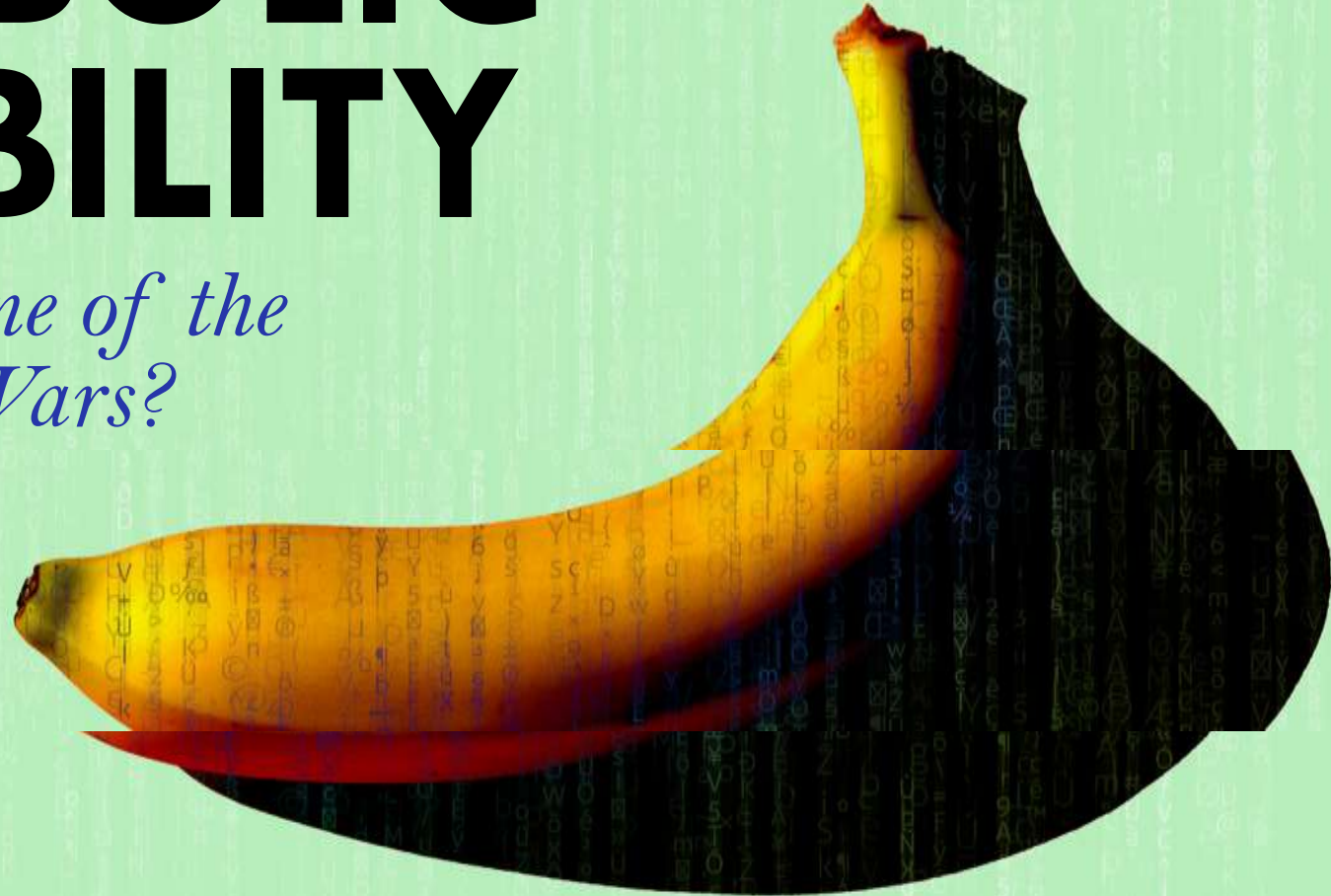


METABOLIC FLEXIBILITY

*The Rosetta Stone of the
Macronutrient Wars?*



ROBB WOLF *revolutionary solutions
to modern life*



optimal

optimal

optimal **definition**

optimal **blue**

optimal **outbreeding**

optimal **health**

optimally

optimal **health systems**

optimal **resume**

optimal **nutrition**

optimal **arousal theory**

Only the fringes care about optimal?

Seems a reasonable question,
but *really hard to pin down!*

NOTHING
in Pubmed



Google optimal human diet

All Videos News Shopping Images More Settings Tools

About 961,000 results (0.87 seconds)

Scholarly articles for optimal human diet
Optimal intakes of protein in the human diet - Millward - Cited by 71
... , foraging goals and the evolution of the human diet - Hawkes - Cited by 283
The ancestral human diet: what was it and should it be ... - Eaton - Cited by 184

What is the Best Diet For Human Beings? - Beverly Meyer
<https://www.ondietandhealth.com/what-is-the-best-diet-for-human-beings/> ▼
Mar 8, 2017 - The best diet for human beings includes the foods we evolved to eat. What our teeth, enzymes and intestines can process. We didn't used to eat hybridized grains, sugars, or dairy products. We did eat fishes and animals and gathered plants, flowers, some eggs, seeds, herbs and fruit. No vegetable oils ...

The Natural Human Diet | NutritionFacts.org
<https://nutritionfacts.org> > Dr. Greger's Medical Nutrition Blog ▼
Nov 15, 2016 - Our epidemics of dietary disease have prompted a great deal of research into what humans are meant to eat for optimal health. In 1985, an influential article highlighted in my video The Problem With the Paleo Diet Argument was published proposing that our chronic diseases stem from a disconnect ...

Is There a Perfect Diet? | Psychology Today
<https://www.psychologytoday.com/blog/perfect-health-diet/.../is-there-perfect-diet/> ▼
Jan 18, 2012 - Longer colons allow more fermentation of plant fiber, but they don't dramatically change macronutrient ratios of the diet. Across human populations, the optimal human diet probably doesn't vary in any macronutrient by more than 5% of energy or so. So there is little support for a "blood type diet" or ...

What is the "Optimal" Diet for Humans? (Part 1) | Denise Minger
<https://deniseminger.com/2010/03/08/what-is-the-optimal-diet-for-humans-part/> ▼
Mar 8, 2010 - Part of what first led me to raw foods was a curiosity about our "optimal diet." It seemed like such a simple concept: a combination of foods that our bodies are best adapted to, that we could easily discern by looking at our anatomy, that evolutionary history supported, and that would lead to the best...

nutrition - From a purely biological perspective, how does an ...
<https://biology.stackexchange.com/.../from-a-purely-biological-perspective-how-does-...> ▼
Mar 11, 2014 - No, there isn't a single diet that can be recommended from a biological perspective. The most popular diet from a pseudo-scientific perspective is the Paleo diet, saying we should eat what our ancestors in the Paleolithic were eating, but it makes a mistake of forgetting that our metabolism has evolved since ...

