Eating Precisely: Merging Nutrition with Individualized Factors to Optimize Metabolic Health

Suneil K. Koliwad, MD, PhD

Chief of Endocrinology and Metabolism, UCSF Health

Gerold Grodsky/JAB Chair in Diabetes Research

Mount Zion Health Fund Distinguished Professor in Endocrinology

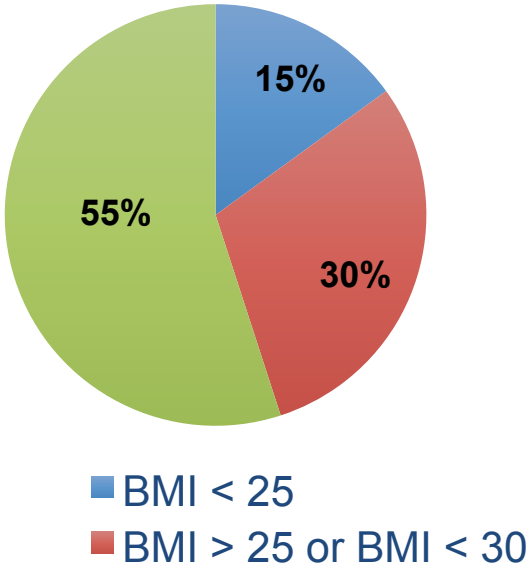
Cardiometabolic Health: Human Beings are Genetically and Functionally Heterogeneous

Human Heterogeneity: Cardiometabolic Health is a Classic Gene x Environment Interaction. Example: The Pima Indians

Subsistence….Lean….
NO DIABETES

Modernity….Obesity….
50% DIABETES!!!!

The Impact of Obesity on Diabetes Risk In the US Reflects Human Heterogeneity



Among people diagnosed with Type 2 diabetes,
55% are BMI ≥ 30 (obese),

30% are BMI ≥ 25 or ≤30 (overweight)

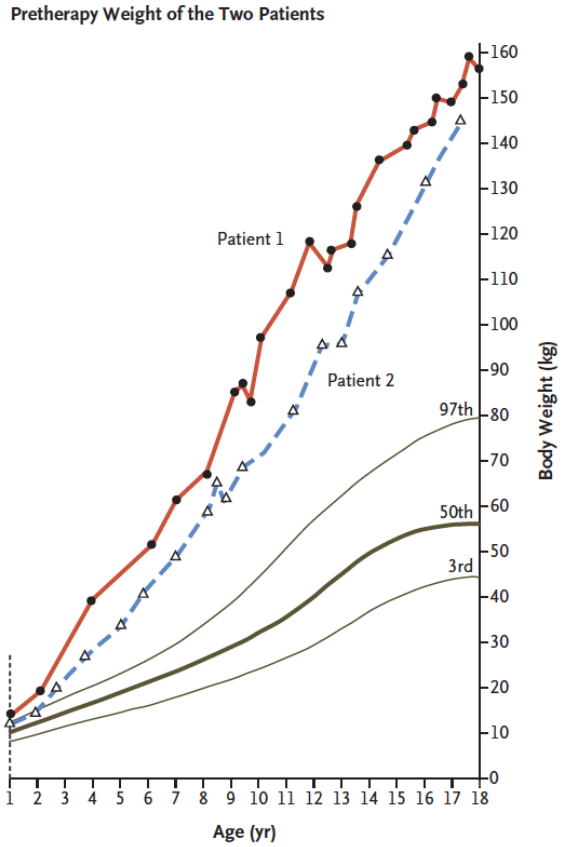
15 percent have a BMI ≤ 25 (classified as normal weight).

Moreover, ~70% of Overweight and Obese People do not develop T2DM!

Adapted from: http://www.obesityinamerica.org/trends.html

Obesity Alone is Not a Highly Penetrant Risk Factor

Two Individuals with POMC Mutations



Patient	1	2
Glucose (mg/dl)	65	76
Insulin (mU/L)	26.7	9.8
Triglycerides (mg/dl)	99	63
HbA1C	5%	5.4%

Kuhnen, et al., NEJM 2016

Precision Medicine: Understanding Ethnicity-Associated T2DM Risk

China and Japan : overweight BMI of 24, obesity BMI > 28.
India: overweight BMI of 23, and obesity BMI > 27

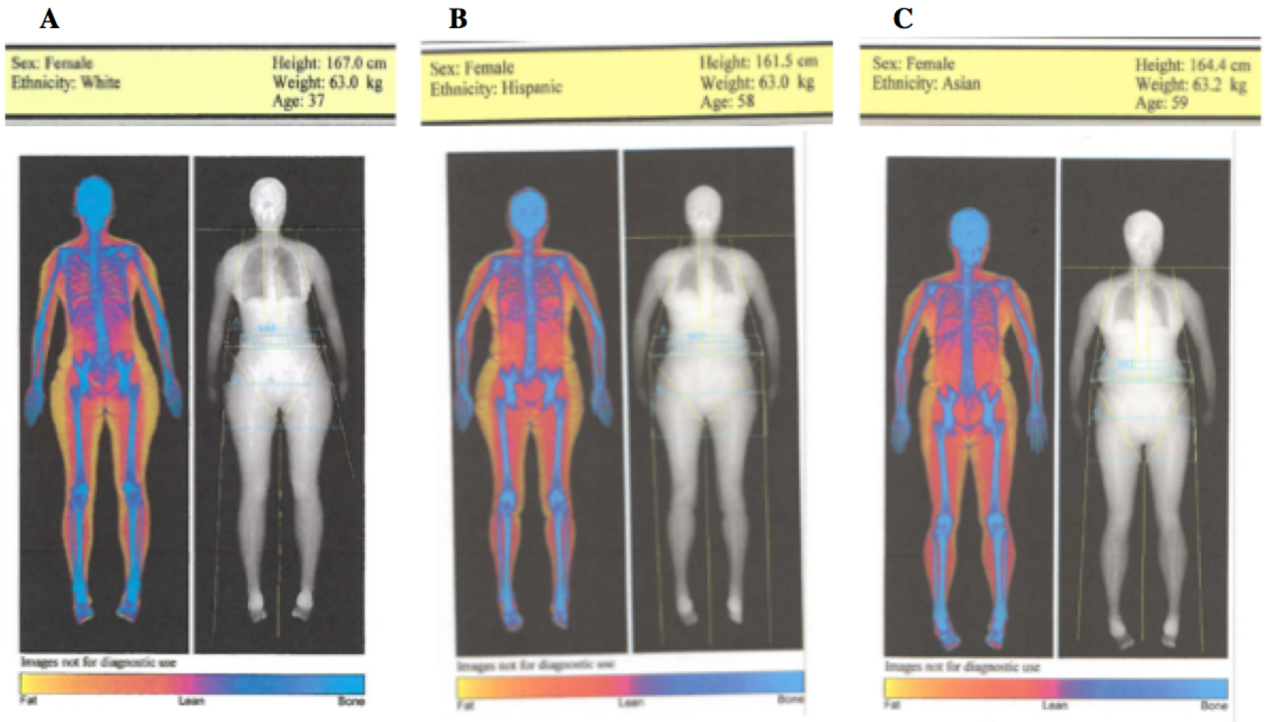
http://screenat23.org

Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet*. 2004;

Non-Obese People can be Insulin Resistant

Clausen et al. JCI 98:1195 (1996)

