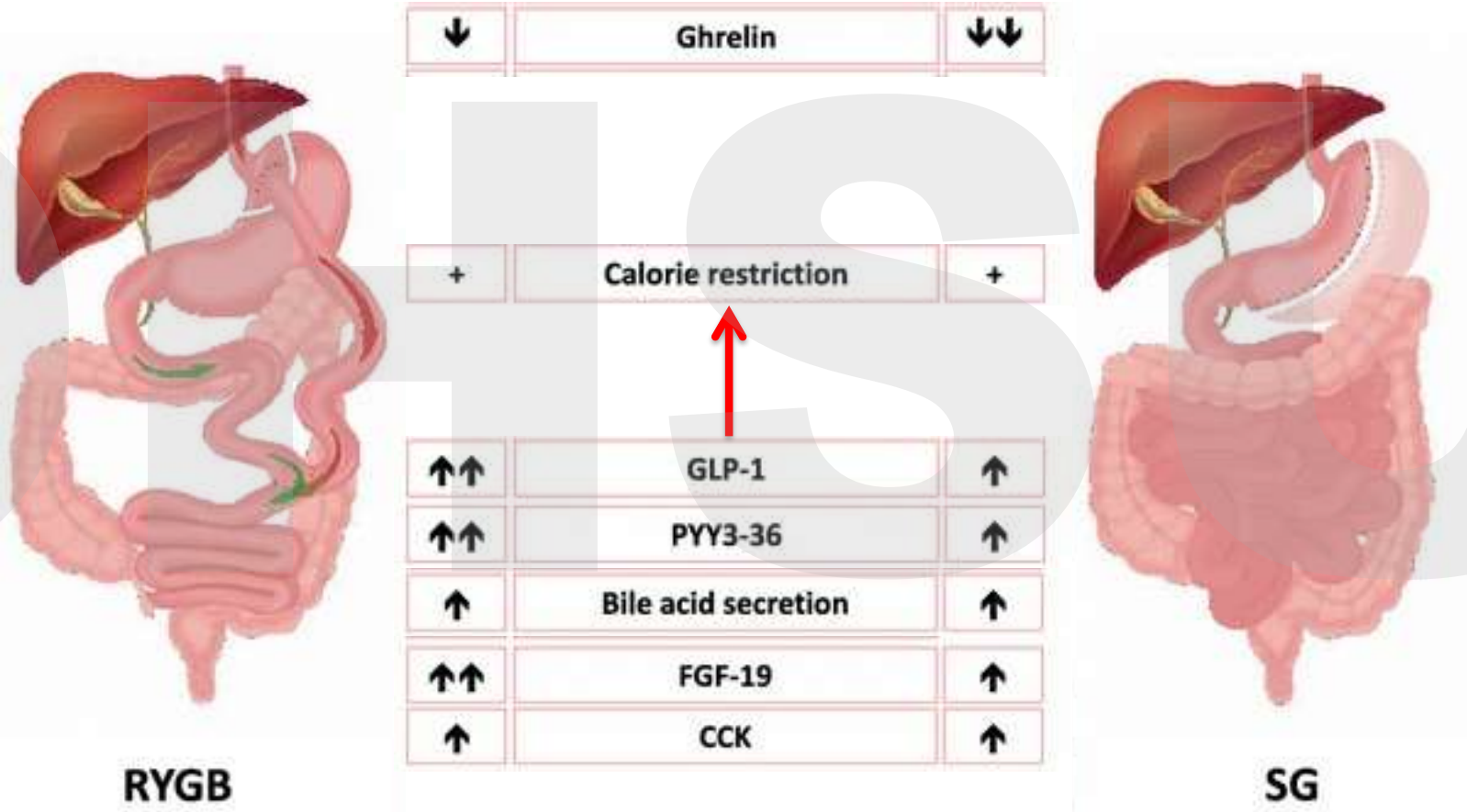
OHSU

Sustained Appetite Reduction after Bariatric Surgery: 10-year Follow-up

Sjostrom, et al. NEJM. 351:2683-93, 2004.

