



Metabolic Basis for Low-Carbohydrate and Ketogenic Diets

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Professor, The Ohio State University



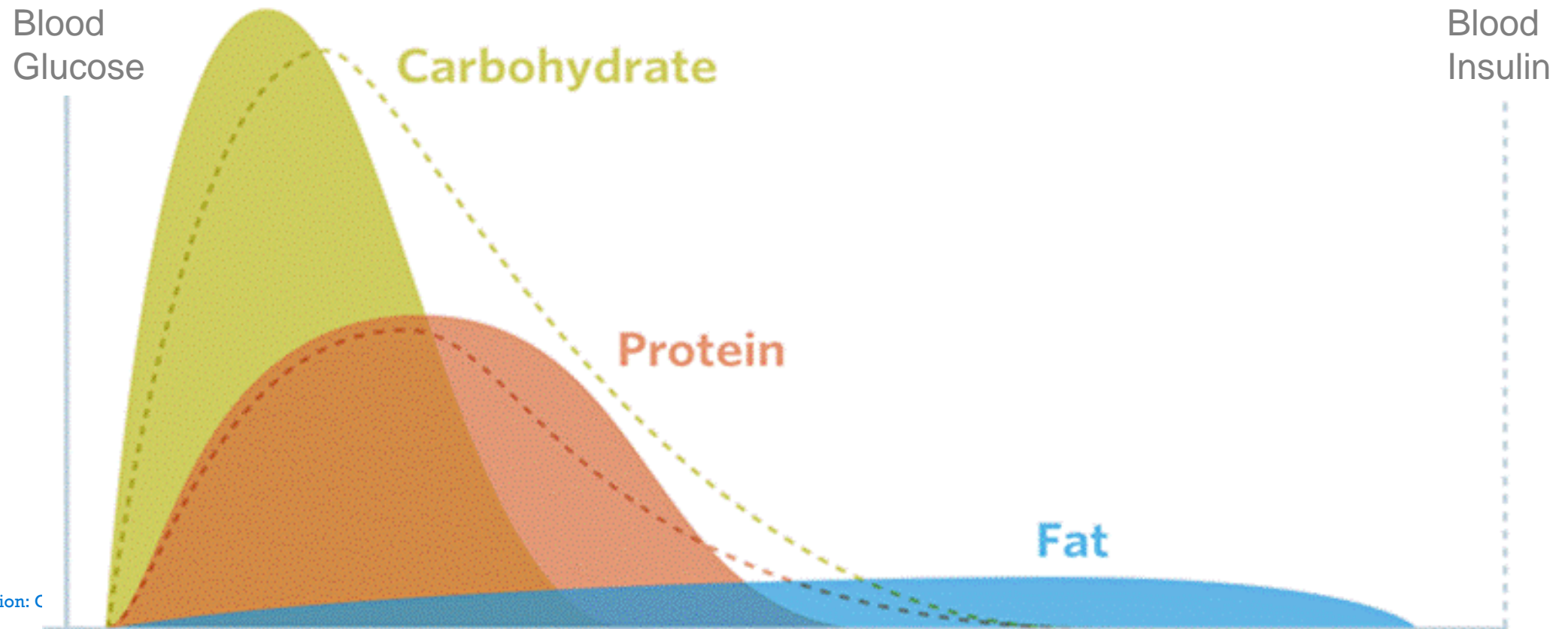
Goal for Today

Examine insulin resistance from the perspective of being a carbohydrate intolerant condition and the metabolic basis and evidence for why low-carbohydrate ketogenic dietary patterns are therapeutic

- 1. Metabolic effects of dietary carbohydrate**
2. Emerging aspects of ketone physiology
3. Ketone nomenclature
4. Ketogenic diet formulation
5. Overview of ketogenic diet literature in obesity & prediabetes
6. Safety concerns

What is Driving Insulin Resistance and Type 2 Diabetes

- ❑ Dietary fat and excess body fat have traditionally been viewed as drivers of both the obesity and T2D epidemics.
- ❑ Alternatively, these epidemics are likely driven by a systemic metabolic distortion of fuel partitioning from overconsumption of sugars and starches.

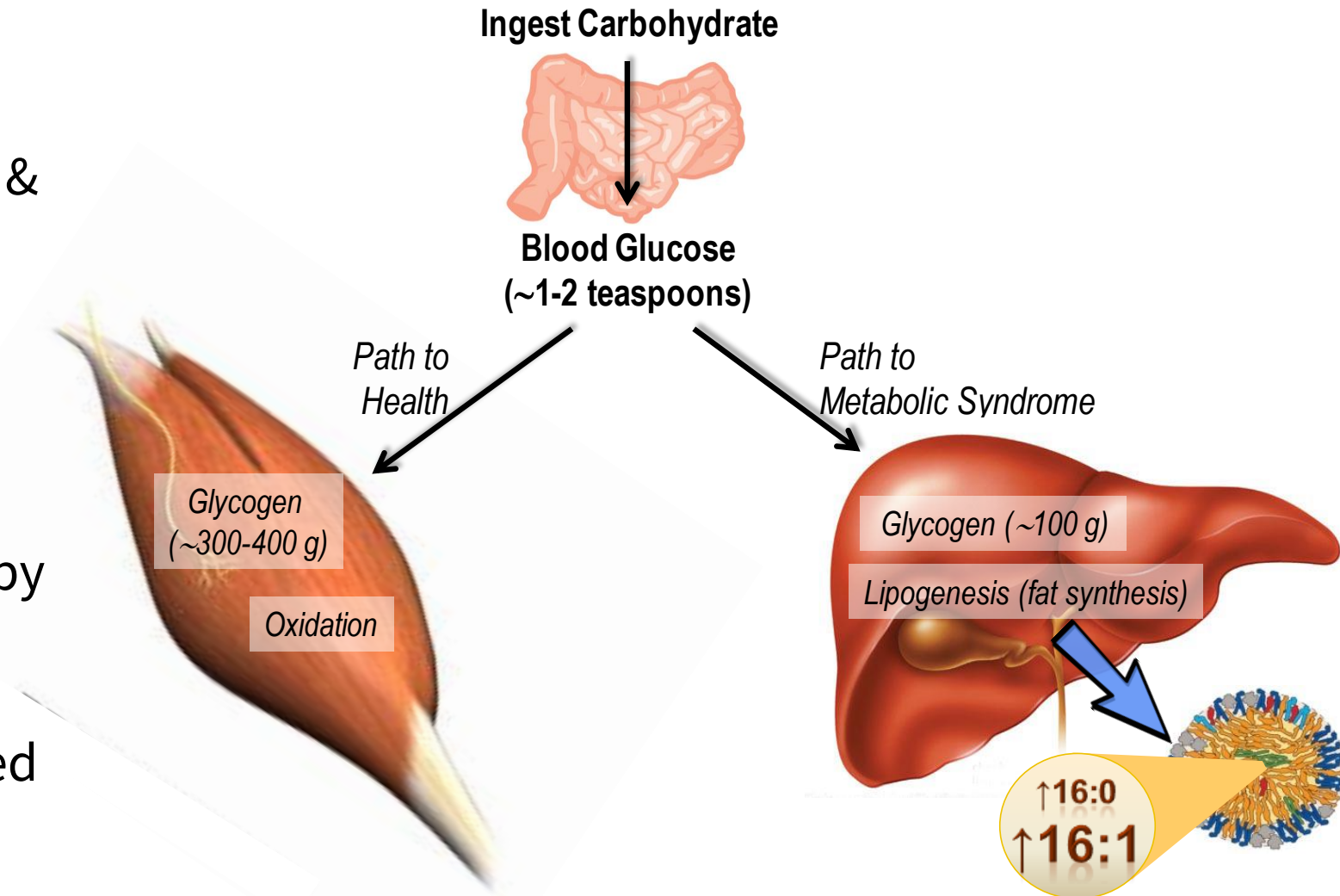


Insulin resistance from a carbohydrate perspective

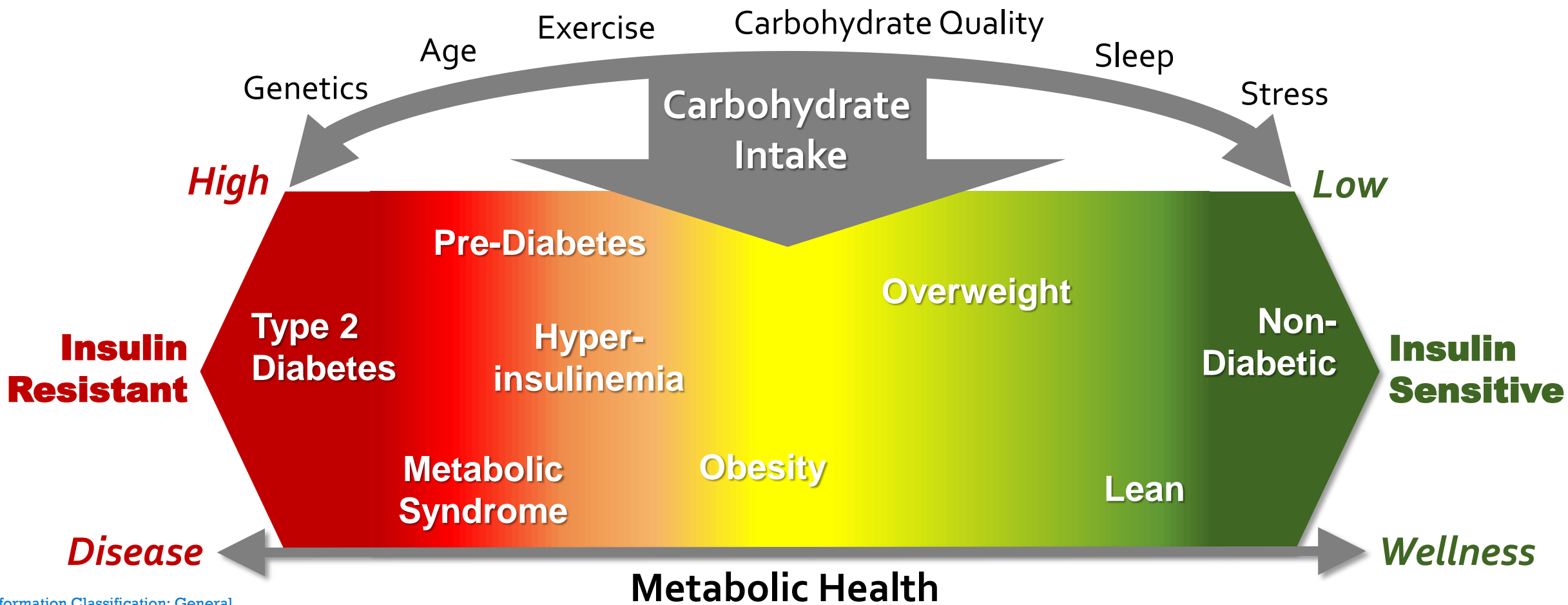
❑ T2D is a disease of insulin resistance (**carbohydrate intolerance**) defined by some combination of hyperglycemia & hyperinsulinemia