IDEO: A Cohort Revealing Ethnicity-Specific Differences in Body Composition



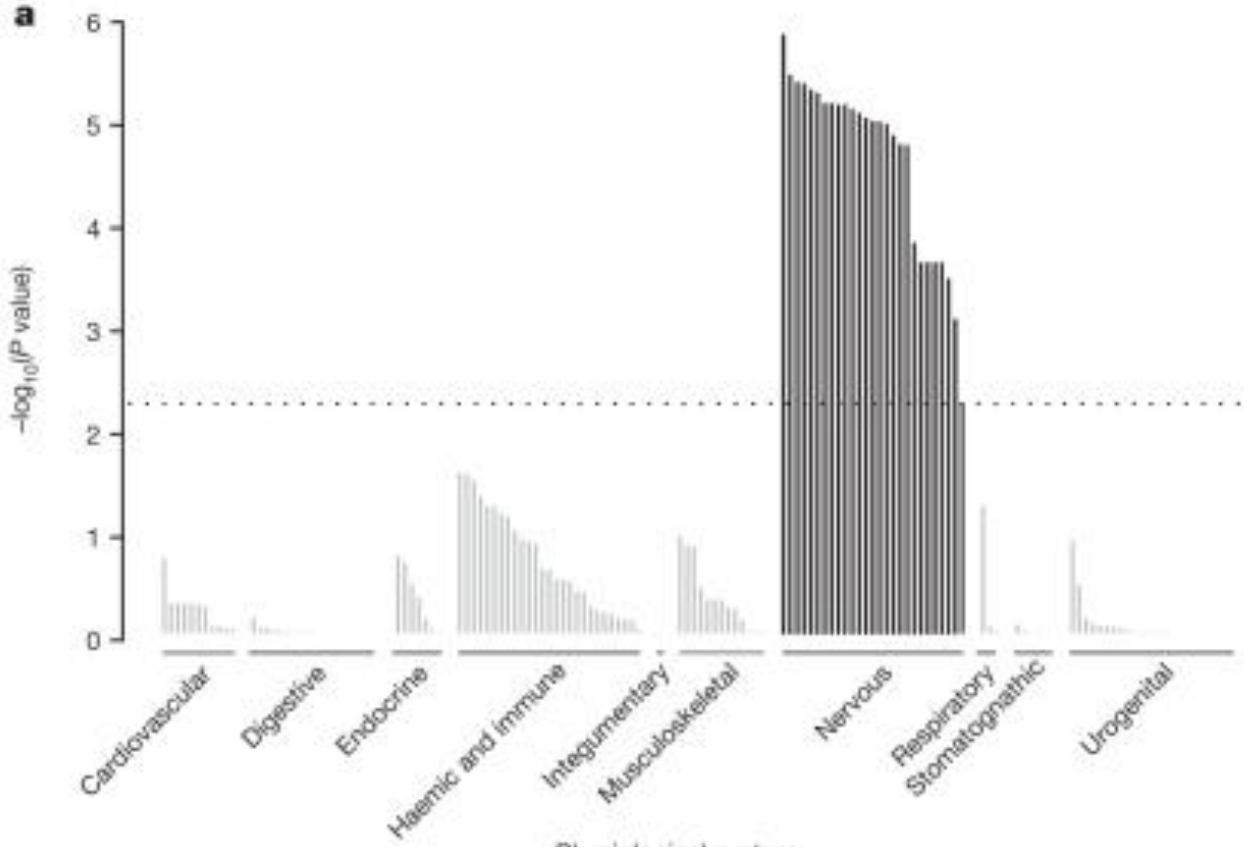
BMI: 22.6 kg/m^2
VWAT mass: 208 g

BMI: 24.2 kg/m^2
VWAT mass: 561 g

BMI: 23.4 kg/m^2
VWAT mass: 601 g

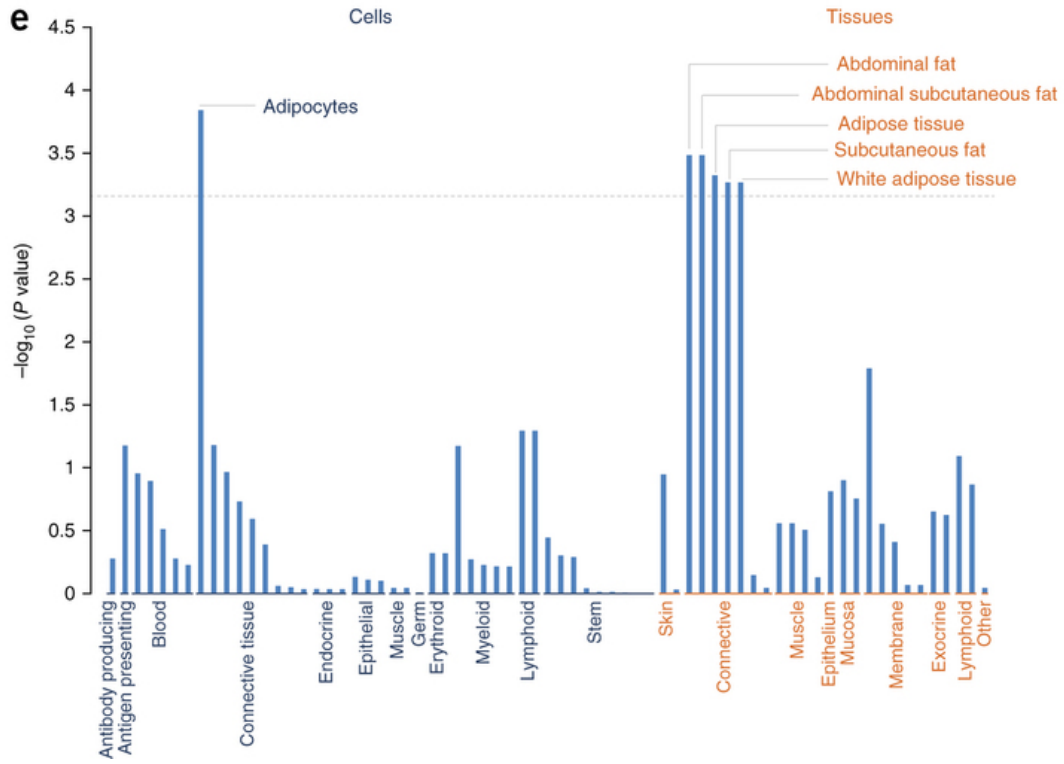
Diana Alba, Karin Sandlund, John Shepherd, UCSF Nutrition and Obesity Research Center (*NORC)*

GWAS Meta-Analysis: Heritable Component of BMI is Dominated by “Brain Genes”



Locke, et al. 2015. *Nature.* 518(7538): 197-206. DEPICT analysis

DEPICT: Heritable Aspect of Insulin Resistance is Dominated by Fat Tissue and Its Storage Capacity



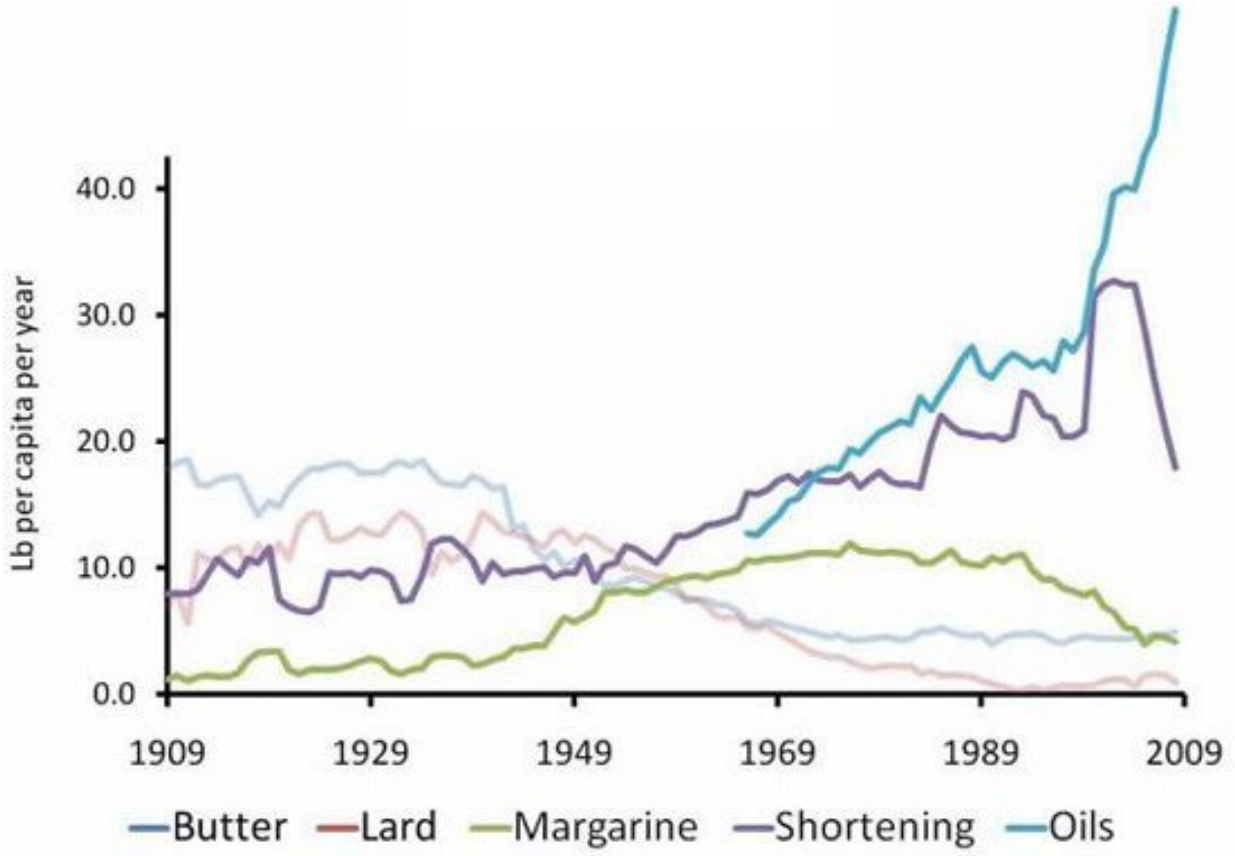
Lotta, et al. *Nature Genetics* 49, 17–26 (2017); Involved Two Large Cohorts and a PFLD1 Cohort

Dietary Overlay: A Deeper Understanding of Risks and Benefits

“Wonderbread” and The Story of Processed Carbohydrates

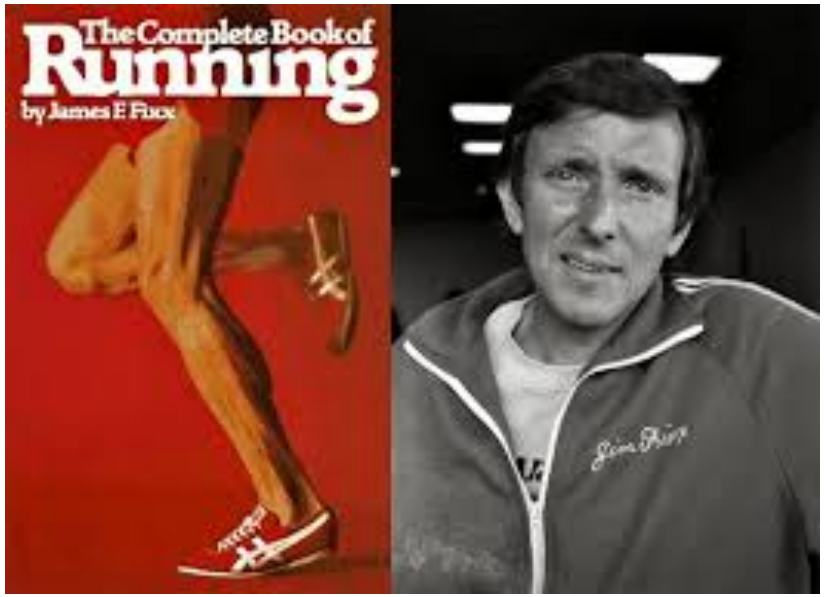
1980s: LDL-Cholesterol, Heart Disease, and the Low-Fat Diet

Success: A Half-Century of Lowering Dietary Fat

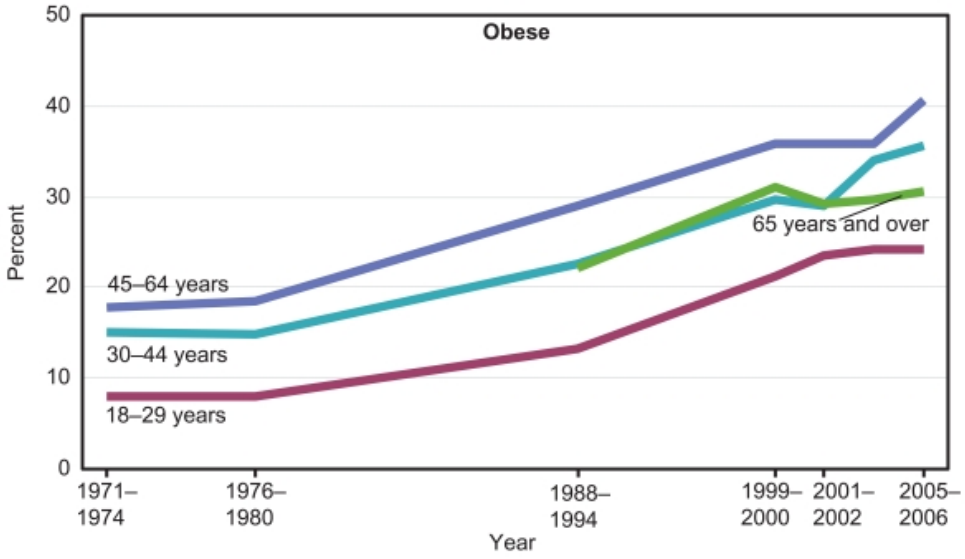


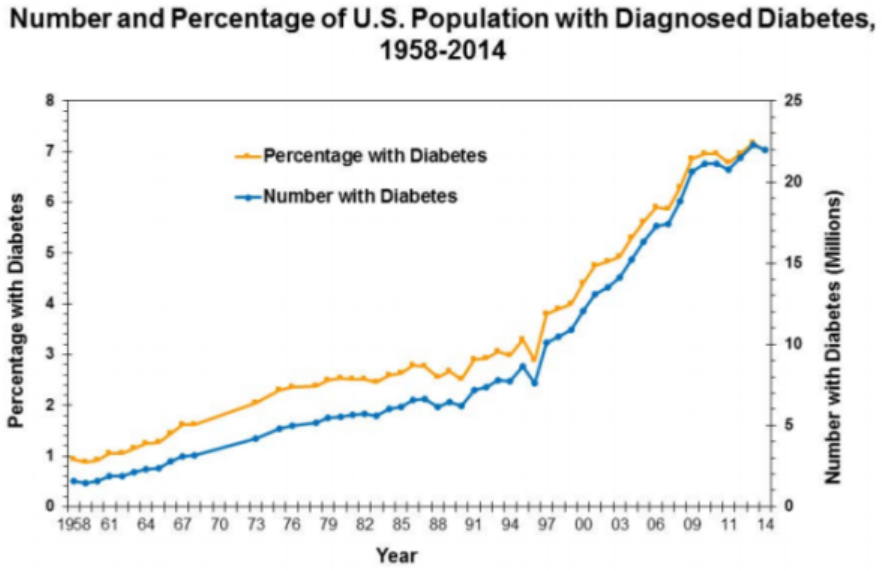
Stephan Guyenet "The American Diet" 2012

