Carbohydrate-Insulin Model

A physiological perspective on the obesity pandemic

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On Sabbatical: Novo Nordisk Foundation and University of Copenhagen

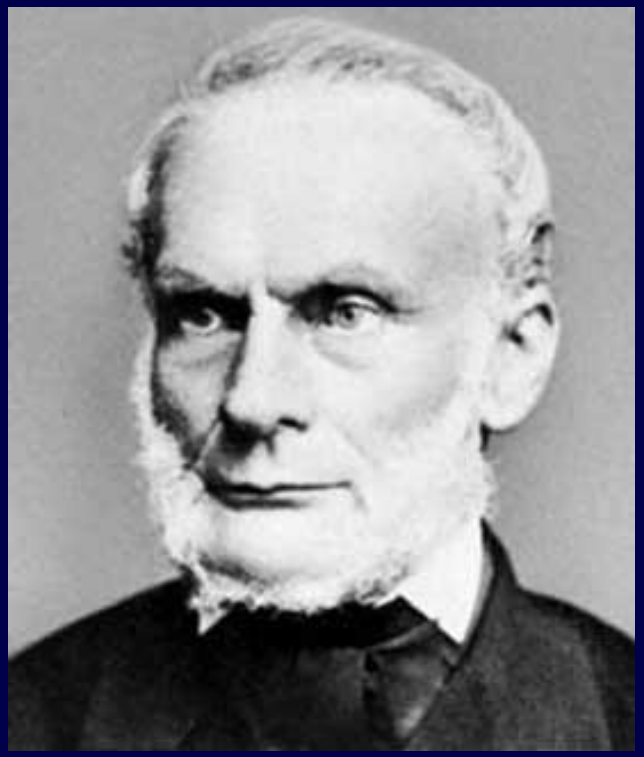
Disclosures:

Grants from the NIH and philanthropic organizations for studies of carbohydrate-modified diets (no food industry affiliation)

Royalties for books that recommend a carbohydrate-modified diet.

First Law of Thermodynamics

Energy can neither be created nor destroyed



Rudolf Clausius, German Physicist,1822-1888

Applied to body weight:

Calorie intake - Calorie expenditure

= Calories stored (body fat)

Thermodynamics and Obesity

Physics invoked to explain pathophysiology

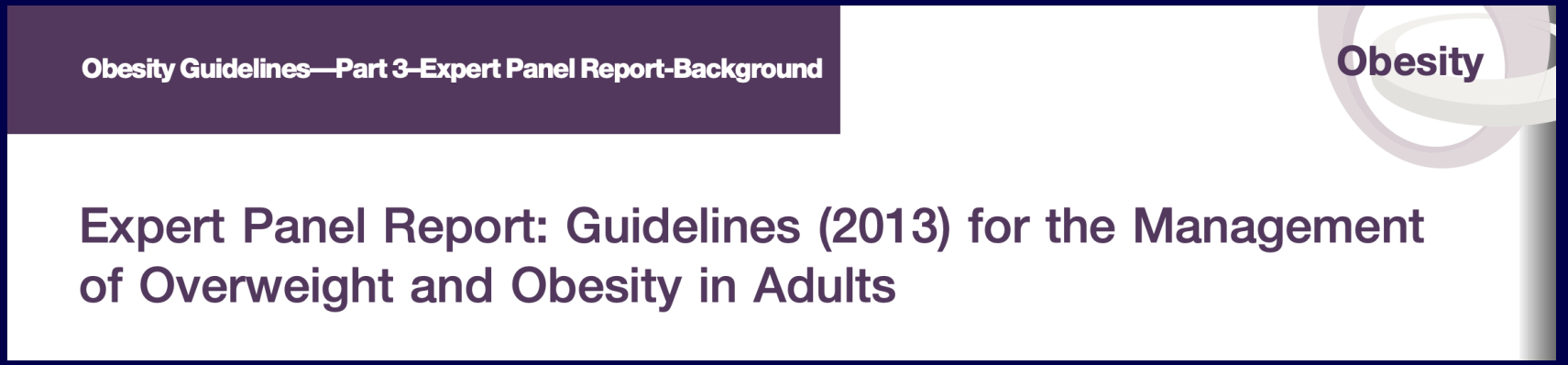
Obesity Pathogenesis:
An Endocrine Society Scientific Statement

"Obesity pathogenesis involves … sustained positive energy balance (energy intake > energy expenditure)"

Endocr Rev 2017;38(4):267–96

Thermodynamics and Obesity

Physics invoked to explain pathophysiology



"To achieve weight loss, an energy deficit is required"
[High evidence strength]

ACC/AHA. Obesity. 2014;22 Suppl 2:S41-410

Energy Balance and Pathogenesis

Tautology?

Positive calorie balance = Increased energy storage (body fat)

Energy Balance and Pathogenesis

Tautology?

Positive calorie balance	=	Increased energy storage (body fat)
Positive heat balance	=	Increased body temperature (fever)

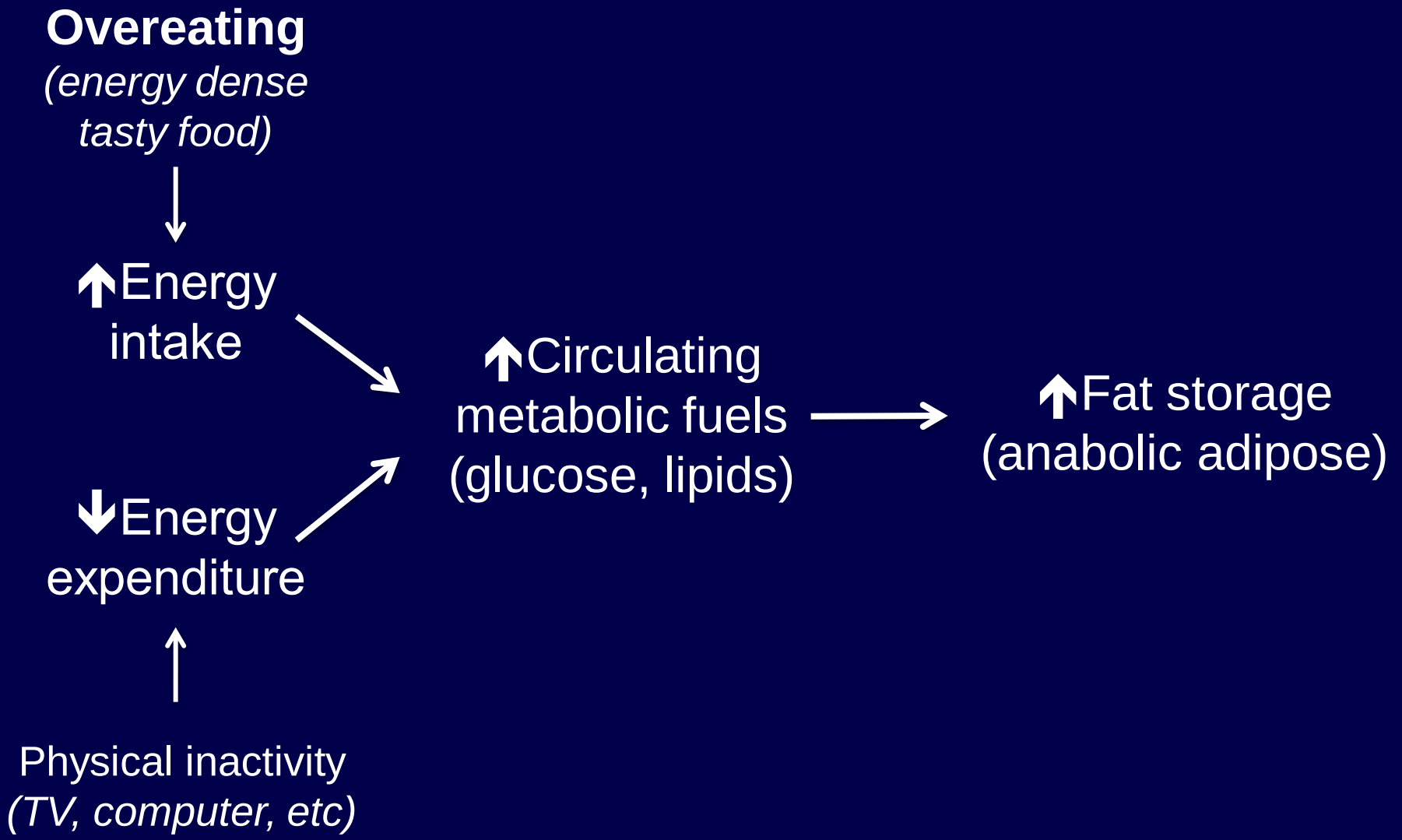
Energy Balance and Pathogenesis

Cause versus effect

Positive calorie balance ⇄ Increased energy storage (body fat)

Conventional View: Energy Balance Model

Obesity, a failure to control energy balance



Energy Balance Model

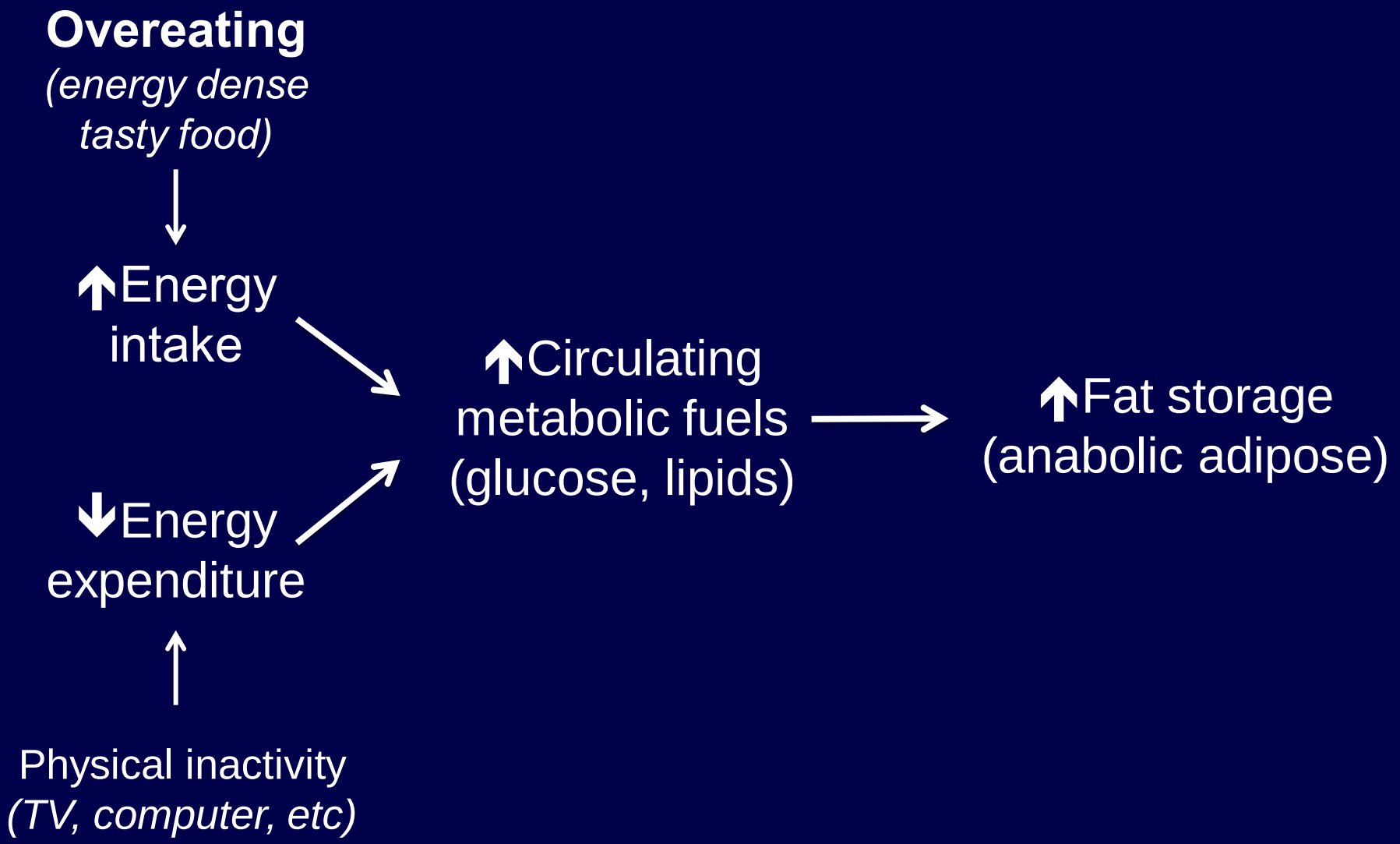
Central precept: All calories are alike to the body

Schwartz et al. Endocr Rev 2017, 38:267–96 (Endoc Society)

"The impact of diet on obesity risk is explained largely by its effect on calorie intake, rather than by changes of either energy expenditure or the internal metabolic environment. Stated differently, 'a calorie is a calorie.' "