In Search of the Perfect Human Diet | Eat Naked Now
www.eatnakednow.com/in-search-of-the-perfect-human-diet/ ▼
Apr 17, 2013 - The movie follows filmmaker CJ Hunt's 10-year search for the "perfect human diet " after the raw vegan diet he adopted following a near-death experience failed to sustain him. Stepping

Is there an
OPTIMAL ancestral
diet?

NO.

Cultures with “diets” that work

Inuit



Kitavan



Okinawan



“Blue-zones”



Images Source:

U.S. Air Force photo/Tech. Sgt. Rey Ramon, <http://www.kadena.af.mil/News/Article-Display/Article/418168/okinawan-ancestors-rejoin-families-during-obon/>

Anziano Sardo by Jean Bajean - <https://www.flickr.com/photos/jeanbajean/4095162162/sizes/o/in/photostream/>, CC BY-SA 2.5, <https://commons.wikimedia.org/w/index.php?curid=27437962>

Commonalities



Largely whole
unprocessed foods



Many common **lifestyle features** (*much more on this later*)



Oddly missing?
~~**Macronutrients**~~

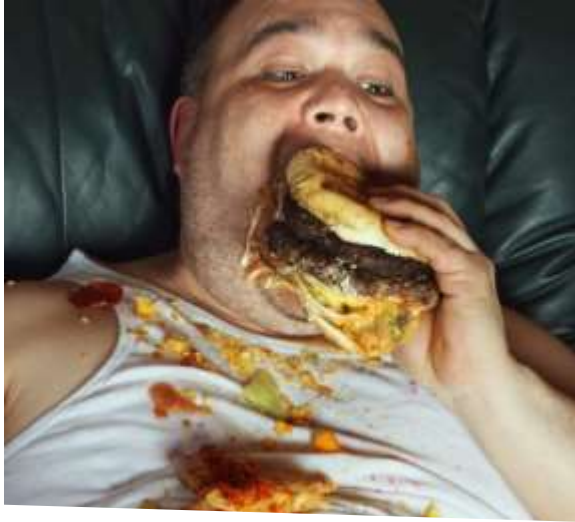
Outcomes

Population is largely
free of Western
degenerative
disease



Cultures with “diets” that *do not* work





US (*Why??*)



Processing



Increasing palate complexity



Dedicated engineering to make food hyperpalatable

hyperpalatable

(Betcha can't eat just one)

TITANFALL | 2

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2XP TITAN CONTENT

DEWANDDORITOS.COM

Doritos

BRAND

GUARANTEED FRESH
* UNTIL PRINTED DATE

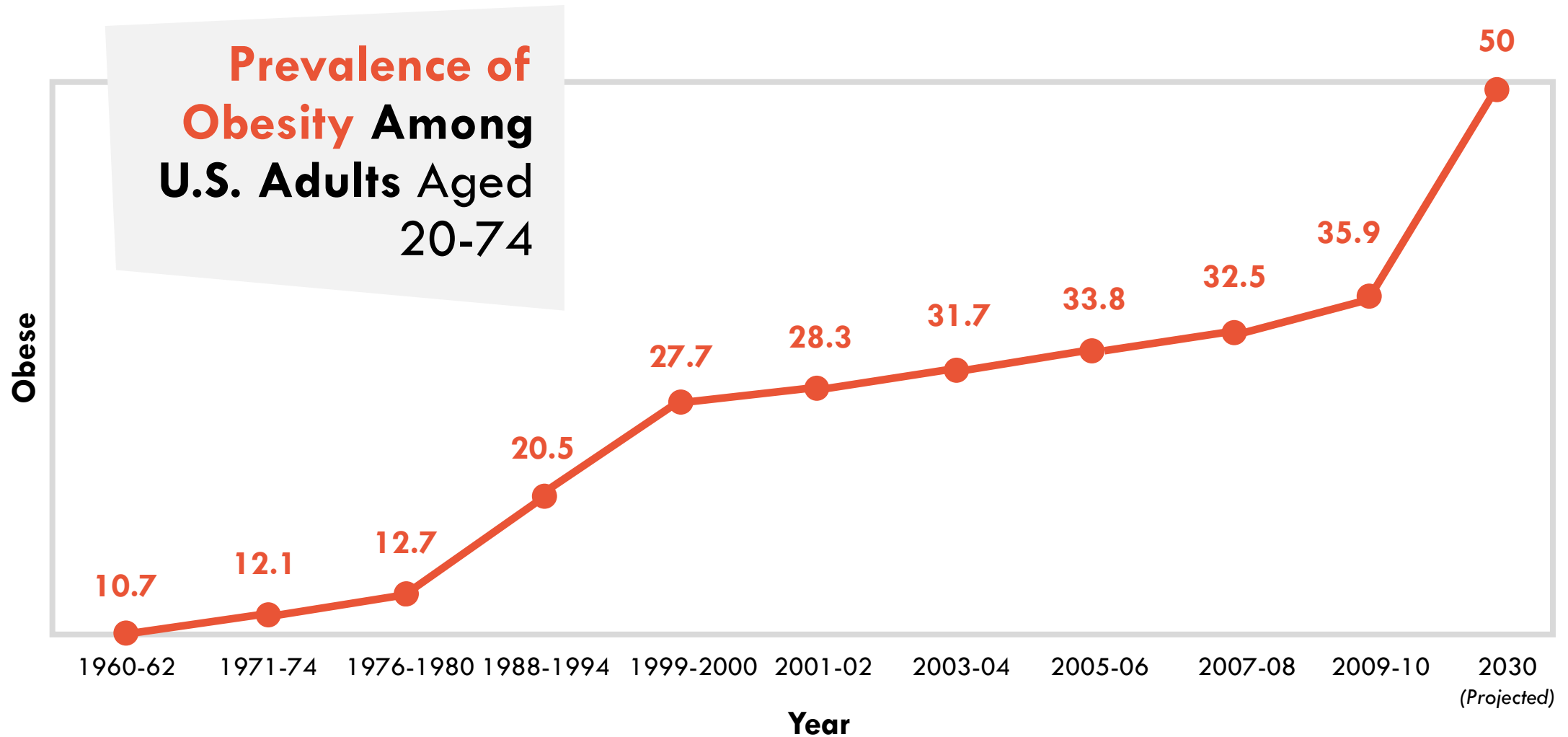
Roulette



FLAVORED TORTILLA CHIPS

NET WT. 3 OZ. (85 g)

Outcomes



Time for

**Optimal
Outcomes**

vs.

**Optimal
DIET**

When might a **set macro ratio** make sense?

High level athletics?