Dietary Fat, Smoking, and Sedentary Lifestyle are Not the Sole Contributors to Heart Disease Risk: Emerging Interaction Between Genetics and Other Dietary Components



Success?: Lowering Dietary Fat is Associated with Increased Rates of Obesity and Diabetes



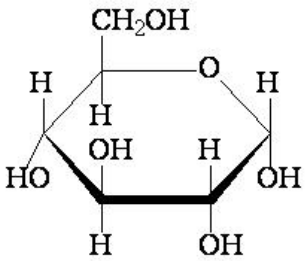


American Heart Association

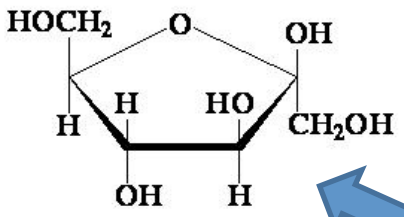
CDC's Division of Diabetes Translation

Low Fat Diets Increased the Consumption of Processed Carbohydrates

Sucrose and Fructose in Processed Carbohydrates

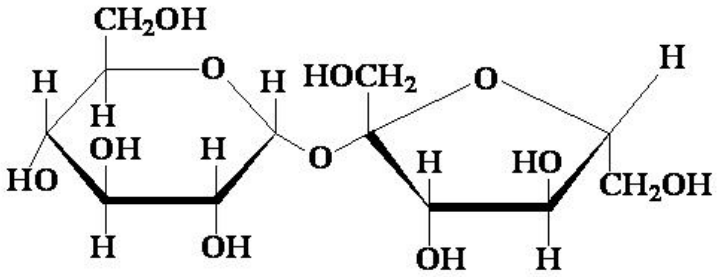


glucose



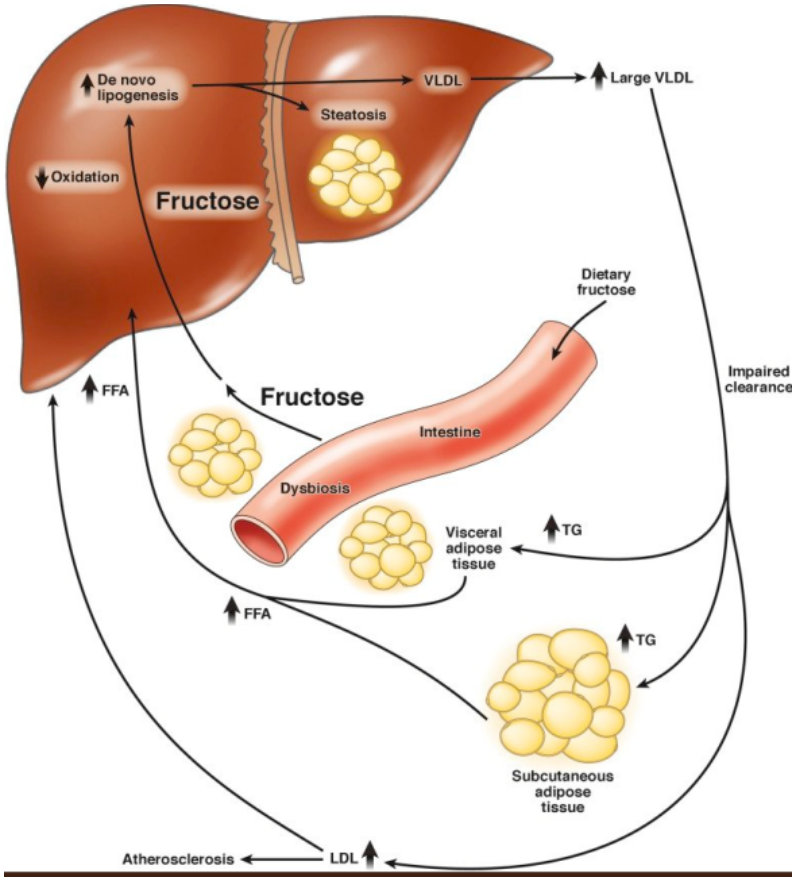
fructose

Unhealthy



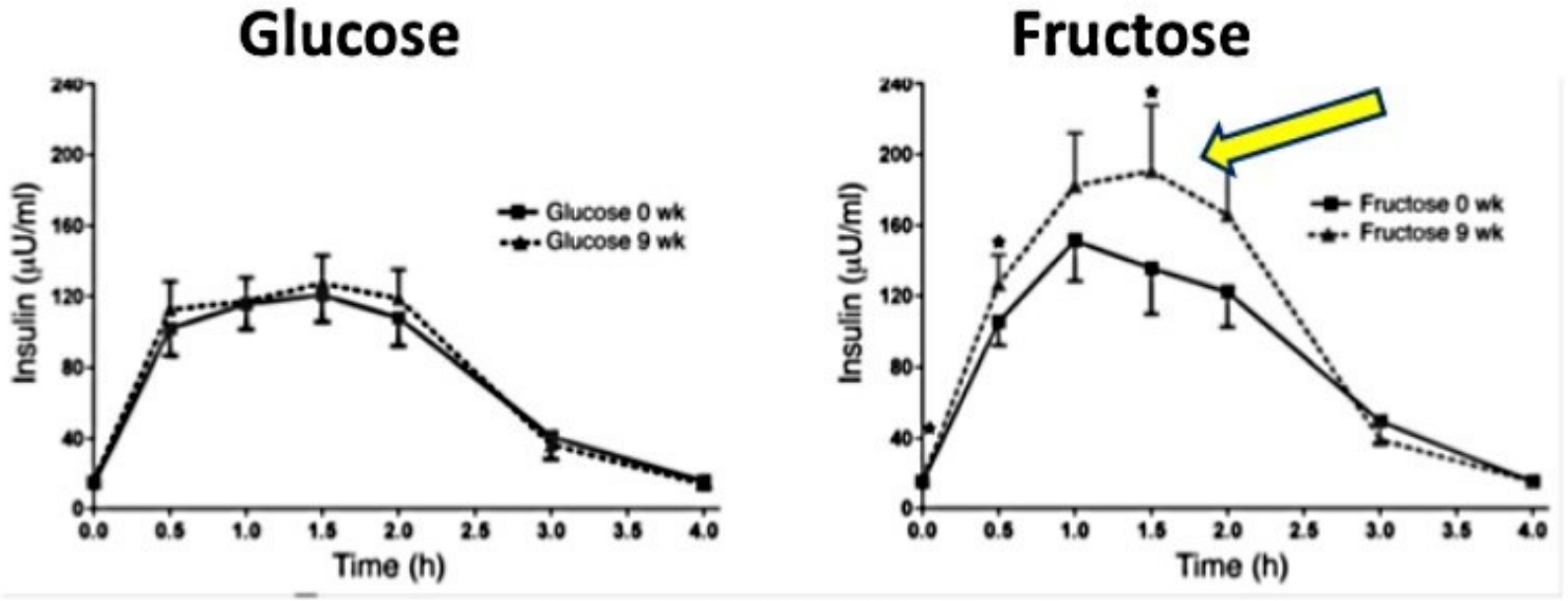
sucrose

Sugar: The Stealth Enemy of Metabolic Health



J-M Schwarz et al. Gastroenterol 2017; 153: 743-52, editorial MB Vos, IR Goran Gastroenterol 2017; 153: 642-5

Fructose Consumption Also Causes Hyperinsulinemia



JCI April 20, 2009 Havel et al.

Health Benefits of Minimizing Dietary Sugar

J-M Schwarz et al. Gastroenterol 2017; 153: 743-52, editorial MB Vos, IR Goran Gastroenterol 2017; 153: 642-5

Whole-Grain Processing and Glycemic Control in Type 2 Diabetes: A Randomized Crossover Trial

Sebastian Åberg,[1,2] Jim Mann,[1,3] Silke Neumann,[4] Alastair B. Ross,[5] and Andrew N. Reynolds[1,3]

https://doi.org/10.2337/dc20-0263

Table 1—Nutrient information of intervention foods

	Less-processed whole-grain intervention			Finely milled whole-grain intervention		
	Traditional oats (cooked)	Brown rice (cooked)	Coarsely milled bread	Instant oats (cooked)	Brown rice pasta (cooked)	Finely milled bread
Nutrients per 100 g						
Energy (kJ)	512	850	862	512	822	852
Carbohydrates (g)	18.4	39.5	35.77	18.4	40.5	36.49
Protein (g)	4.8	4.9	6.99	4.8	4.3	7.03
Fat (g)	2.3	2.2	2.45	2.3	1.6	1.79
Fiber (g)	4.0	1.6	9.2	4.0	1.4	9.1
Sodium (mg)	<5	<5	290	<5	6.5	290
Retention of whole grains on particle-size sieves (μm), %						
>2,800	93	0	23	40	0*	0
1,000–2,799	7	100	39	52	0*	0
180–999	0	0	16	4	6*	59
<180	0	0	22	4	94*	41

*These measurements were made on brown rice flour as the only listed ingredient in brown rice pasta.