❑ Characteristics:

- Insulin Resistance = Carb Intolerance
- Inherited condition triggered by over-consumption of carbs
- Inflammatory antecedents
- Correlated with, but not caused by obesity



Expression of an insulin resistant or sensitive phenotype is a continuum that is strongly influenced by carbohydrate intake, with modulation based on genetic predisposition, age, and lifestyle choices



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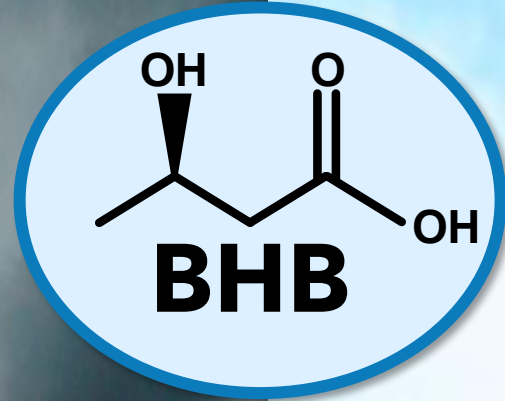
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Introduction to Nutritional Ketosis

Until recently, much of what is taught about ketones to health care providers is flawed or outright wrong

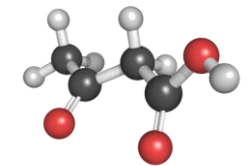
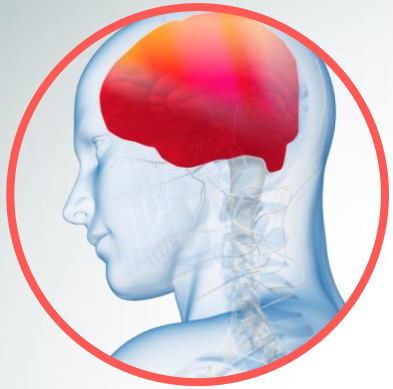
- Most have not been taught to differentiate between physiological ketones as a fuel source and the pathophysiology of diabetic keto-acidosis



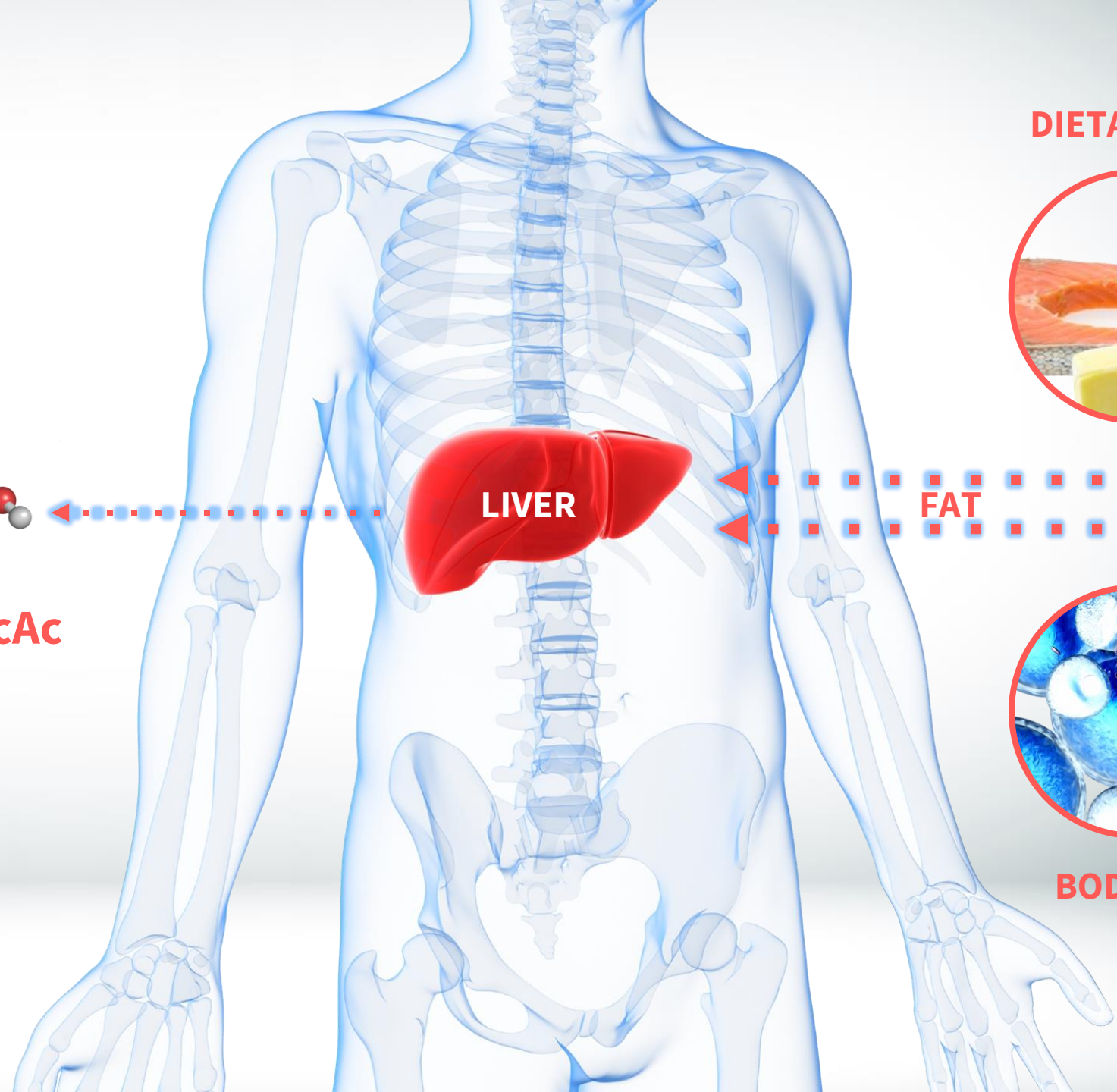
In the last decade, our perspective and appreciation of BHB has changed radically