Likely a case for seasonal fueling choices

Near competition, “serial killer consistent”
(Physique competitors)



Illness/conditions that likely benefit from Low Carb



**Gut
Disbiosis**



**Mitochondrial
Insufficiency**



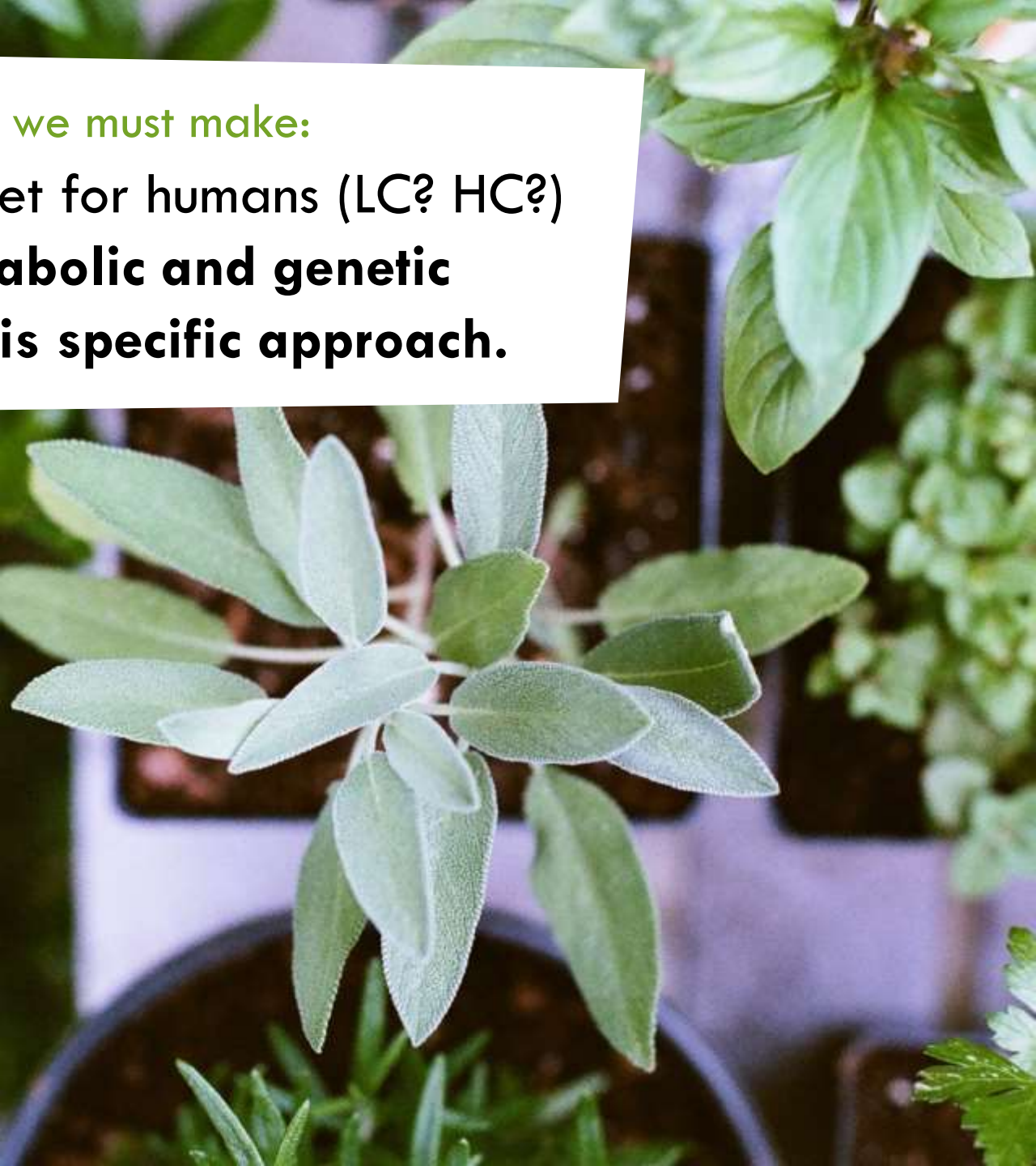
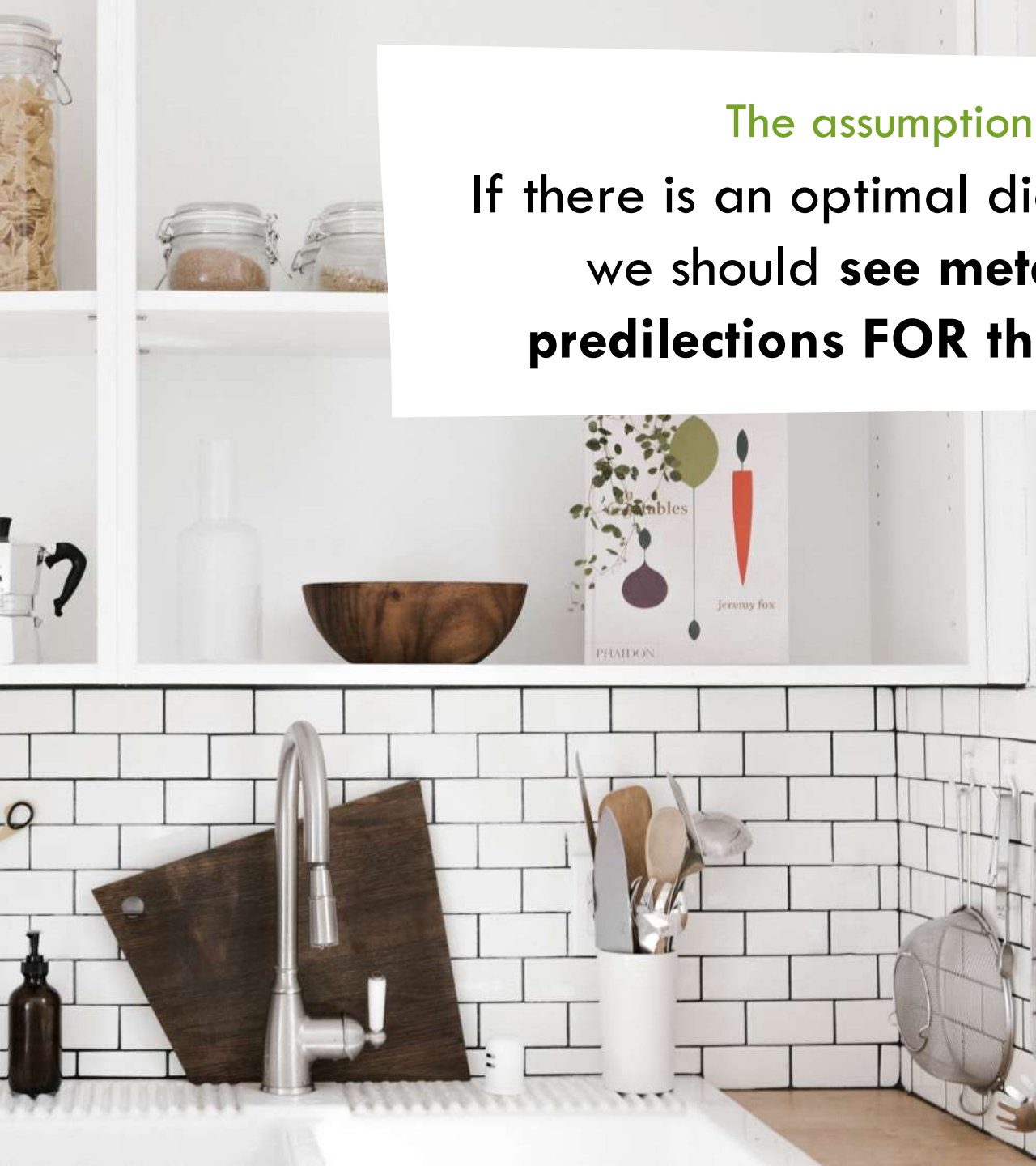
**IR/substrate
depletion**

Key to fat loss?