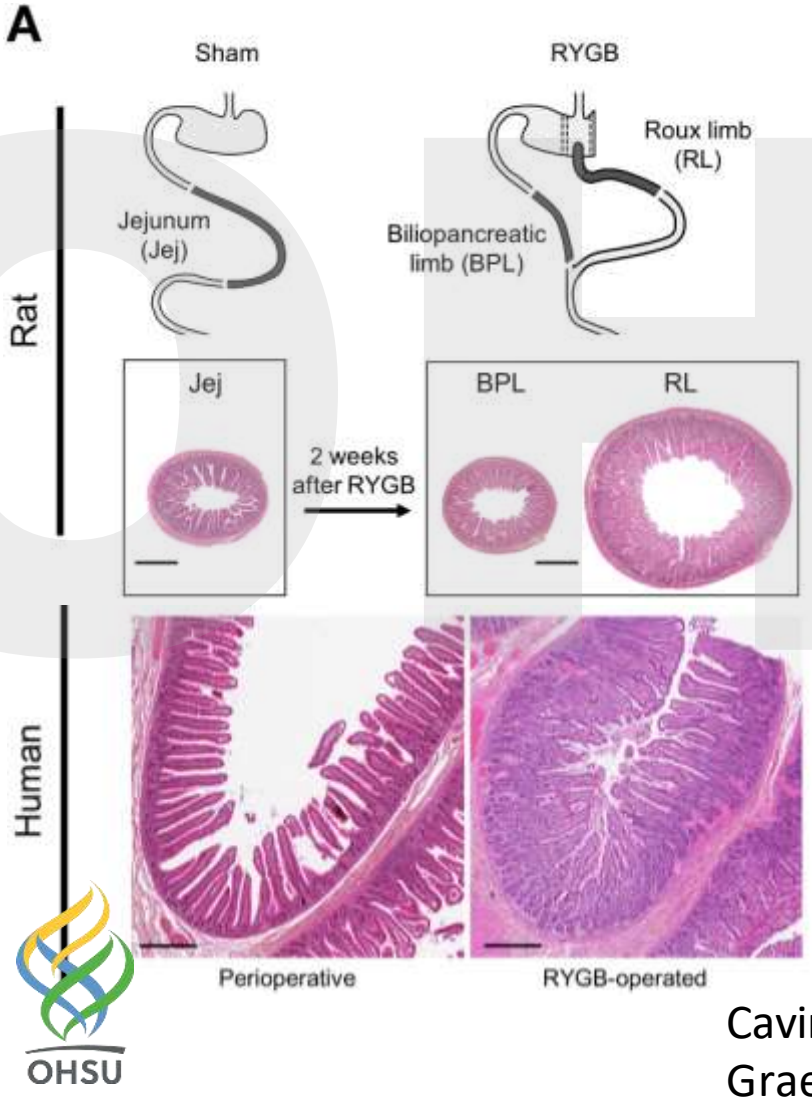


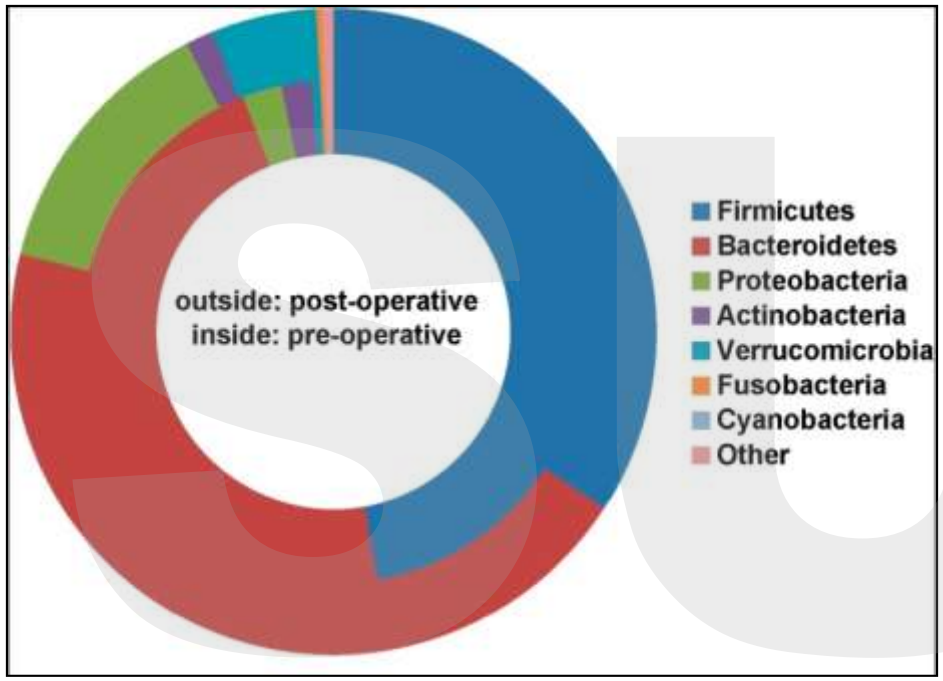
Primer on Mechanisms/Effects of Bariatric Surgery



Pucci and Batterham. J Endocrinol Invest. 2019 Feb;42(2):117-128.

Primer on Mechanisms/Effects of Bariatric Surgery: Gut Adaptation



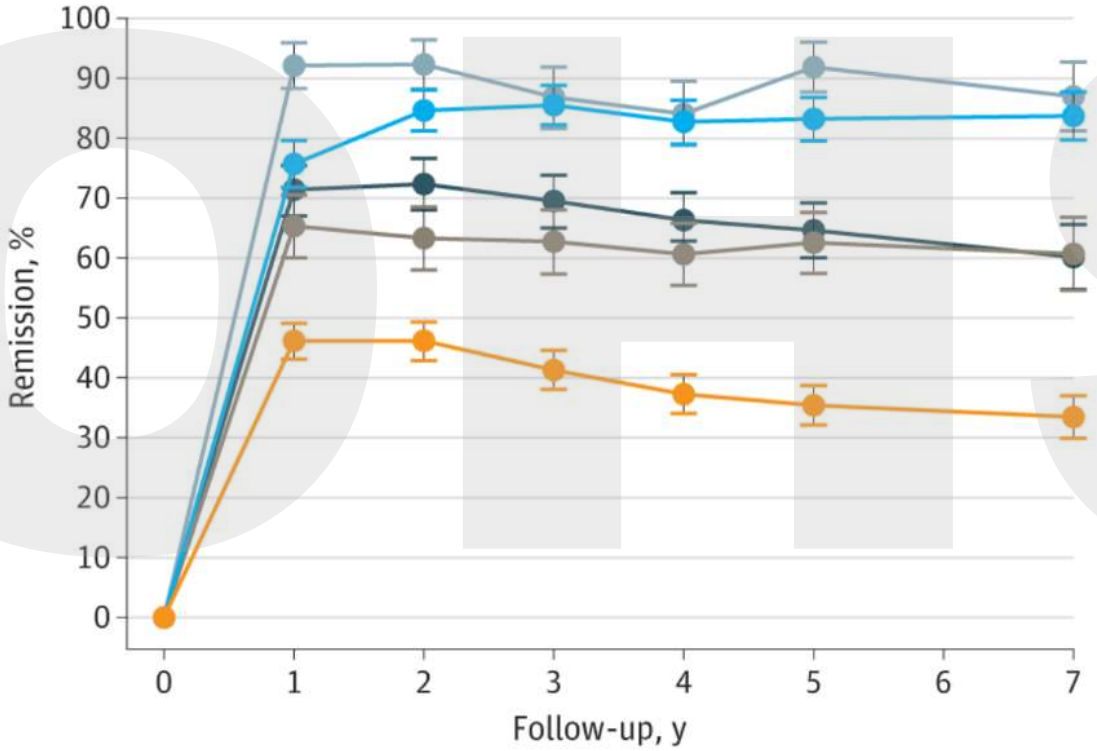


Cavin J-B, et al. Gastroenterology. 2016. 150:454–464.
Graessler J, et al. Pharmacogenomics J. 2013.13: 514–522

Weight Change and Health Outcomes after Bariatric Surgery: The Longitudinal Assessment of Bariatric Surgery (LABS) Study

Courcoulas, et al. JAMA Surg. 2018;153(5):427-434

Roux-en-Y gastric bypass

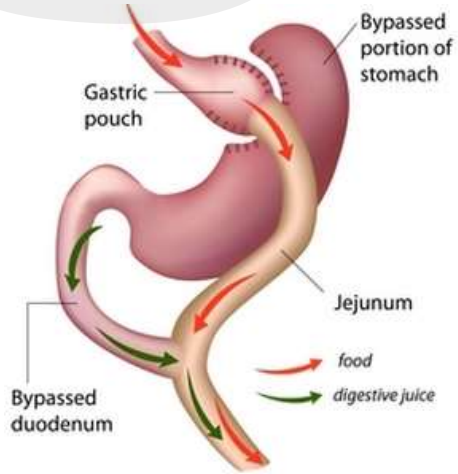


Median (95% CI), %

- Diabetes
- High LDL cholesterol level
- High triglyceride level
- Low HDL cholesterol level
- Hypertension