- Superior energy supply
- Robust signaling activities
- Hemodynamic effects





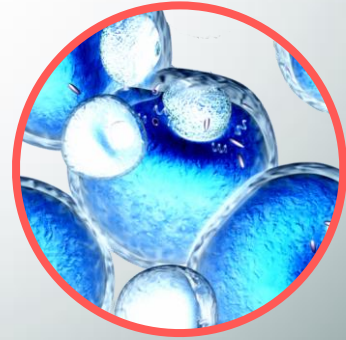
BHB/AcAc



DIETARY FAT



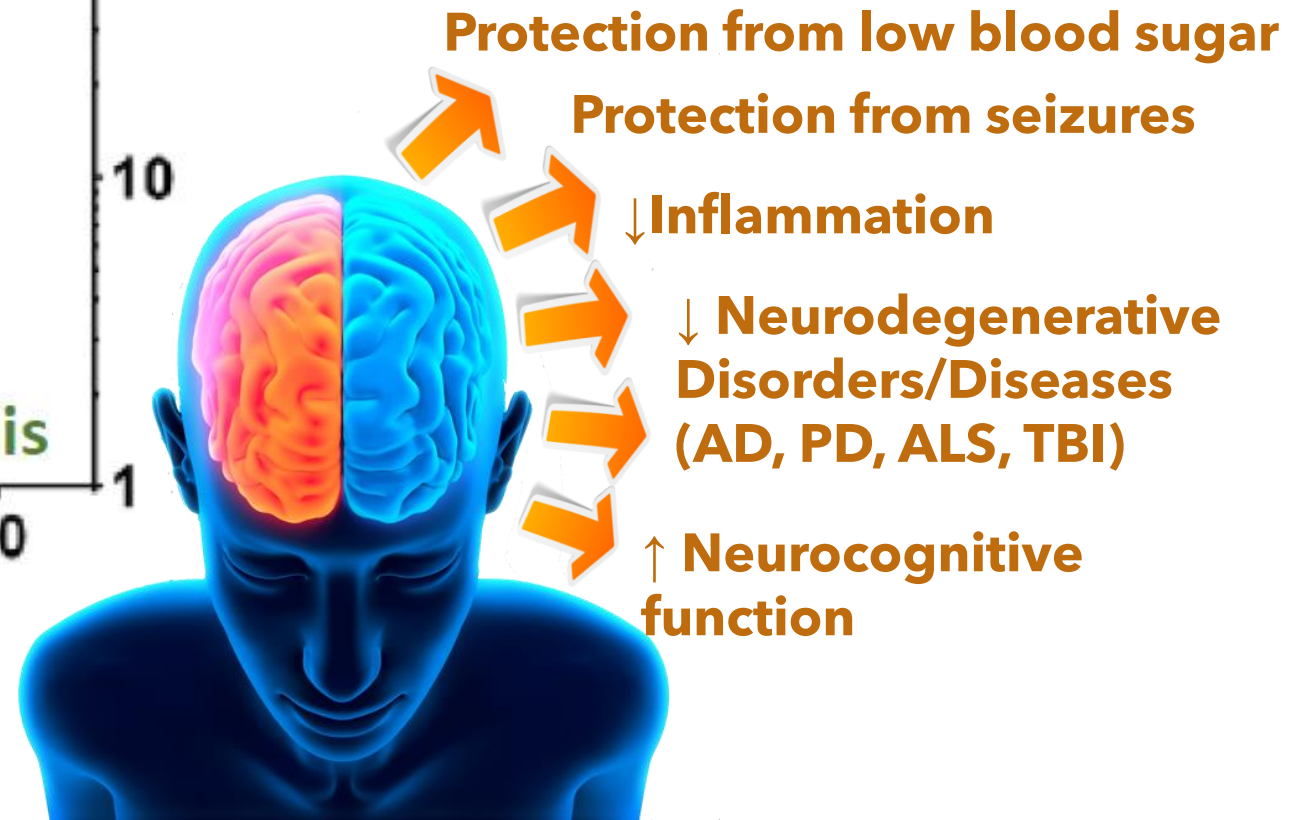
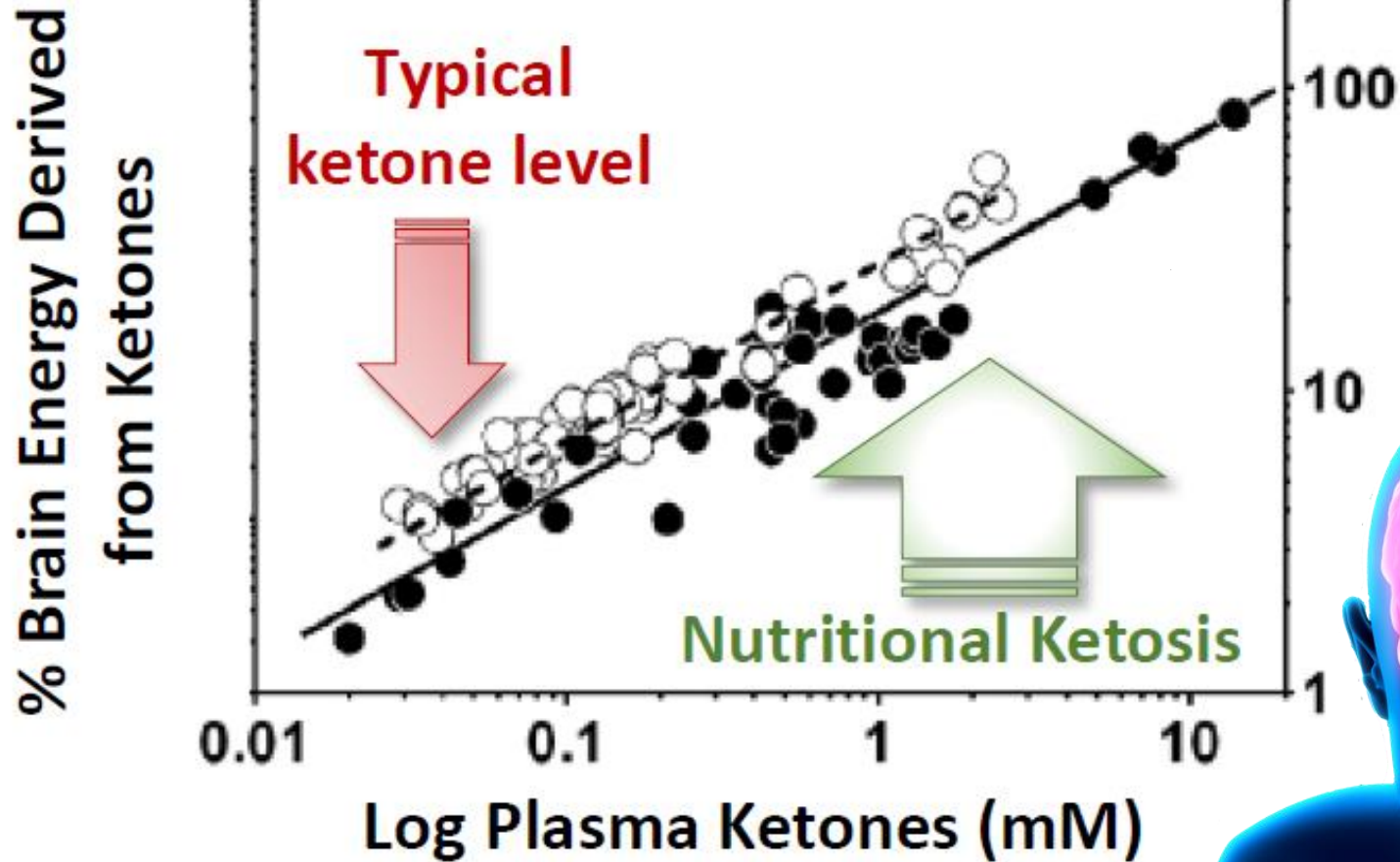
FAT



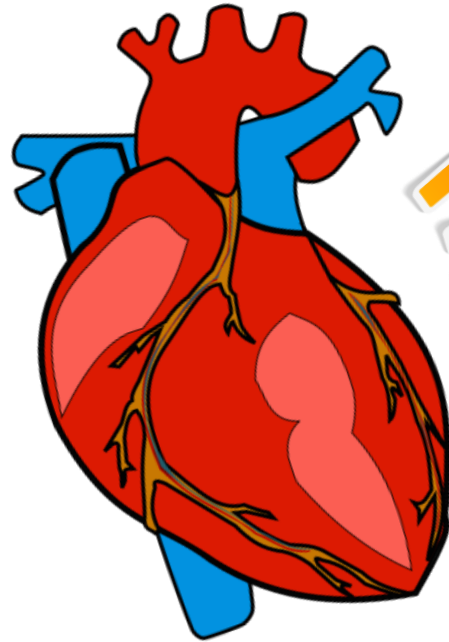
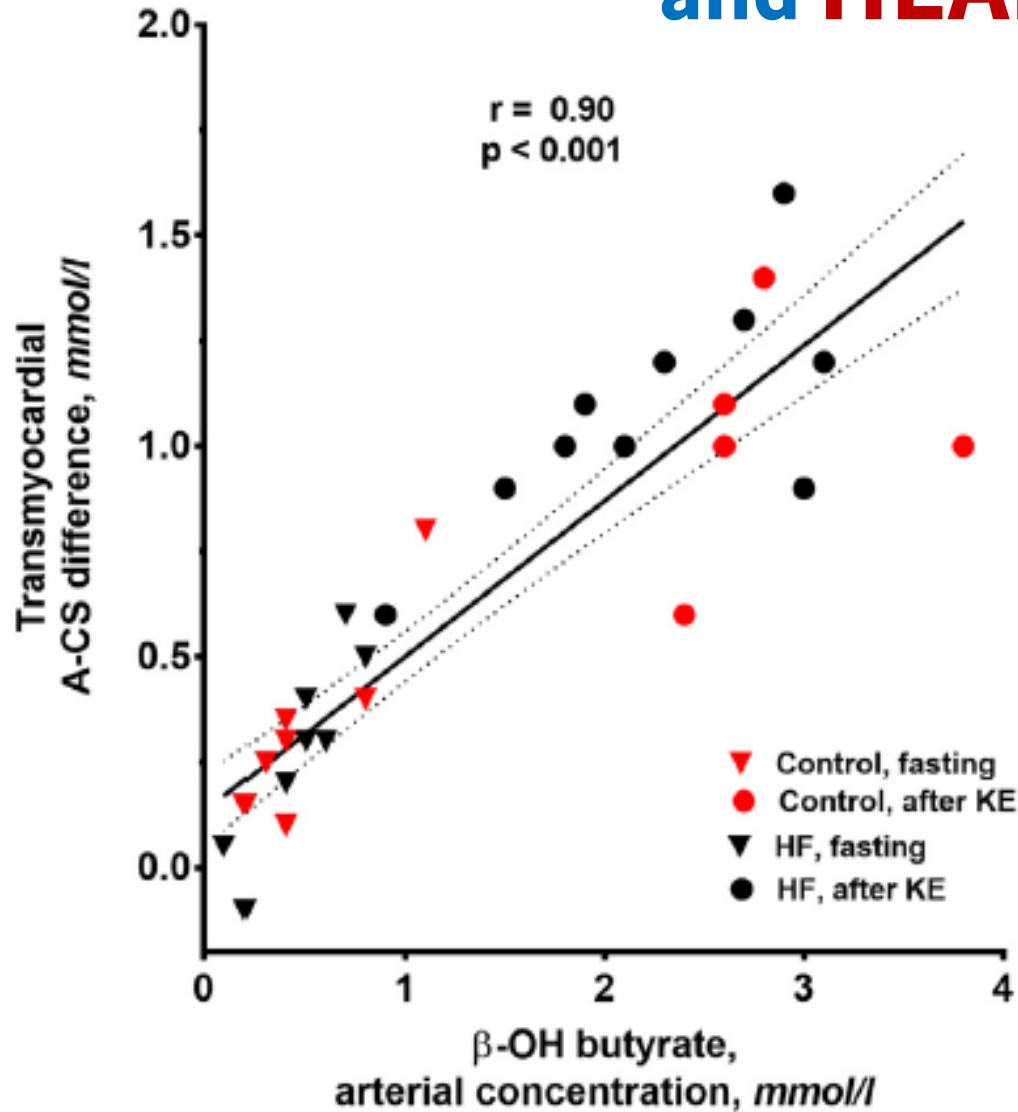
BODY FAT