Appetite
suppression

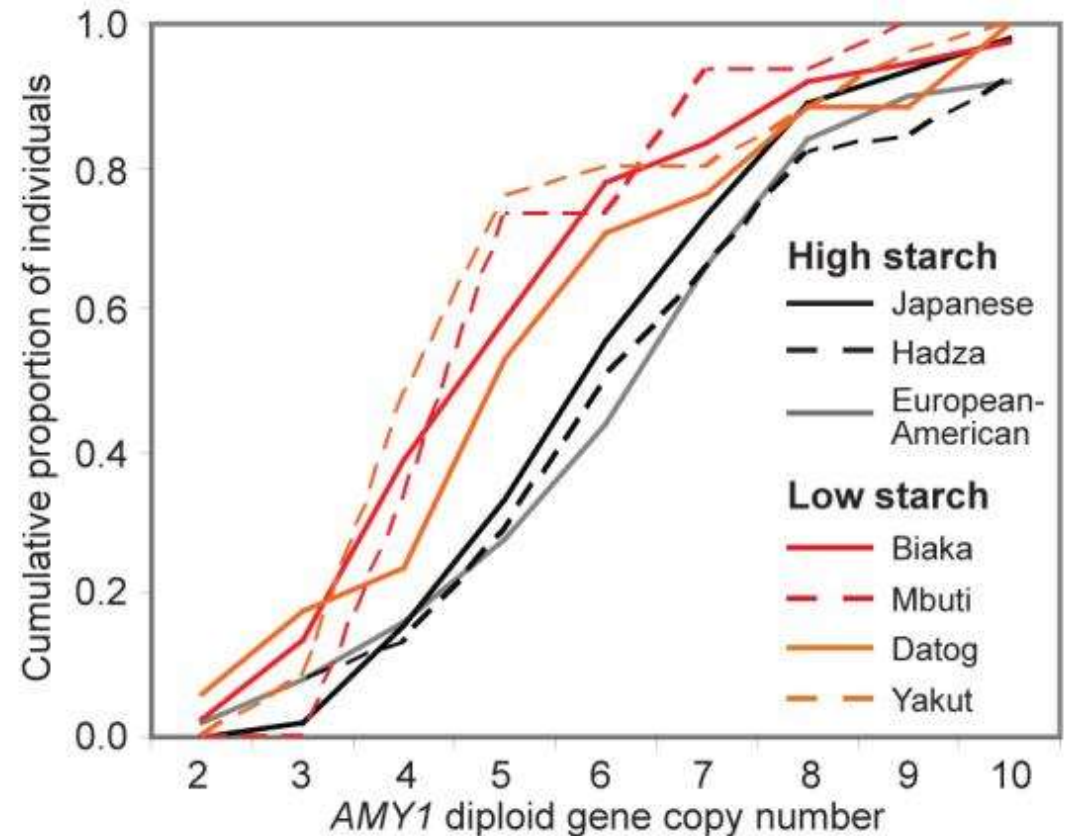
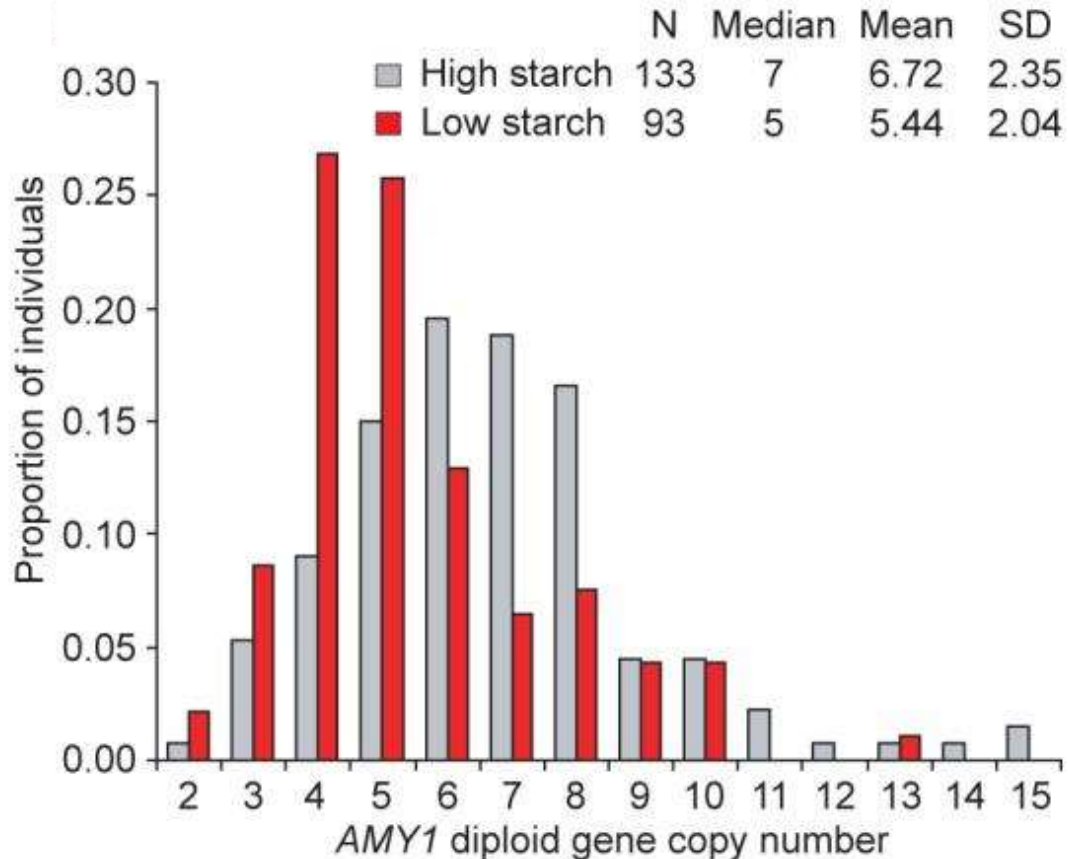
The assumption we must make:

If there is an optimal diet for humans (LC? HC?)
we should see **metabolic and genetic**
predilections FOR this specific approach.