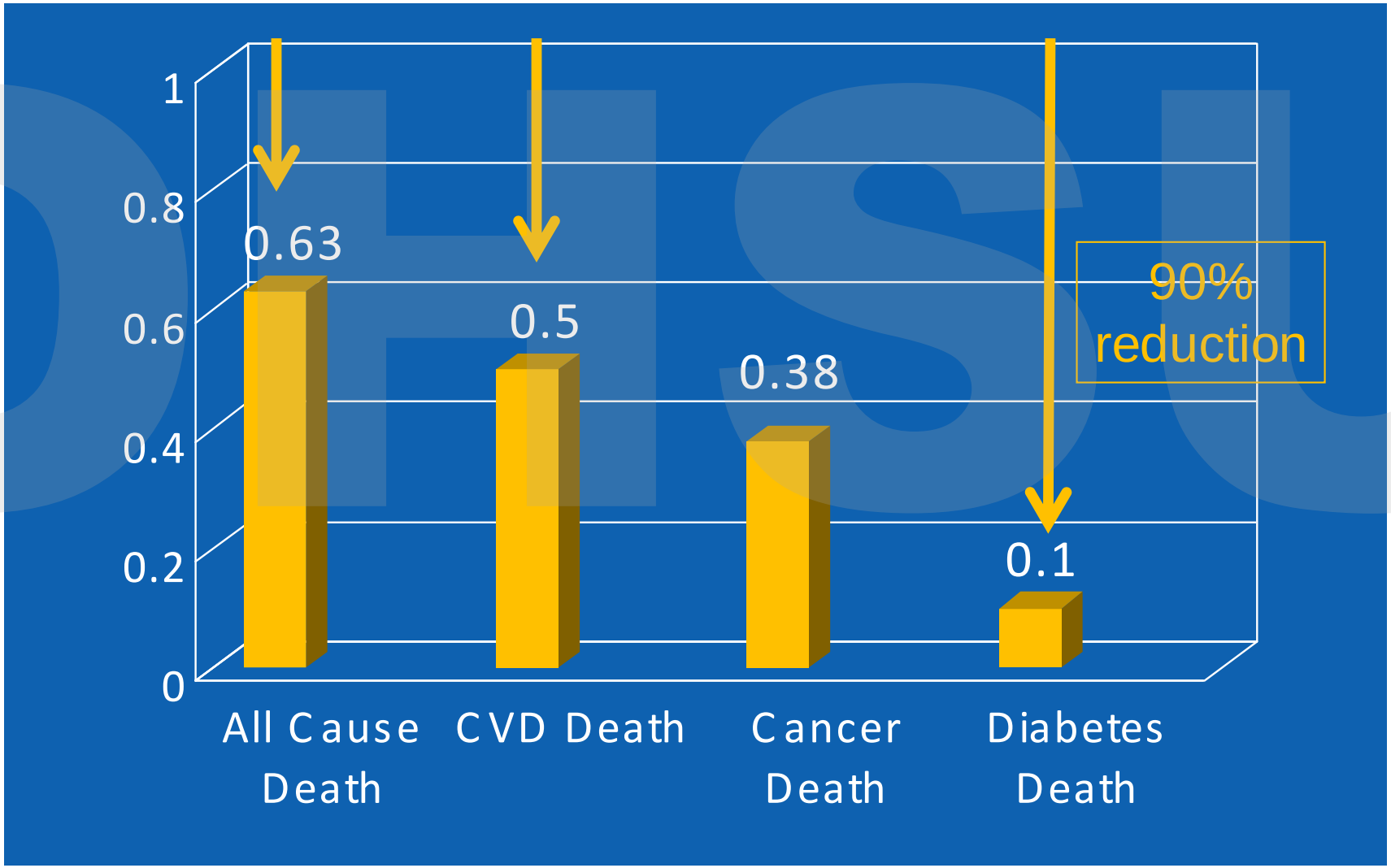
No. at risk

Diabetes	379	327	320	342	345	219
High LDL cholesterol level	292	246	253	253	260	167
High triglyceride level	201	166	162	161	164	120
Low HDL cholesterol level	437	353	342	341	354	241
Hypertension	960	786	741	751	782	520

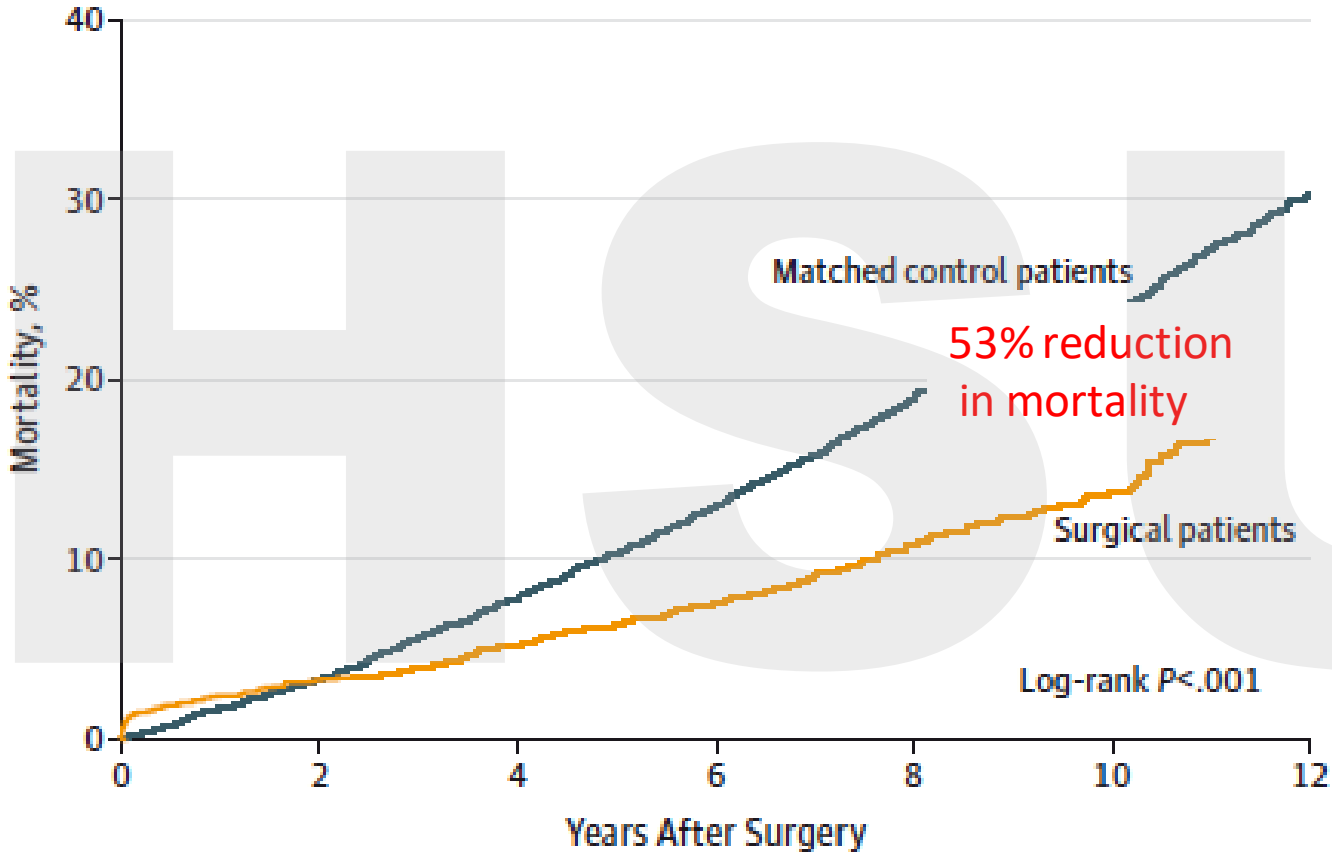


Hazards Ratios for Death: Surgery (n=7000) vs. Control Group (n=7000)

Adams, et al. N Engl J Med. 2007 357(8):753-61, 2007.