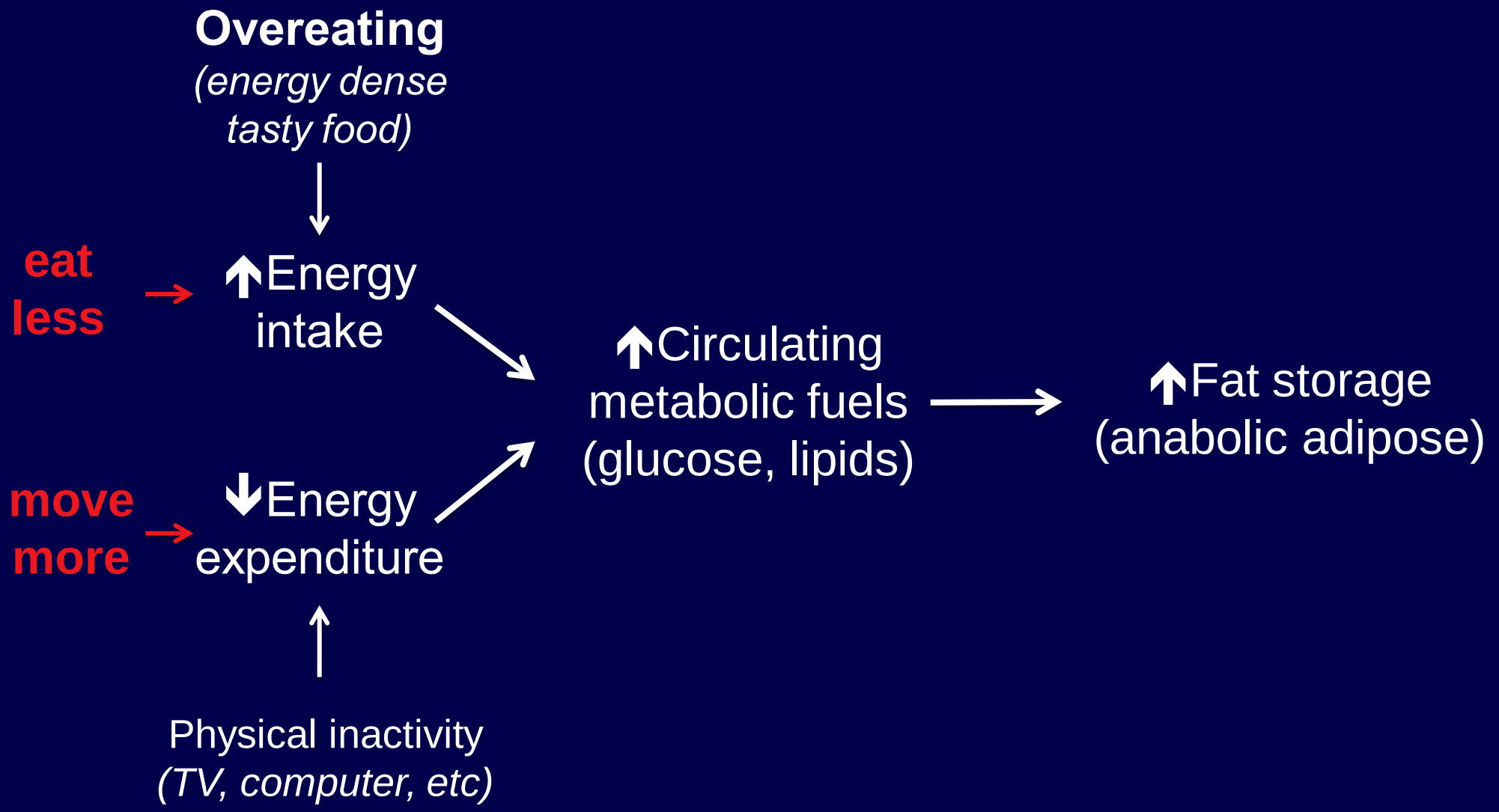
Energy Balance Model

Obesity, a failure to control energy balance



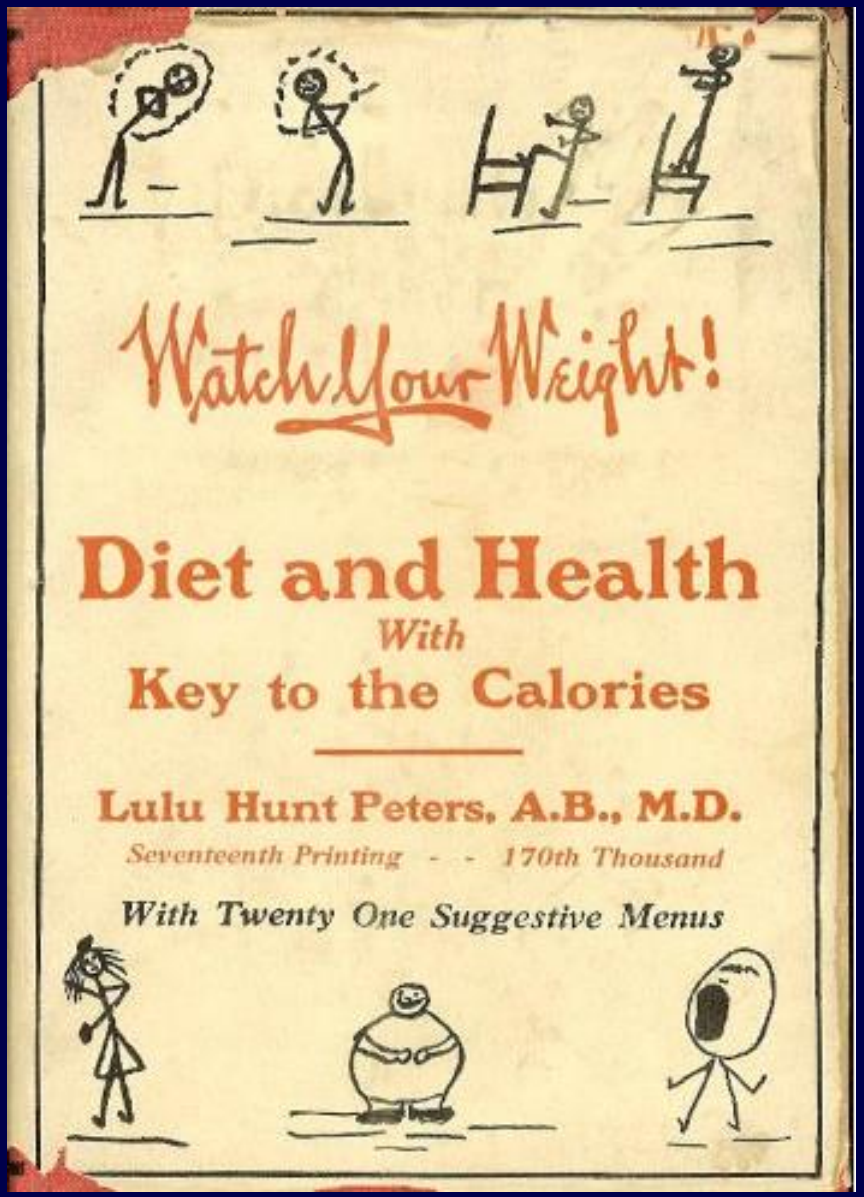
Energy Balance Model

Obesity, a failure to control energy balance



Energy Balance Model, Early 1900s

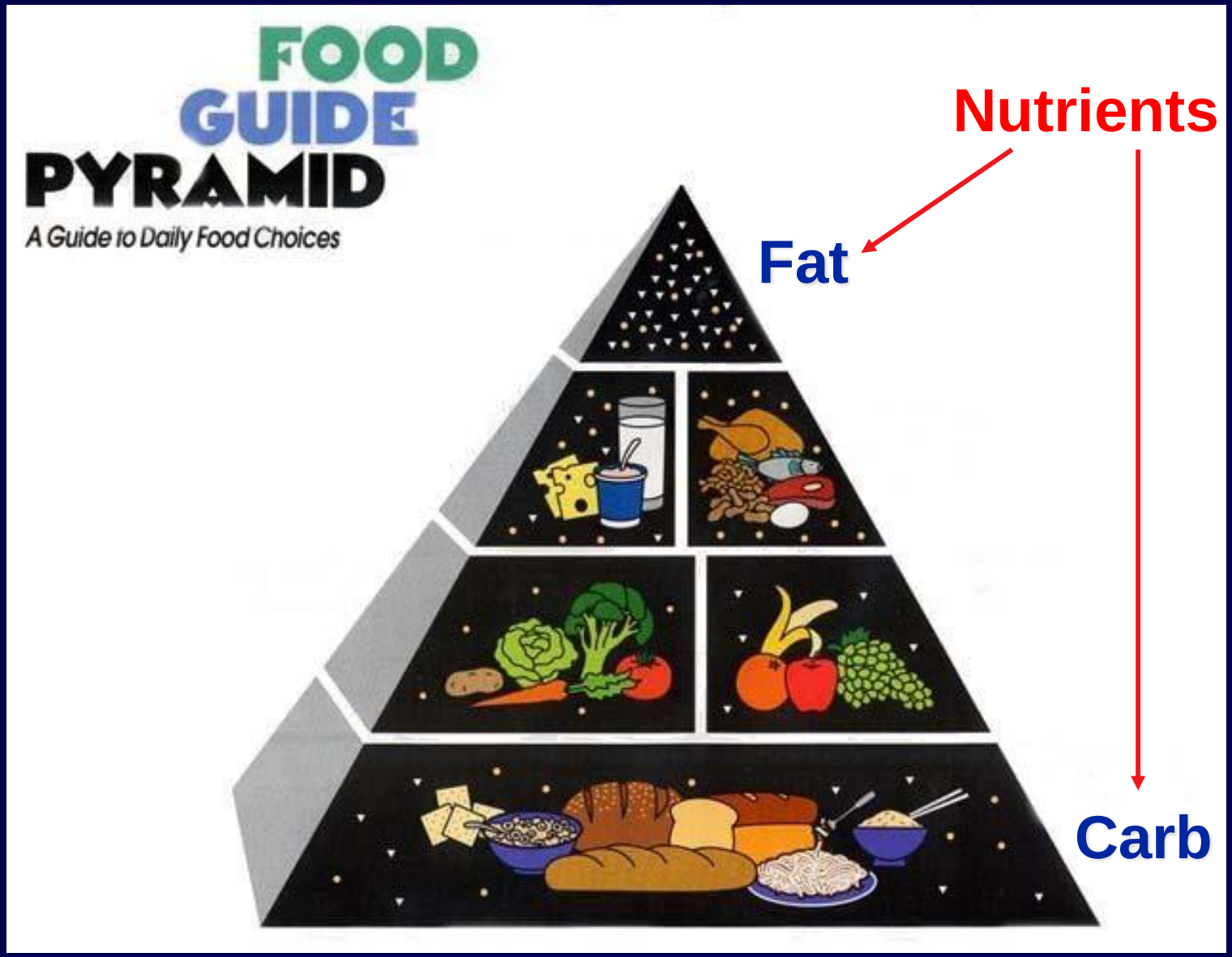
Calorie counting



Published 1918

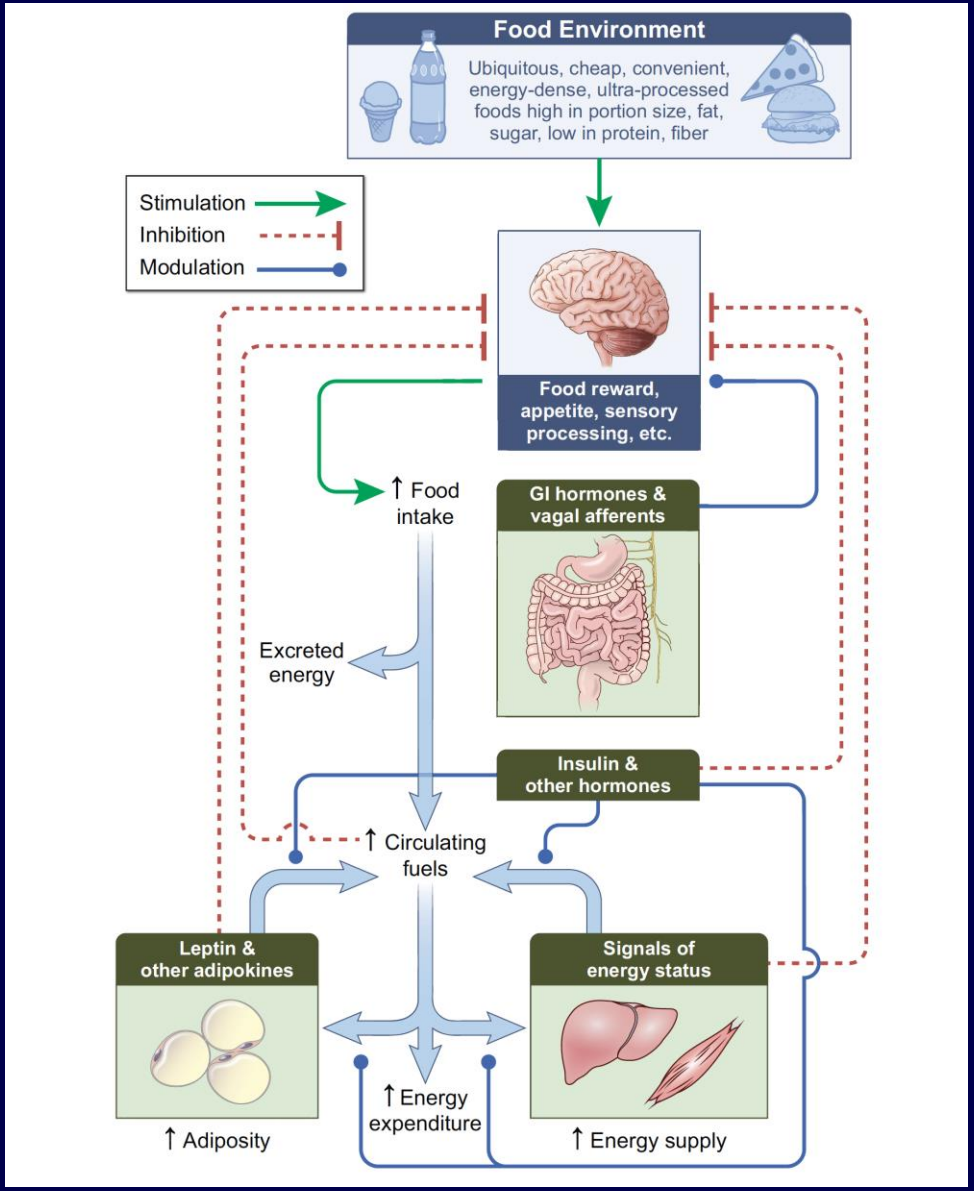
Energy Balance Model, Late 1900s

The low-fat diet



Energy Balance Model, 2000s

A focus on modern processed foods



- "Ubiquitous, cheap, convenient, energy dense, ultra-processed foods high in portion size, fat, sugar, low in protein, fiber"
- Acting through "food reward, appetite, sensory processing"
- Below conscious level

Hall et al. AJCN 2022,115:1243-1254

Four EBM Anomalies

EBM Anomaly #1

Persistent failure to control the epidemic

Inexorable increase in obesity rates, despite long-term public health campaign based on energy balance

EBM Anomaly #2

Rising BMI among genetically stable populations

Unsolved puzzle:

- Body weight is defended by metabolic mechanisms
  - 1960s – average man weighed 165 lb
  - 2020s – average man weighs 195 lb

Why has defended body weight – the observed "Set Point" – increased so rapidly among genetically stable populations?

Leibel. NEJM 1995;332:621-8

EBM Anomaly #3

Difficulty compensating for small effects driving weight gain

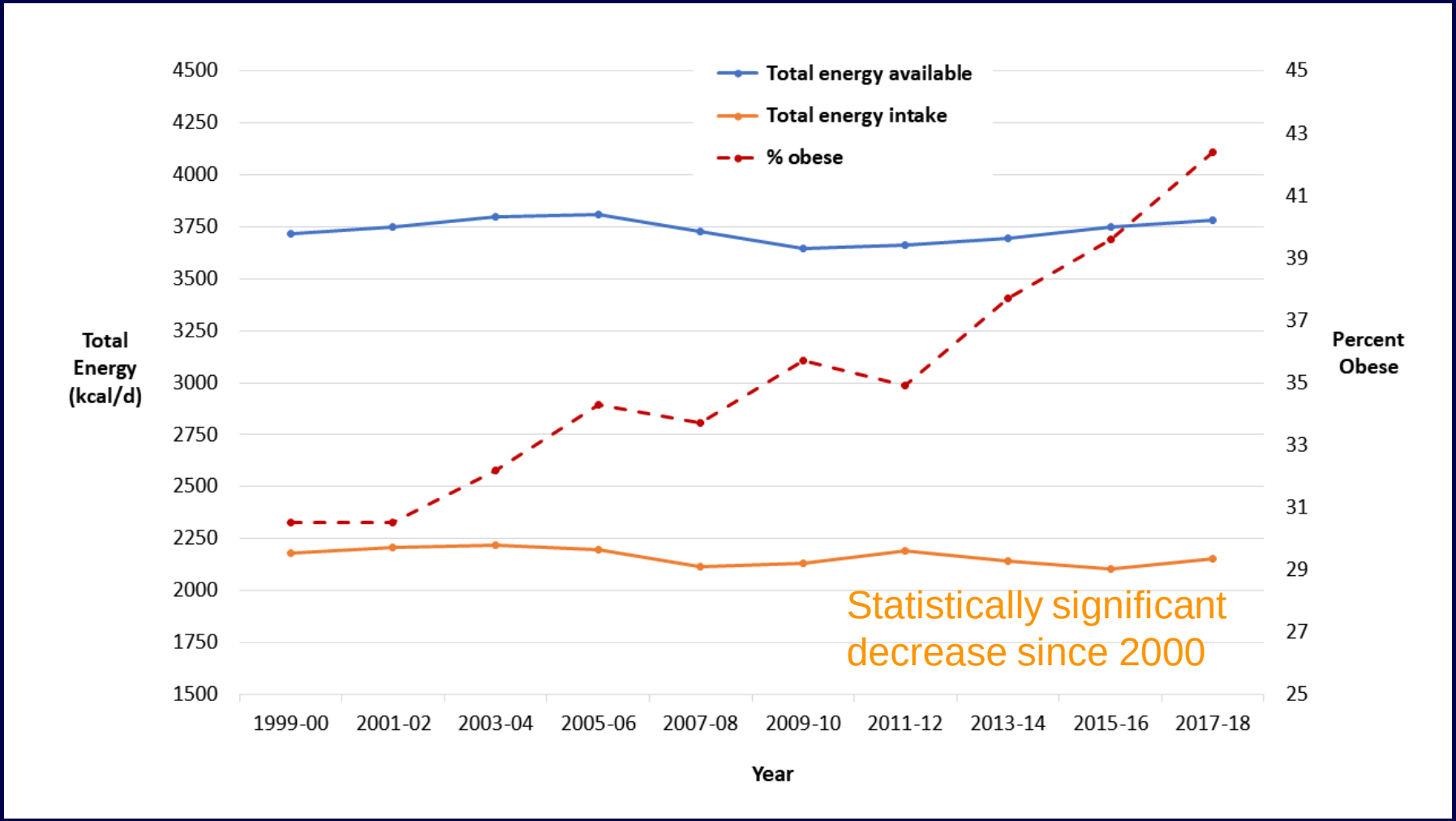
- Obesity typically develops slowly, about 1 g excess body fat/d
  - ~ 10 kcal/d (< 1 teaspoon sugar)
- Increase in average energy intake since 1970:
  - ~ 200 kcal/d (12 oz grape juice)

Why is it so difficult to compensate for these small daily effects?

Ford, Deitz. AJCN 2013;97:848-53
Mozaffarian. AJCN 2022 Apr 23:nqac075

EBM Anomaly #4

Secular trends challenge primary role of "overeating"



Mozaffarian. AJCN 2022 Apr 23:nqac075

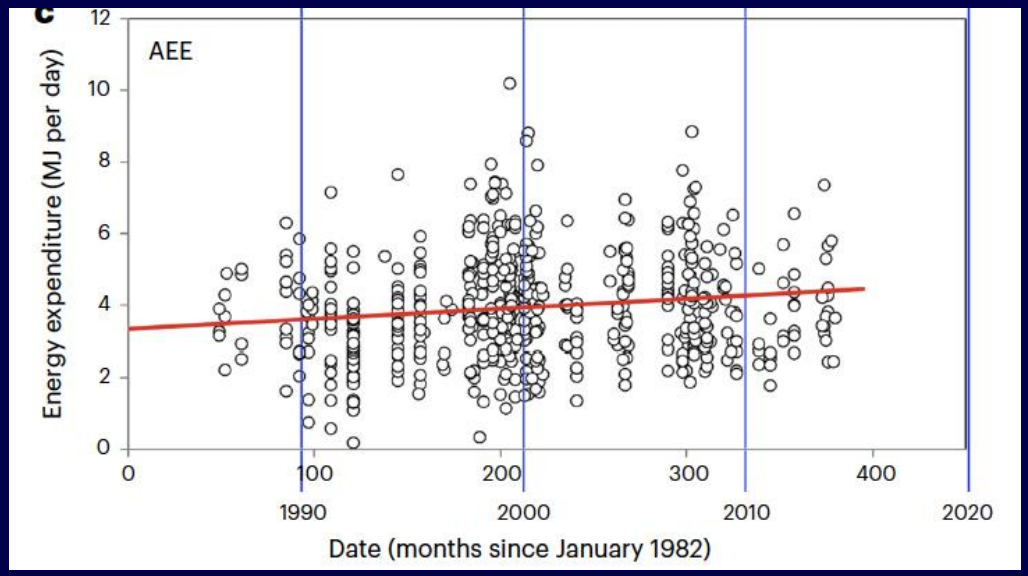
EBM Anomaly #4

Secular trends challenge primary role of "overeating"

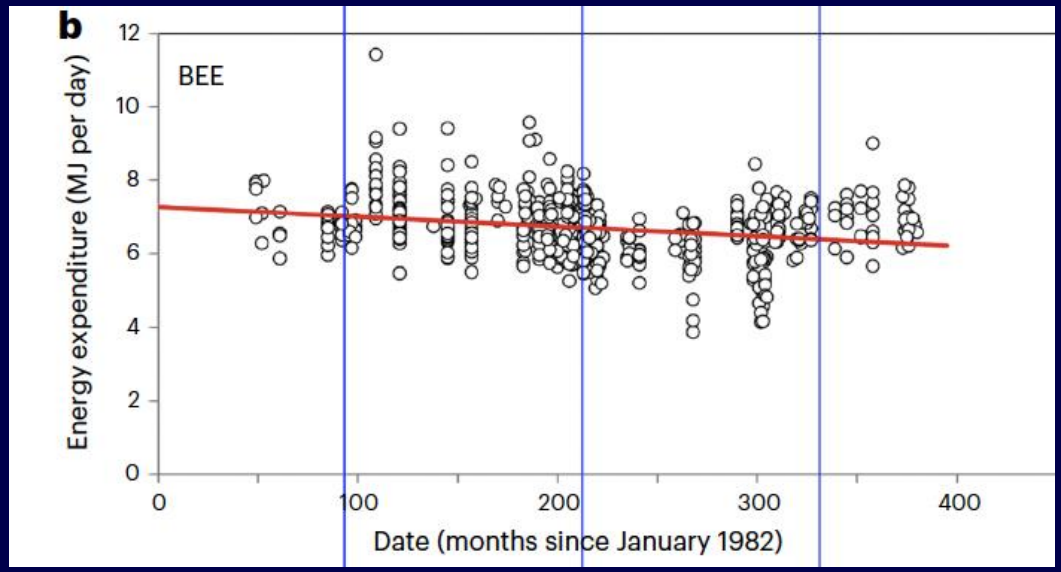
nature metabolism

Letter https://doi.org/10.1038/s42255-023-00782-2

Total daily energy expenditure has declined over the past three decades due to declining basal expenditure, not reduced activity expenditure



Activity Energy Expenditure (men)

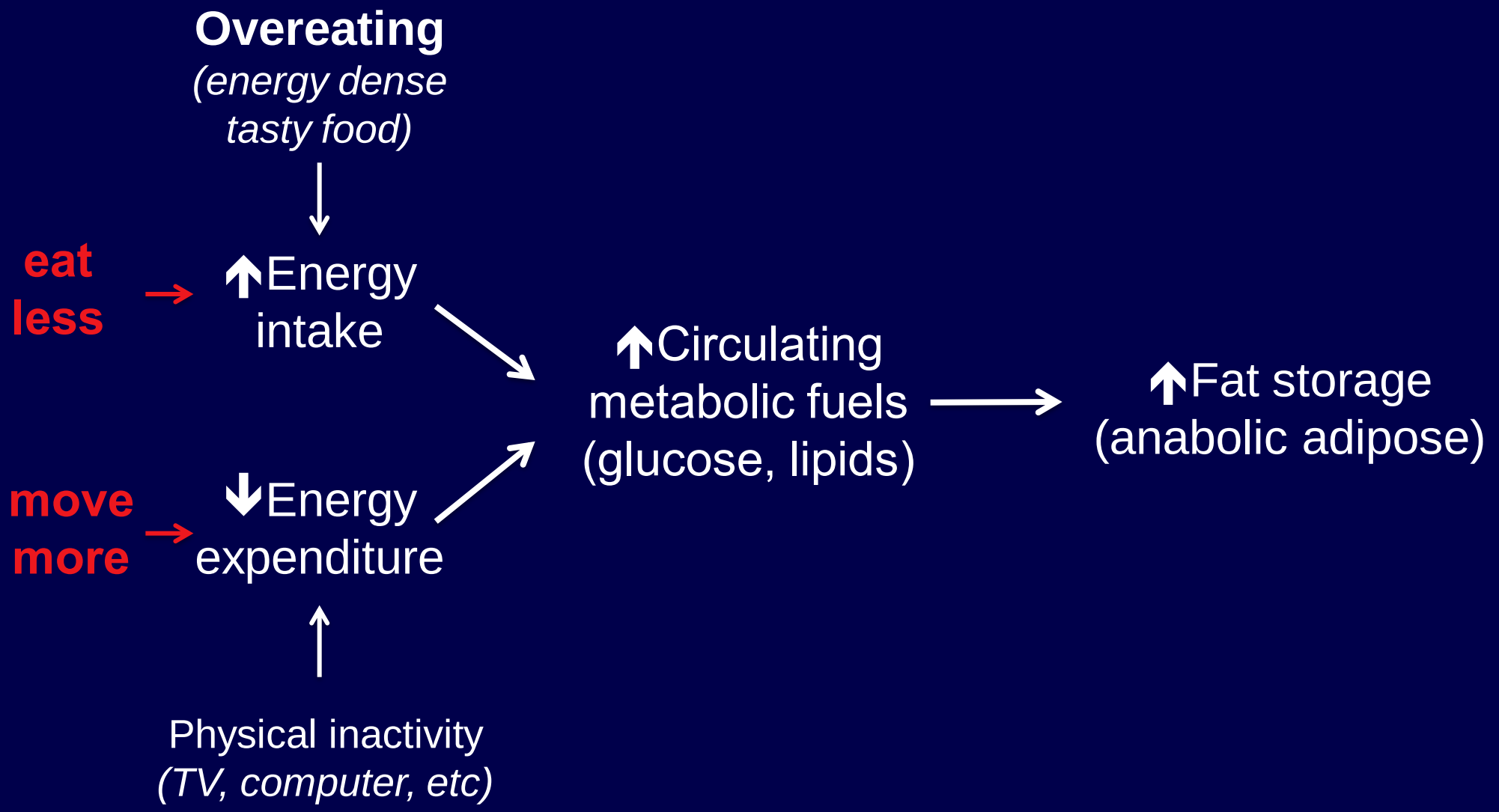


Basal Energy Expenditure (men)