The Case for Carbs

**Humans SHOULD be able to eat carbs,
likely more than all other primates!**



So,
what about
Ketosis



The Case Against Ketosis, pt. 1

Body actively “tries”
to **get out of Ketosis**



What are the recommended carb levels per day?

#context



A person is balancing on a thin yellow tightrope stretched across a deep valley. The person is wearing a black long-sleeved shirt, patterned leggings, and a blue belt. They are barefoot and have their arms outstretched for balance. The background shows a vast, hazy landscape with a dense forest of trees in shades of green and brown, suggesting an autumn or winter setting. The sky is a pale, hazy blue.

If Ketosis is *THE*
preferred state...
why it is **so hard**
to maintain?

A bit of a **razors**
edge to maintain
VIA NUTRITION
ALONE

The Case Against Ketosis, pt. 2

The Inuit largely do not
USE Ketosis!

CPT-1a

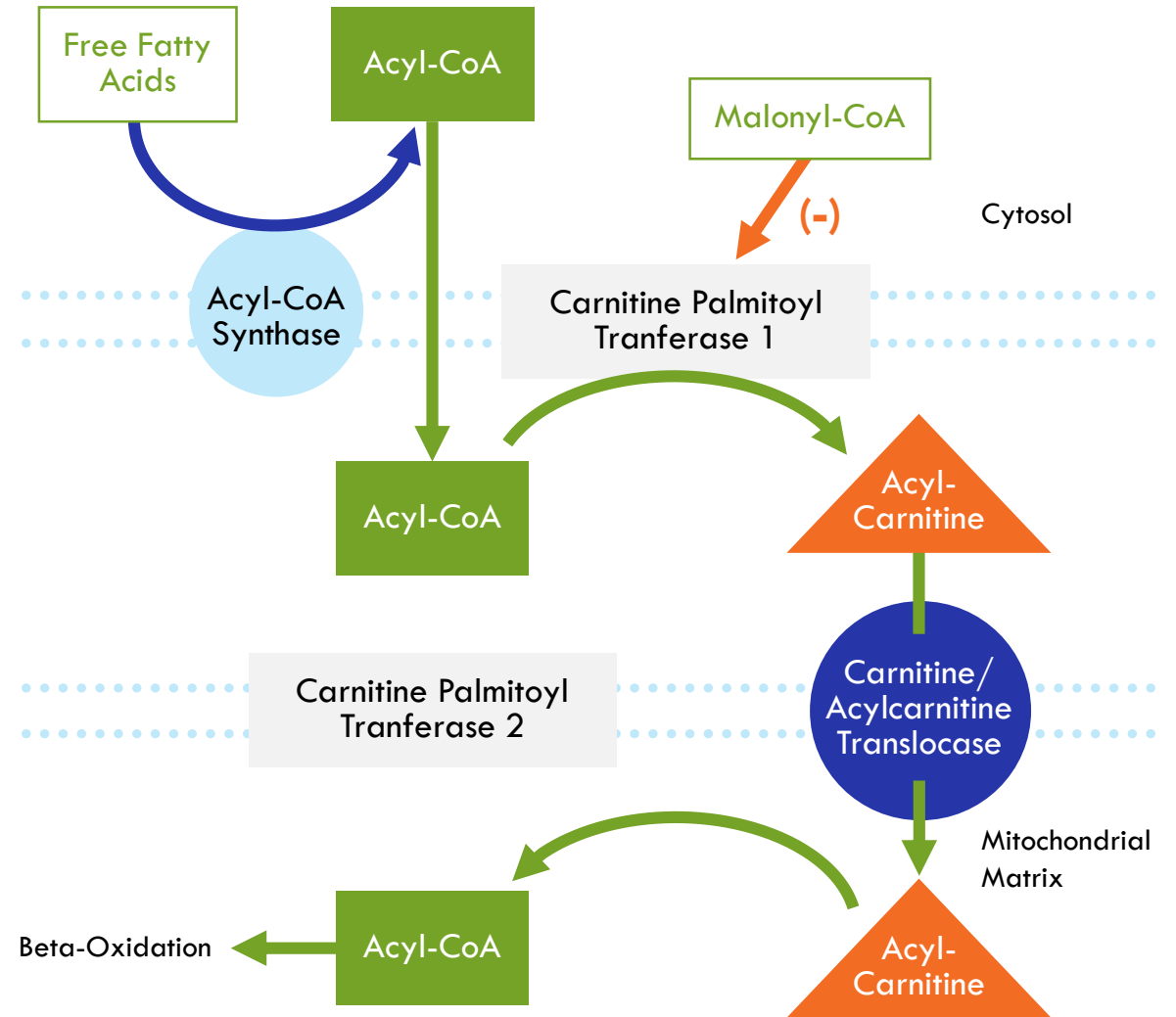
(Carnitine palmitoyltransferase)

Increases hypoglycemia

Largely blocks ability to enter ketosis

3X increase in infant mortality!

Stunning speed of gene spread



Mitochondrial carnitine palmitoyltransferase system

Carnitine Palmitoyl Transferase (CPT1 and CPT2). The fatty acids are transferred from cell cytoplasm to mitochondrial matrix for beta-oxidation. The CPT1 activity is regulated by malonyl-CoA feedback inhibition.

Gene that once aided survival in the Arctic is found to have negative impact on health today



Published

24 Oct 2014

Image

Ig-loos or Snow Villages at Oo-pung-ne-wing

Credit: [Toronto Public Library](#)

Millennia-old genetic variant that once provided advantages for survival in cold climates increases risk of hypoglycemia and infant mortality.

In individuals living in the Arctic, researchers have discovered a genetic variant that arose thousands of years ago and most likely provided an evolutionary advantage for processing high-fat diets or for surviving in a cold environment; however, the variant also seems to increase the risk of hypoglycemia, or low blood sugar, and infant mortality in today's northern populations.

The findings, published online in the [American Journal of Human Genetics](#), provide an example of how an initially beneficial genetic change could be detrimental to future generations.