Direct association of plasma ketones and **BRAIN** ketone oxidation

Ketones 0.5 mM = ~5%
Ketones 1.5 mM = ~20%
Ketones 4-5 mM = ~50%



Also...Direct association of plasma ketones and **HEART** ketone oxidation



Provide more energy per carbon than glucose

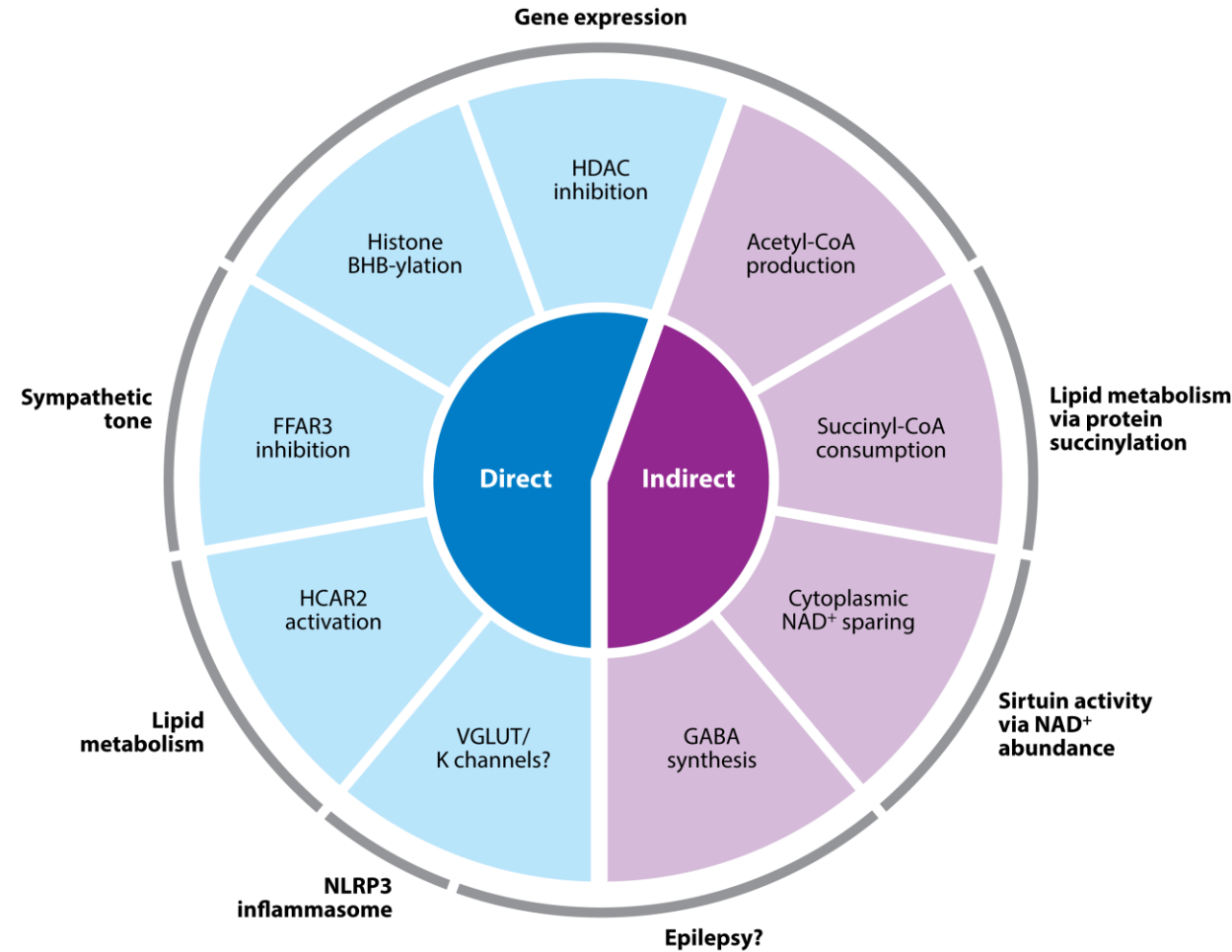
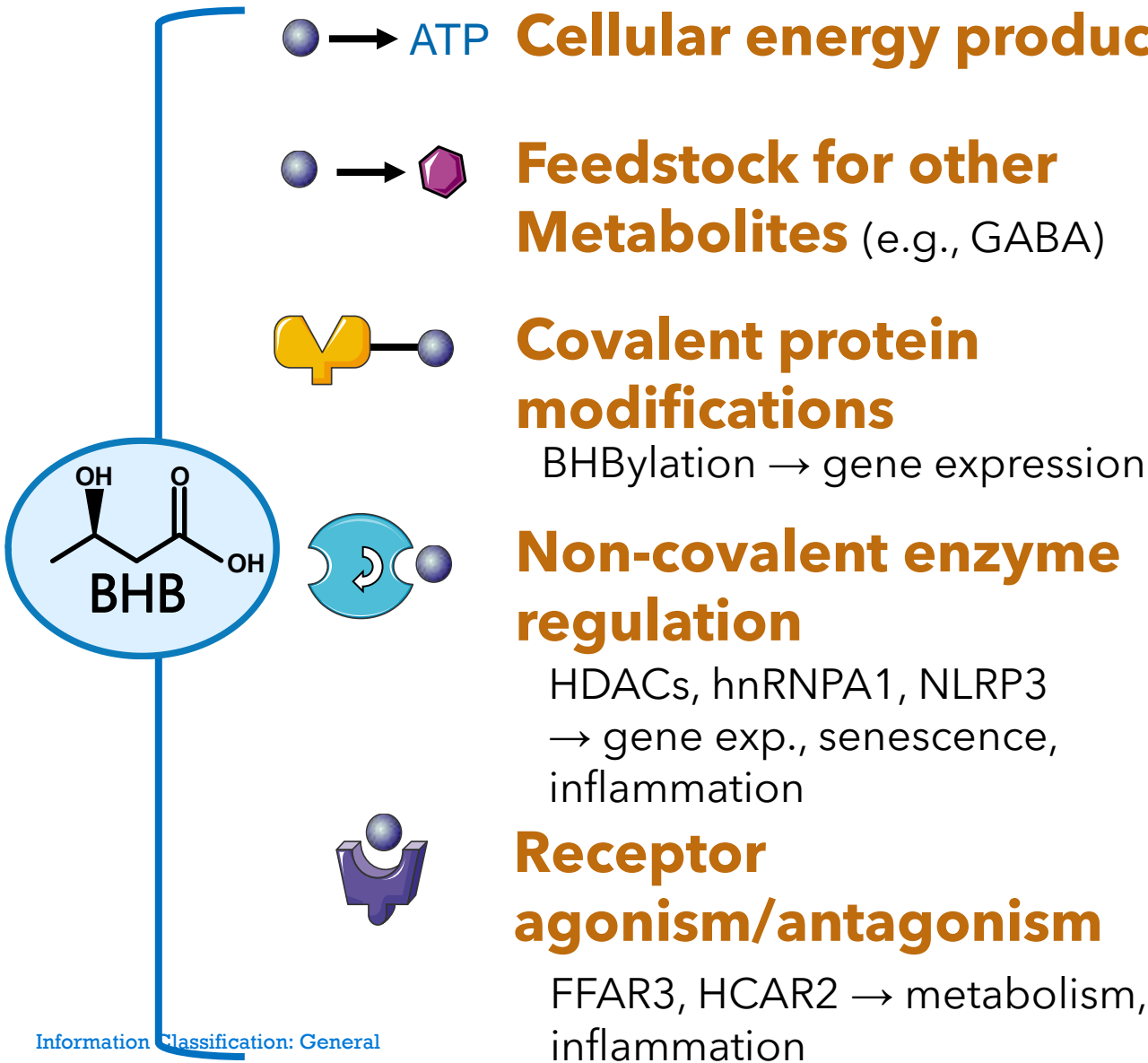
Require less O₂ for ATP than fatty acids