Speakman. Nat Metab 2023, 579–588

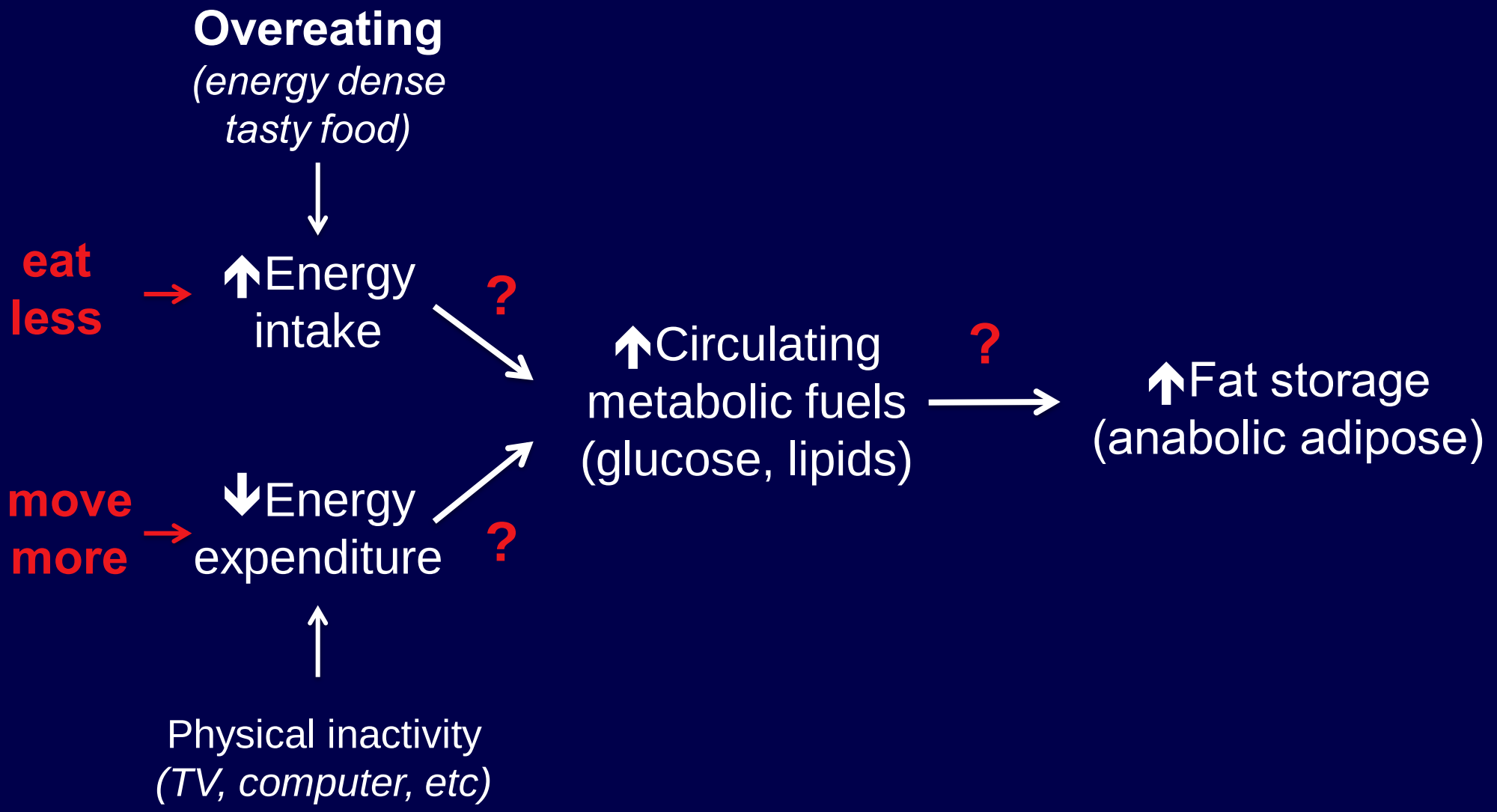
Energy Balance Model

Obesity, a failure to control energy balance



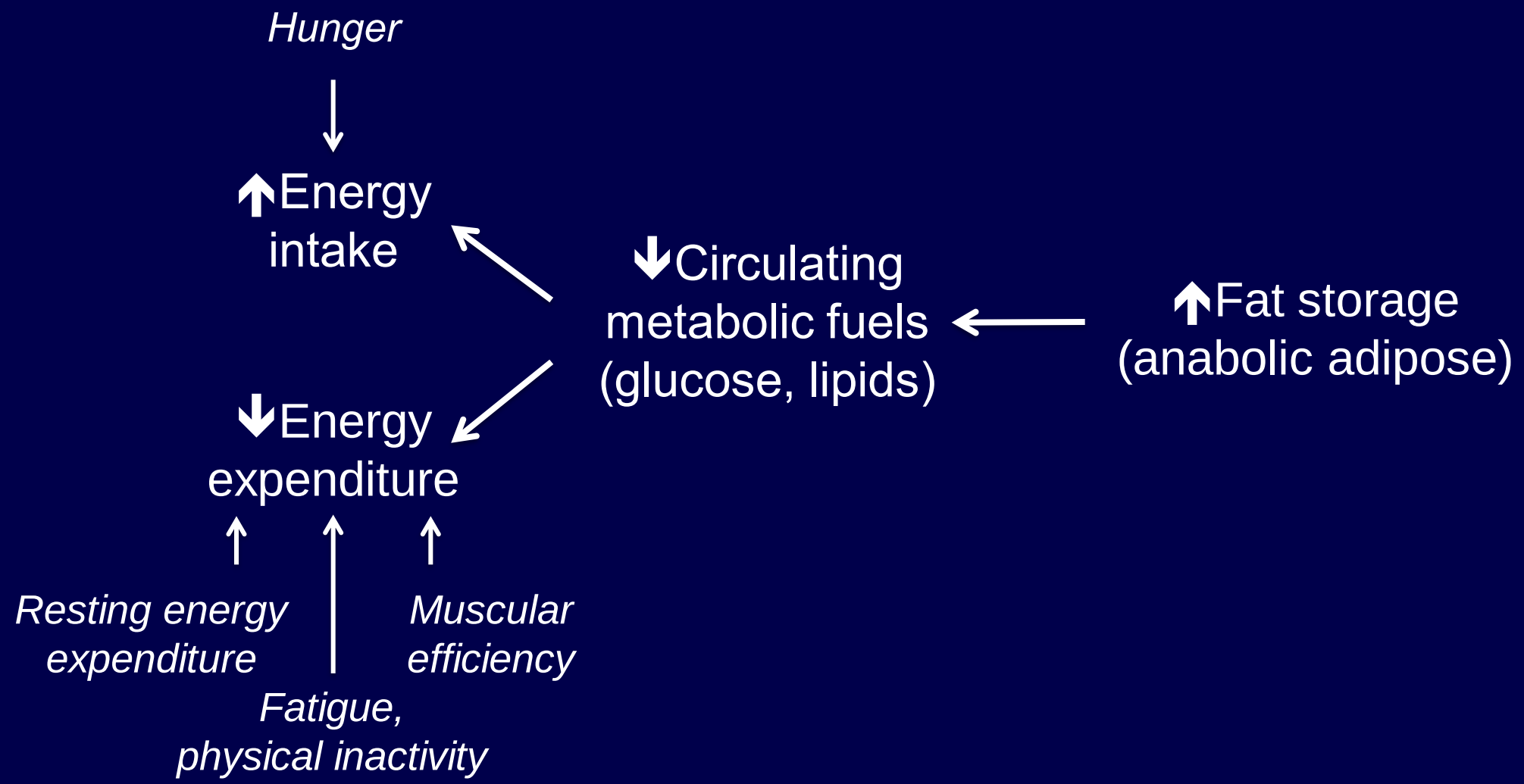
Energy Balance Model

Obesity, a failure to control energy balance



Carbohydrate-Insulin Model

A metabolic disorder of fat storage



Carbohydrate-Insulin Model

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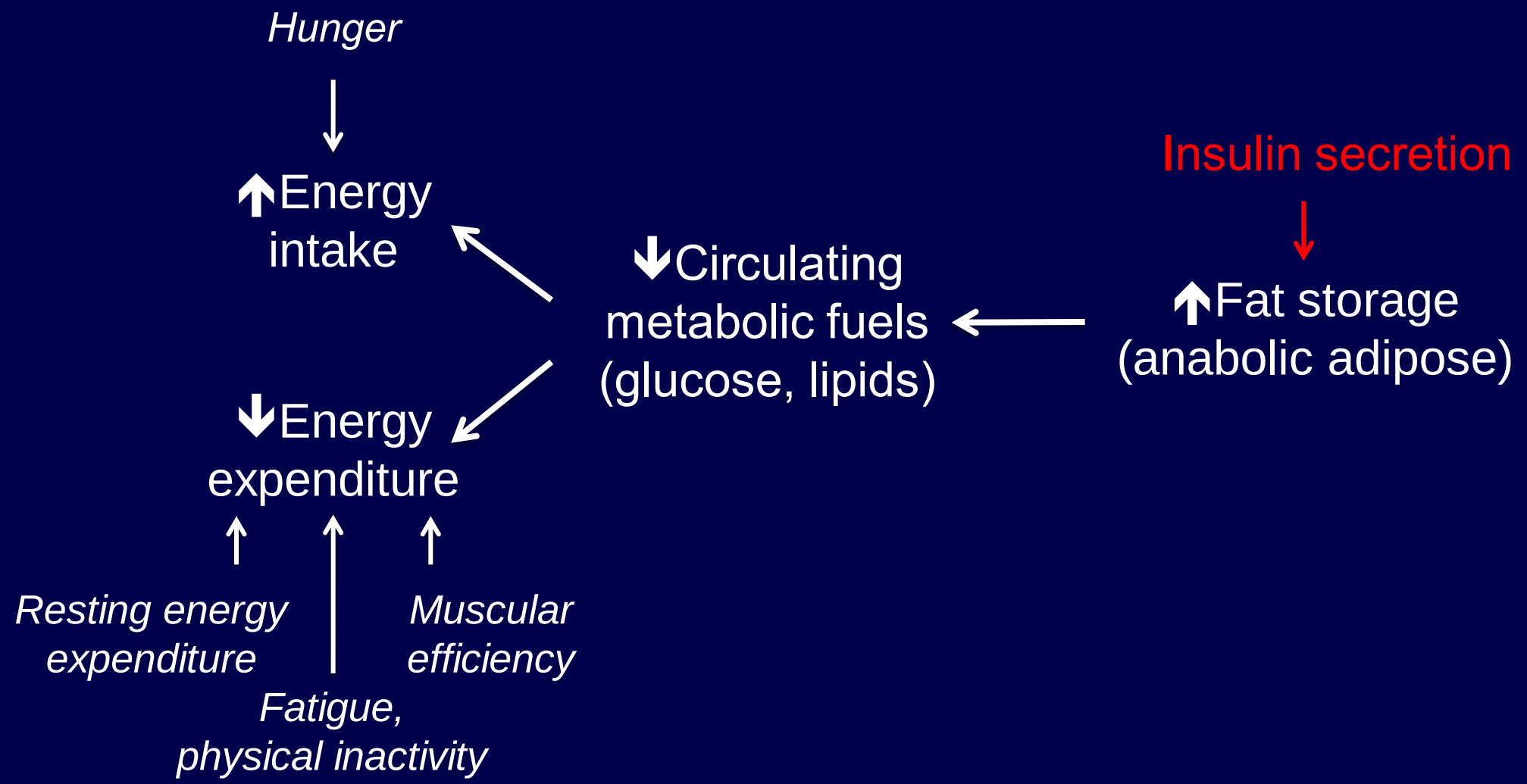

Insulin & Body Weight

A dominant anabolic hormone

- Regulates availability of all key metabolic fuels
  - Stimulates fat synthesis and deposition
  - Inhibits fat release and oxidation
- Increased action causes weight gain
  - Excessive insulin treatment in diabetes
  - Human genetic variants affecting insulin secretion
- Decreased action causes weight loss
  - Under-treatment of type 1 diabetes
  - Insulin knock down genetic models

UKPDS Lancet 1998, 352:837; Carlson. Diabetes 1993, 42:1700; Le Stunff, Nat Gen 2000, 26:444-6; Lustig, IJO 2006, 30:331-41; Templeman. J Endo 2017, 232:R173-83

Carbohydrate-Insulin Model

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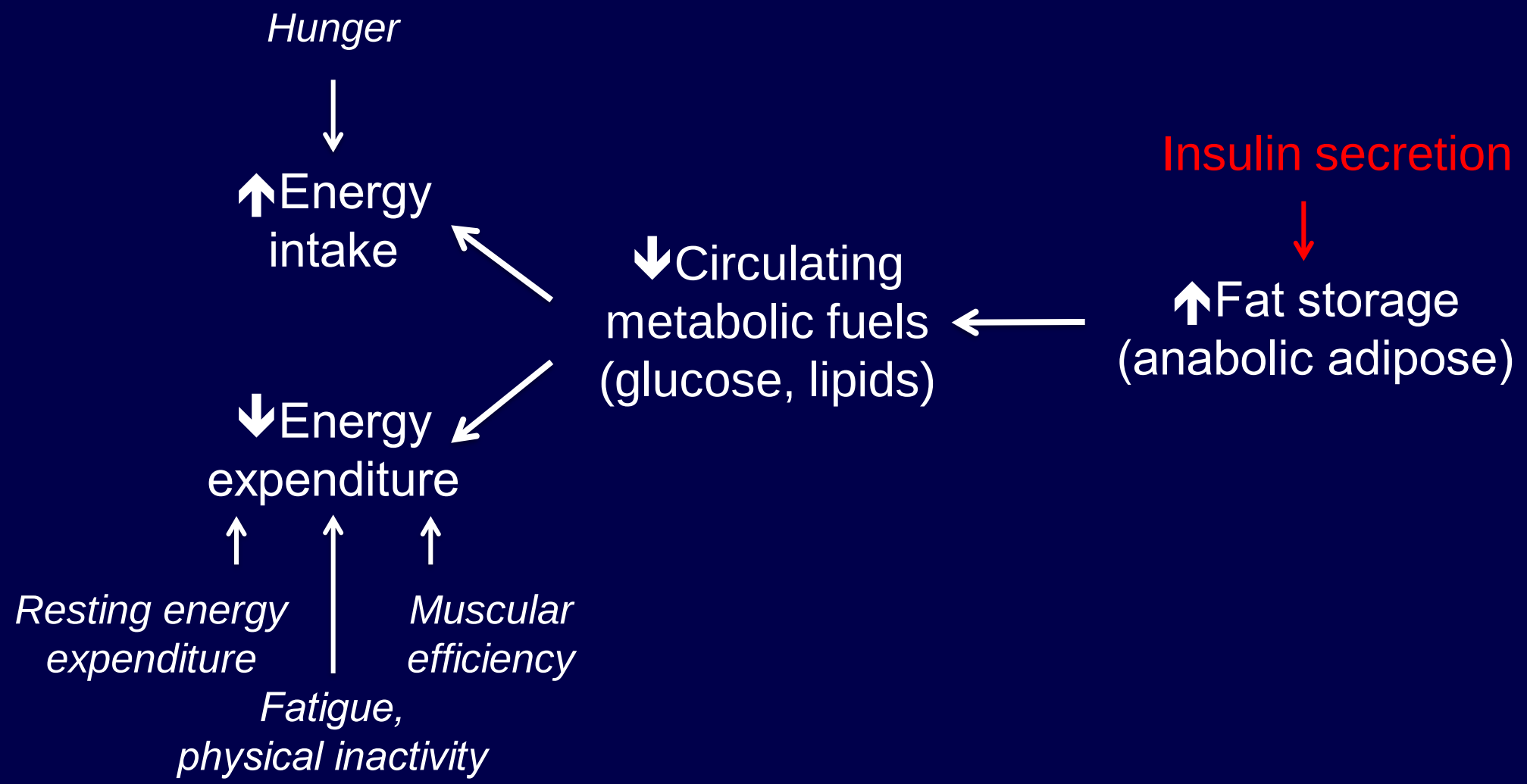

Carbohydrate-Insulin Model

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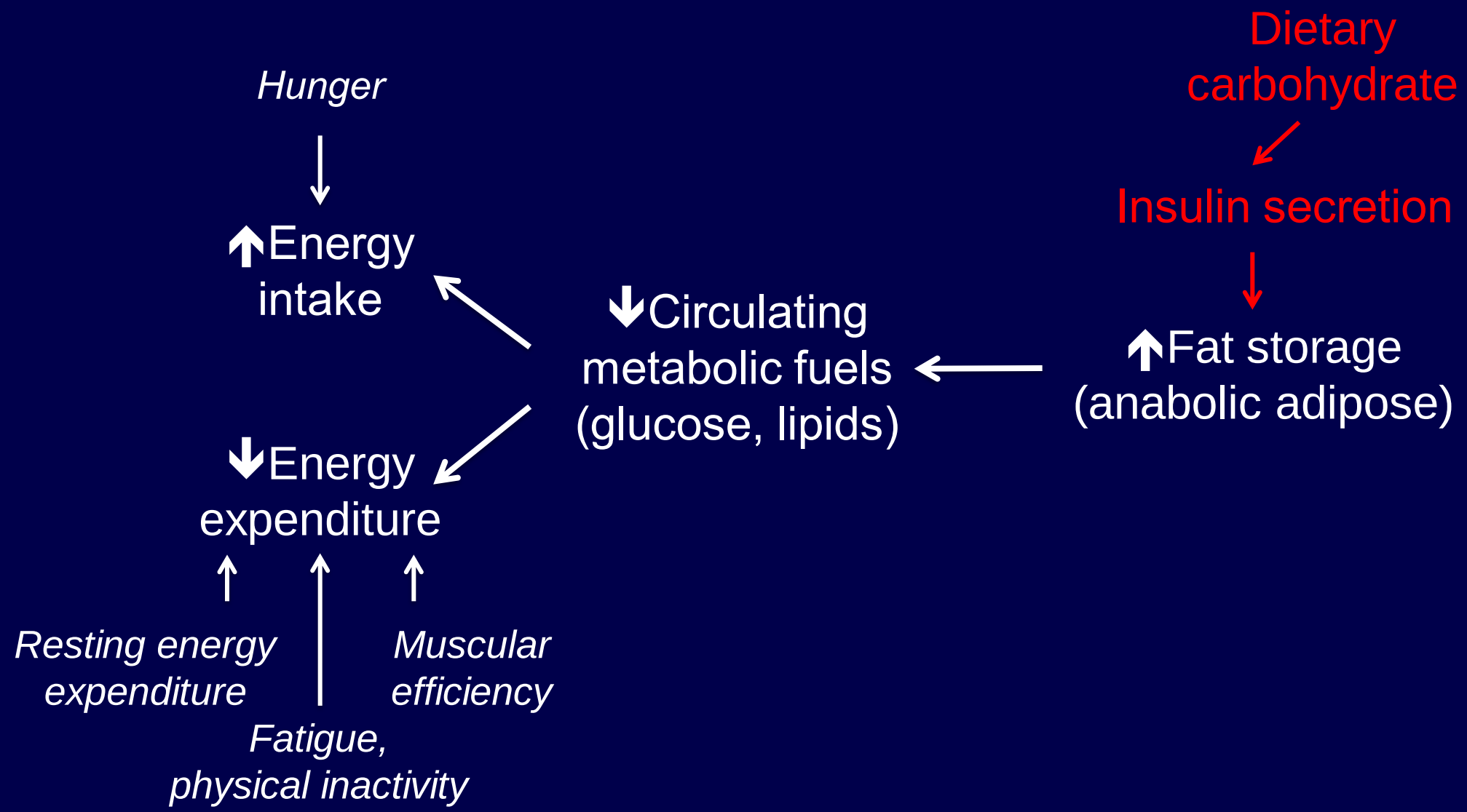