“ Evolutionary impacts on health might be more prevalent than currently appreciated ”
— Florian Clemente

Share

Email	1	reddit	0
Share	0	in Share	0
Tweet	2	Share	60
Like	0		

- Subjects
- Arctic
 - Genetics
 - Genetic Variant

“
Evolutionary impacts on health might be more prevalent than currently appreciated.
— Florian Clemente

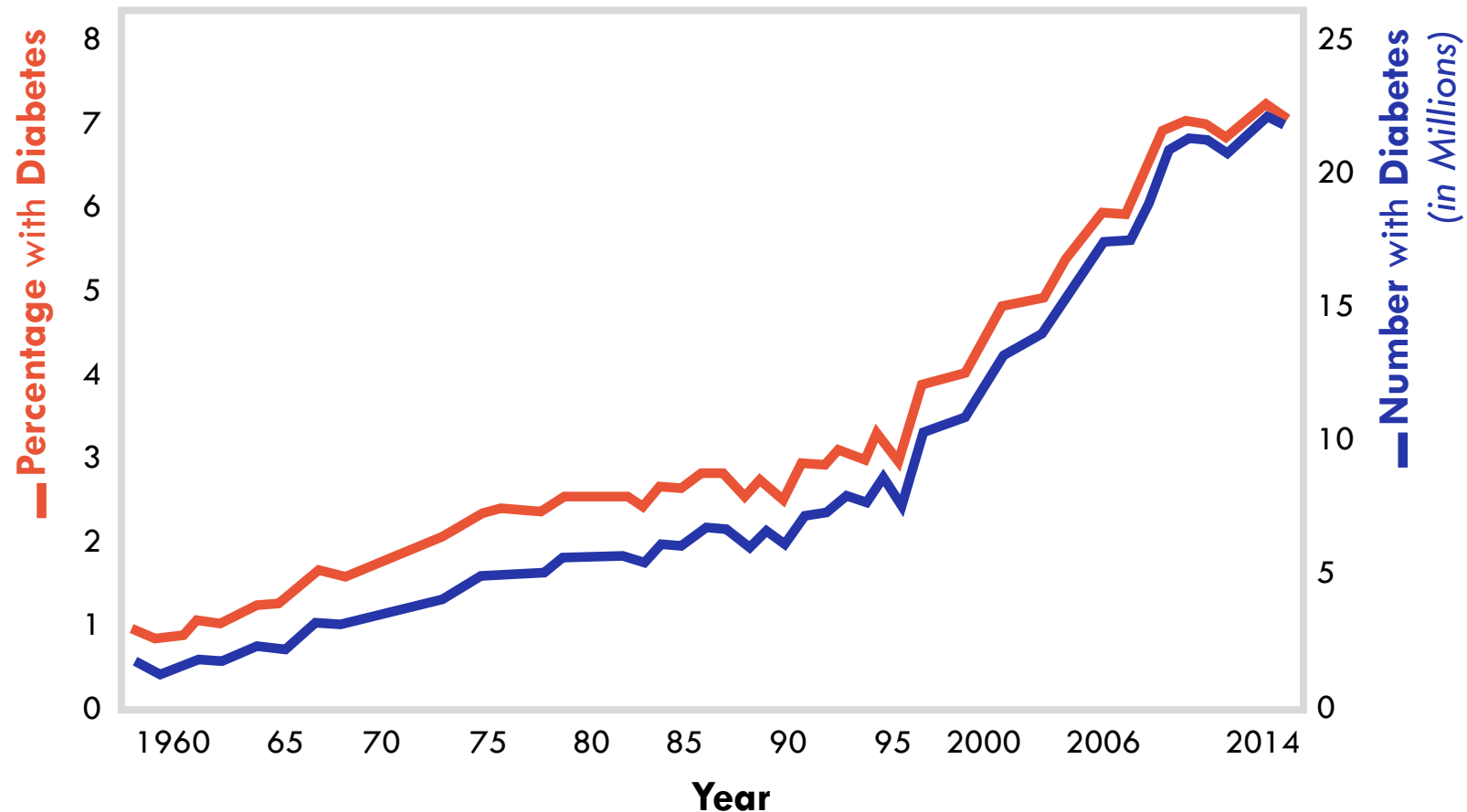
So,
carbs good,
low carb bad
right?

A solid green shape at the bottom of the page, starting as a vertical line on the left and tapering to a point on the right.

context



This is NOT the paleolithic, most of us don't have numbers like HG's



Reference: Centers for Disease Control and Prevention (CDC), "Long-Term Trends in Diabetes," April 2016. Americans diagnosed with diabetes, 1958 through 2014.

There *ARE* laudable characteristics of **time restricted feeding, exercise and low carb intake.**

SAY HELLO TO MY LITTLE FRIEND!!!

A dramatic scene from the movie Heat featuring Al Pacino. He is in a dark, ornate office, wearing a dark suit and a white shirt with a red collar. He is holding a handgun and has a wide-eyed, shouting expression. The room is filled with luxury furniture, including a large desk, ornate chairs, and a chandelier. The lighting is low and moody, with a red carpet leading to the desk.

Hysteresis.



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Interdiscip Top Gerontol. Author manuscript; available in PMC 2009 Oct 1:
 Published in final edited form as:
[Interdiscip Top Gerontol. 2007; 35: 39–68.](#)
 doi: [10.1159/000096555](#)

PMCID: PMC2755292
 NIHMSID: NIHMS134099

Glucose Hysteresis as a Mechanism in Dietary Restriction, Aging and Disease

Charles V. Mobbs, Jason Mastaitis, Minhua Zhang, Fumiko Isoda, Hui Cheng, and Kelvin Yen

[Author information](#) | [Copyright and License information](#)

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 See other articles in PMC that [cite](#) the published article.

Abstract

Go to:

Elevated blood glucose associated with diabetes produces progressive and apparently irreversible damage to many cell types. Conversely, reduction of glucose extends life span in yeast, and dietary restriction reduces blood glucose. Therefore it has been hypothesized that cumulative toxic effects of glucose drive at least some aspects of the aging process and, conversely, that protective effects of dietary restriction are mediated by a reduction in exposure to glucose. The mechanisms mediating cumulative toxic effects of glucose are suggested by two general principles of metabolic processes, illustrated by the *lac* operon but also observed with glucose-induced gene expression. First, metabolites induce the machinery of their own metabolism. Second, induction of gene expression by metabolites can entail a form of molecular memory called hysteresis. When applied to glucose-regulated gene expression, these two principles suggest a mechanism whereby repetitive exposure to postprandial excursions of glucose leads to an age-related increase in glycolytic capacity (and reduction in β -oxidation of free fatty acids), which in turn leads to an increased generation of oxidative damage and a decreased capacity to respond to oxidative damage, independent of metabolic rate. According to this mechanism, dietary restriction increases life span and reduces pathology by reducing exposure to glucose and therefore delaying the development of glucose-

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An intervention resembling caloric restriction prolongs life span and retards aging in yeast. [FASEB J. 2000]

Decreased energy metabolism extends life span in *Caenorhabditis elegans* without reducing oxidative [Genetics. 2010]

Metabolic phenotype modulation by caloric restriction in a lifelong dog study. [J Proteome Res. 2013]

Caloric restriction in primates and relevance to humans. [Ann N Y Acad Sci. 2001]

Caloric restriction and aging: an update. [Exp Gerontol. 2000]

[See reviews...](#)

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Cited by other articles in PMC

Retinol as a cofactor for PKC δ -mediated impairment of insulin sensitivity in a mouse model of diet-inc [The FASEB Journal. 2015]

Evidence for the Cost of Reproduction in Humans: High Lifetime Reproductive Effort Is Associated with Greater [PLoS ONE. 2016]

Regulation of peripheral metabolism by substrate partitioning in the brain [Endocrinology and metabolism c...]