Association Between Bariatric Surgery and Long-term Survival: VA Study

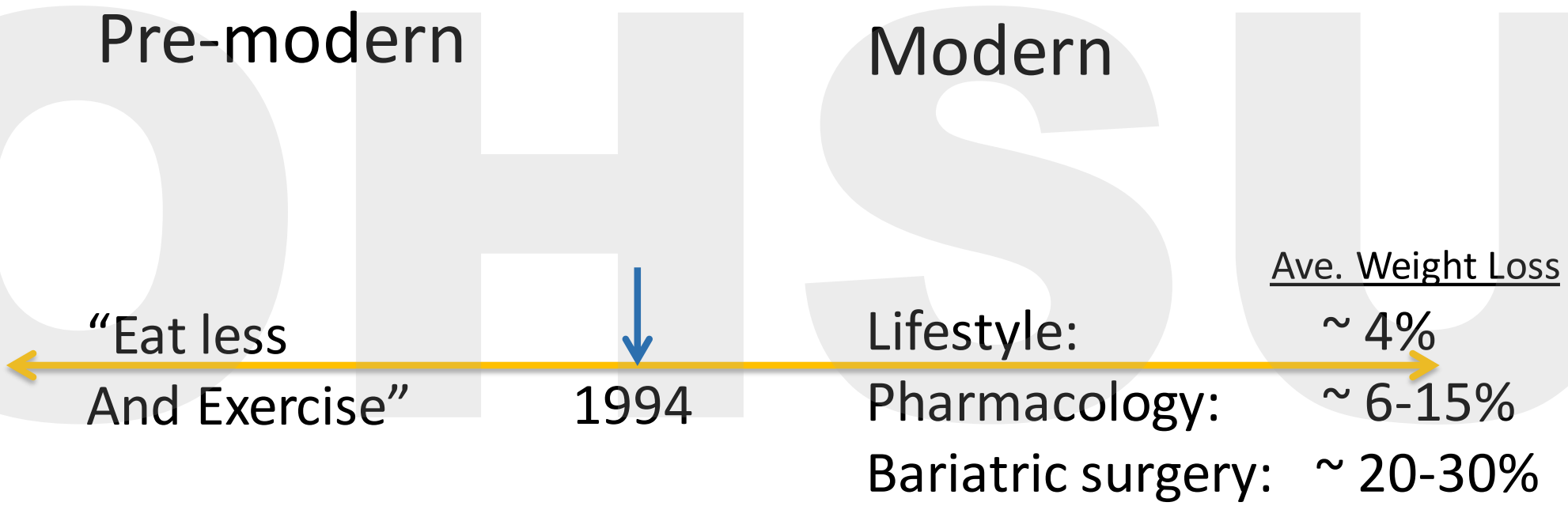


No. at risk							
Matched control patients	7462	7114	5306	3878	2641	1407	472
Surgical patients	2500	2416	1868	1412	1004	552	185

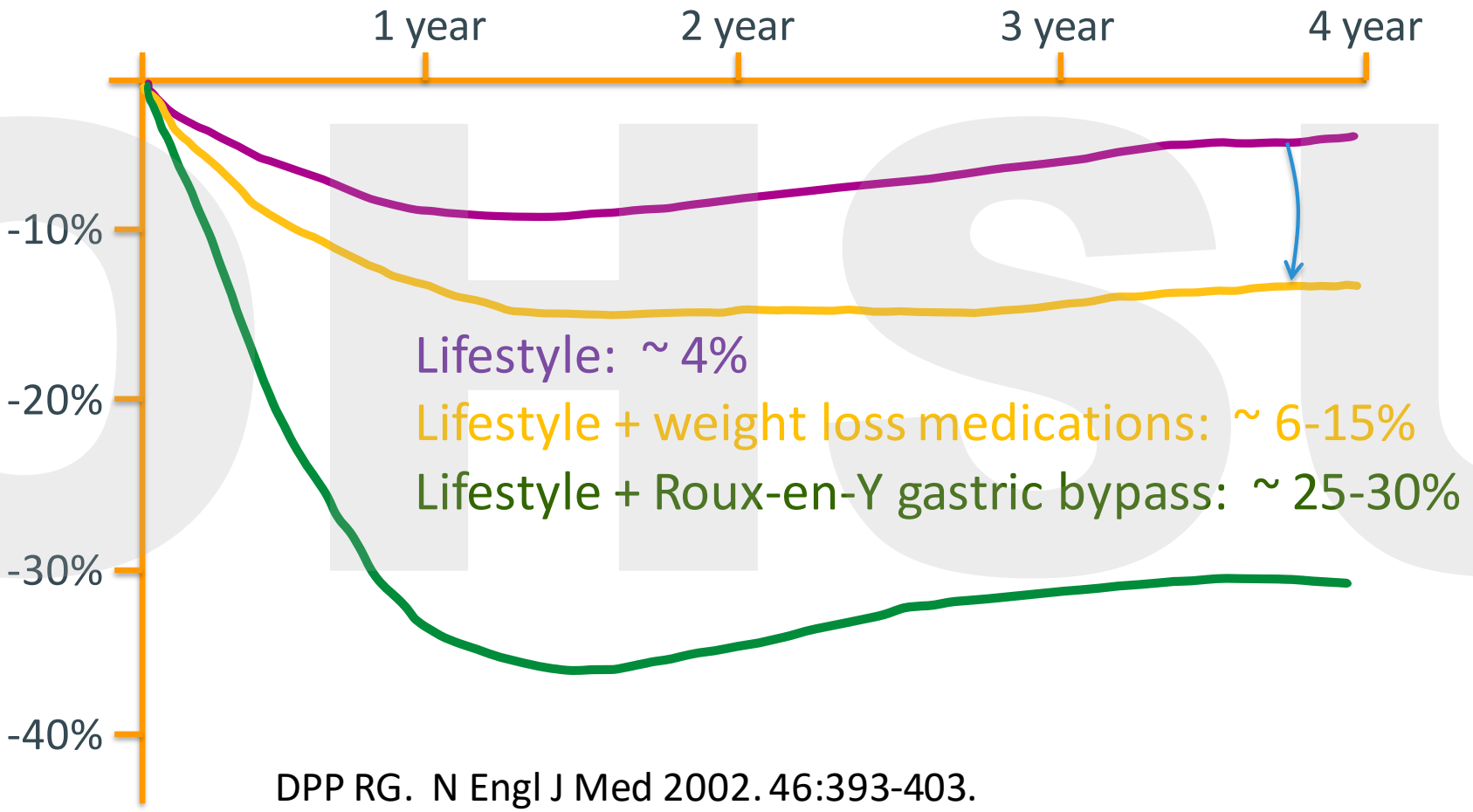
Arterburn D et al., **JAMA** January 6, 2015

OHSU

Obesity (as a disease) Management: Timeline



Weight Loss Averages by Approach



DPP RG. N Engl J Med 2002. 46:393-403.
LOOK AHEAD. N Engl J Med 2013. 369:145-54.
Wilding JPH, et al. N Engl J Med 2021; 384:989-1002.
LABS Study. JAMA Surg. 2018 May 1;153(5):427-434.

OHSU

Pharmacological Weight Management

SPECIAL FEATURE

Clinical Practice Guideline

Pharmacological Management of Obesity: An Endocrine Society Clinical Practice Guideline

Caroline M. Apovian, Louis J. Aronne, Daniel H. Bessesen, Marie E. McDonnell, M. Hassan Murad, Uberto Pagotto, Donna H. Ryan, and Christopher D. Still

(*J Clin Endocrinol Metab* 100: 342–362, 2015)

Welcome to Endotext

The best Clinical Endocrinology source in the world, and FREE.