Carbohydrate Amount & Type

Most potent effects of all macronutrients on insulin secretion

- Amount – total carbohydrate (grams)
- Type – glycemic index

>> Glycemic load

Acute effects of glycemic load on hunger

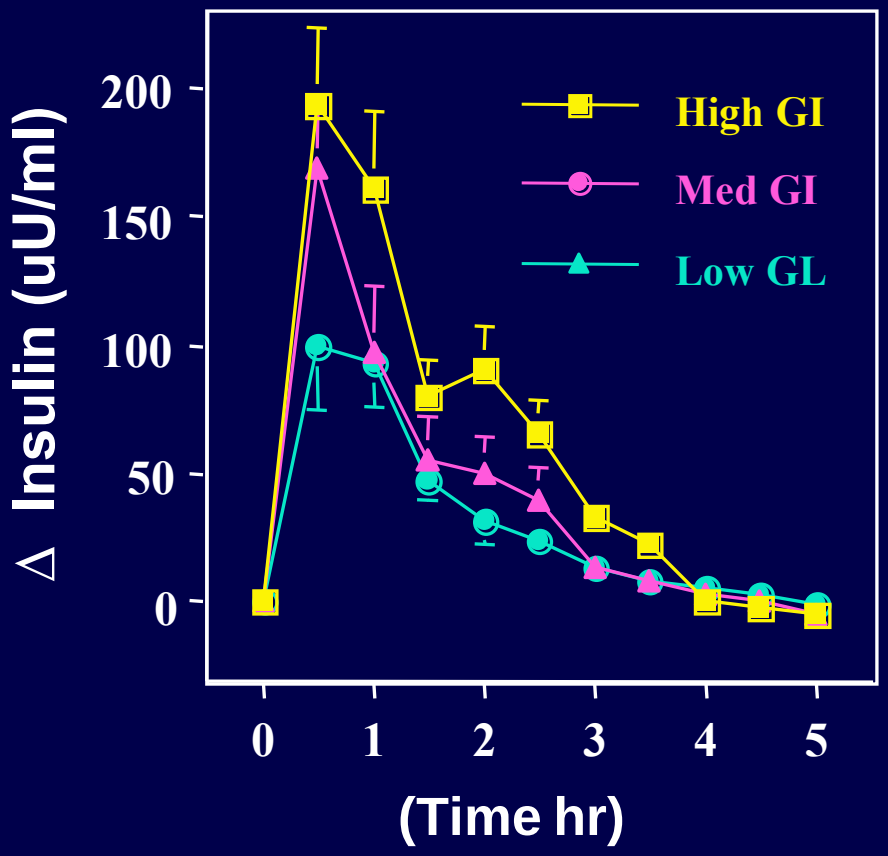
Glycemic Load and Hunger

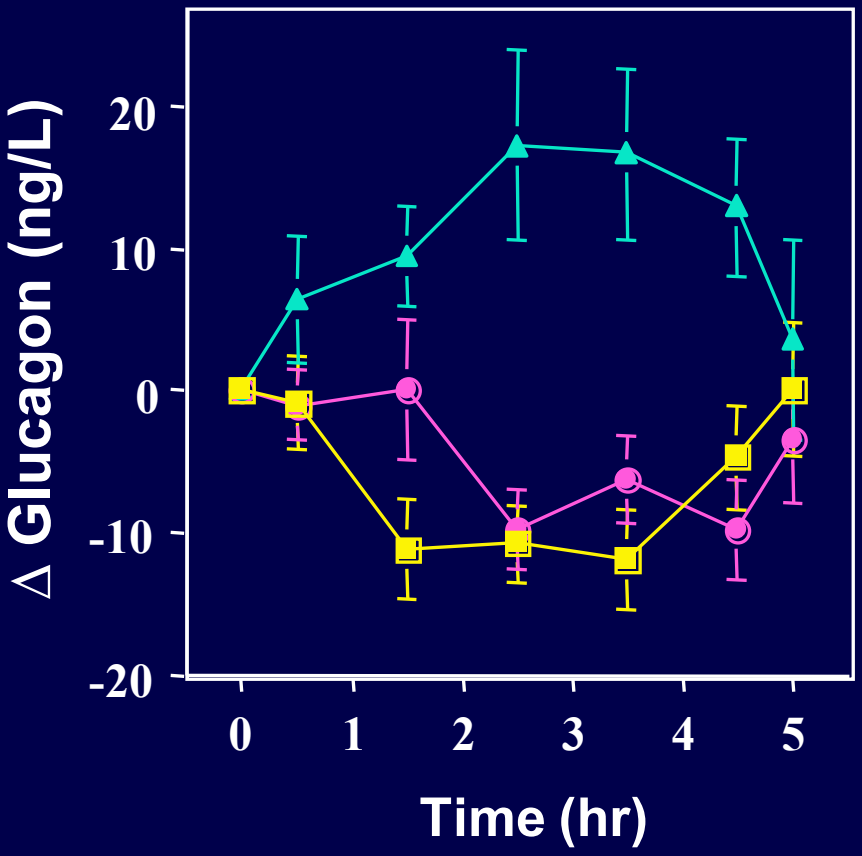
Methods

- Subjects: 12 adolescents with obesity
- Design: cross-over feeding study on 3 separate days
- Intervention: breakfasts with identical calories:
  - Highly processed carbohydrate (instant oatmeal)
  - Minimally processed carbohydrate (steel-cut oatmeal)
  - No processed carbohydrate (vegetable omelet with fruit)
- Blood tests and hunger followed through the morning