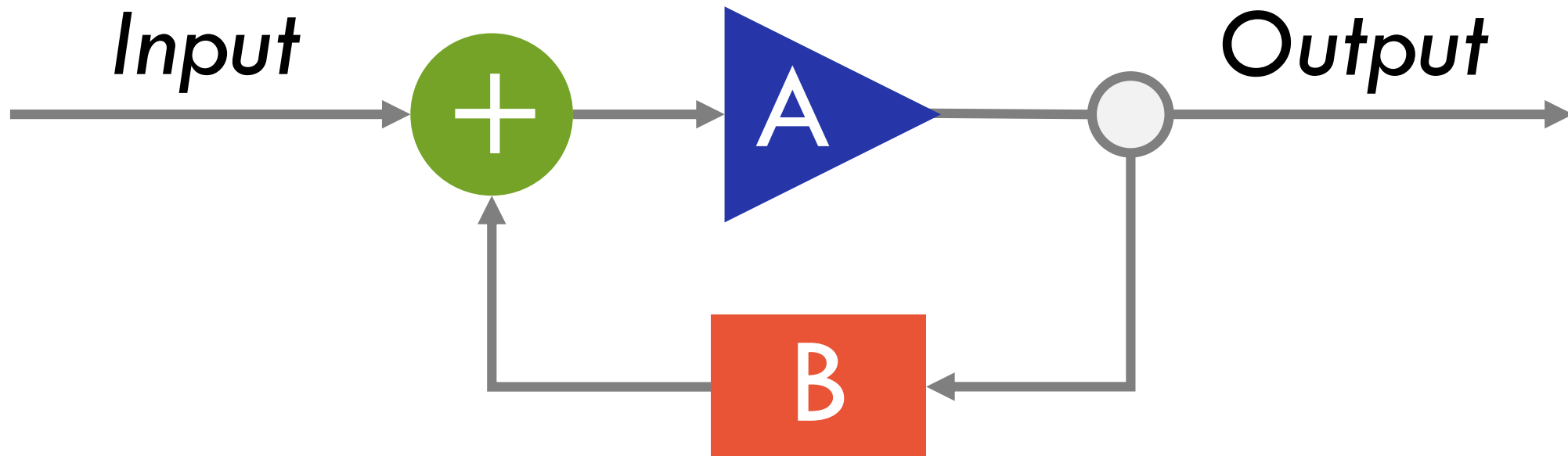
A novel kinase regulates dietary restriction-mediated longevity in *Caenorhabditis elegans*. [Aging Cell. 2014]

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What is **Hysteresis**?

Dependence of the state of a system on its **HISTORY**
(A type of memory)