Whole-Grain Processing and Glycemic Control in Type 2 Diabetes: A Randomized Crossover Trial

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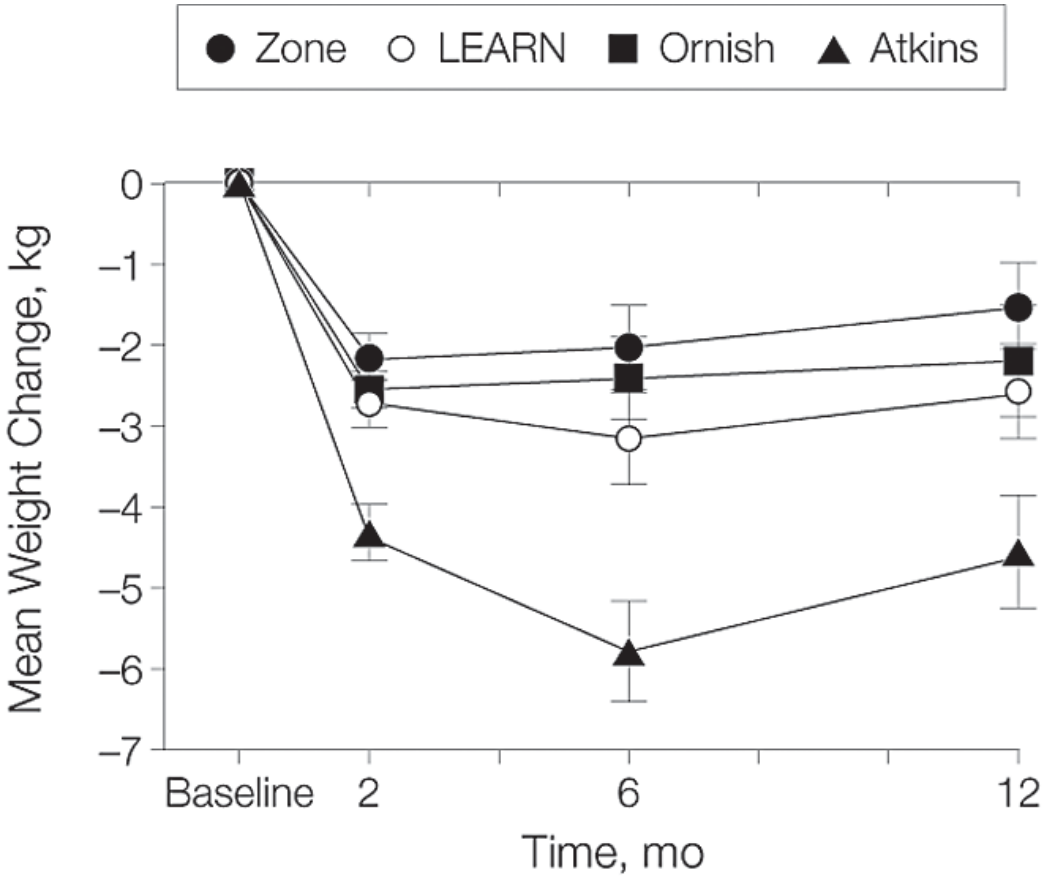
https://doi.org/10.2337/dc20-0263

Table 3—Measures of glycemia calculated from CGM

Measure	Less-processed whole grains	Finely milled whole grains	*P* value difference between interventions	*P* value interaction with weight change
Meal responses (mmol/L/min)				
All-meal iAUC	423 ± 210	466 ± 192	0.022	0.555
Breakfast iAUC	449 ± 256	525 ± 248	0.007	0.984
Lunch iAUC	412 ± 287	440 ± 304	0.614	0.321
Dinner iAUC	391 ± 293	415 ± 277	0.117	0.118

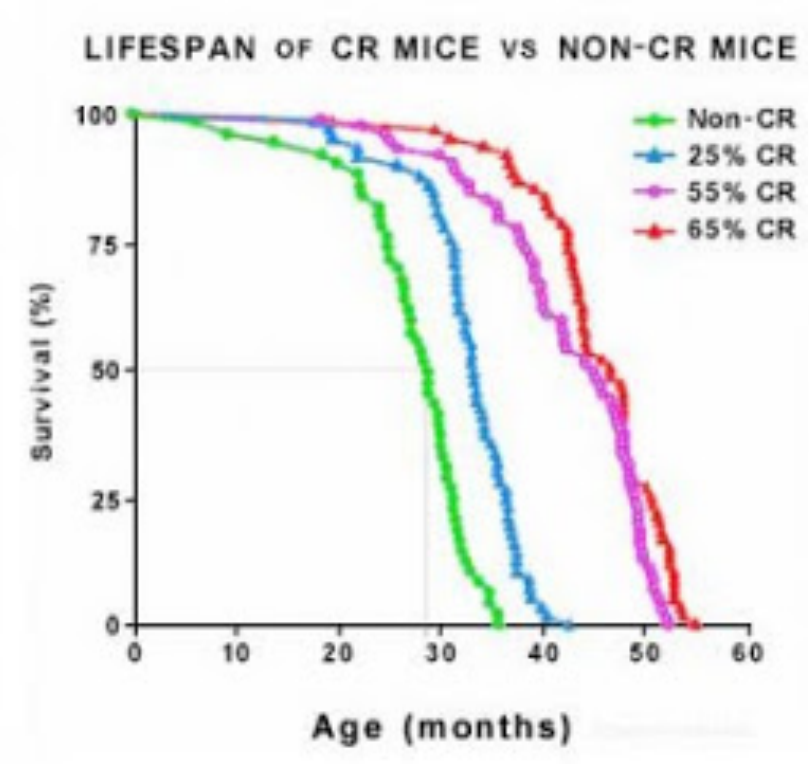
Calories and Dieting For Weight Loss vs Healthspan

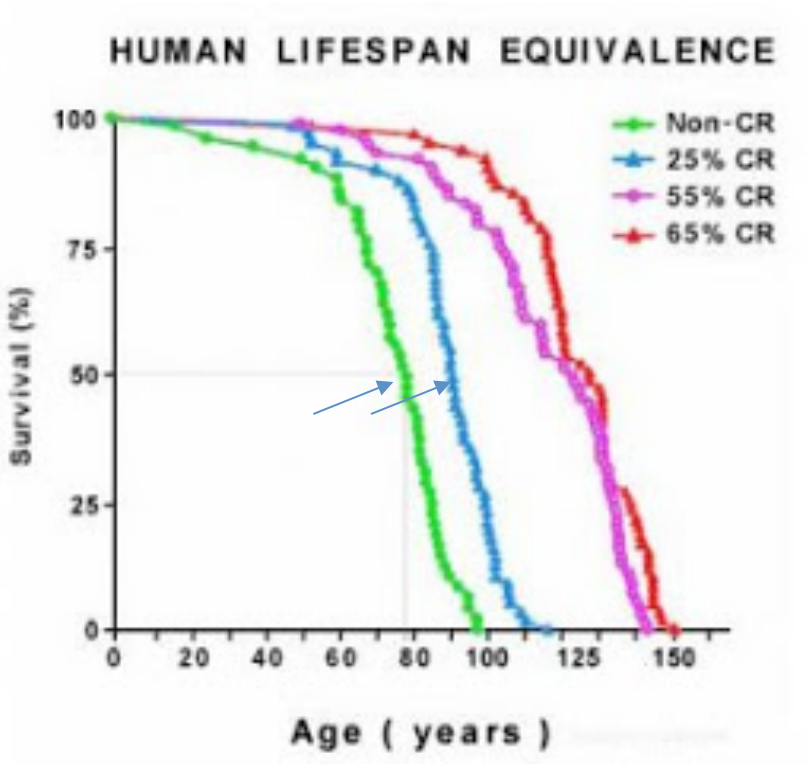
All Diets Produce Weight Loss! (But The Effects Don't Last)



Gardner, C. D. et al. JAMA 2007;297:969-977.

Simply Reducing Overall Caloric Intake Increases both Lifespan and Healthspan





Caveats: Multiple inputs beyond calories, and interaction with individual genetics

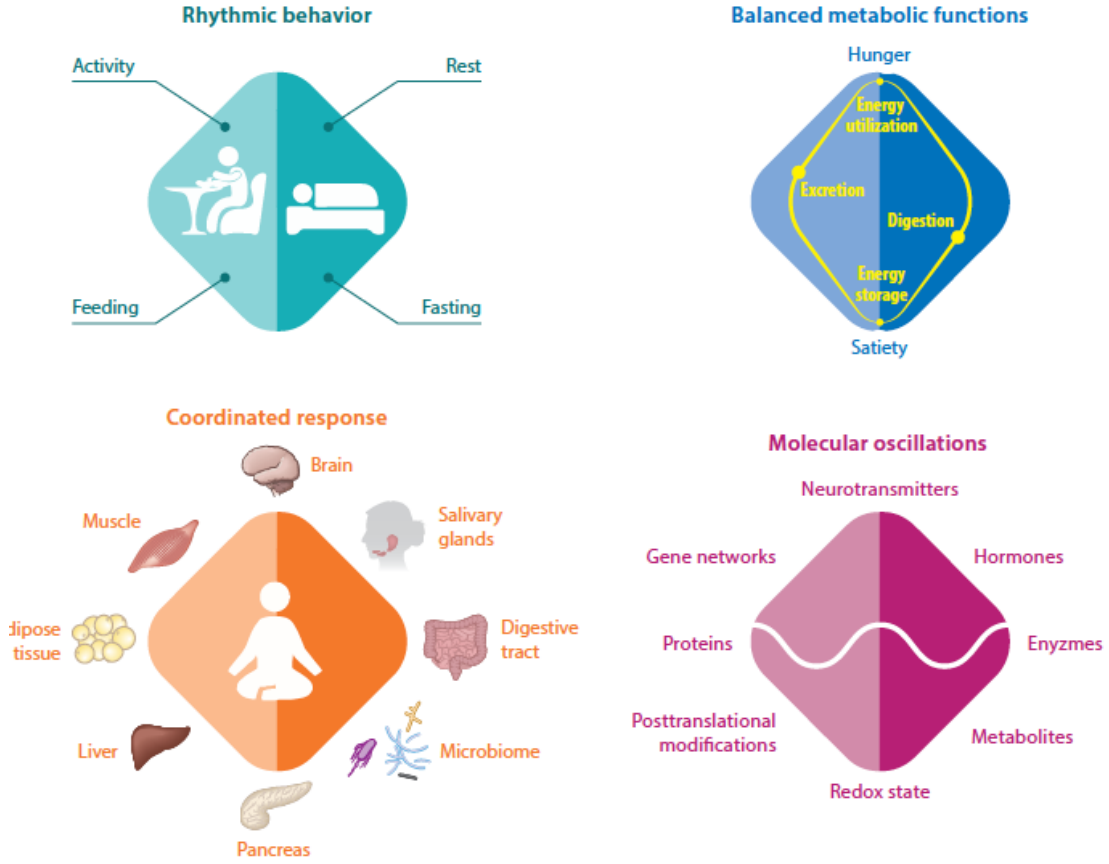
Luigi Fontana,*† Timothy E. Meyer,* Samuel Klein,* and John O. Holloszy*
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC404101/

Simply Reducing Overall Caloric Intake Increases both Lifespan and Healthspan

Goal: Discover potentially “druggable” mechanisms underlying this,
and biomarkers to indicate responders and non-responders to facilitate precision medicine