Minimize uncoupling & oxidative stress

↑ myocardial blood flow

↑ Cardiac output & ejection fraction

Signaling Activities of BHB

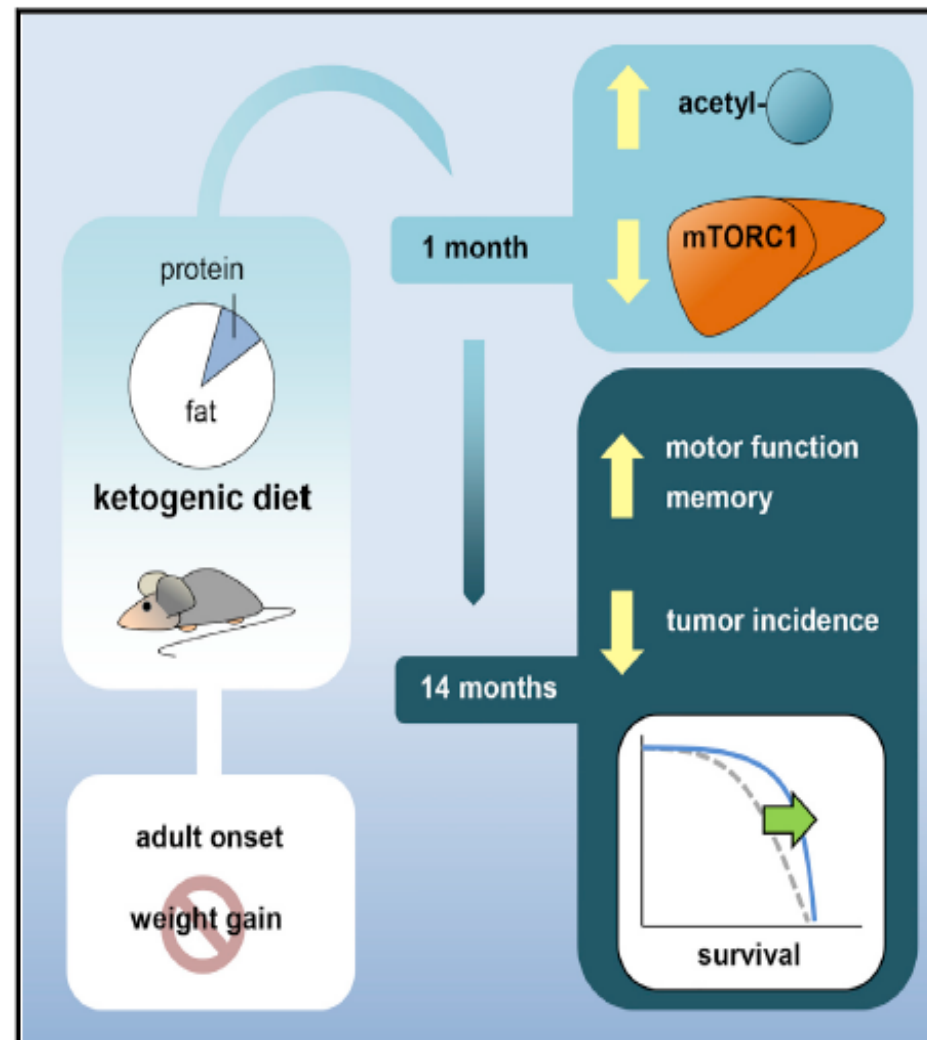


Newman JC, Verdin E. 2017. *Annu. Rev. Nutr.* 37:51-76

Cell Metabolism

A Ketogenic Diet Extends Longevity and Healthspan in Adult Mice

Graphical Abstract



Authors

Megan N. Roberts, Marita A. Wallace,
Alexey A. Tomilov, ...,
Gino A. Cortopassi, Jon J. Ramsey,
Jose Alberto Lopez-Dominguez

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In Brief

Roberts et al. show that a ketogenic diet extends longevity in adult male mice and preserves motor function, memory, and muscle mass in aged mice. The ketogenic diet increased protein acetylation levels and regulated mTORC1 signaling in a tissue-dependent manner. See related paper by Newman et al.



**Ketones extend
healthspan**



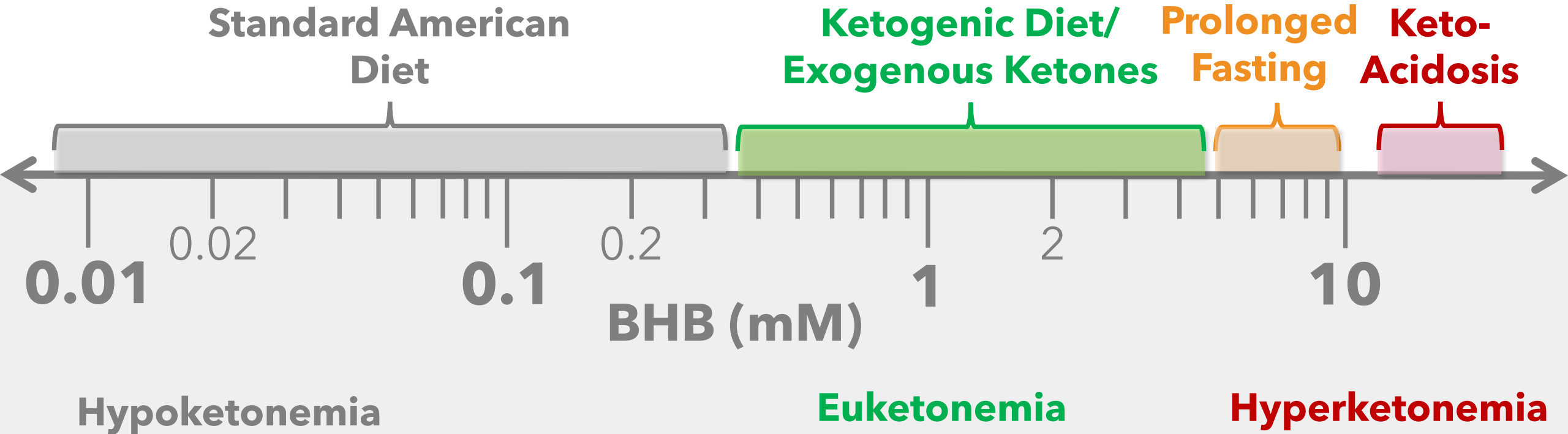
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Ketone Concentrations

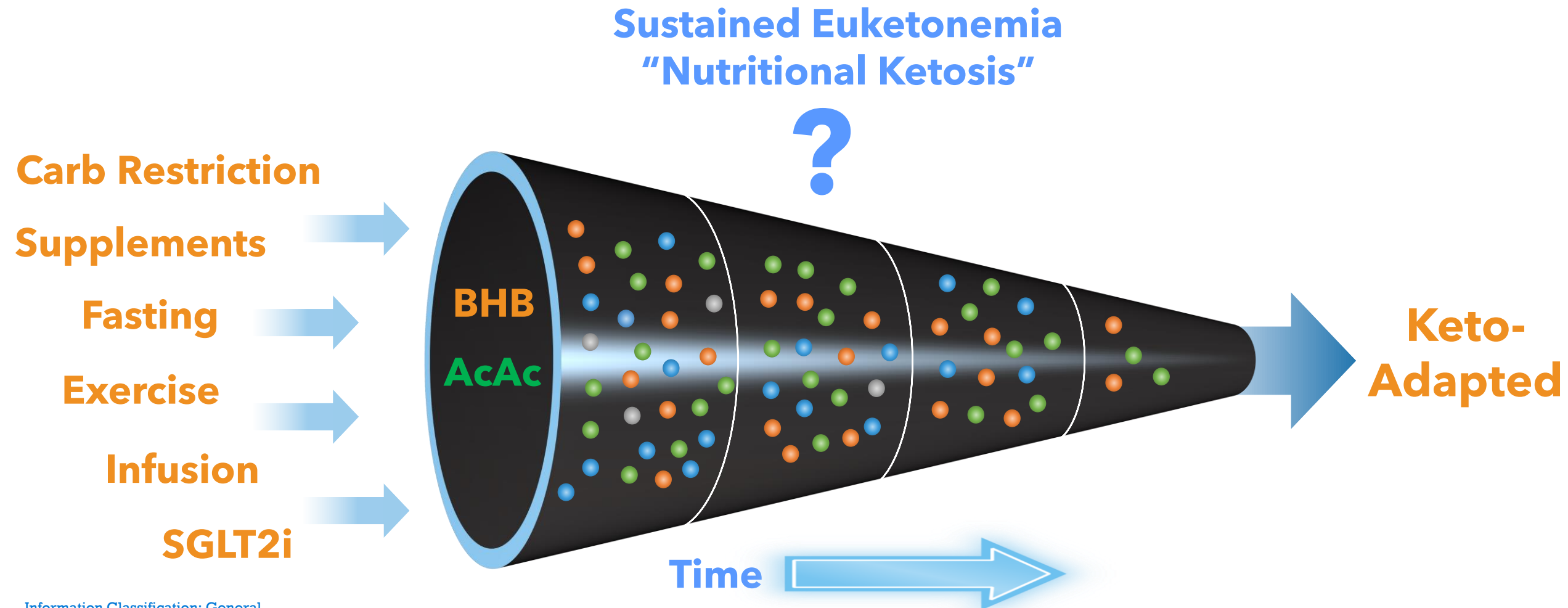
Span over 4 orders of magnitude [<0.01 to >10 mM]!!!



What is Normal?

What is Optimal?

Many Ways to Achieve “Nutritional Ketosis”, but this is not equivalent to “Keto-Adaptation”



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Principles of a WFKD*

- ✓ Achieving nutritional ketosis (0.5 up to 5 mM)
- ✓ Biofeedback to personalize carb & protein intake
- ✓ Individualized carb restriction (30-70 g/d)
- ✓ Not high or low in protein (1.2-2.0 g/kg ref wt)
- ✓ Eat until satisfied, no kcal counting, exercise not required
- ✓ Fat is your friend (fuel, flavor/pleasure, satiety)
- ✓ Fat type/quality more important than quantity
- ✓ Saturated fat embraced, not feared or shunned
- ✓ PUFA limited, but good source of EPA/DHA
- ✓ Whole food based, nutrient adequacy
- ✓ Plenty of non-starchy vegetables & some fruits
- ✓ ↑ sodium (4-5 g/d for most people) to prevent "keto-flu"
- ✓ Attention to micronutrients (e.g., K, Mg, Zn)
- ✓ ↓ requirement for fiber?

*WFKD=well-formulated ketogenic diet

Sustainable



à la Keto

TODAY ON THE MENU

Eggs and Peanut Butter Smoothie

Scrambled eggs in butter and cheddar cheese featuring an almond and heavy cream protein shake with peanut butter, MCT and strawberries.