HOME / SECTIONS | CLINICAL GUIDELINES | ASK AN EXPERT | EDITORIAL TEAM | COUNTRY ASSOCIATES | ABOUT

Endocrine Emergencies
Editor: Leslie J De Groot

Pituitary Disease and Neuroendocrinology
Editor: Ashley Grossman, MD and Marta Korbonits, MD

Diabetes Mellitus and Carbohydrate Metabolism---DiabetesManager
Editor: Kathleen Dungan, MD, MPH

Endocrinology of Male Reproduction
Editor: Robert McLachlan

Diagnosis and Treatment of Diseases of Lipid and Lipoprotein Metabolism in Adults and Children
Editor: Kenneth Feingold, MD and Don P Wilson, MD

Endocrinology of Female Reproduction
Editor: Robert Rebar

Thyroid Disease-www.thyroidmanager.org
Editor: Leslie J De Groot

Adrenal Disease and Function
Editor: George Chrousos

Diseases of Bone and Mineral Metabolism
Editor: Frederick Singer

Diffuse Hormonal Systems and Endocrine Tumor Syndromes
Editor: Aaron Vinik

Pediatric Endocrinology
Editor: Maria New

Obesity
Editor: Jonathan Purnell, MD, and Leigh Perreault, MD

Endocrine Disease and Pregnancy
Editor: Bruce R Carr

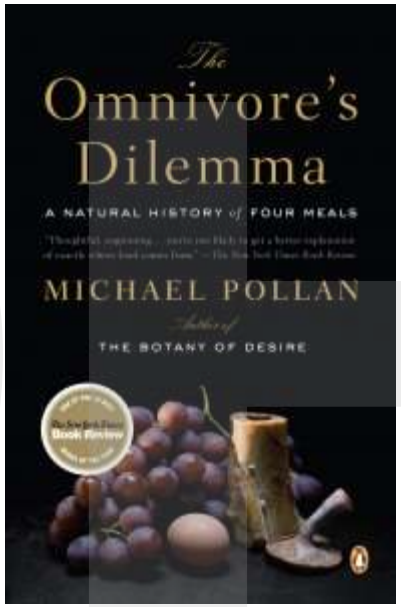
Endocrine Testing Protocols
Editor: Christian Koch

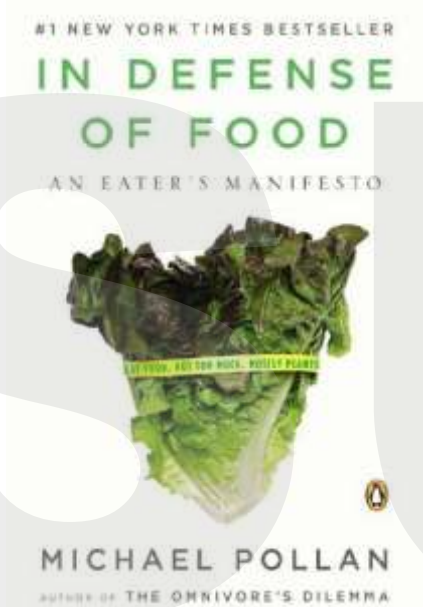
Endocrinology of Aging
Editor: Jerome M Hershman and John E. Morley, MB, BCh

Through 12/31/2017 FREE CONTINUING MEDICAL EDUCATION credits available on ENDOTEXT.ORG (All modules also offer equivalent credit for the ABIM MOC program.) Click here

OHSU

Thank You





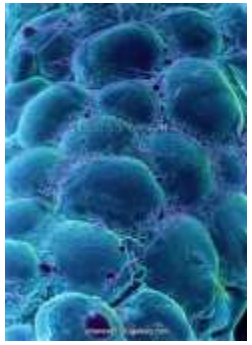
Eat food. Not too much. Mostly plants.

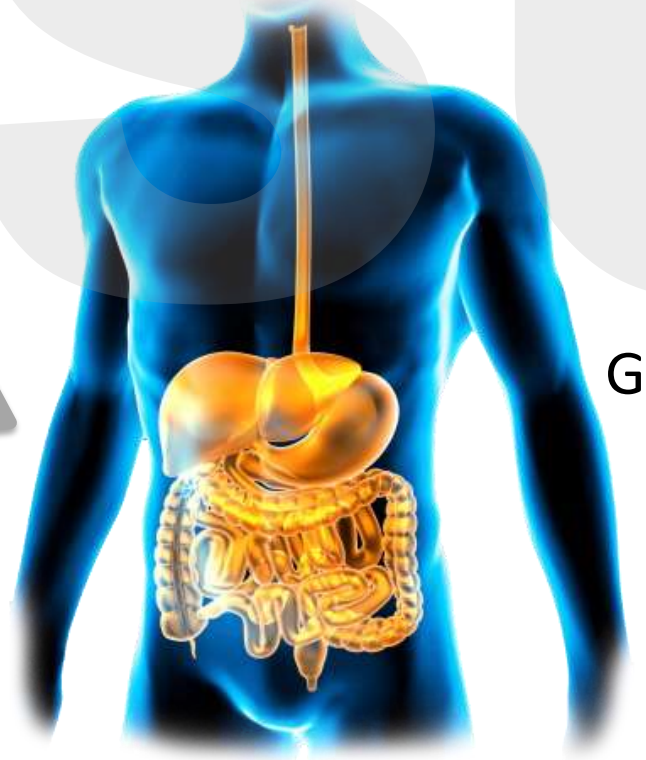
OHSU

Weight Is Regulated Through the Interaction of Three Major Organ Systems

Brain:
Hypothalamus
and Brainstem

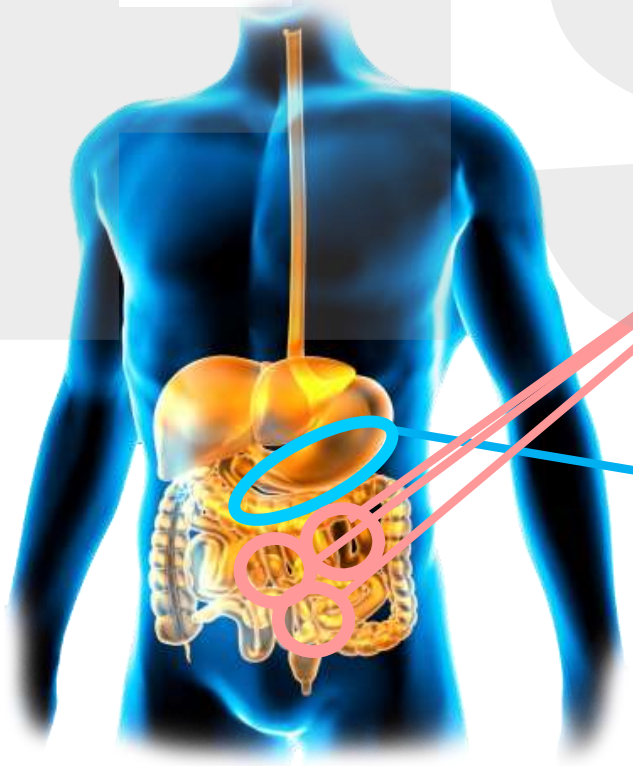
Adipose Tissue Stores





Gastrointestinal (GI)
System

Nutrient Absorption Triggers Secretion of Gut Hormones: "Sensing Food" and Conveying Biologic Appetite Signals to CNS