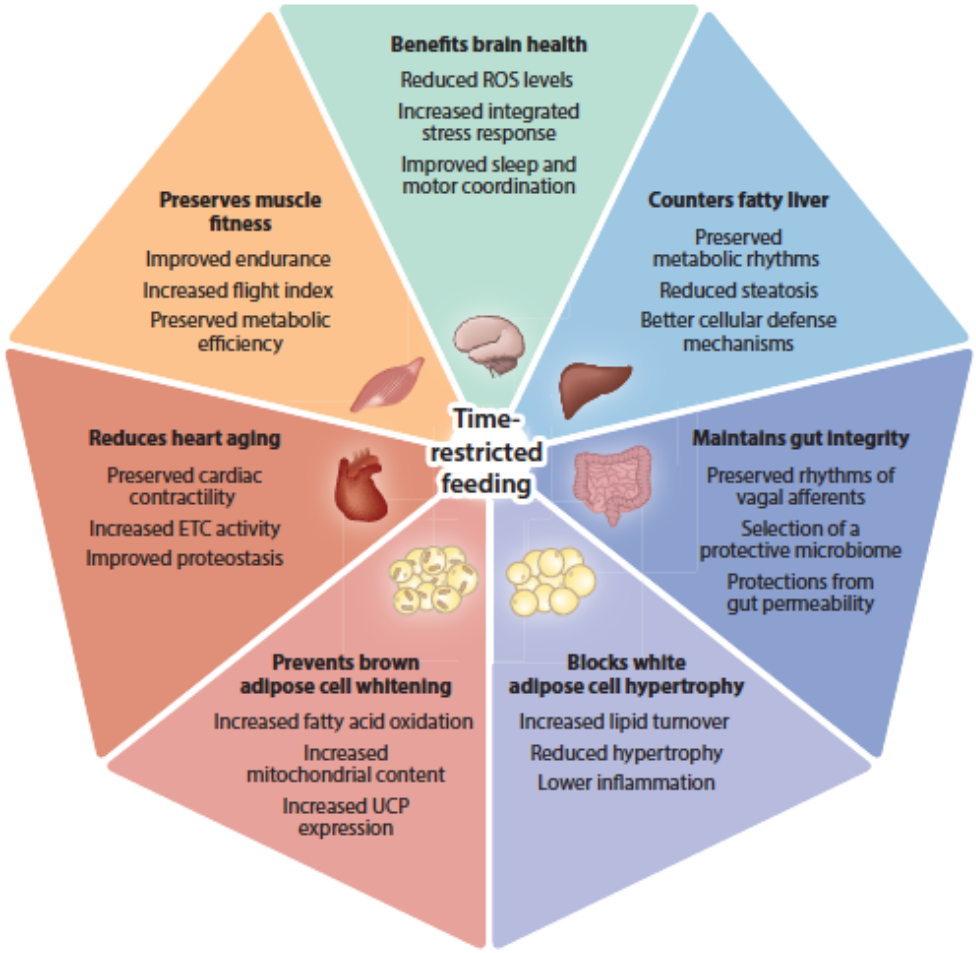
Ricki J. Colman, Mark T. Beasley, David B. Allison, and Richard Weindruch
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2812805/

Fasting: Levering our Biological and Metabolic Clocks to Recapture Health Benefits of CR



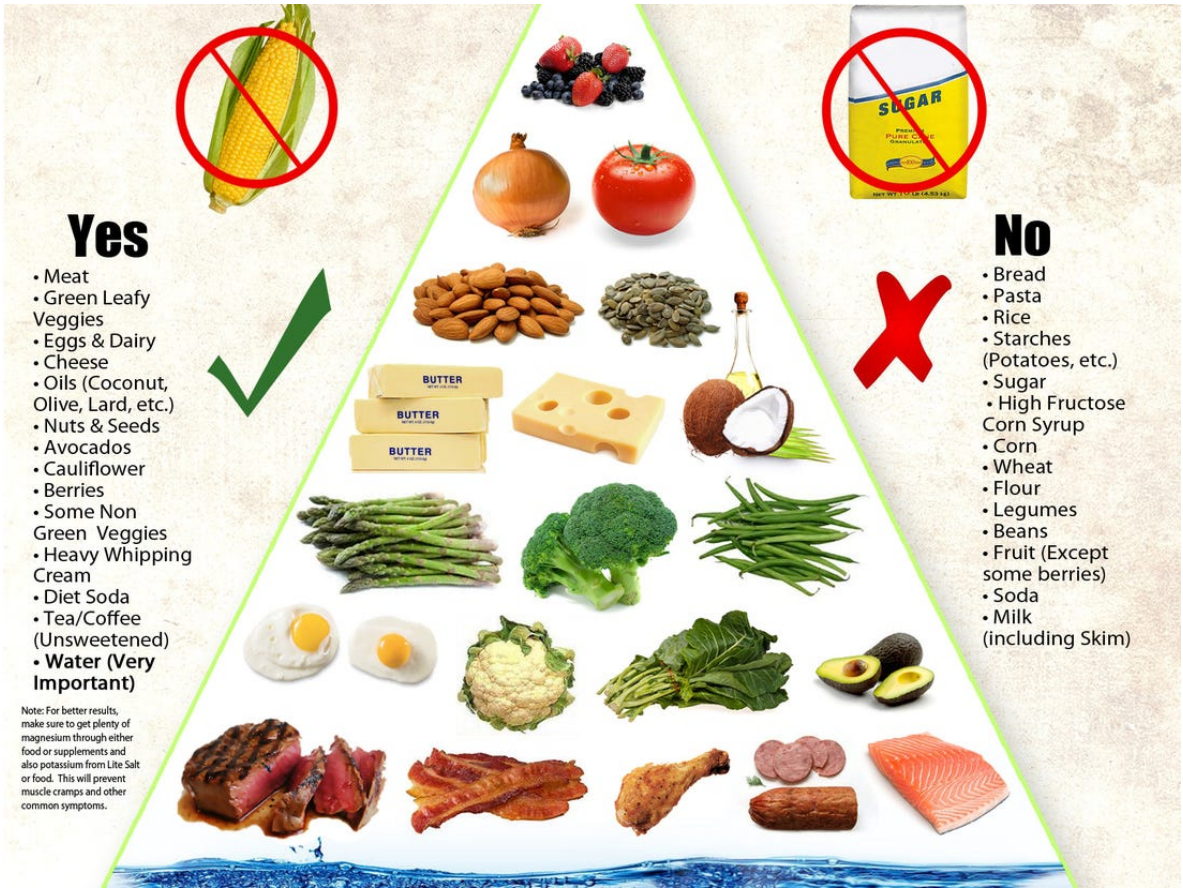
Chaix, Manoogian, Melkani, and Panda. S. Annu. Rev. Nutr. 2019. 39: 291-315.

TRF: Levering our Biological and Metabolic Clocks to Recapture Health Benefits of CR



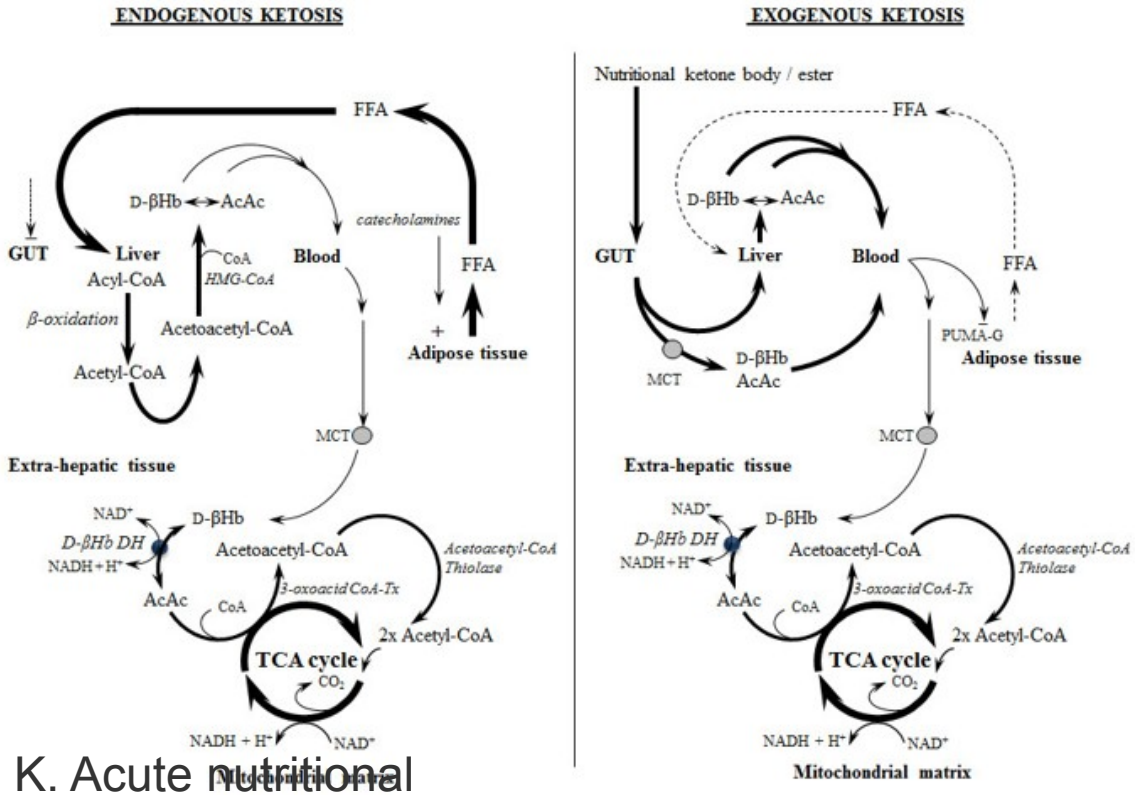
Chaix, Manoogian, Melkani, and Panda. S. Annu. Rev. Nutr. 2019. 39: 291-315.

The Ketogenic Diet: Dietary Recapitulation of Fasting



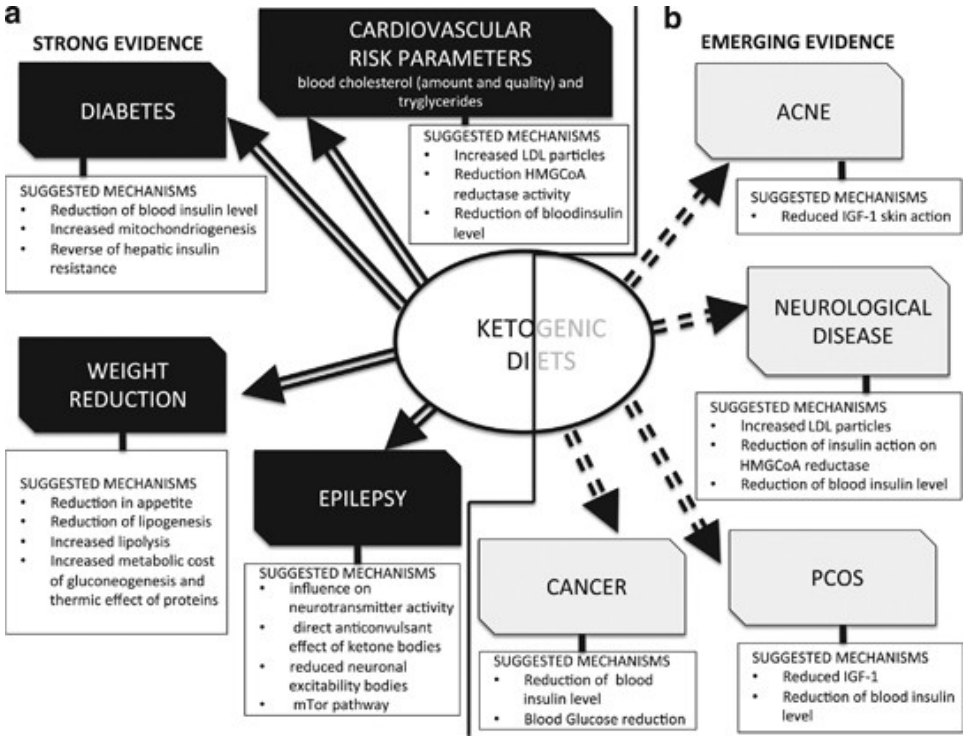
M. Robinson, Business Insider 2017.