Greek Vinaigrette Salad

Uncured ham served on romaine and spinach with cherry tomatoes, cucumbers, feta, bell peppers and olive oil vinaigrette.

Afternoon Snack

Cottage cheese with almonds and MCT

Cheddar Ranch Chicken

Chicken thigh seared in butter topped with mayo, ranch seasoning, garlic powder and cheddar cheese. Served with parmesan broccoli.



Varied

Tasty

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Effects of low-carbohydrate diets v. low-fat diets on body weight and cardiovascular risk factors: a meta-analysis of randomised controlled trials

Nadia Mansoor^{1*†}, Kathrine J. Vinknes^{1†}, Marit B. Veierød^{1,2} and Kjetil Retterstøl^{1,3}

British Journal of Nutrition (2016), **115**, 466–479

Dietary Intervention for Overweight and Obese Adults: Comparison of Low-Carbohydrate and Low-Fat Diets. A Meta-Analysis

Jonathan Sackner-Bernstein^{1*}, David Kanter², Sanjay Kaul³

PLOS ONE | DOI:10.1371/journal.pone.0139817 October 20, 2015

Effect of carbohydrate restriction on body weight in overweight and obese adults: a systematic review and dose–response meta-analysis of 110 randomized controlled trials

Sepideh Soltani¹, Ahmad Jayedi², Shima Abdollahi³, Azam Ahmadi Vasmehjani⁴, Fatemeh Meshkini⁵ and Sakineh Shab-Bidar^{6*}

Front. Nutr. 10:1287987.

doi: 10.3389/fnut.2023.1287987

Effectiveness of low-carbohydrate diets for long-term weight loss in obese individuals: A meta-analysis of randomized controlled trials

Giovanni Antonio Silverii MD¹ | Claudia Cosentino MD² |
Federica Santagiuliana RD³ | Francesco Rotella MD⁴ | Federica Benvenuti MD⁴
Edoardo Mannucci MD¹ | Barbara Cresci MD³

Diabetes Obes Metab. 2022;24:1458–1468.

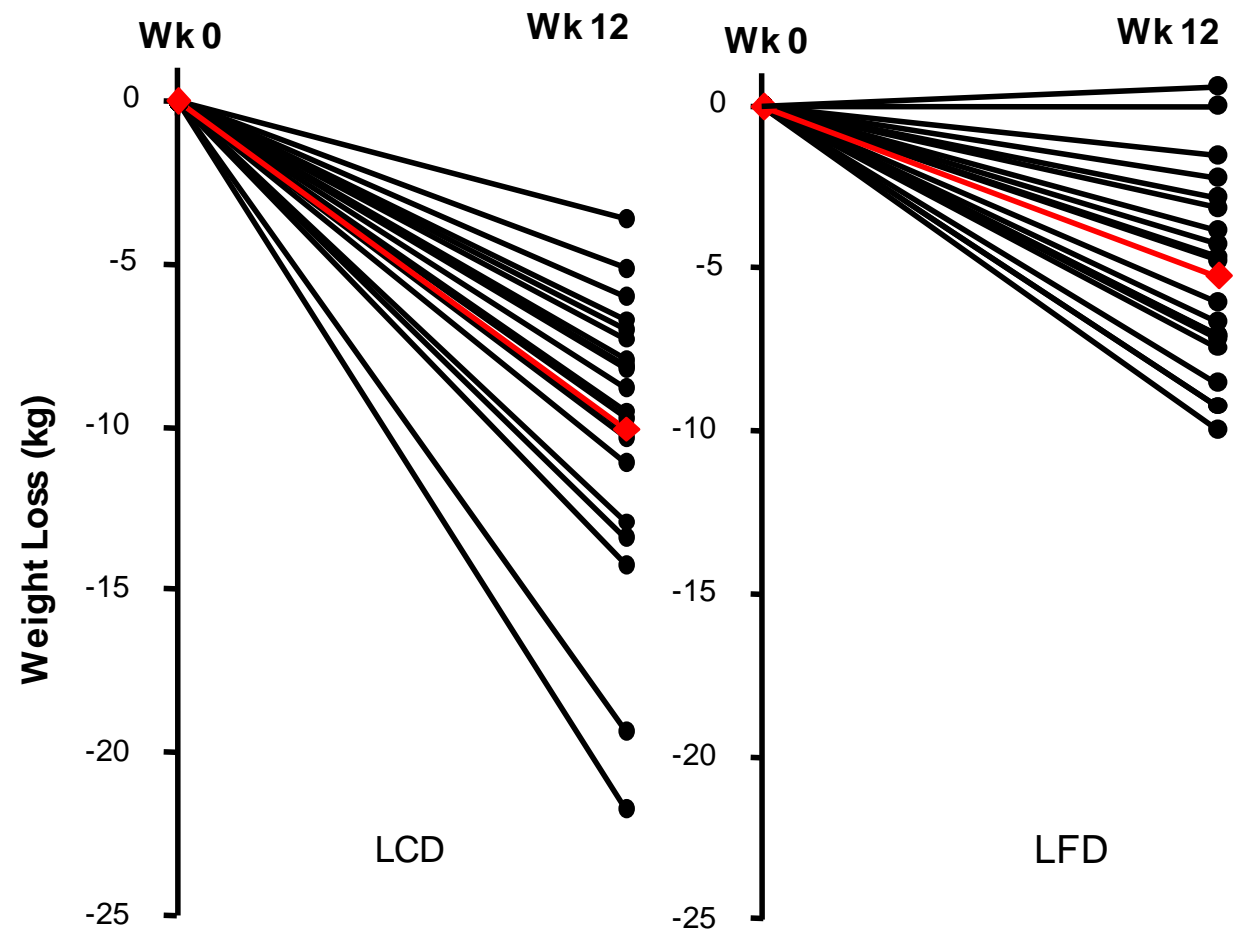
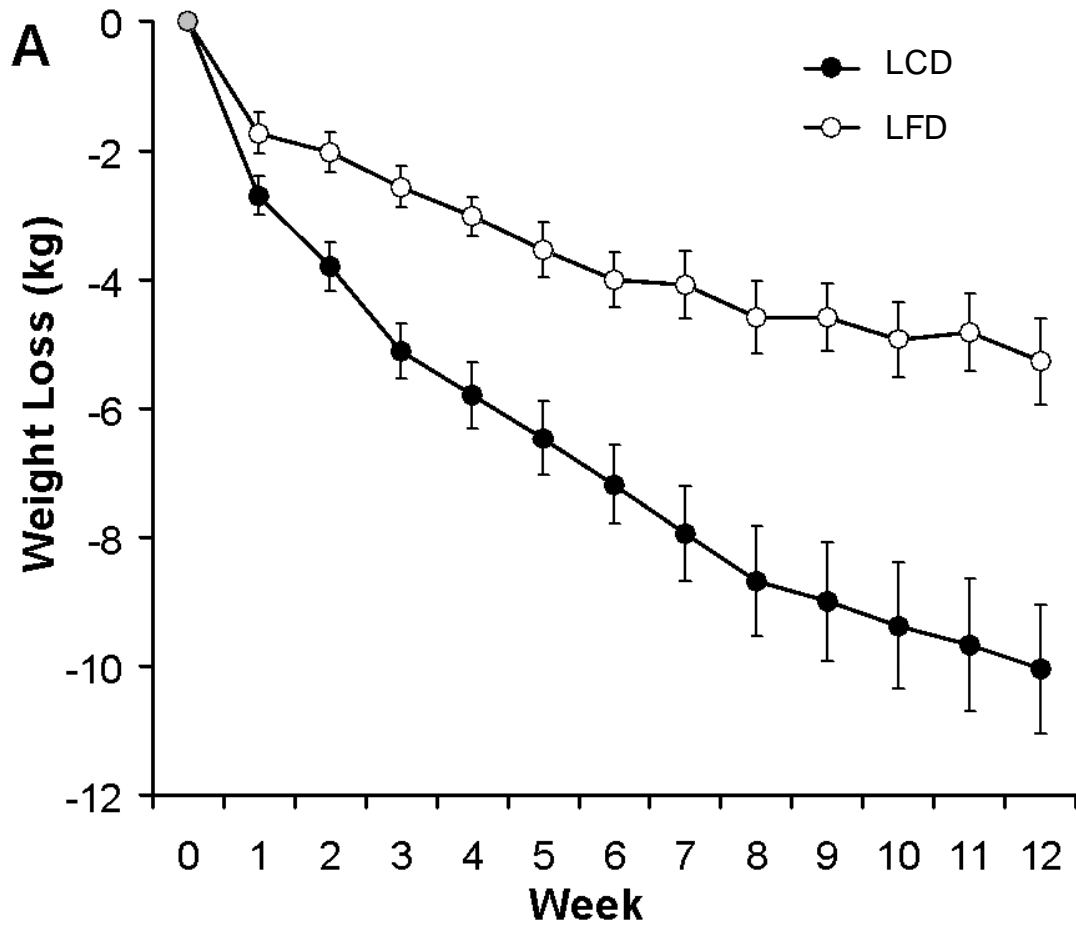
The Effect of Low-Fat and Low-Carbohydrate Diets on Weight Loss and Lipid Levels: A Systematic Review and Meta-Analysis

Shreya Chawla¹, Fernanda Tessarolo Silva², Sofia Amaral Medeiros², Rania A. Mekary^{3,4,†}
and Dina Radenkovic^{5,*,†}