Glycemic Load and Hunger

Pancreatic hormones

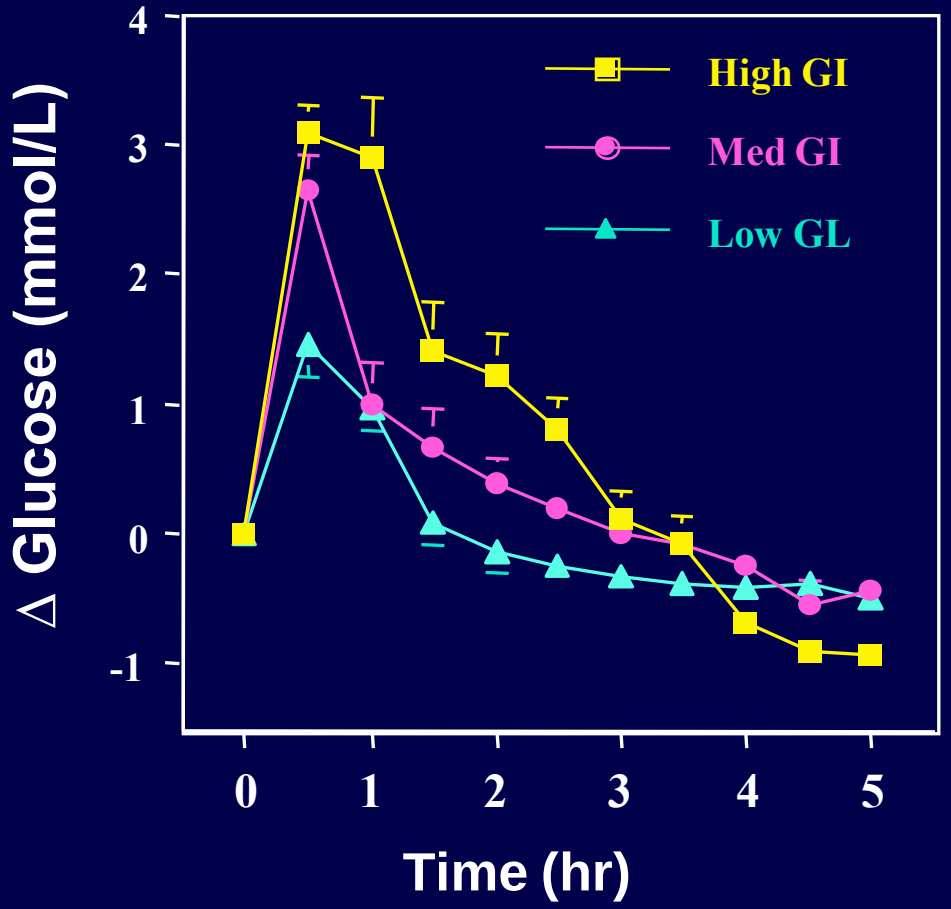


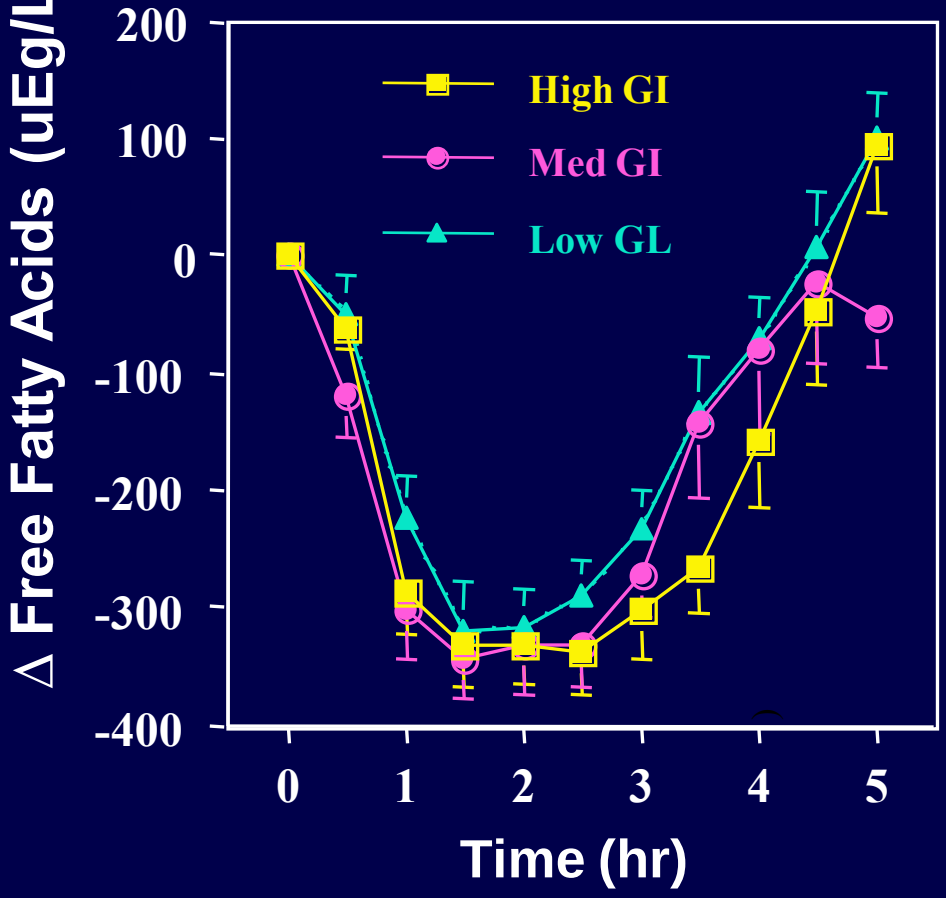


Ludwig. Pediatrics 1999, 103:e26

Glycemic Load and Hunger

Metabolic fuels

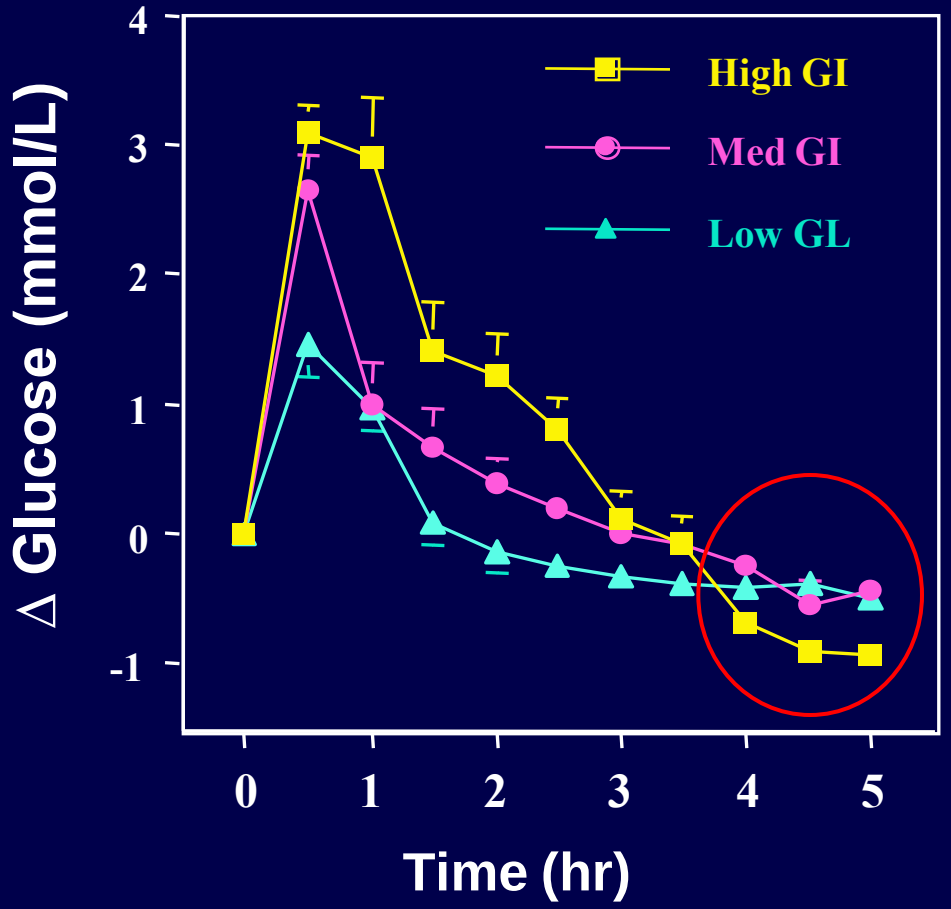


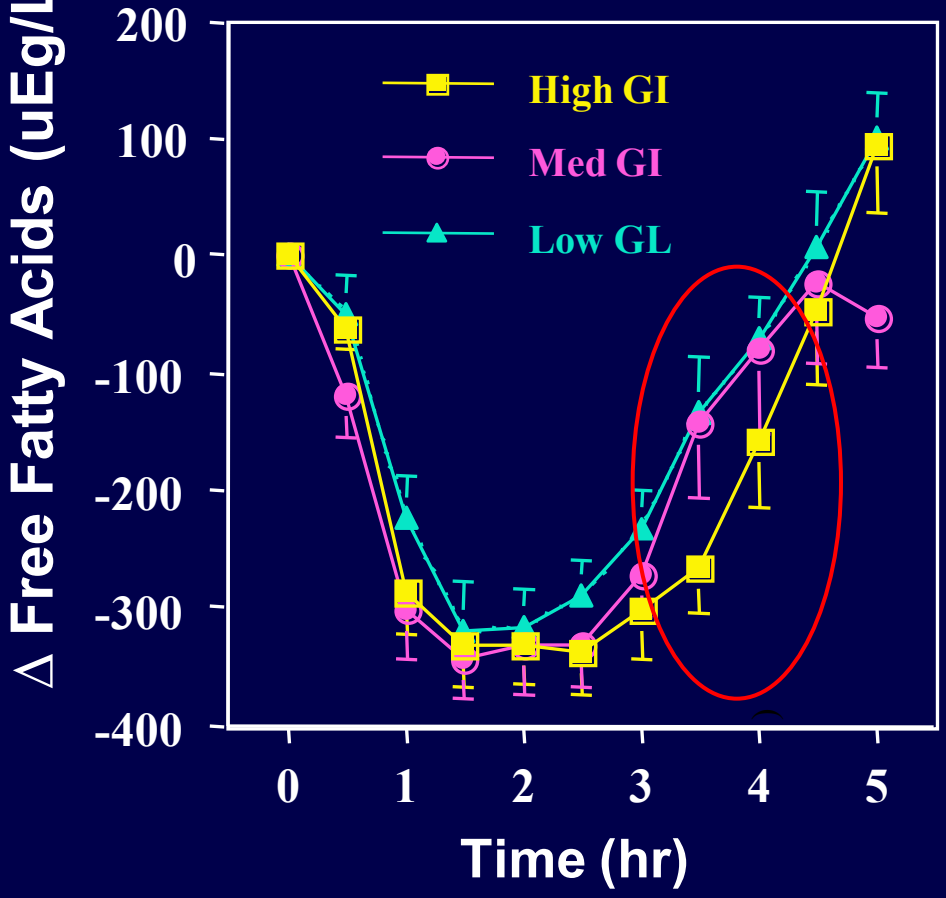


Ludwig. Pediatrics 1999, 103:e26

Glycemic Load and Hunger

Metabolic fuels

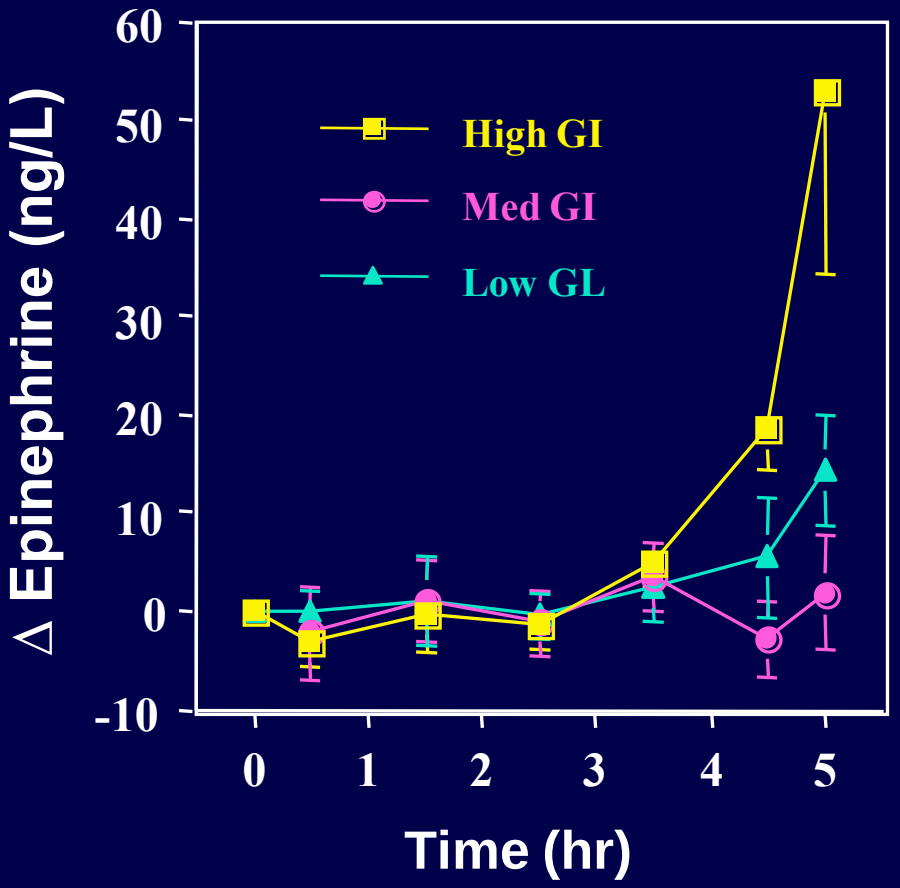




Ludwig. Pediatrics 1999, 103:e26

Glycemic Load and Hunger

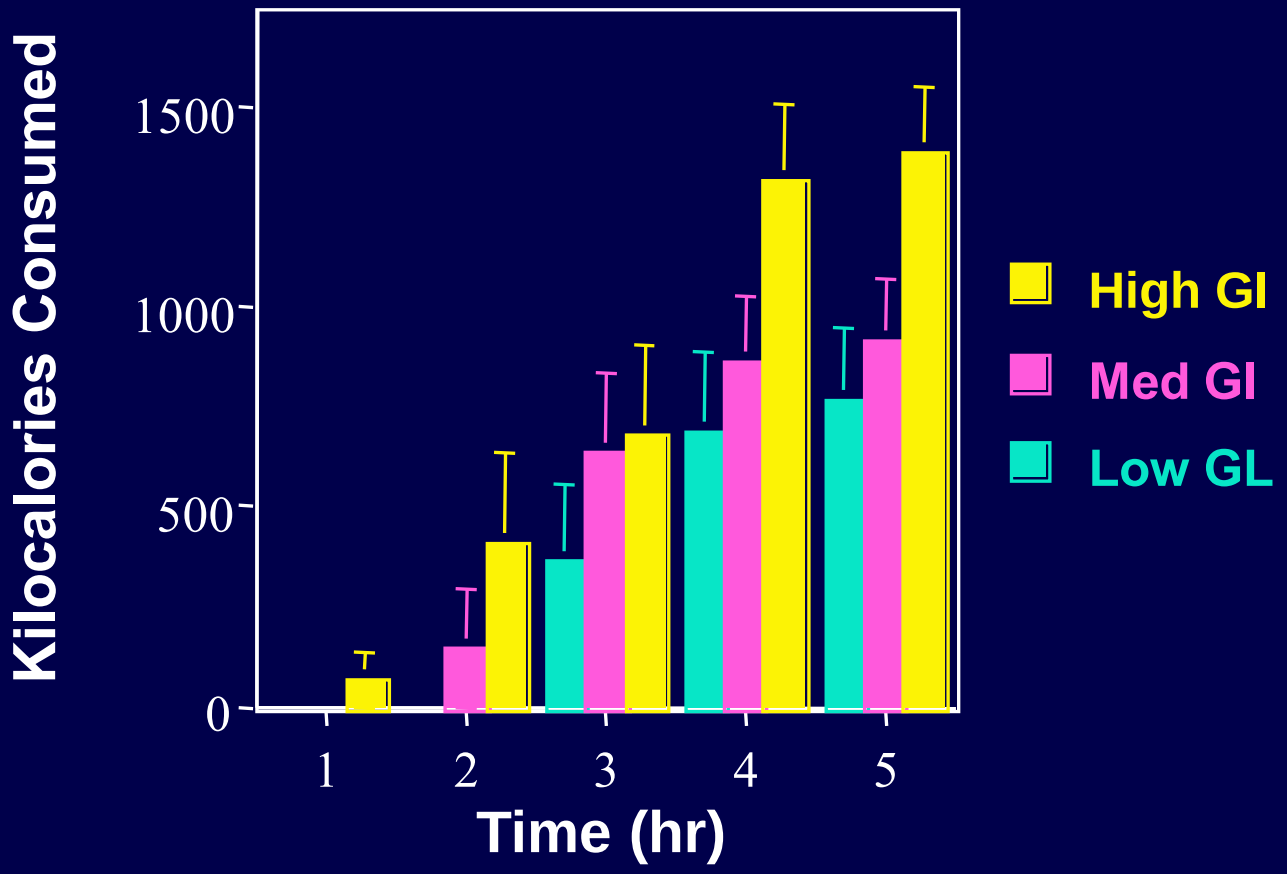
Plasma epinephrine



Ludwig. Pediatrics 1999, 103:e26

Glycemic Load and Hunger

Cumulative food intake



Ludwig. Pediatrics 1999, 103:e26

Chronic effects in an animal model

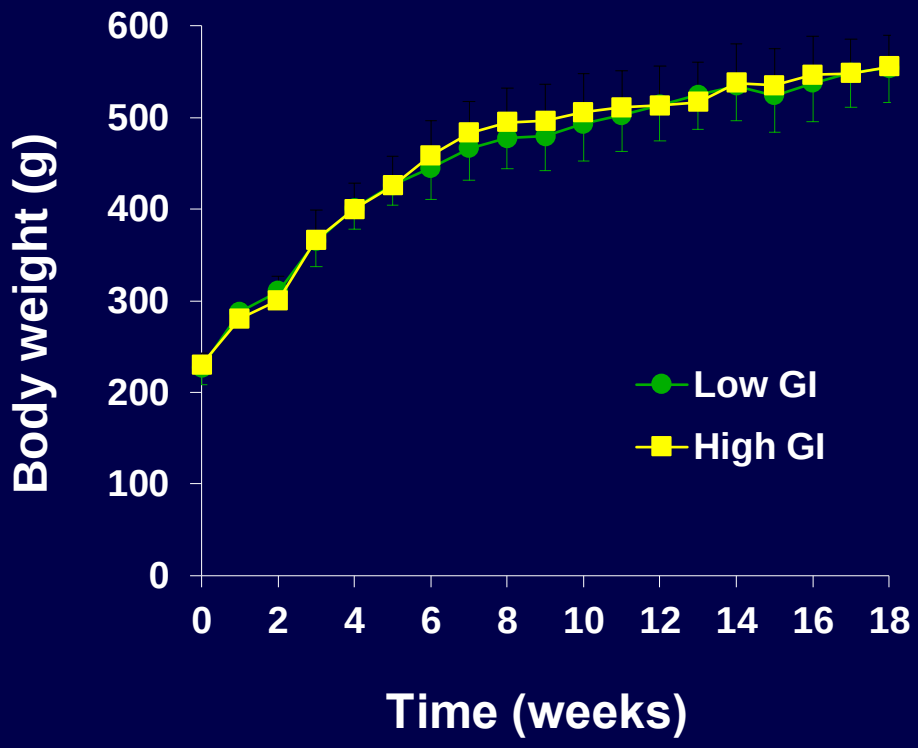
Effects of Glycemic Index in Rodents

Study Design

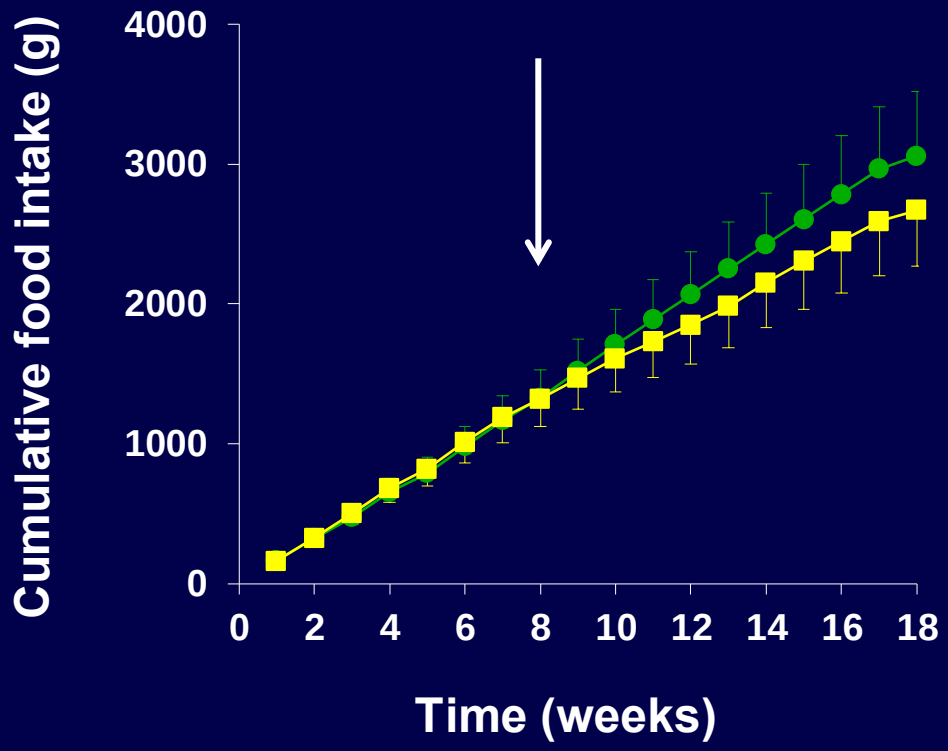
- Sprague-Dawley rats given diets with identical macronutrients
  - high GI (amylopectin starch) , n = 11
  - low GI (high amylose starch), n = 10
- Energy intake controlled to maintain identical mean body weight between groups
- Body composition measured at 18 weeks with tritiated water

Effects of Glycemic Index in Rodents

Food intake and body weight



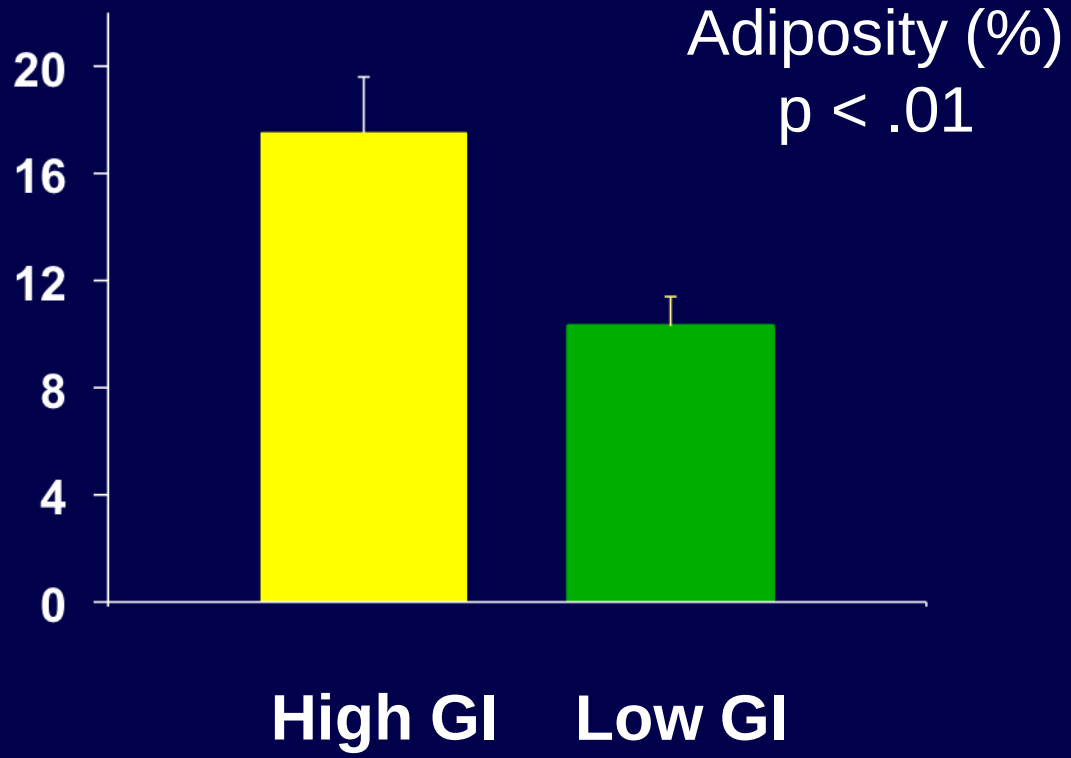
Energy restriction required, suggesting metabolic changes



Pawlak. Lancet 2004, 364:778-85

Effects of Glycemic Index in Rodents

Differences in body composition



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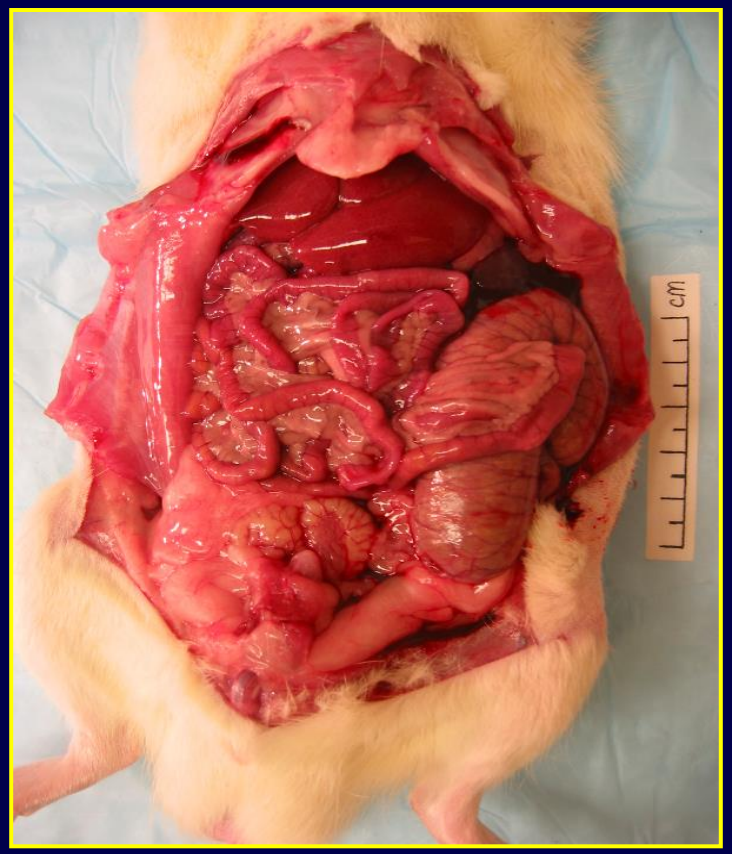
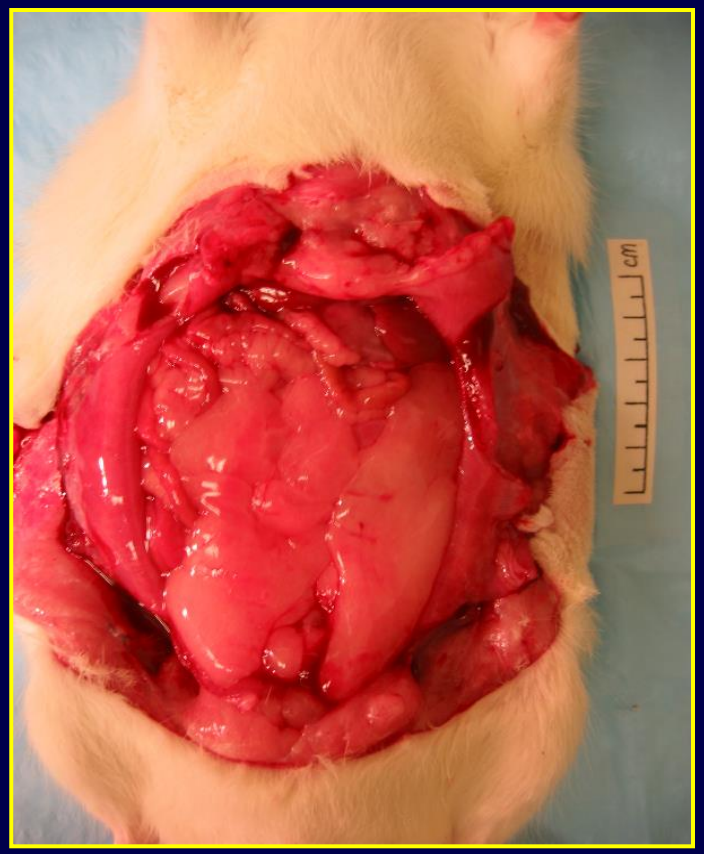
Effects of Glycemic Index in Rodents

Differences in body composition



Low GI



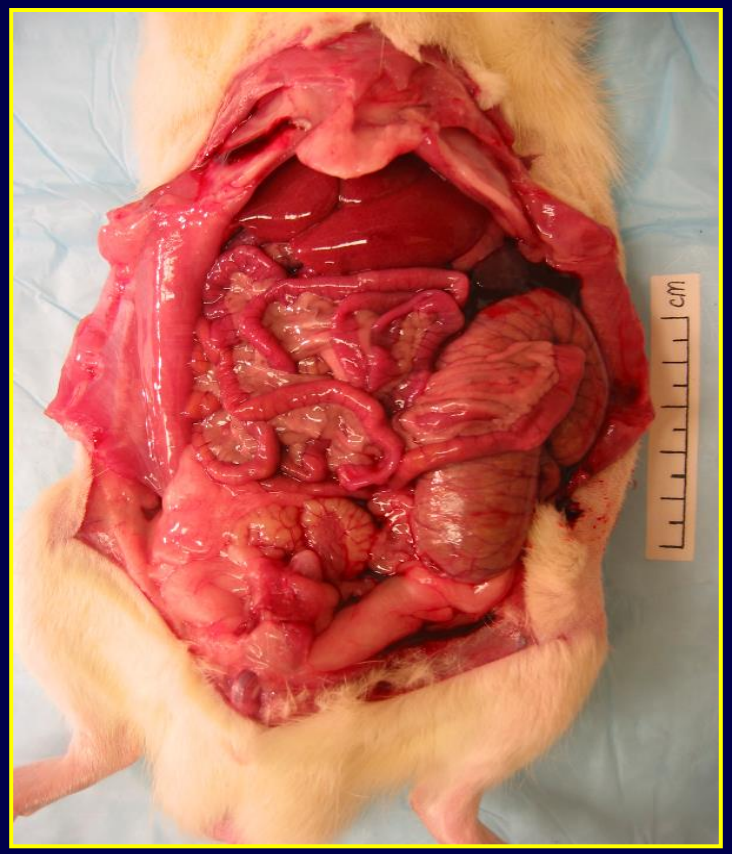
High GI

Pawlak. Lancet 2004, 364:778-85

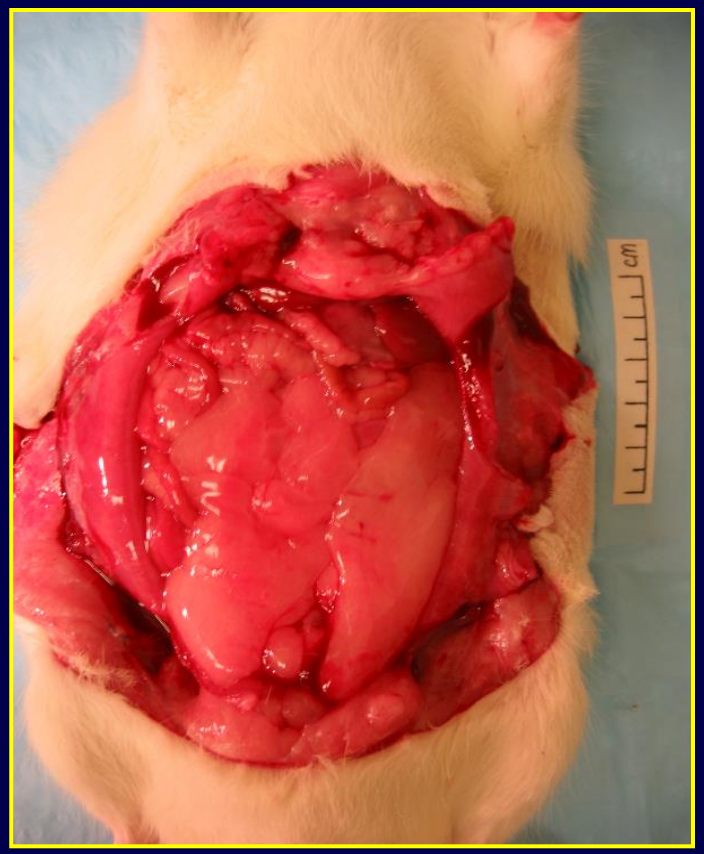
Effects of Glycemic Index in Rodents

Differences in body composition

Prima facie case for disorder in substrate partitioning:



Low GI



High GI

- ↓ Energy intake
- ↓ Lean mass
- ↑ Fat mass

Pawlak. Lancet 2004, 364:778-85

Effects on metabolism

Framingham State Food Study

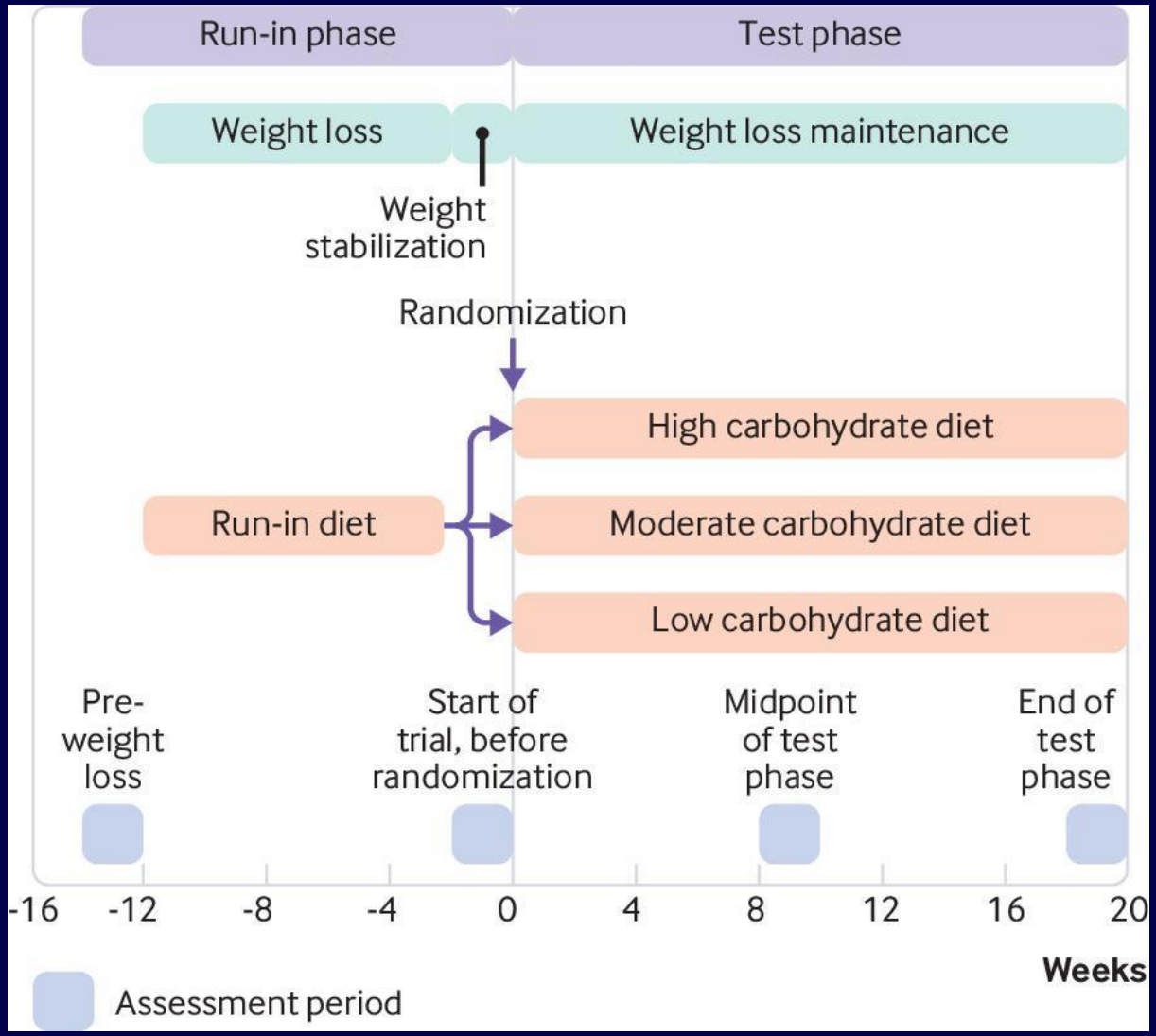
(FS2)

Specific Aim

To evaluate the effect of three diets varying in carbohydrate-to-fat ratio on energy expenditure during weight-loss maintenance over 5 months in a well-powered feeding study

Framingham State Food Study

164 young adults with high body weight



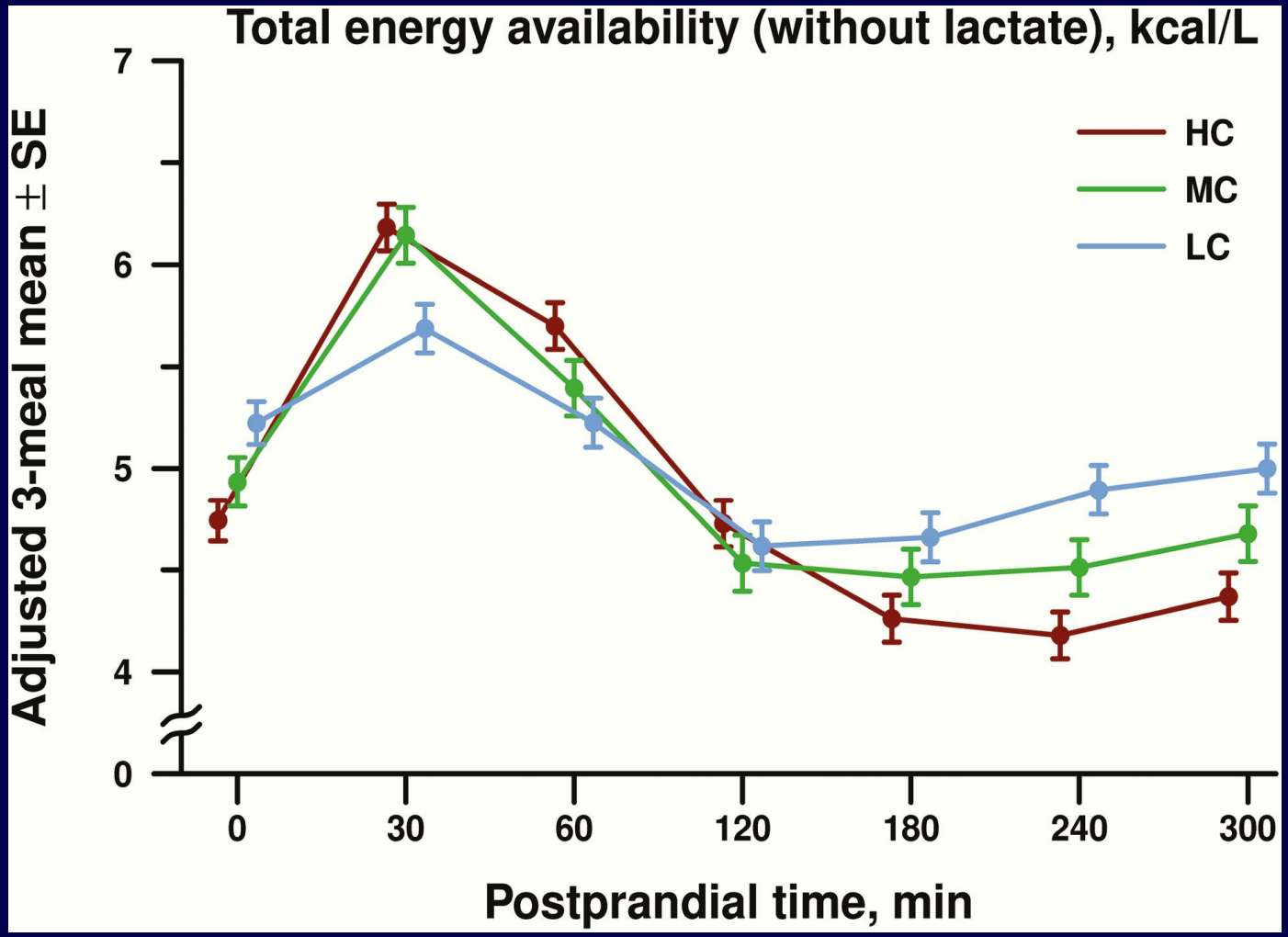
Framingham State Food Study

Diet composition

	HI Carb	MOD Carb	LO Carb
Targets	Consistency and Differentiation		
Carbohydrate (% energy)	**60**	**40**	**20**
Added Sugar (% total carbohydrate)	15	15	15
Fat (% energy)	**20**	**40**	**60**
Saturated Fat (% total fat)	35	35	35
Protein (% energy)	20	20	20

Framingham State Food Study

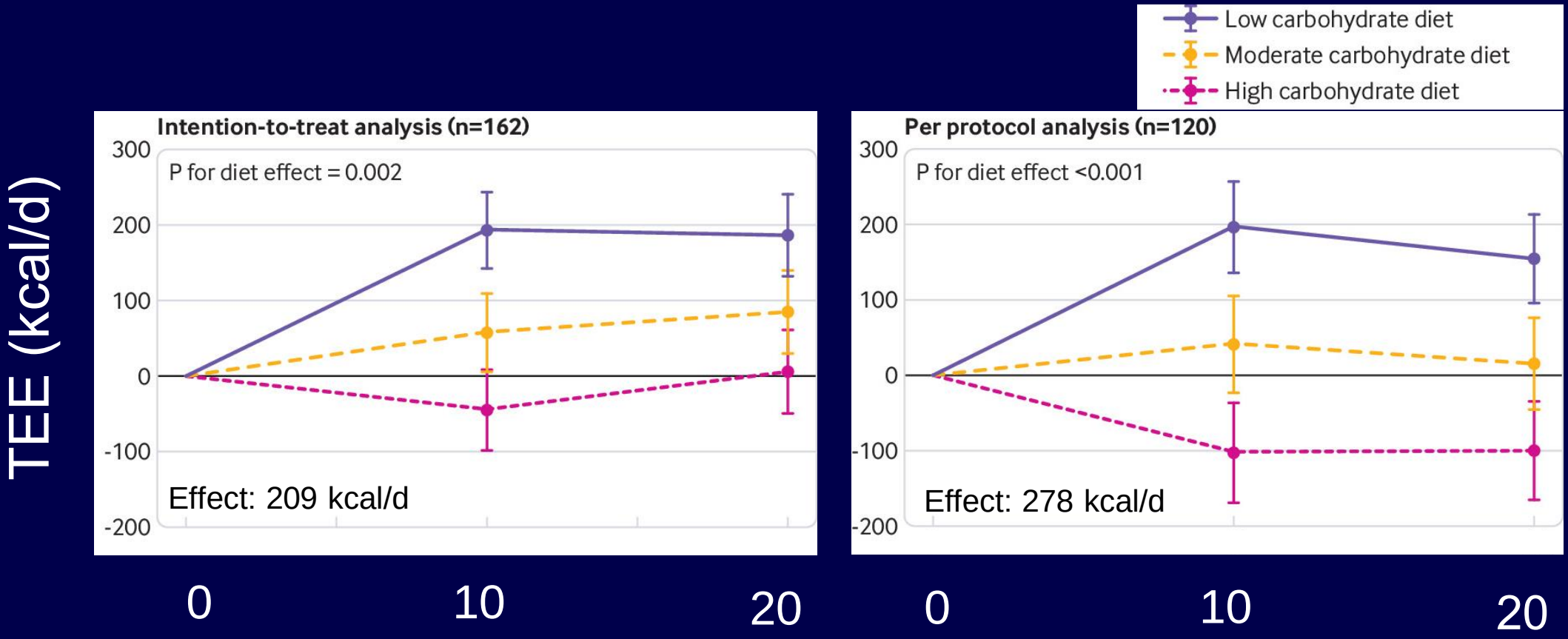
Metabolic fuels



Shimy et al. J Endo Soc 2020 (July) bvaa062

Framingham State Food Study

Primary outcome: TEE by DLW



Ebbeling. BMJ, 2018; 363:k4583

Chronic effects on body weight: Problem of low intensity behavioral trials

Meta-analyses of Low-Fat Diets

INFERIOR to all higher fat/low-carb comparisons

- Moderate-carbohydrate Mediterranean diets
  Nordmann AJ. Am J Med 2011, 124:841-51
- Low-carbohydrate diets
  Sackner-Bernstein J. PLoS One, 2015 20;10:e0139817
- Very low-carbohydrate diets.
  Bueno NB. Br J Nutr 2016, 115:466-79
- Ketogenic (ultra-low carbohydrate) diets
  Mansoor N. Br J Nutr 2013, 110:1178-87
- All lower-carb / higher-fat diets
  Tobias DK. Lancet Diabetes Endocrinology 2015, 3:968-79

Macronutrient Feeding Studies

Characteristically substantial effect of dietary composition

DIRECT Study

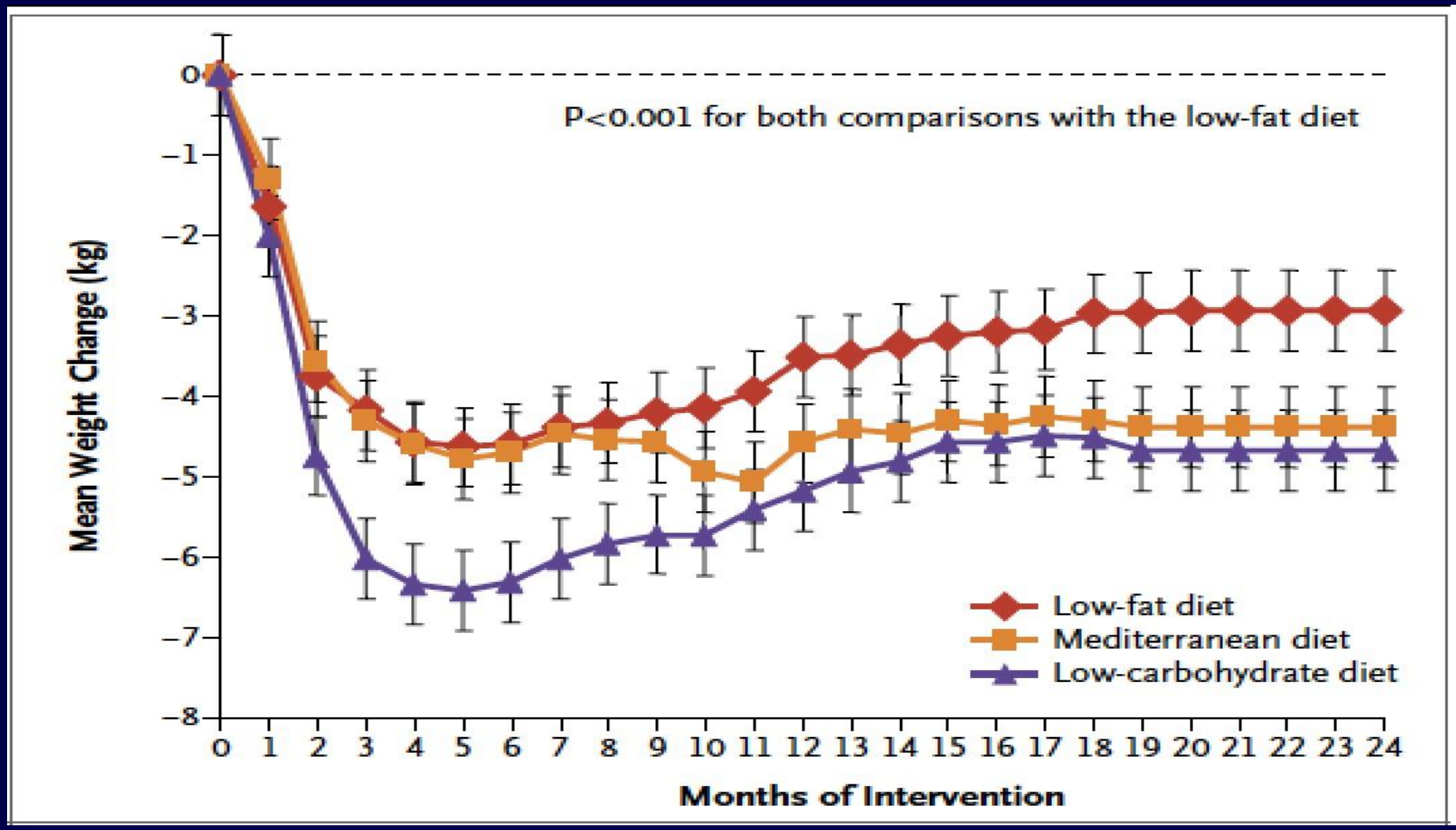
Methods

- 322 obese adults, studied for 2 years
- Assigned to 3 diets designed to differ in macronutrients
  - Low fat, calorie-restricted
  - Mediterranean, calorie-restricted
  - Low carbohydrate, not calorie-restricted
- Intervention based at a work site, with partial food provision
- Completion rates approaching 90%

Shai. NEJM 2008, 359:229-41

Macronutrient Feeding Studies

Characteristically substantial effect of dietary composition

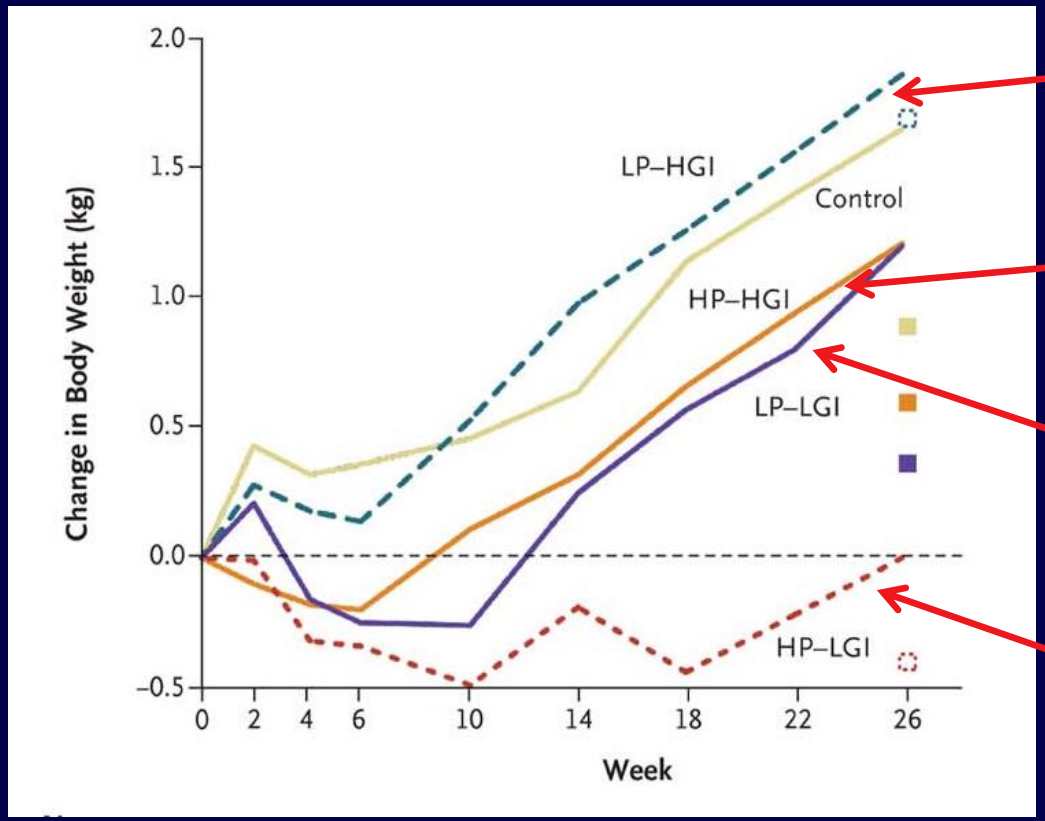


Shai. NEJM 2008, 359:229-41

Feeding Studies

Substantial effect of dietary composition

- 773 adults from 8 European countries who initially lost >8% body weight
- Diet: Low vs high protein; low vs high GI for 26 weeks – *ad libitum*



High GL
(low protein, high GI)

Medium GL
(high protein, high GI)

Medium GL
(low protein, low GI)

Low GL
(high protein, low GI)

Diogenes Study, NEJM 2010, 363:2102-13

Drugs & Body Weight

Diabetes Drugs

Adipose insulin action and weight gain

↑ Insulin Action

- Insulin
- Sulfonylureas
- Thiazolidinediones

Weight Gain

Diabetes Drugs

Adipose insulin action and weight gain

↑ Insulin Action

- Insulin
- Sulfonylureas
- Thiazolidinediones

Weight Gain

↓ Insulin Action

- Metformin
- SGLT-2 inhibitors
- Alpha-glucosidase inhibitors

Weight Loss

Diabetes Drugs

Adipose insulin action and weight gain

↑ Insulin Action

- Insulin
- Sulfonylureas
- Thiazolidinediones

Weight Gain

↓ Insulin Action

- Metformin
- SGLT-2 inhibitors
- Alpha-glucosidase inhibitors

Weight Loss

What about GLP-1 receptor agonists?