↑ CCK
↑ Insulin
↑ Amylin
↑ PYY
↑ GLP-1

→ ↑ satiety

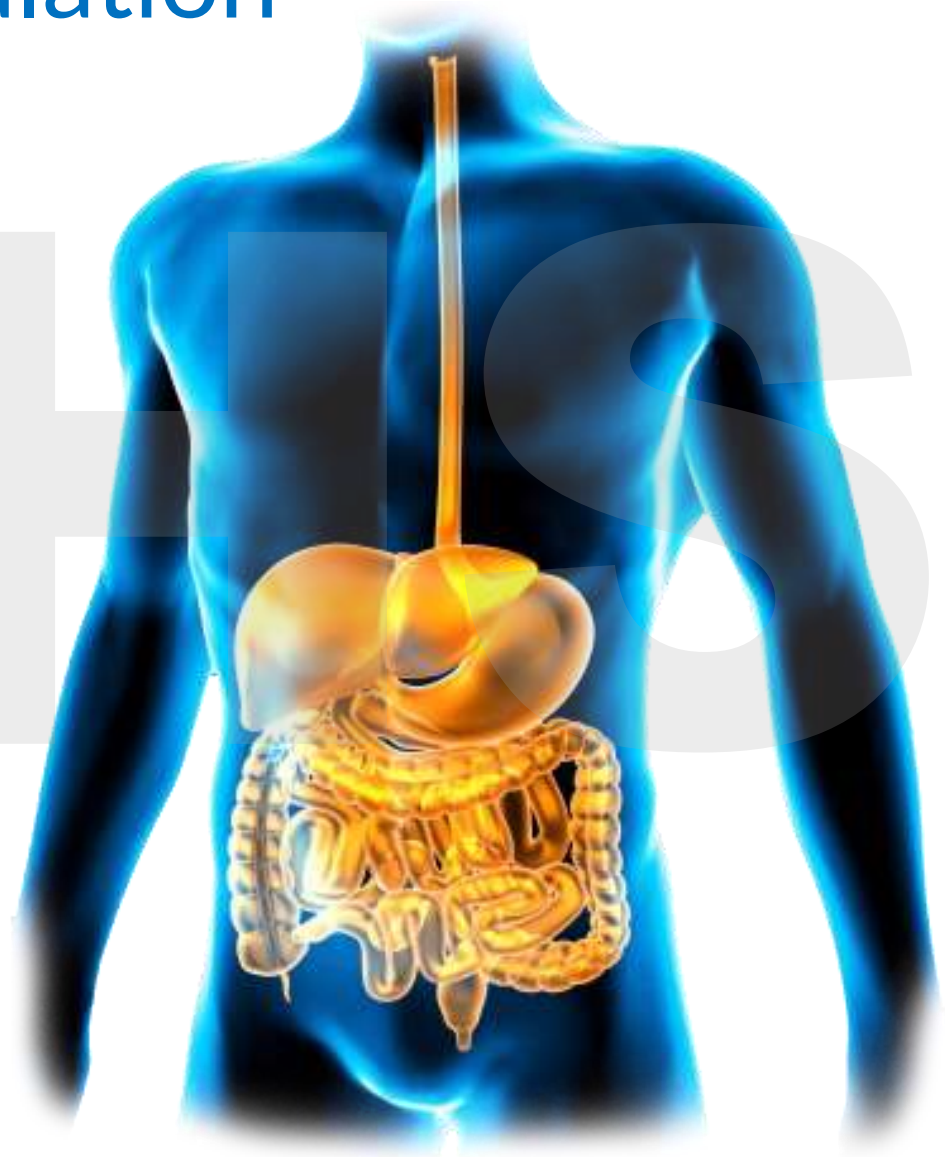
↓ Ghrelin → ↓ hunger

Signals from the GI tract have a key role in body weight regulation

Duodenum
- CCK
- GIP
- Ghrelin

Jejunum
- GIP
- GLP-1
- ApoA-IV
- Guanylin
- Uroguanylin

Ileum
- GLP-1
- ApoA-IV
- Guanylin
- Uroguanylin
- PPY
- Oxyntomodulin
- Neurotensin