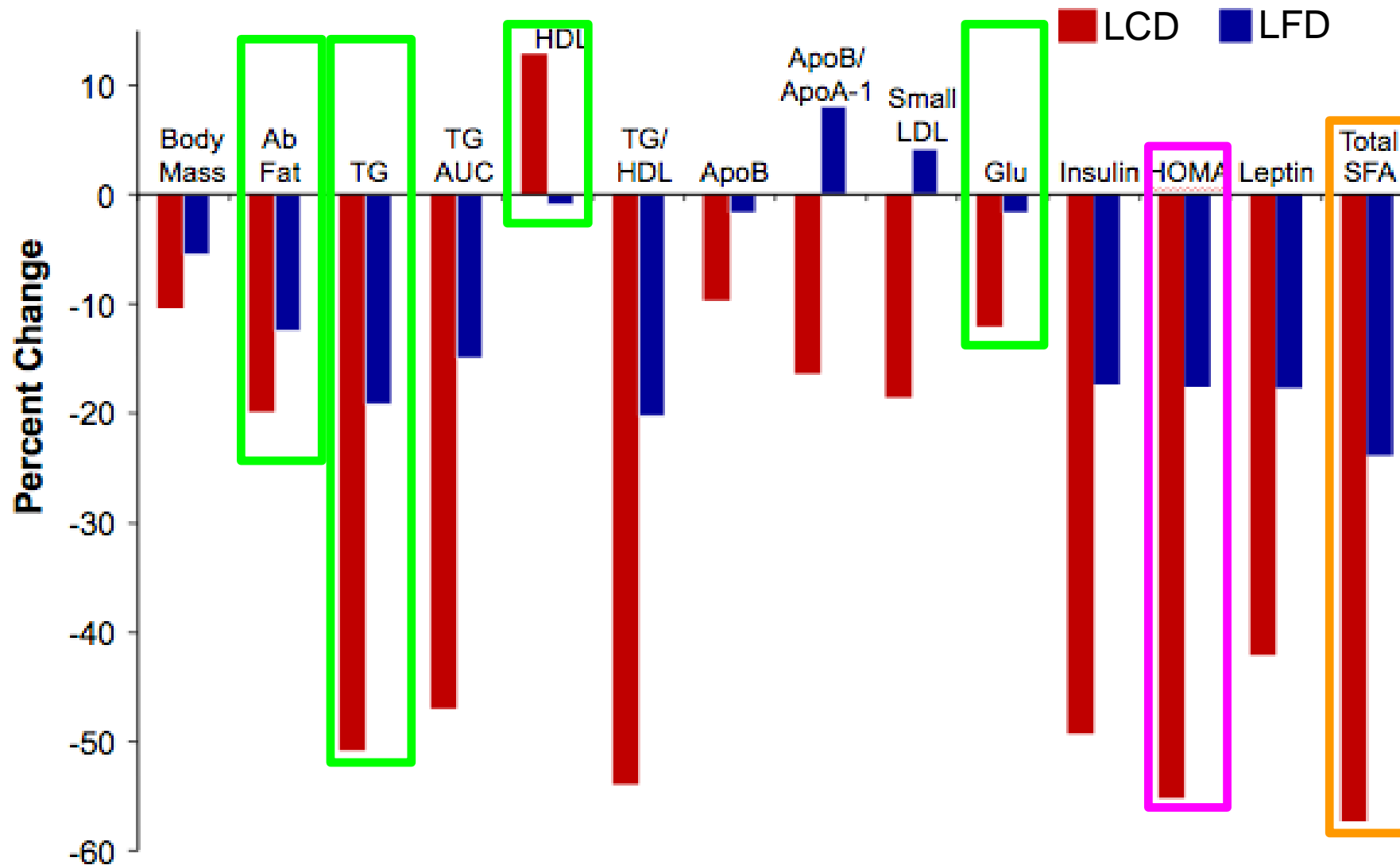
Nutrients 2020, 12, 3774

A ketogenic diet is superior at facilitating weight loss in individuals with metabolic syndrome

Without explicit instruction to reduce calories



A ketogenic diet is superior at improving metabolic syndrome



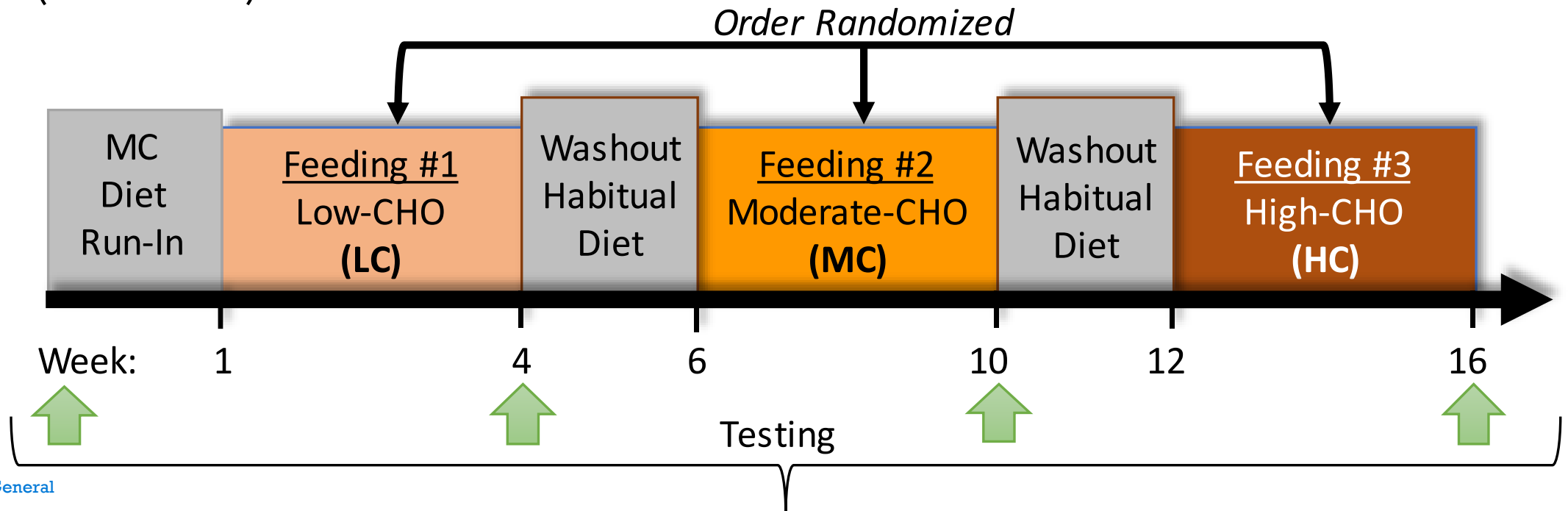
- All the markers of MetS improved, significantly better in LC than LF
 - Except BP (not shown)
- Marker of insulin resistance (HOMA-IR) improved dramatically for LC than LF
- Total SFA was dramatically lower in LC than LF in serum, even though dietary intake was 3x higher
 - Likely because patients are so much better at oxidizing it

Dietary carbohydrate restriction improves metabolic syndrome independent of weight loss

Parker N. Hyde,¹ Teryn N. Sapper,¹ Christopher D. Crabtree,¹ Richard A. LaFountain,¹ Madison L. Bowling,¹ Alex Buga,¹ Brandon Fell,¹ Fionn T. McSwiney,² Ryan M. Dickerson,¹ Vincent J. Miller,¹ Debbie Scandling,³ Orlando P. Simonetti,³ Stephen D. Phinney,⁴ William J. Kraemer,¹ Sarah A. King,⁵ Ronald M. Krauss,⁵ and Jeff S. Volek¹