GLP-1 Receptor Agonists

Commonly believed to raise insulin secretion

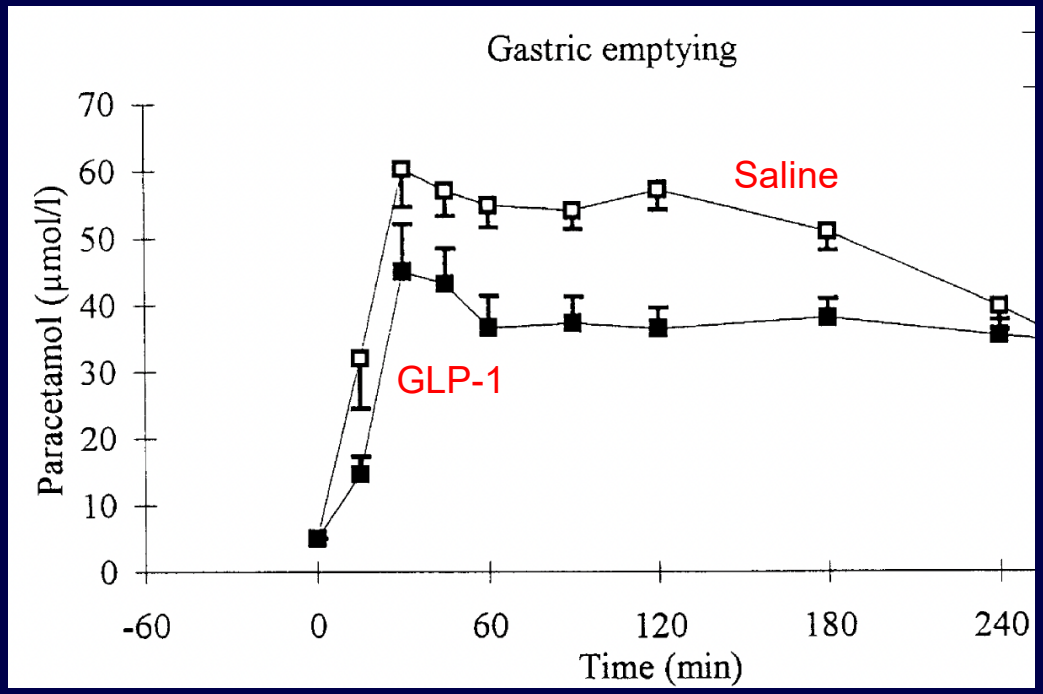
"despite acutely increasing insulin secretion, GLP-1Ra are currently the most effective approved medication to treat obesity"

Hall et al. AJCN 2022, 115:1243-1254

GLP-1 Receptor Agonists

Do their weight loss effects "disprove" the CIM?

- GLP-1, as an incretin, stimulates β-cell insulin secretion
- ALSO has major effect slowing gastric emptying



GLP-1 vs saline, acute

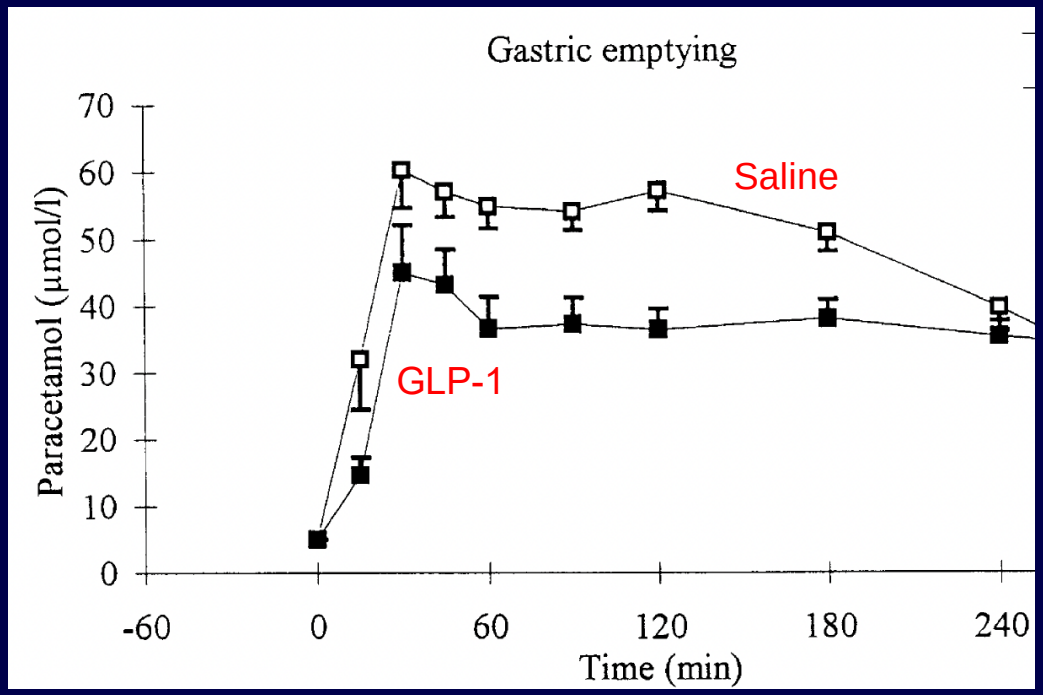
Flint. IJO 2001, 25:781-792

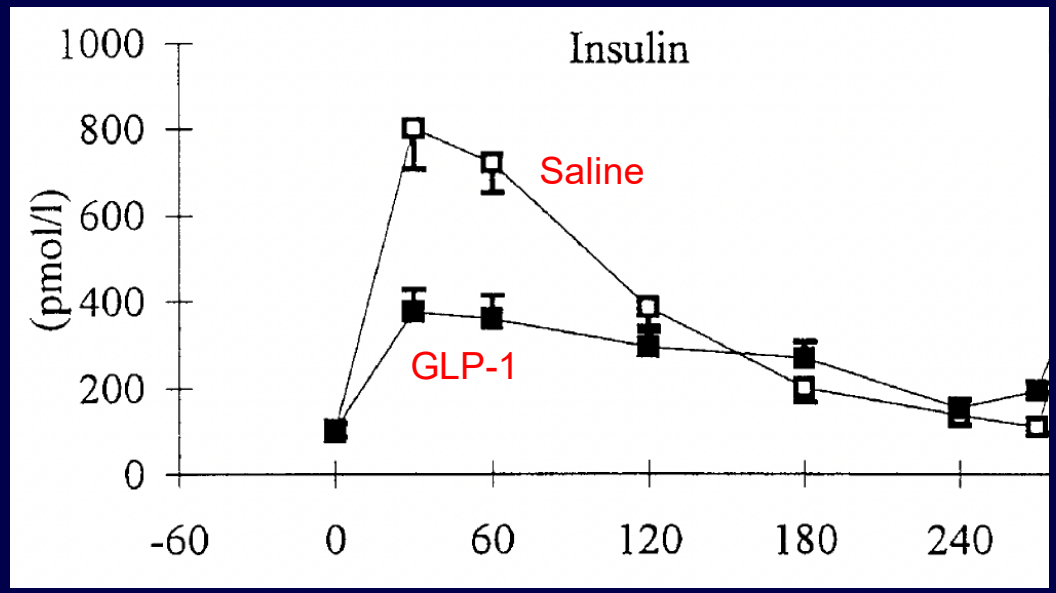
GLP-1 Receptor Agonists

Do their weight loss effects "disprove" the CIM?

- GLP-1, as an incretin, stimulates β-cell insulin secretion
- ALSO has major effect slowing gastric emptying
- Consequently, insulin levels usually decreased with treatment

GLP-1 vs saline, acute





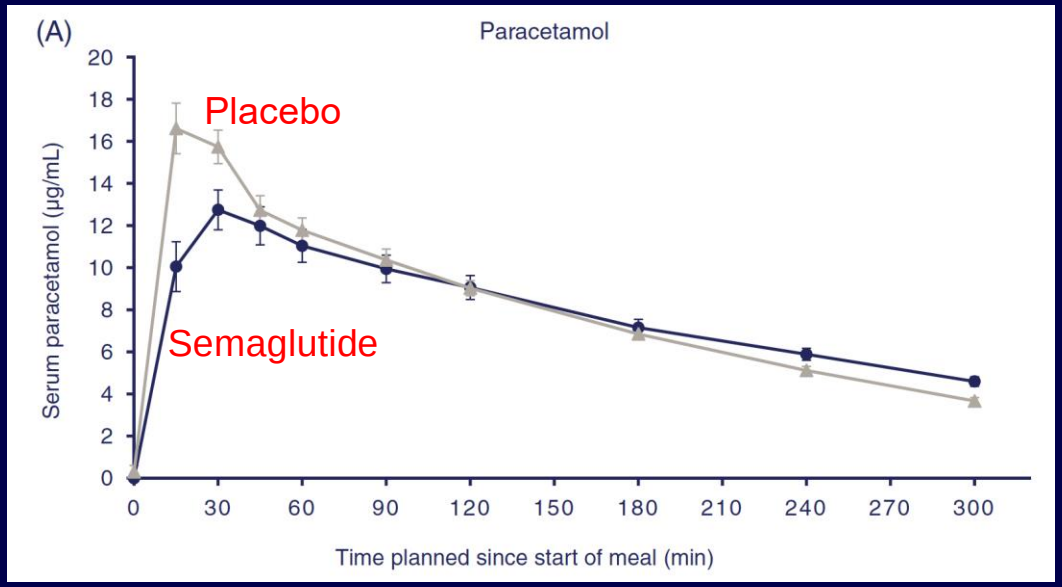
Flint. IJO 2001, 25:781-792

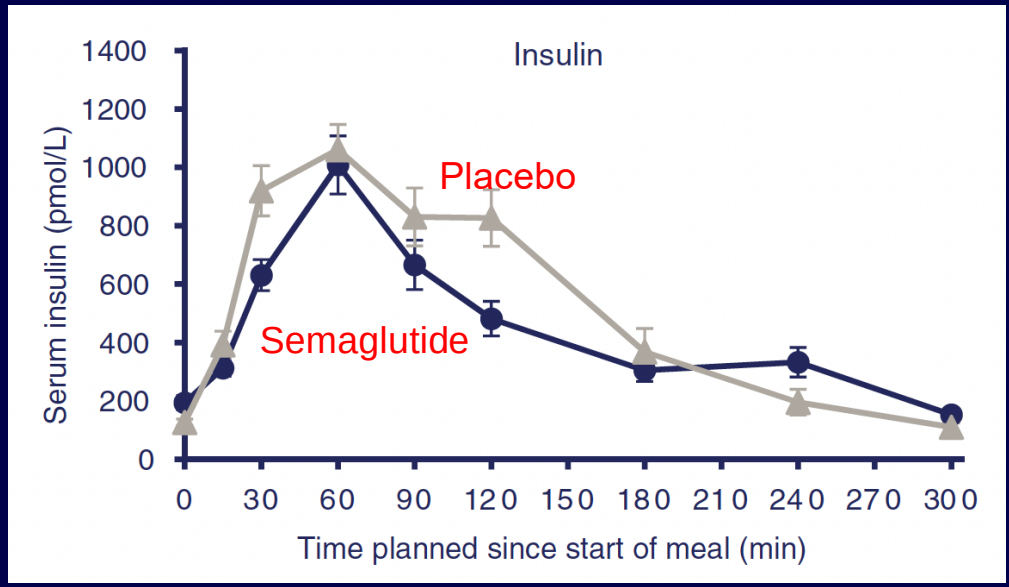
GLP-1 Receptor Agonists

Do their weight loss effects "disprove" the CIM?

- Although tachyphylaxis occurs, effects on gastric emptying and insulin secretion persist.

Semaglutide vs placebo, 12 weeks





Hjerpsted Diab Obes Metab 2018, 20:610-19

GLP-1 Receptor Agonists

Do their weight loss effects "disprove" the CIM?

- Case reports of surgical patients on GLP-1 RA with residual gastric content, even after many hours fasting

Journal of Clinical Anesthesia 87 (2023) 111091

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journal homepage: www.elsevier.com/locate/jclinane

Original Contribution

Relationship between perioperative semaglutide use and residual gastric content: A retrospective analysis of patients undergoing elective upper endoscopy

Saullo Queiroz Silveira, MD [a], Leopoldo Muniz da Silva, MD, PhD [b], Arthur de Campos Vieira Abib, MD [a], Diogo Turiani Hourneaux de Moura, MD, PhD [c], Eduardo Guimarães Hourneaux de Moura, MD, PhD [c], Leonardo Barbosa Santos, MD [d], Anthony M.-H. Ho, MD [e], Rafael Souza Fava Nersessian, MD [b], Filipe Lugon Moulin Lima, MD [a], Marcela Viana Silva, APRN [c], Glenio B. Mizubuti, MD, MSc [e,*]

Can J Anesth/J Can Anesth
https://doi.org/10.1007/s12630-023-02521-3

CASE REPORTS / CASE SERIES

Regurgitation under anesthesia in a fasted patient prescribed semaglutide for weight loss: a case report

Régurgitation sous anesthésie chez une personne à jeun à qui du sémaglutide a été prescrit pour une perte de poids : une présentation de cas

Michael A. Gulak, MD · Patricia Murphy, MD, FRCPC

OXFORD

BJS Open, 2023, zrac169
https://doi.org/10.1093/bjsopen/zrac169
Research Letter

Gastroparesis with bezoar formation in patients treated with glucagon-like peptide-1 receptor agonists: potential relevance for bariatric and other gastric surgery

Veronica Preda[1], Skylar Su-Yee Khoo[1], Tamara Preda[2] and Reginald V. Lord[2,*]

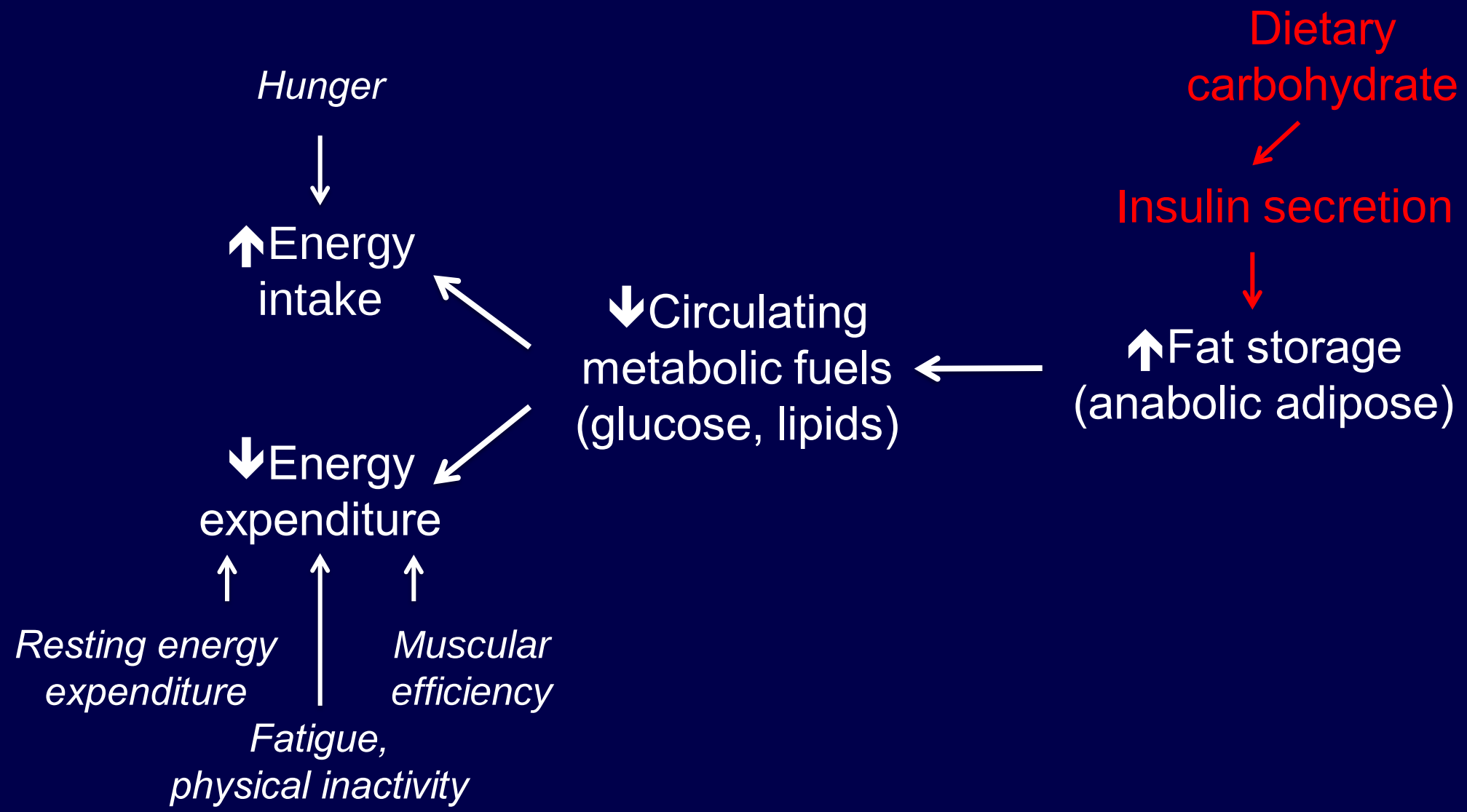
GLP-1 Receptor Agonists

Lower insulin secretion in real life conditions

- Peripheral actions consistent with, not opposed to, the CIM:
  - Slow gastric emptying
  - Delay nutrient absorption
  - Lower insulin
  - Lower ghrelin
  - Raise adiponectin
  - Improve measures of leptin sensitivity
- We need a major trial to examine potential synergy between GLP-1 RAs and a low-carbohydrate diet (!)