The Ketogenic Diet: Metabolic Impacts



Cox, P.J., Clarke, K. Acute nutritional ketosis: implications for exercise performance and metabolism. *Extrem Physiol Med* **3,** 17 (2014).

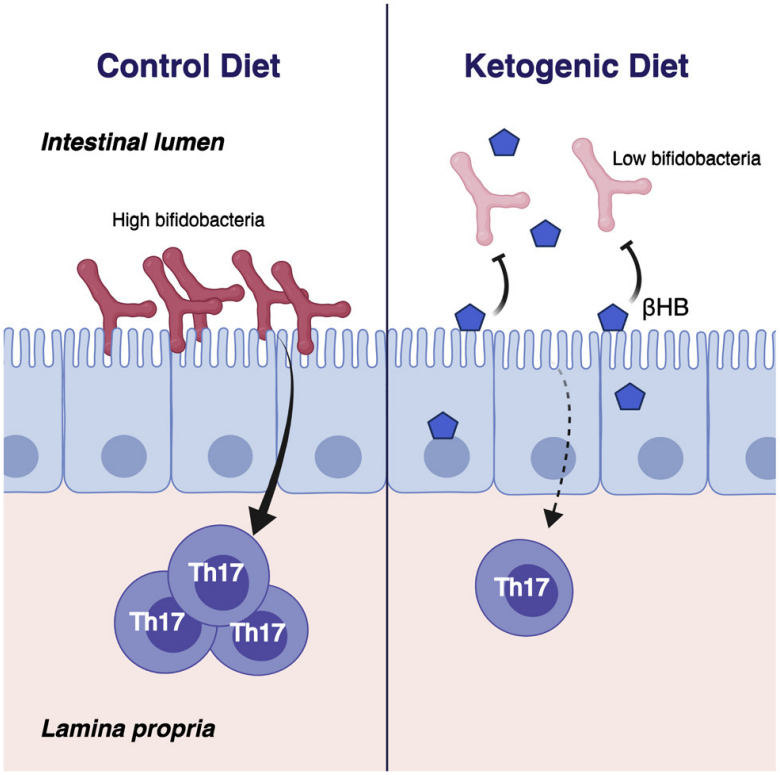
The Ketogenic Diet: Potential Health Benefits



Caveat: Most patients in Keto Studies are obese.
Extrapolation to a diverse population across multiple ethnicities not yet done.
Likely responders and non-responders, with biomarkers needed!

Paoli, A., Rubini, A., Volek, J. *et al.* Beyond weight loss: a review of the therapeutic uses of very-low-carbohydrate (ketogenic) diets. *Eur J Clin Nutr* **67,** 789–796 (2013).

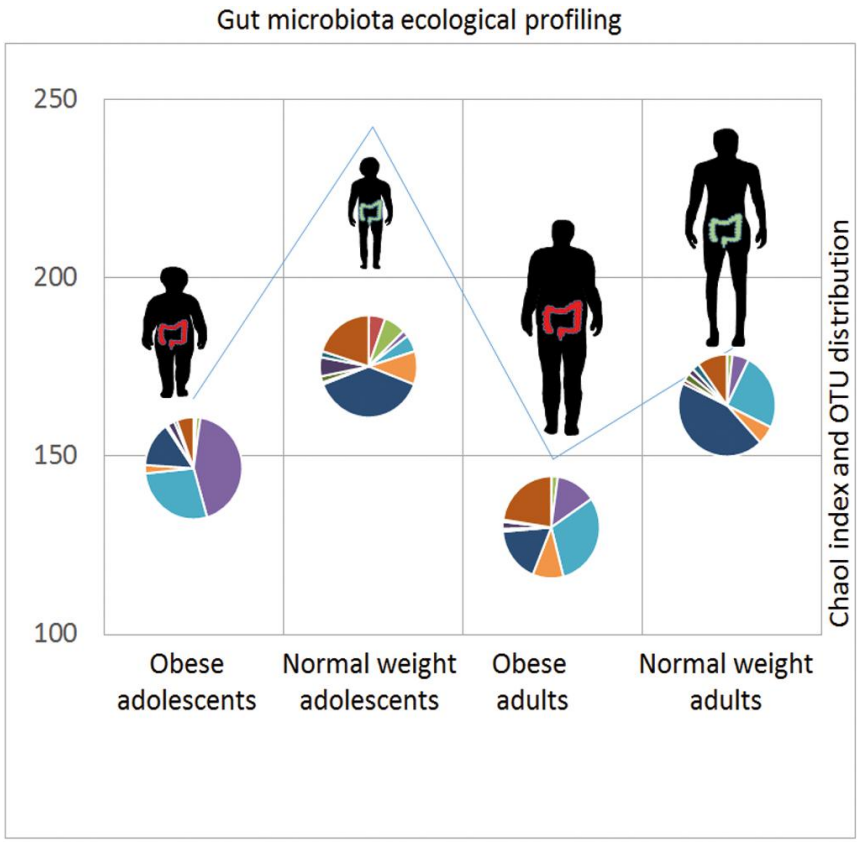
The Gut Microbiome May Link the Ketogenic Diet To Immunological Health:

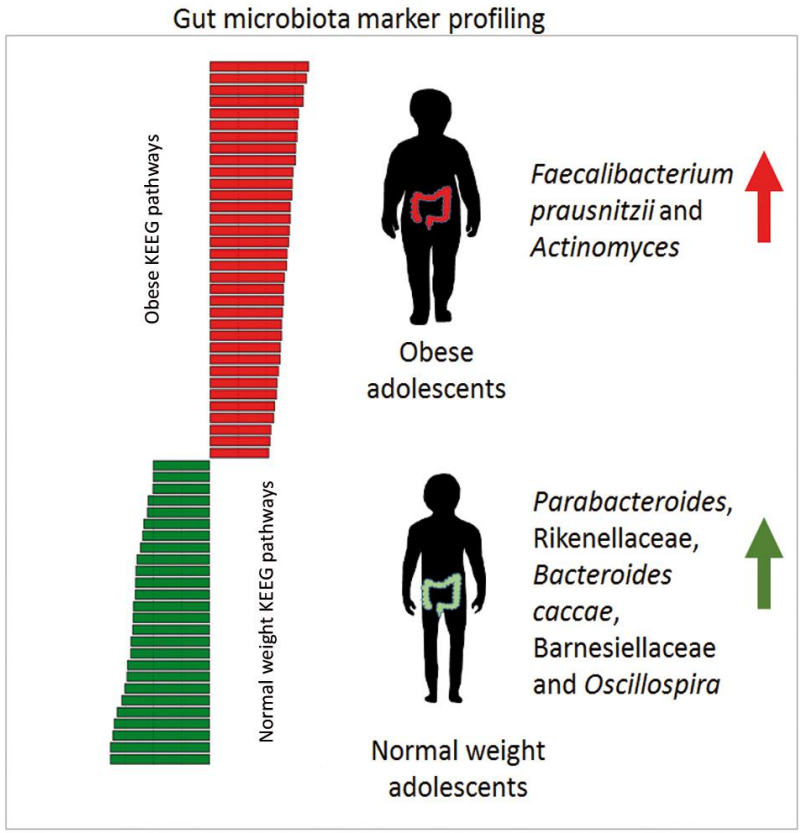


Ketogenic Diets Alter the Gut Microbiome Resulting in Decreased Intestinal Th17 Cells. Ang QY… Turnbaugh PJ., et al. Cell. 2020. S0092-8674(20)30490-6

Further Precision: Age, Genetics, and Diet Interact with the Microbiome

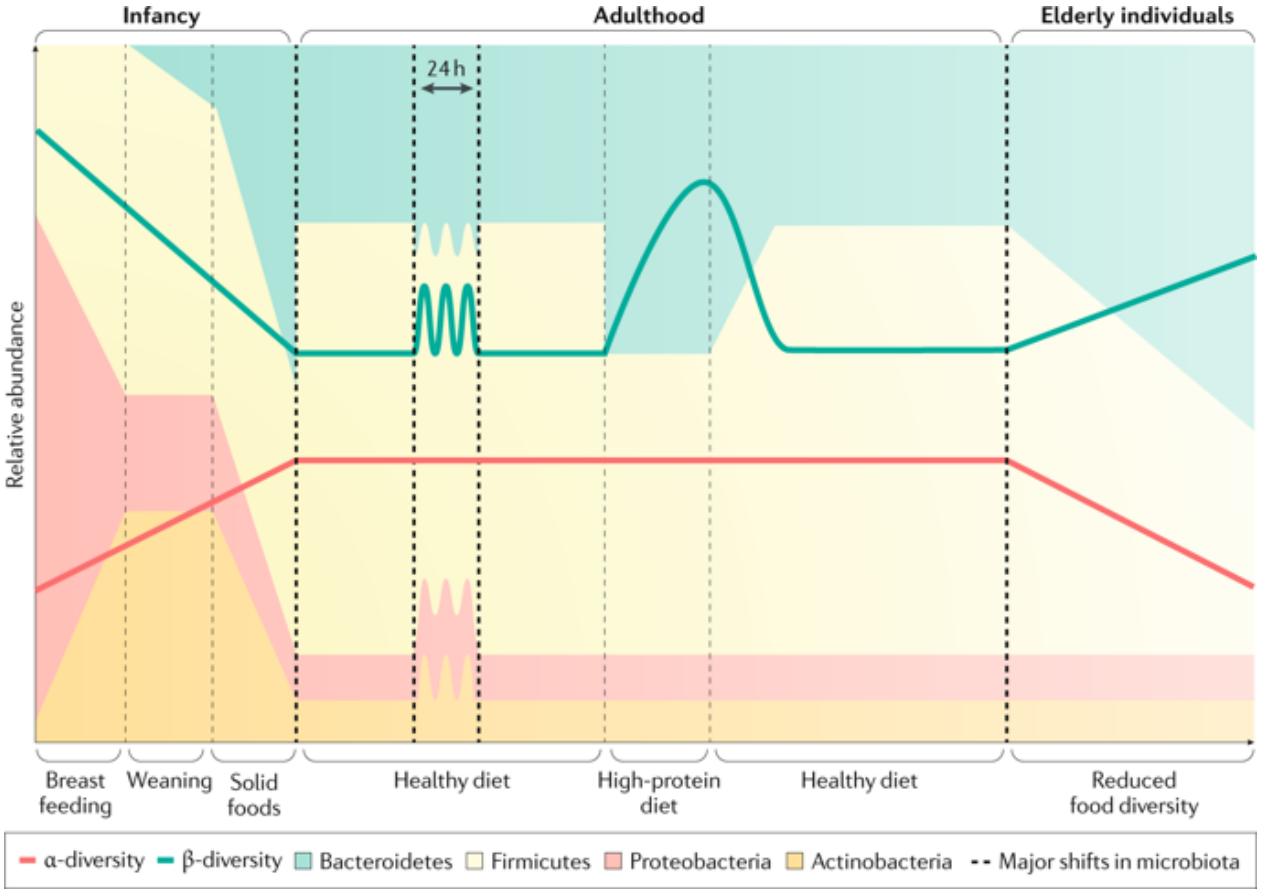
Impact of Age and Obesity on the Composition of Gut Microbiota