Design

- 3-way cross-over controlled-feeding study
- 16 obese (BMI = 39) adults w/ MetS



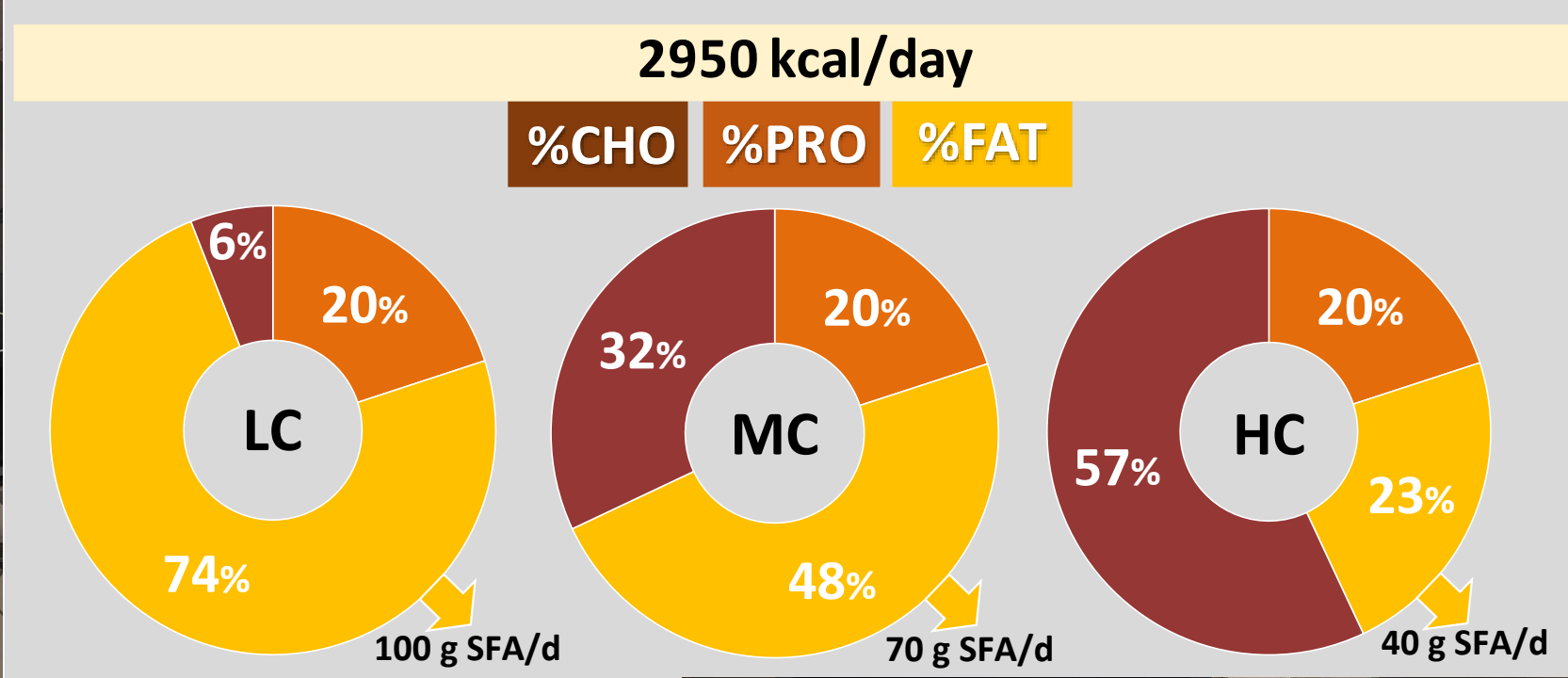


Table 1. Daily nutrient intake of controlled diets

Nutrient	HC	MC	LC
Energy (kcal)		2,950 (2035–3750)	
Protein (g)	144 (100–184)	146 (101–185)	150 (103–190)
Carbohydrate (g)	420 (290–534)	234 (161–297)	45 (31–58)
Fat (g)	77 (53–97)	159 (110–202)	242 (167–307)
Saturated fat (g)	40 (28–51)	70 (48–89)	100 (69–127)
Monounsaturated fat (g)	21 (15–27)	54 (37–69)	86 (59–110)
Polyunsaturated fat (g)	6 (5–8)	21 (14–26)	35 (24–45)
Cholesterol (mg)	334 (231–425)	503 (347–639)	1,015 (701–1291)
Cheese (g)	200 (138–255)	201 (139–256)	201 (139–256)
Calcium (mg)	2,151 (1484–2734)	2,229 (1537–2833)	2,177 (1502–2768)
Fiber (g)	25 (17–32)	20 (14–25)	14 (9–17)

This table is related to Figure 1. Values are mean (range). *n* = 16.

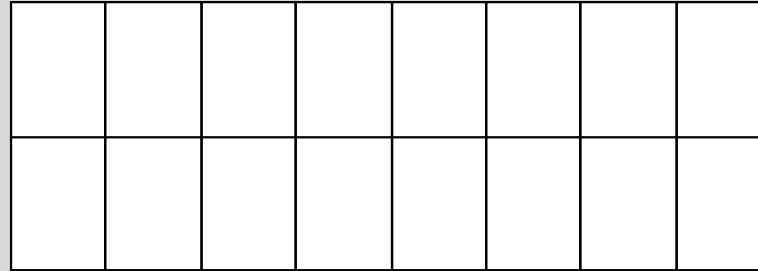
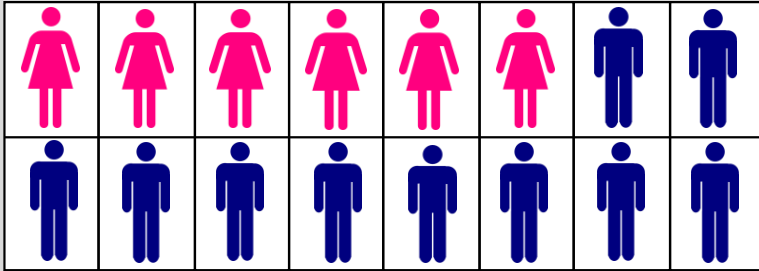


Despite no weight loss, LC more effective in reversing MetSyn

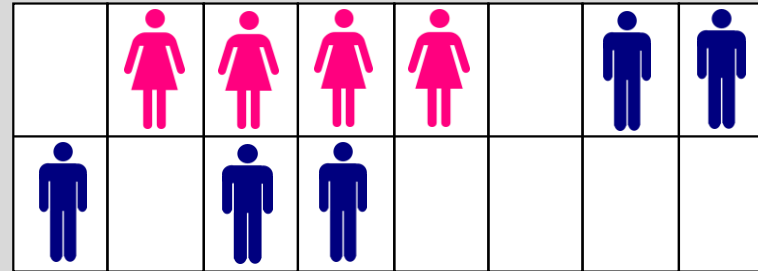
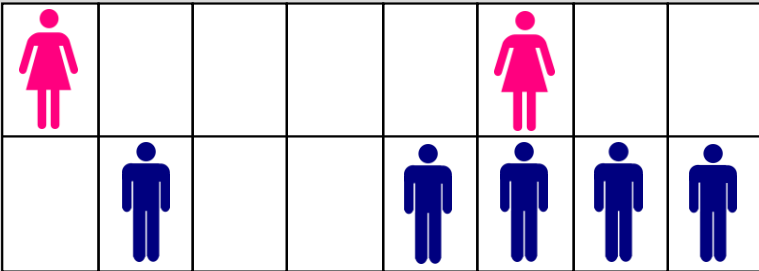
Metabolic Syndrome

No Metabolic Syndrome

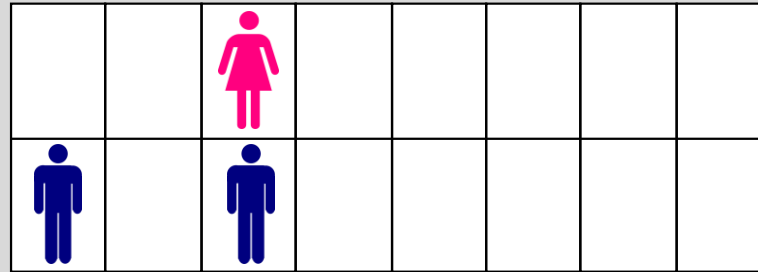
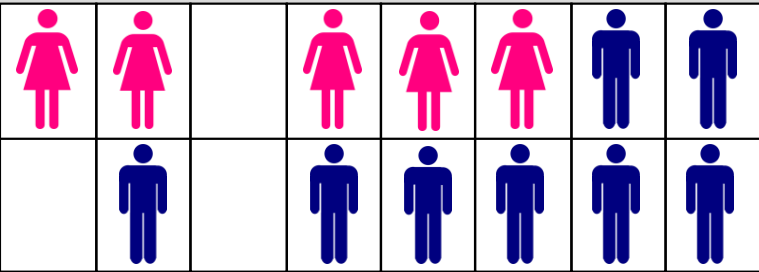
BL



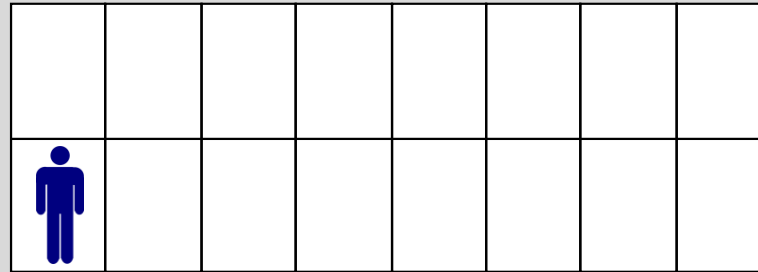
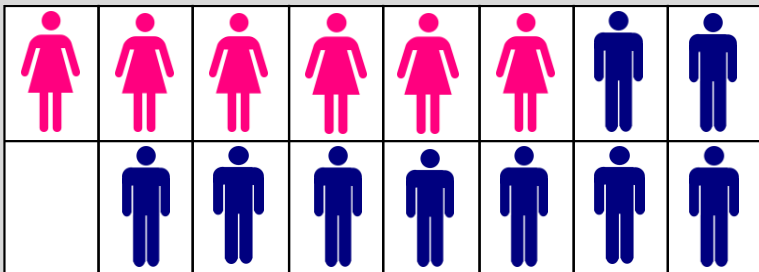
LC



MC



HC



Fraction who reversed MetSyn in 4-weeks

9/16

3/16

1/16

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SAFETY CONCERNS

A lot of myths and hyperbole; little credible evidence

Can humans safely sustain a low carbohydrate diet for decades?

Evidence: Explorers who lived at least 1 year among and reported dietary choices of traditional hunting/herding cultures

- George Catlin, (Great Plains), 1830-1840
- John Rae, (Canadian Arctic), 1840-1855
- Nikolai Przhevalsky , (Mongolia and Tibet), 1870-73
- Frederick Schwatka, (Canadian Arctic), 1880-1882
- Vilhjalmur Stefansson, (Canadian & Alaskan Arctic) 1907-1917,
- Vilhjalmur Stefansson, (inpatient, Bellevue Hospital, NYC) 1928
- Orr and Gilks, (Great Rift Valley, East Africa), 1928

In T2D it is critical to have knowledgeable physicians reduce some glucose-lowering meds at the onset of a ketogenic diet!

Summary

- **Low-carbohydrate, especially ketogenic diets, reverse most signs of metabolic syndrome and prediabetes in many people, and improve a broad range of markers linked with the insulin resistant phenotype and CVD risk; an effect that is largely independent of weight loss**
- **Ketogenic diets can be sustainable, but it requires education and support**

Thank you!

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Buck



USAMRAA
UNITED STATES ARMY
Medical Research
Acquisition Activity



BASZUCKI
BRAIN RESEARCH FUND