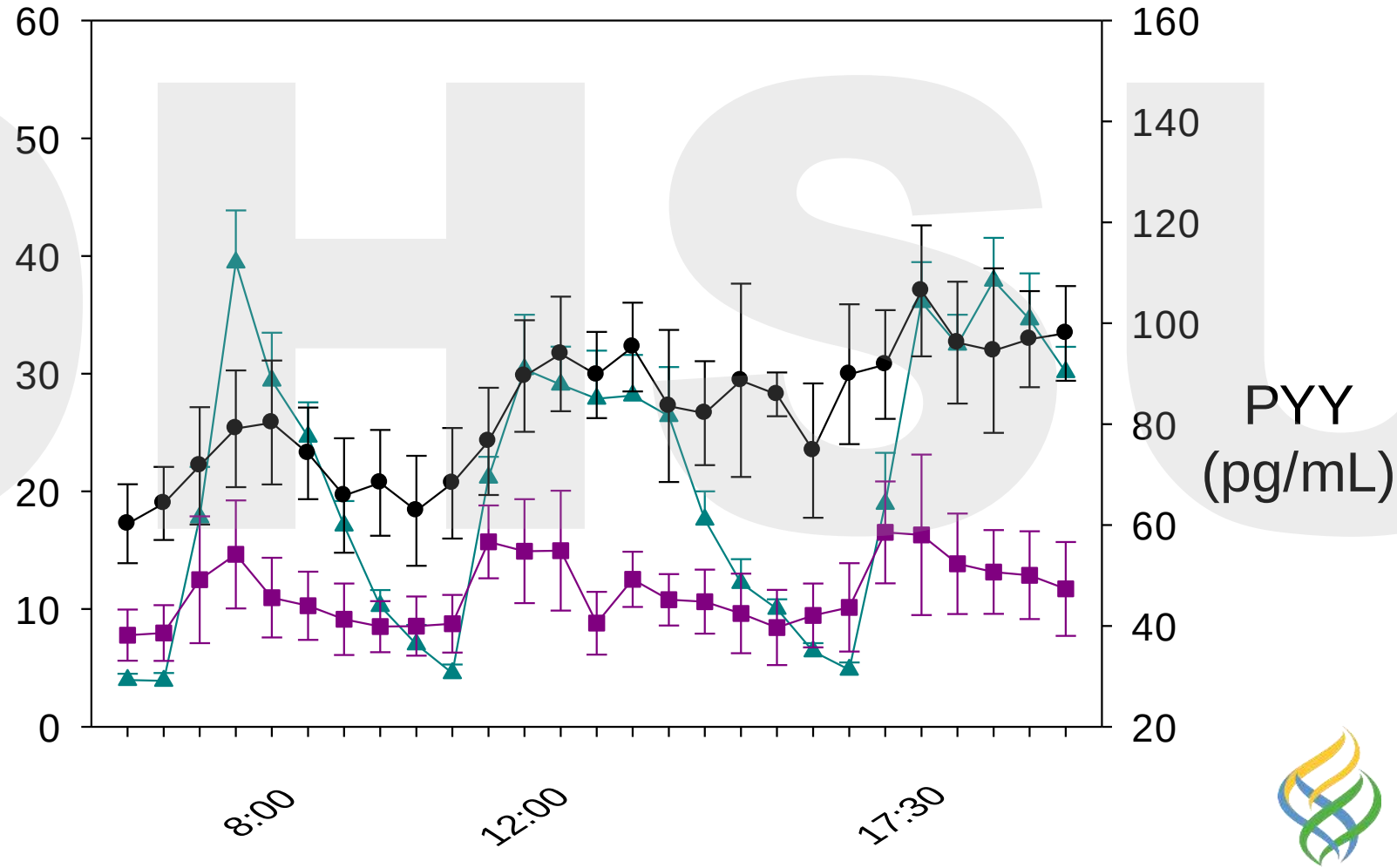


Stomach
- Ghrelin
- Nesfatin-1
- Leptin

Lipid derived molecules
- Endocanabanoid agonists
- Anorexic lipid OEA

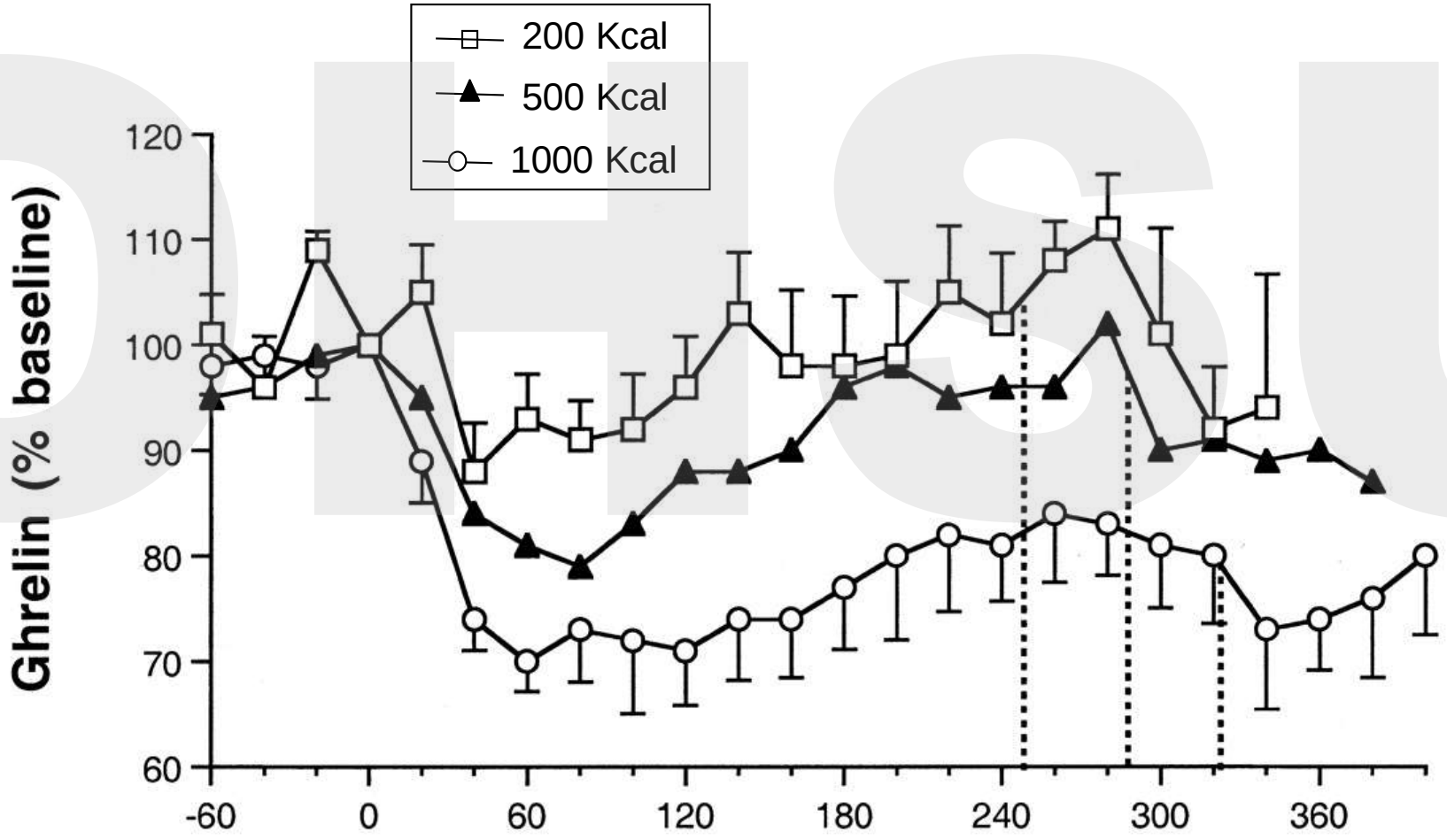
Colon
- GLP-1
- GLP-2
- PPY
- Oxyntomodulin

Meal-related Satiety Gut Hormone Appearance: "Sensing Food Availability"

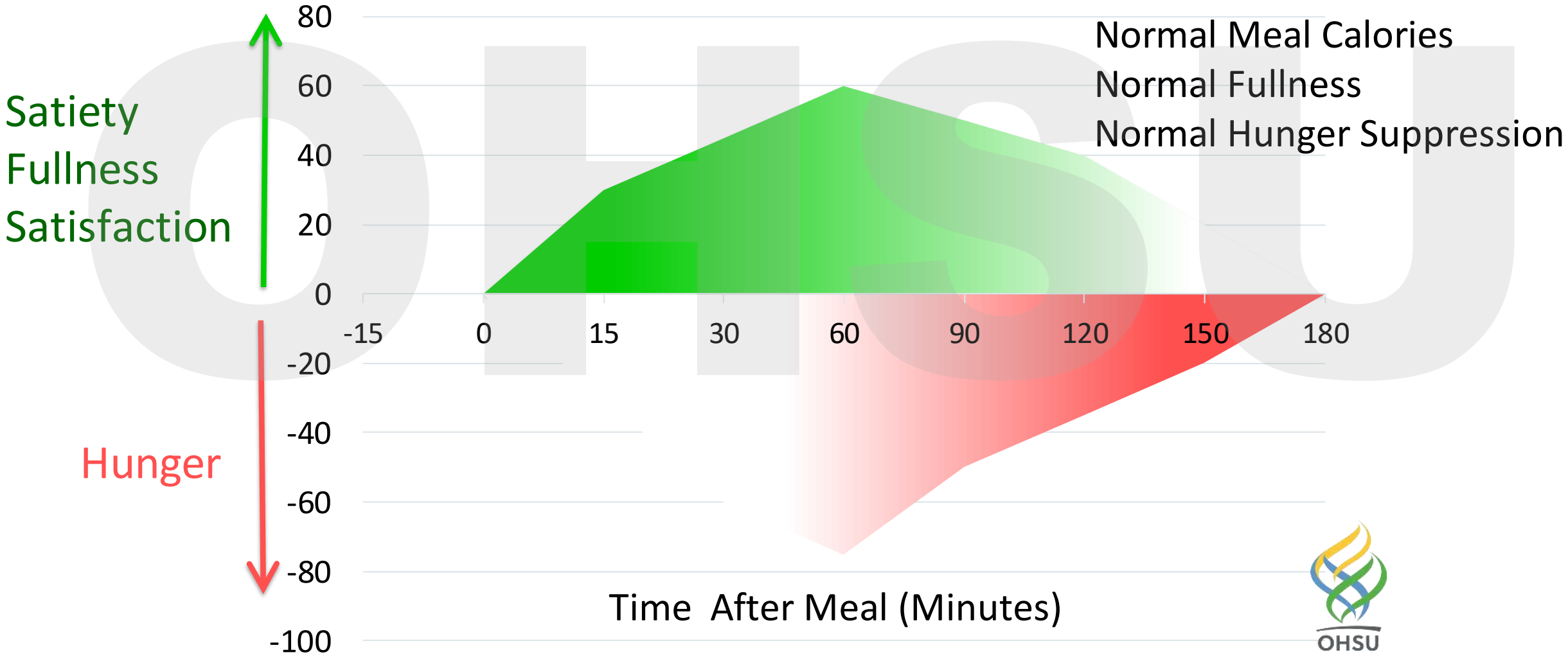


Meal-related Gut Hormone Appearance: Level of Suppression (Stimulation) Determined by Total Calories