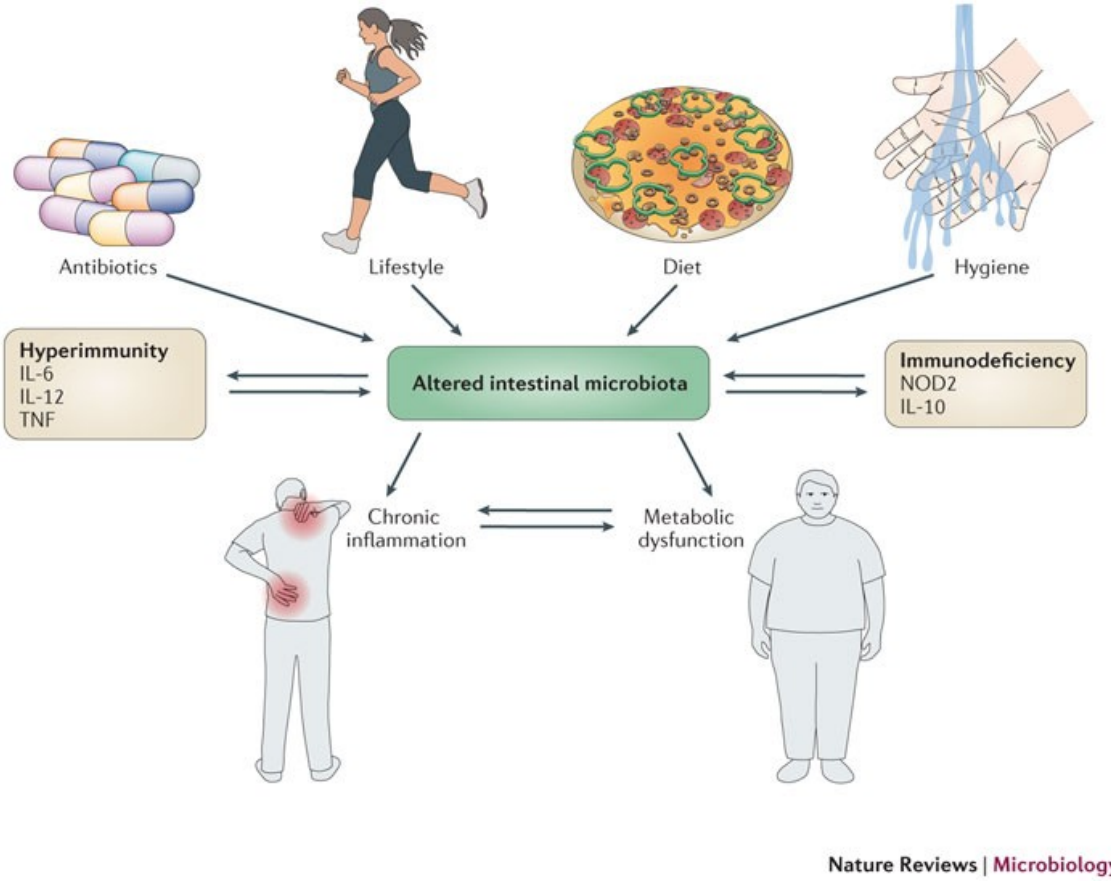
Del Chierico, et al. Front. Microbiol., 05 June 2018

You are What You Eat: Diet, Health and the Gut Microbiota.



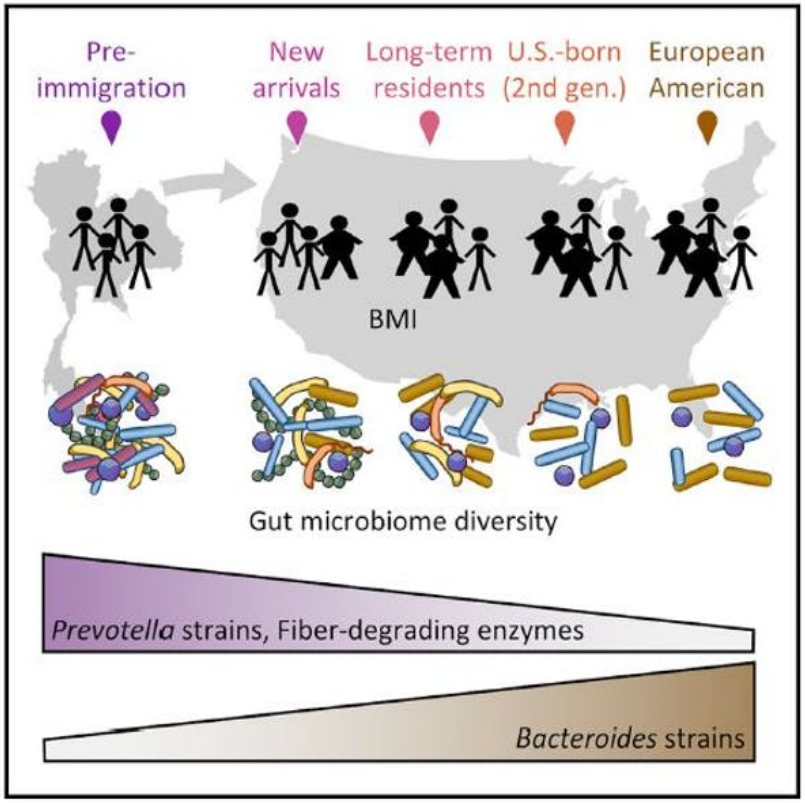
Zmora, N., Suez, J. & Elinav, E. *Nat Rev Gastroenterol Hepatol* **16,** 35–56 (2019).

Dysbiosis: Disease Manifestations of an Altered Gut Microbiome



Sommer, F., Bäckhed, F. The gut microbiota — masters of host development and physiology. *Nat Rev Microbiol* **11,** 227–238 (2013).

Globalization: Impact of Western Lifestyles on the Gut Microbiota of US Immigrants.

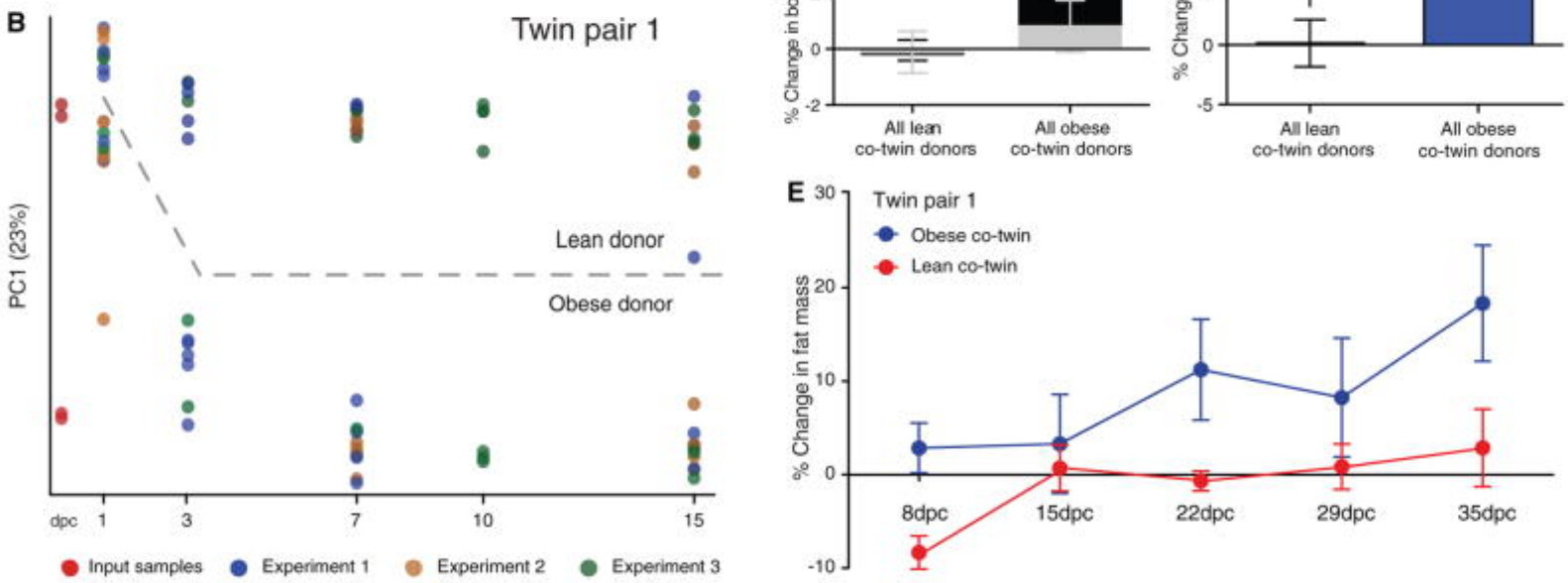


Vangay et al., 2018, Cell 175, 962–972 November 1, 2018

Gut microbiota from twins discordant for obesity modulate metabolism in mice

A

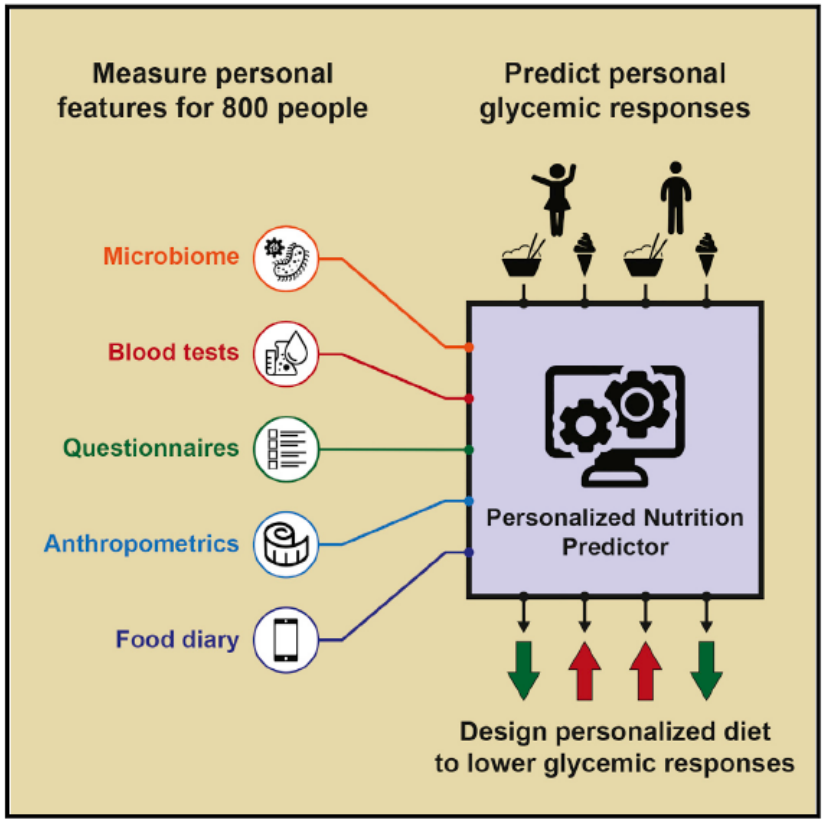
Twin Pair	1 (DZ)		2 (DZ)		3 (DZ)		4 (MZ)	
BMI (kg/m²)	23	32	25.5	31	19.5	30.7	24	33



Ridaura VK, Faith JJ, Rey FE, et al.. *Science*. 2013;341(6150):1241214.