Carbohydrate-Insulin Model

A metabolic disorder of fat storage



Carbohydrate-Insulin Model

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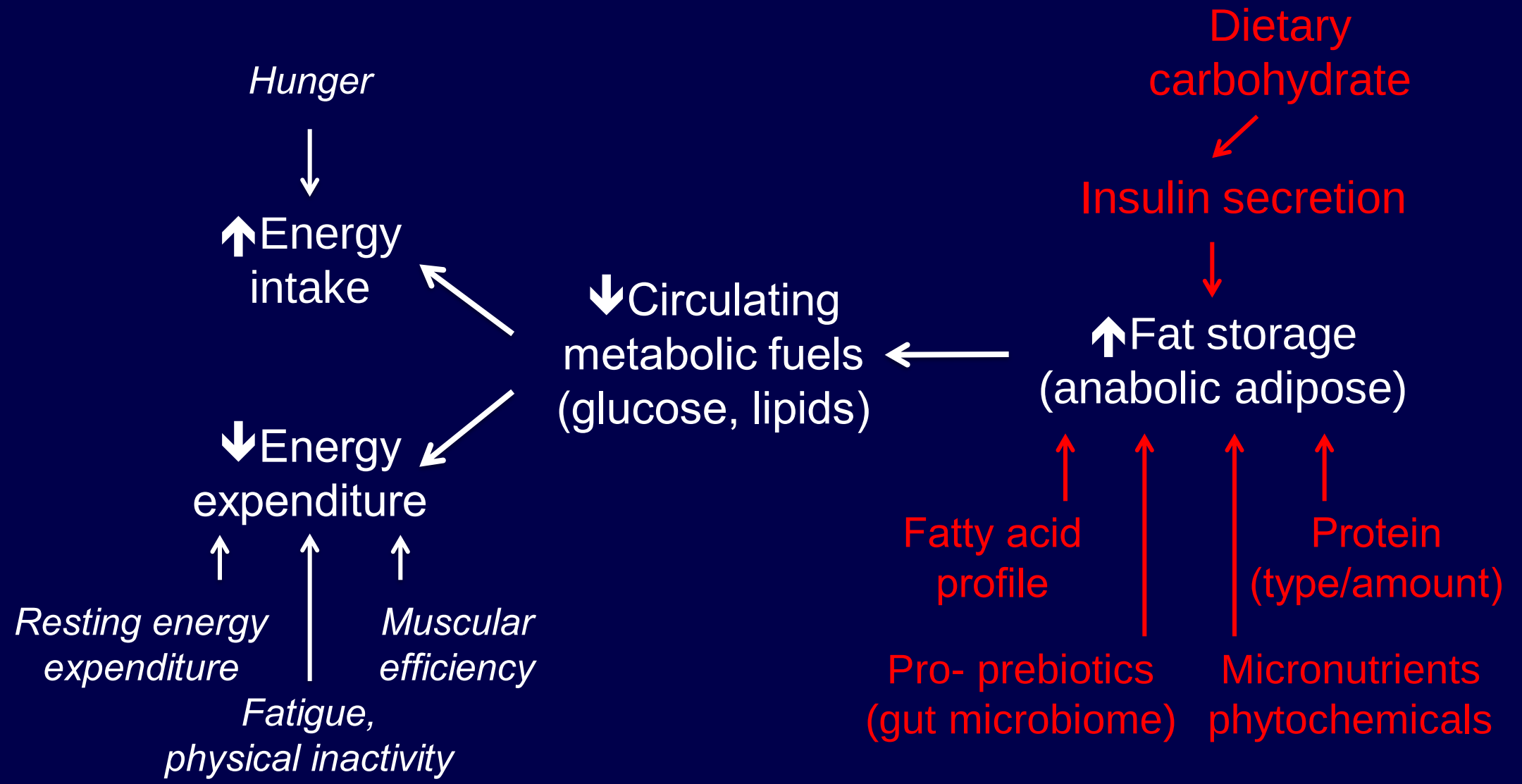

Carbohydrate-Insulin Model

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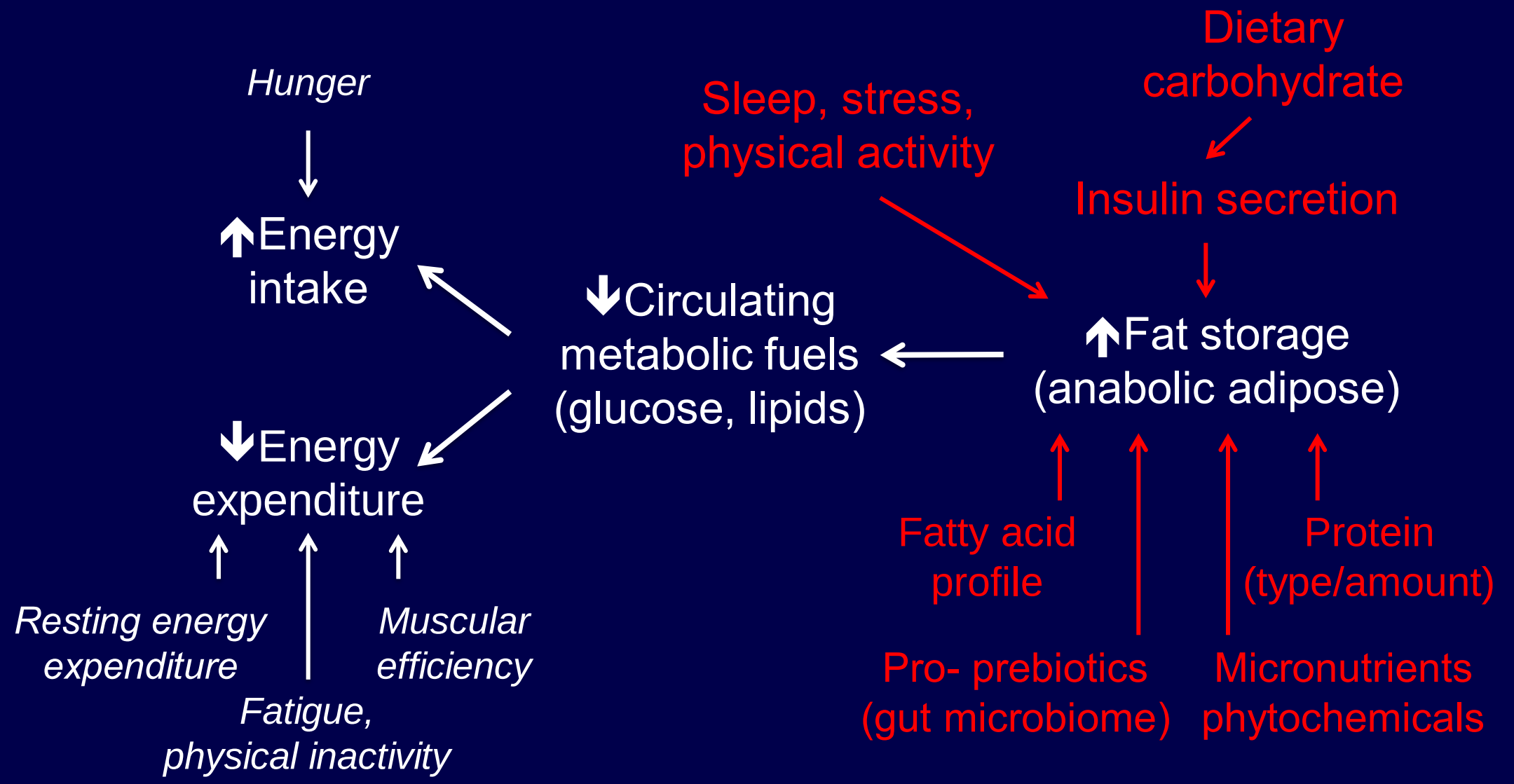

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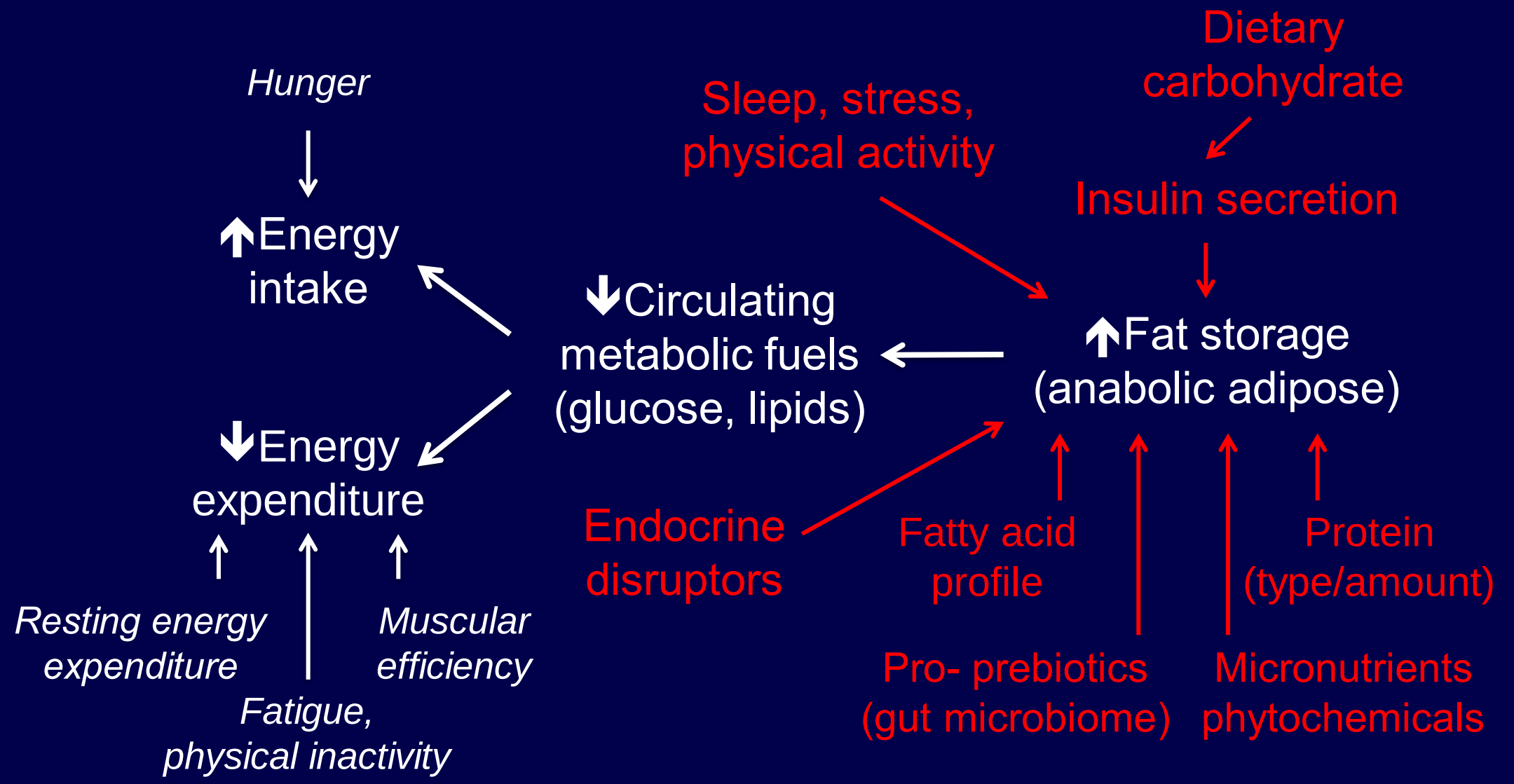
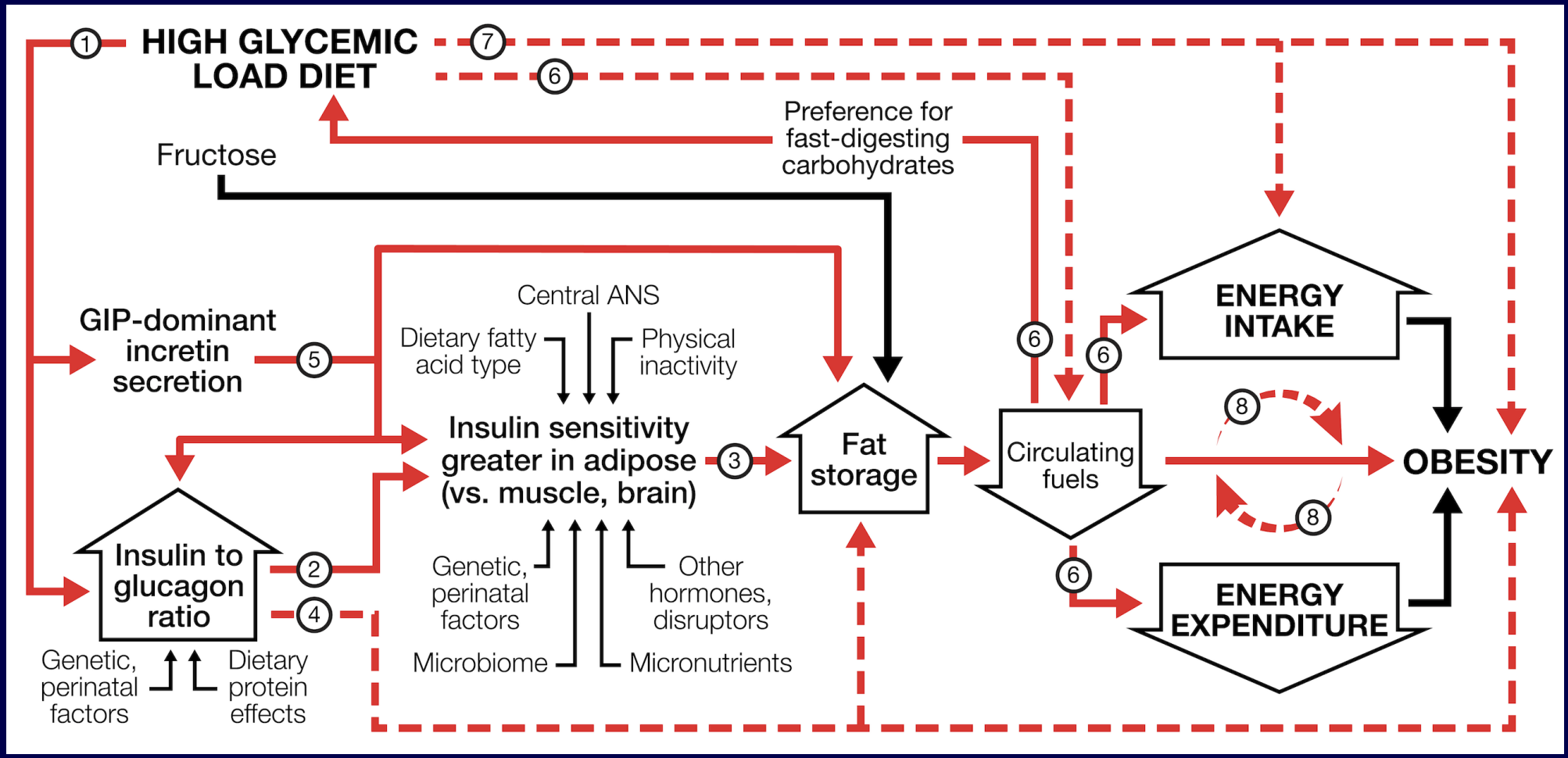


Full Model

Focused on mechanism, with testable hypotheses



Ludwig. AJCN December 2021, 114:1873-

Future Research

Need for complementary, high-quality studies

To produce obesity by age 50 years requires the storage of only *1 gram per day extra fat* – highlighting limitations of short trials

Research needs:

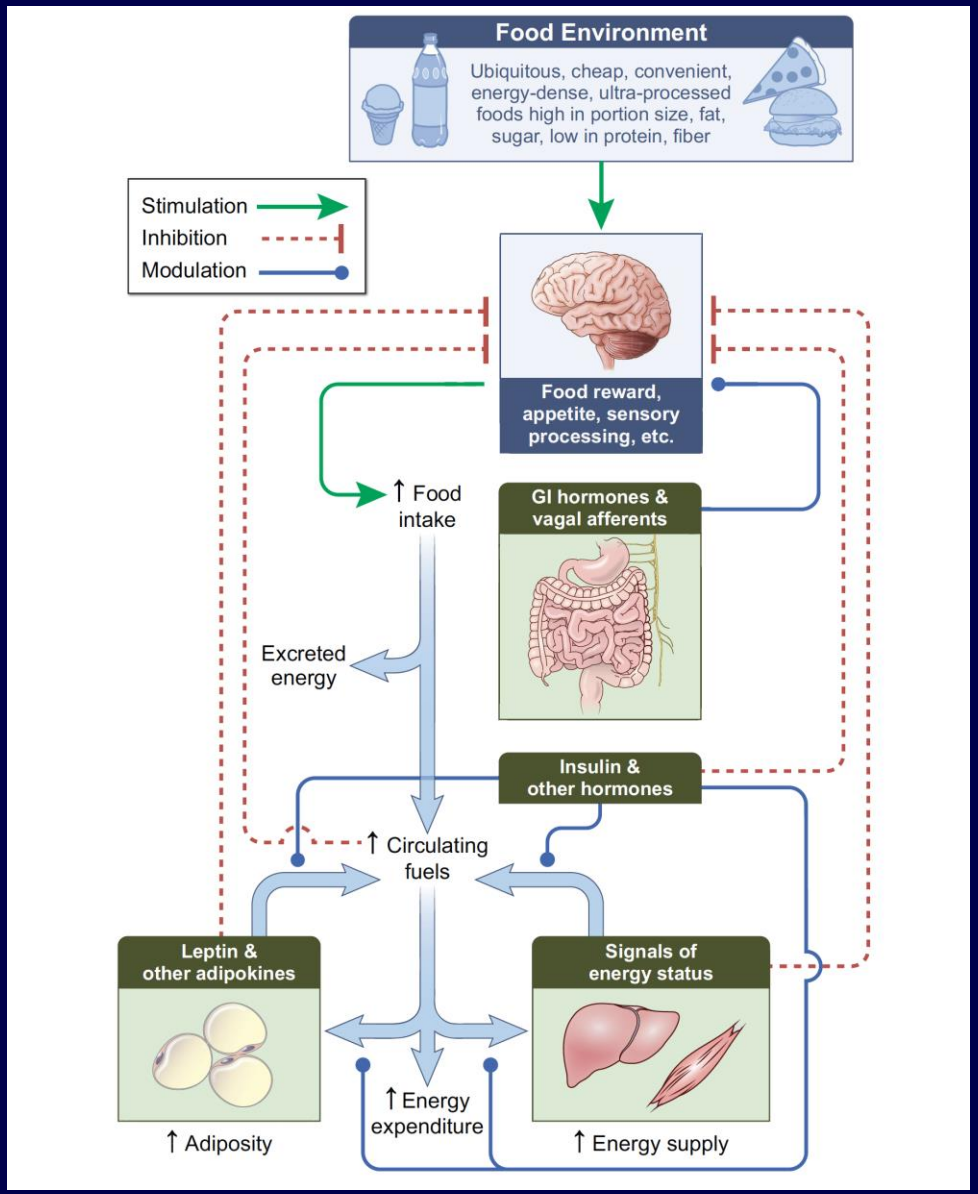
- Metabolic feeding trials long enough to allow for adaptation to changes in macronutrients (≥ 1 month)
- Behavioral obesity trials with sufficient intensity to promote long-term dietary change (≥ 1 year)
- Cohort studies, ideally beginning in childhood, with a mechanistic focus (≥ 10 years)

Importance of getting the science right

Simplistic notions of dietary fat, energy density

Energy Balance Model, 2000s

A focus on modern processed foods



"Ubiquitous, cheap, convenient, energy dense, ultra-processed foods high in portion size, fat, sugar, low in protein, fiber"

Hall et al. AJCN 2022,115:1243-1254

Focus on Food Processing in the New EBM

Risk of unintended consequences?

Great Debates in Nutrition

David S. Ludwig, Section Editor

great debates IN nutrition

See corresponding article on pages 1476 and 1489.

Does the concept of "ultra-processed foods" help inform dietary guidelines, beyond conventional classification systems? NO

TABLE 1 Examples of misclassification of foods as "unhealthy" compared with "healthy" by Nova classification

Healthfulness for weight control (based on scientific evidence)	Healthy by Nova (unprocessed or minimally processed)	Unhealthy by Nova (ultra-processed)
Neutral or beneficial		Pomace olive oil (i.e., extracted after the first olive pressing), noncaloric sweetened yogurts, prepared burger or pizza made on whole wheat flour, plant-based milk alternatives
Unhealthful	White rice, bread products produced with refined wheat or corn flour low in fiber, fruit juice, cream, homemade burger or pizza made with refined wheat flour	

Astrup et al. Am J Clin Nutr 2022, 116:1482-1488

Food Processing from a CIM Perspective

Critical effect of macronutrients

CARBS – ***Major*** *differences in digestion rate, heath outcomes*

- Wheatberries → → → → → white bread
- Steal-cut oats → → → → → instant oatmeal
- Whole fruit → → → → → → fruit juice

Food Processing from a CIM Perspective

Critical effect of macronutrients

CARBS – ***Major*** *differences in digestion rate, heath outcomes*

- Wheatberries → → → → → white bread
- Steal-cut oats → → → → → instant oatmeal
- Whole fruit → → → → → → fruit juice

FATS – ***No major*** *differences in digestion rate, heath outcomes*

- Olives → → → → → → → → olive oil
- Peanuts → → → → → → → peanut butter
- Avocado → → → → → → → guacamole

PROTEINS – ***No major*** *differences in digestion rate, heath outcomes*

- Steak → → → → → → → → hamburger
- Soybean → → → → → → → tofu
- Boiled egg → → → → → → scrambled egg

Provocative, But Not New

"one of the causes of hyperinsulinism [and hypoglycemia] is the excessive ingestion of glucose-forming foods and that, as the result of overactivity induced by overeating, the islands of Langerhans become exhausted and . . . (diabetes) follows. It is possible that the hunger incident to hyperinsulinism may be a cause of overeating, and, therefore, the obesity that so often precedes diabetes.

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Seale Harris (colleague of Fredrick Banting)
JAMA 1924