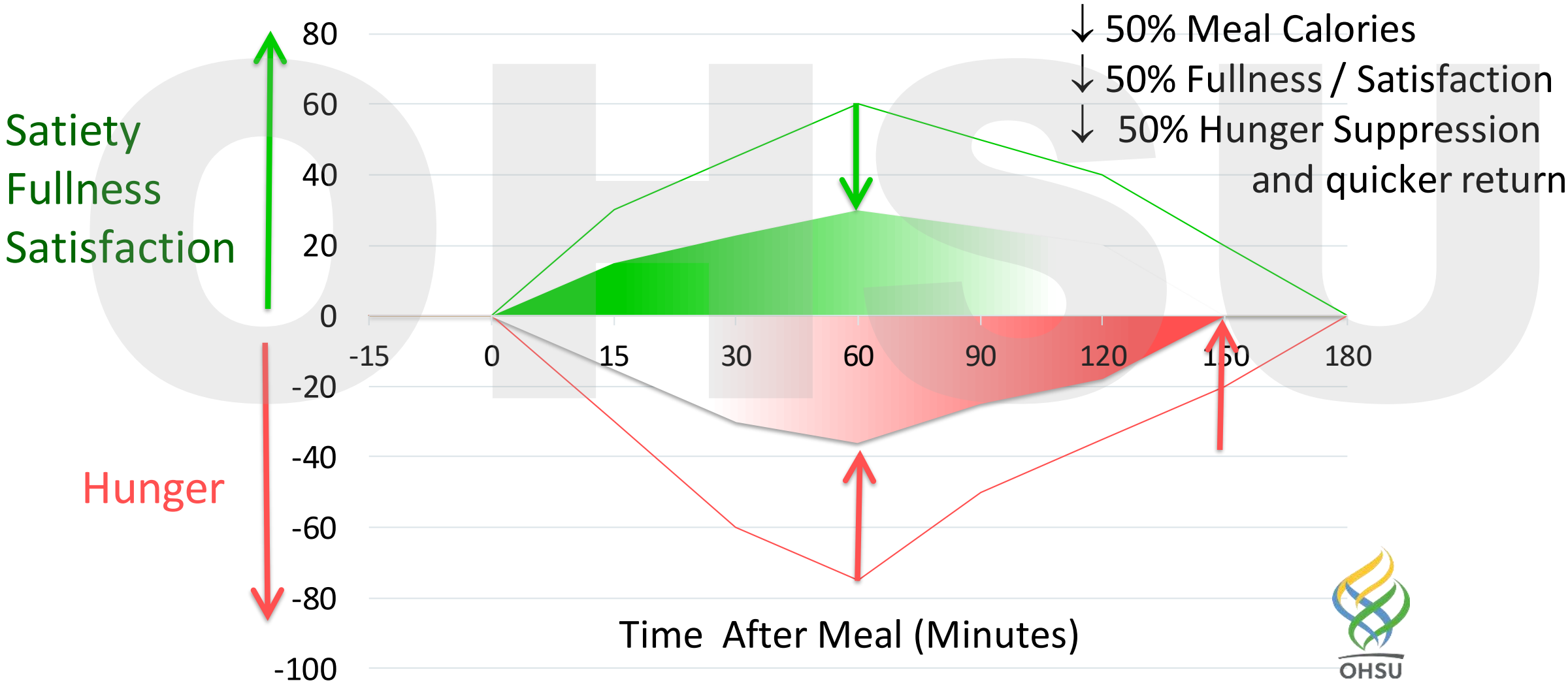
Callahan, et al. JCEM. 89:1319-24, 2004.



Meal-related Satiety Gut Hormone Appearance: Sensing Food Availability and Calories Consumed



Meal-related Satiety Gut Hormone Appearance: Sensing Food Availability and Calories Consumed

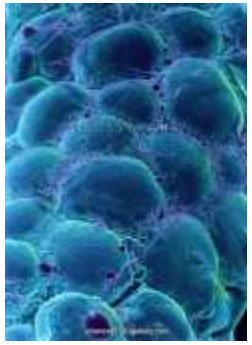


OHSU

CNS Body Weight Regulation Center Receives Adiposity Signal from Fat Depots

Leptin

Adipose Tissue Stores



CNS Integrates Adiposity and Meal-related Signals to Maintain Body Weight Set Point (Range)

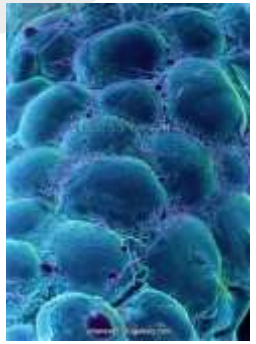
"Are you weighing what I think you should?"

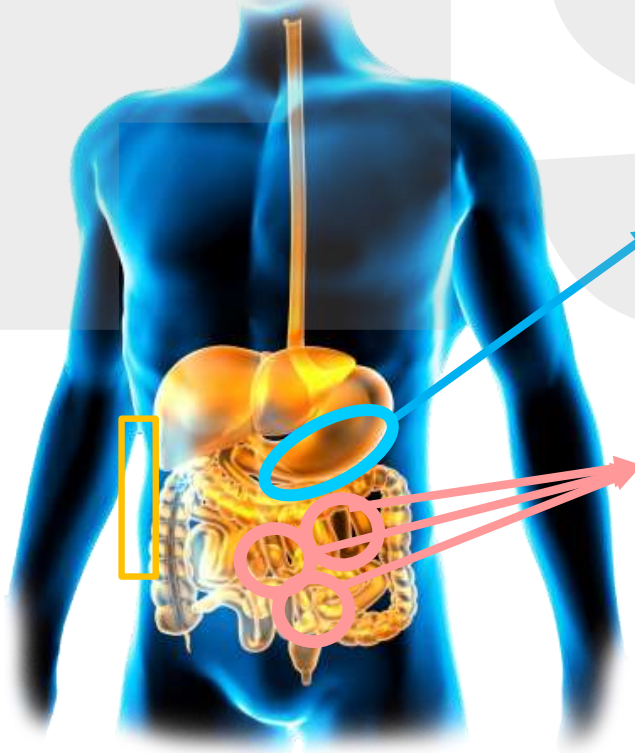
+ 5 lbs.

- 5 lbs.

"Are you eating enough (or too much) to maintain that weight?"

Leptin





Ghrelin
CCK
Insulin
Amylin
PYY
GLP-1
..others

OHSU