Personalized Nutrition by Prediction of Glycemic Responses

Graphical Abstract



Authors

David Zeevi, Tal Korem, Niv Zmora, ..., Zamir Halpern, Eran Elinav, Eran Segal

Correspondence

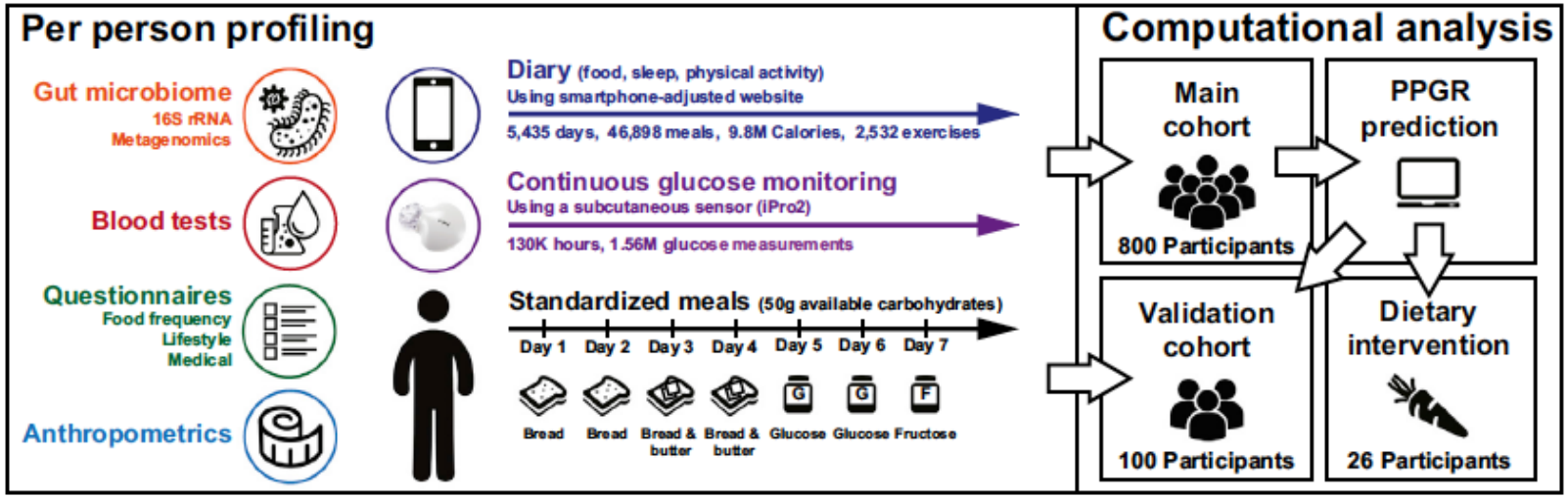
eran.elinav@weizmann.ac.il (E.E.), eran.segal@weizmann.ac.il (E.S.)

In Brief

People eating identical meals present high variability in post-meal blood glucose response. Personalized diets created with the help of an accurate predictor of blood glucose response that integrates parameters such as dietary habits, physical activity, and gut microbiota may successfully lower post-meal blood glucose and its long-term metabolic consequences.

Zeevi, et al. Cell. 2015.

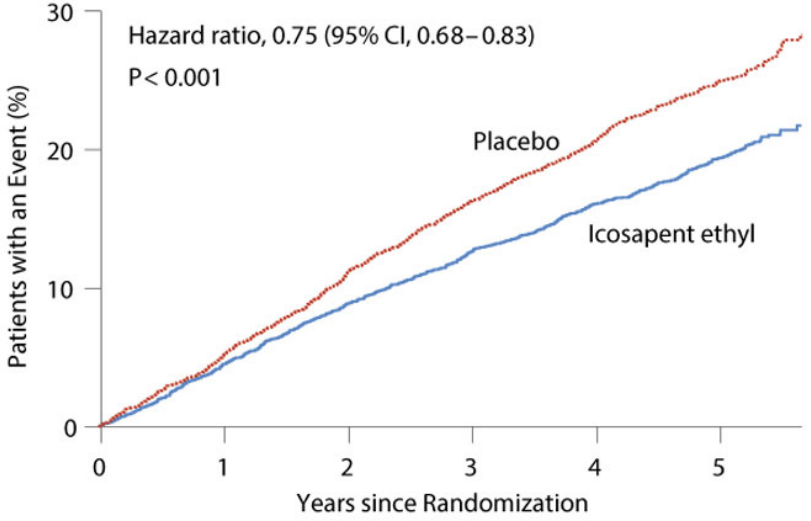
Personalized Nutrition by Prediction of Metabolic Responses



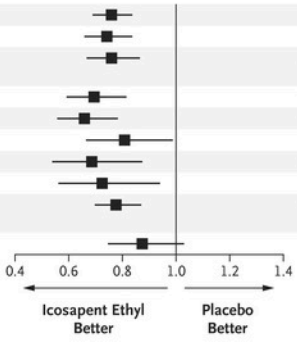
Zeevi, et al. Cell. 2015.

Full Circle: A More Precise Concept of Dietary Fats

Icosapent Ethyl: EPA as a Nutraceutical



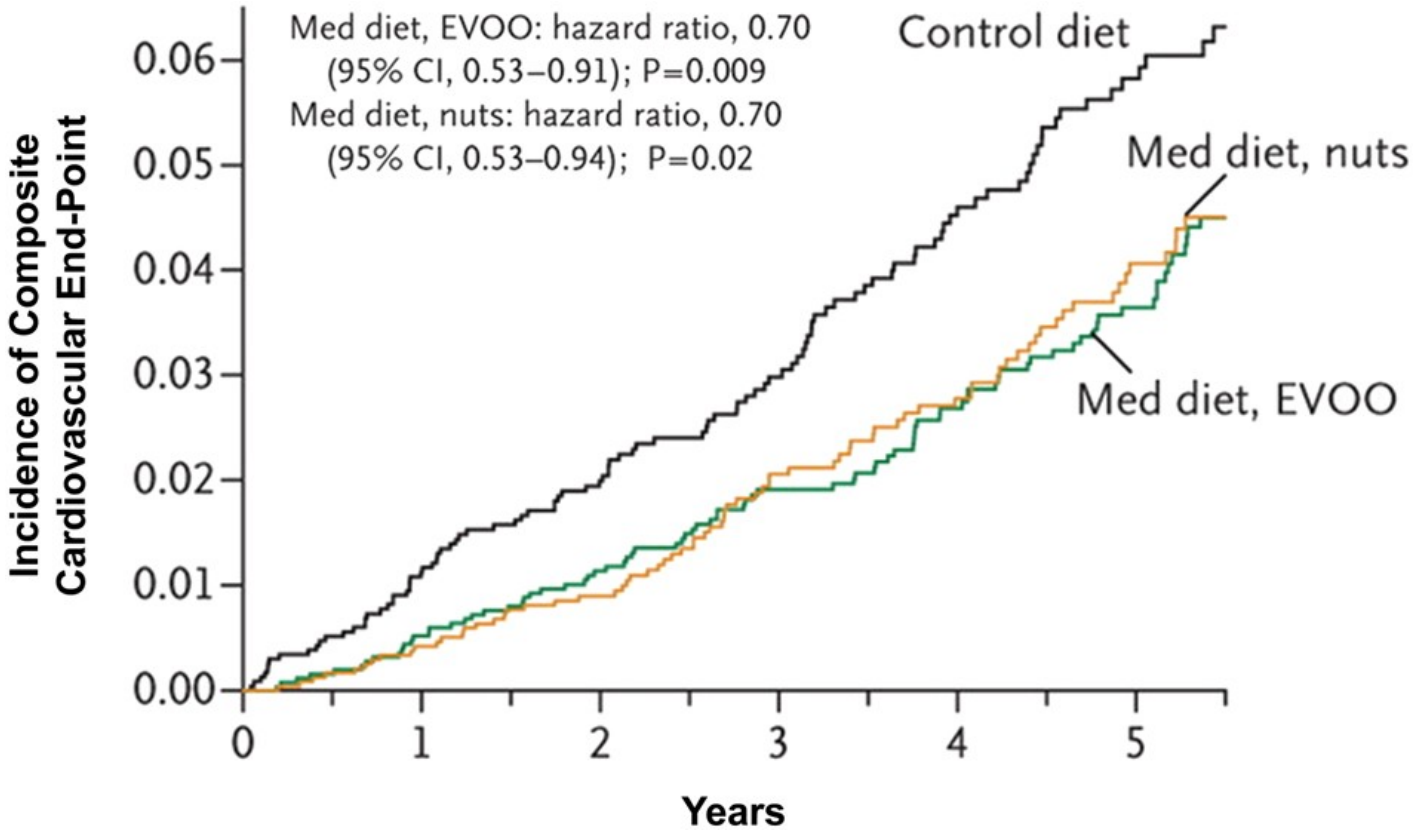
End Point	Icosapent Ethyl (N=4089)	Placebo (N=4090)	Hazard Ratio (95% CI)	P Value
	no. of patients with event (%)			
Primary composite	705 (17.2)	901 (22.0)	0.75 (0.68–0.83)	<0.001
Key secondary composite	459 (11.2)	606 (14.8)	0.74 (0.65–0.83)	<0.001
Cardiovascular death or nonfatal myocardial infarction	392 (9.6)	507 (12.4)	0.75 (0.66–0.86)	<0.001
Fatal or nonfatal myocardial infarction	250 (6.1)	355 (8.7)	0.69 (0.58–0.81)	<0.001
Urgent or emergency revascularization	216 (5.3)	321 (7.8)	0.65 (0.55–0.78)	<0.001
Cardiovascular death	174 (4.3)	213 (5.2)	0.80 (0.66–0.98)	0.03
Hospitalization for unstable angina	108 (2.6)	157 (3.8)	0.68 (0.53–0.87)	0.002
Fatal or nonfatal stroke	98 (2.4)	134 (3.3)	0.72 (0.55–0.93)	0.01
Death from any cause, nonfatal myocardial infarction, or nonfatal stroke	549 (13.4)	690 (16.9)	0.77 (0.69–0.86)	<0.001
Death from any cause	274 (6.7)	310 (7.6)	0.87 (0.74–1.02)	—



Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. Deepak L. Bhatt, M.D., et al. for the REDUCE-IT Investigators.NEJM. N Engl J Med 2019; 380:11-22

The Mediterranean Diet: Precision Fat Consumption

The Mediterranean Diet: Cardiometabolic Disease Prevention



Estruch, et al. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet. NEJM 2013; 368:1279-1290.

Thank You