Glucose Hysteresis: Epigenetics in Action



0

0.3

1

2

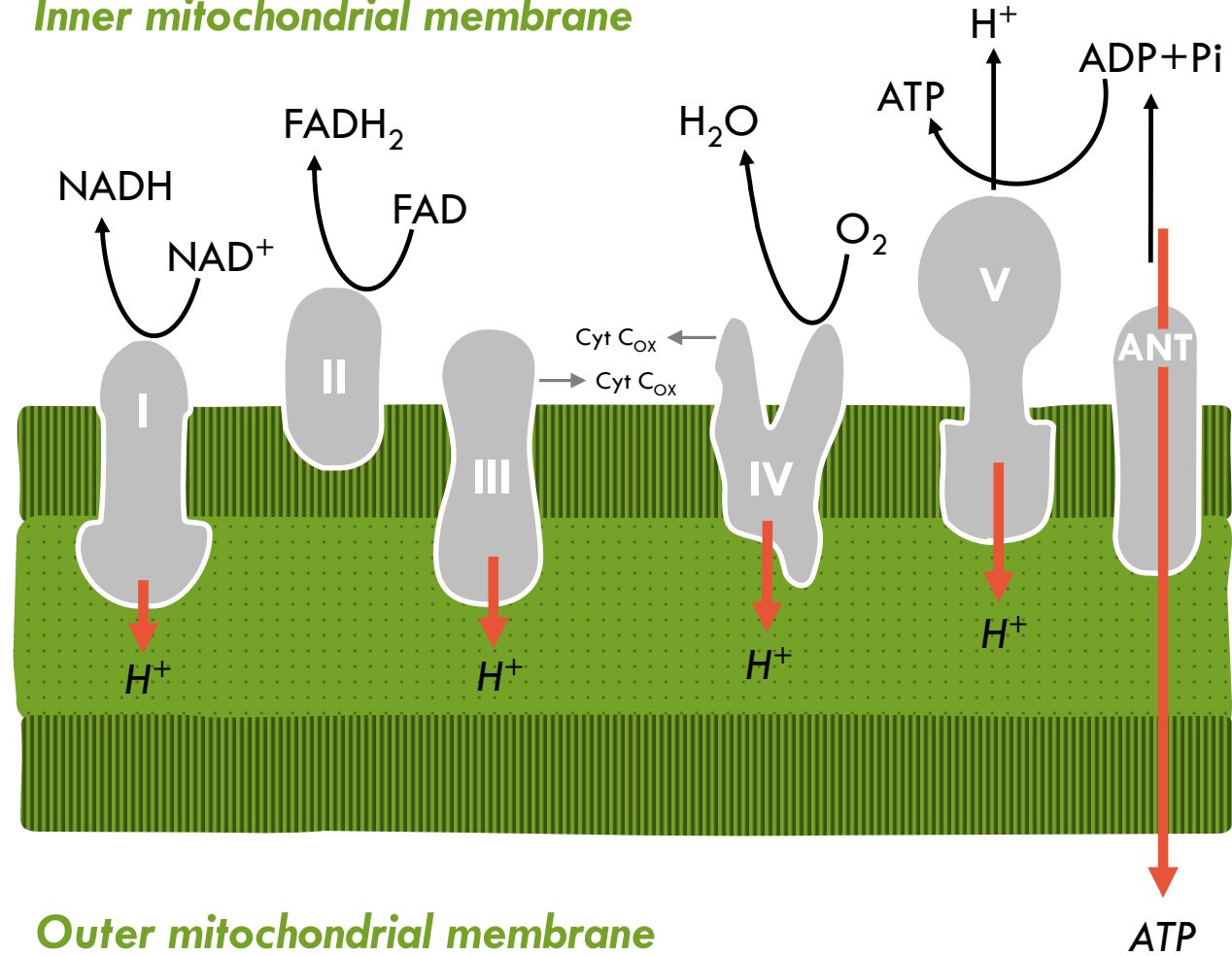
3

4

5

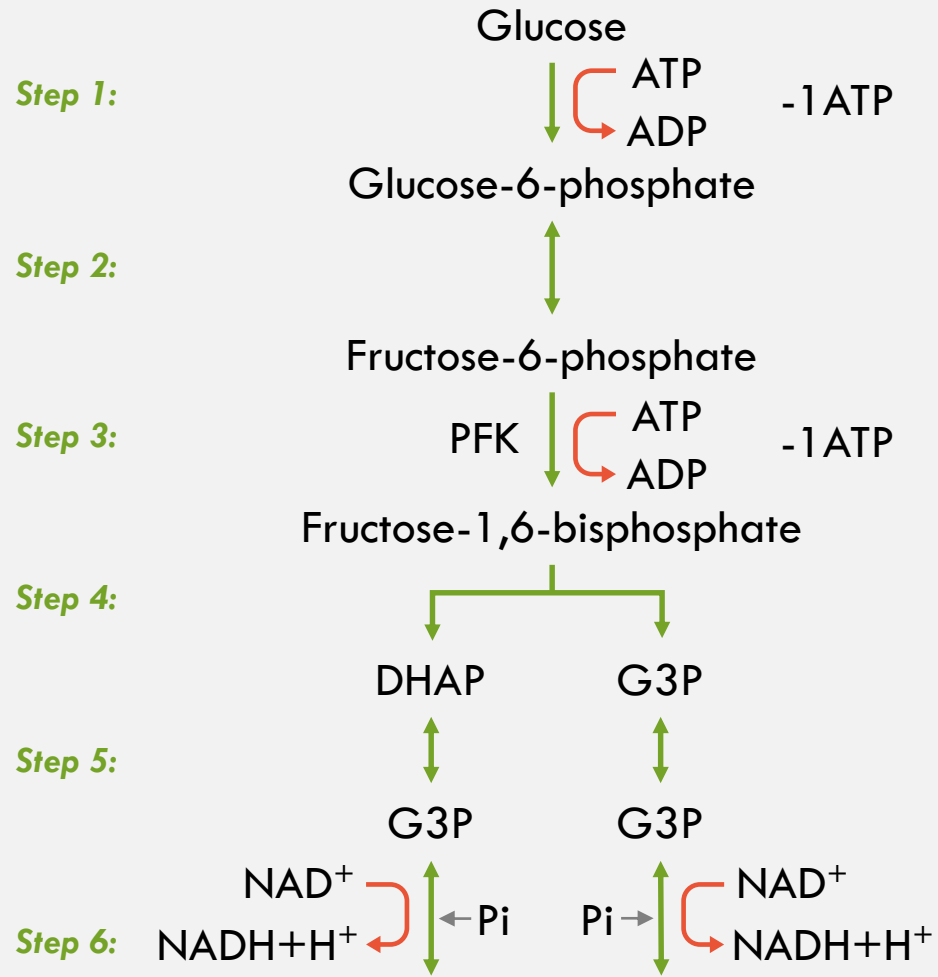


Inner mitochondrial membrane

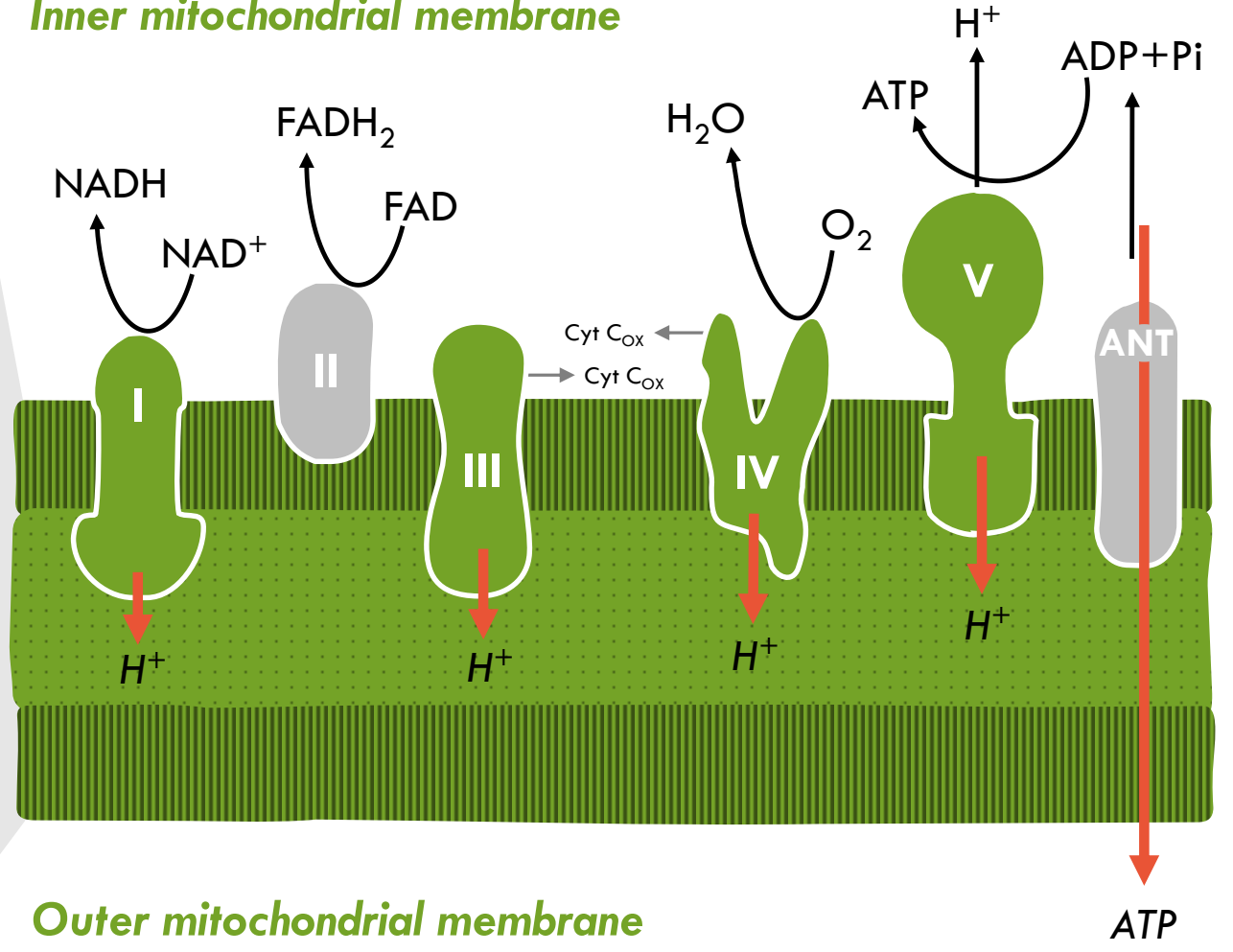


Outer mitochondrial membrane

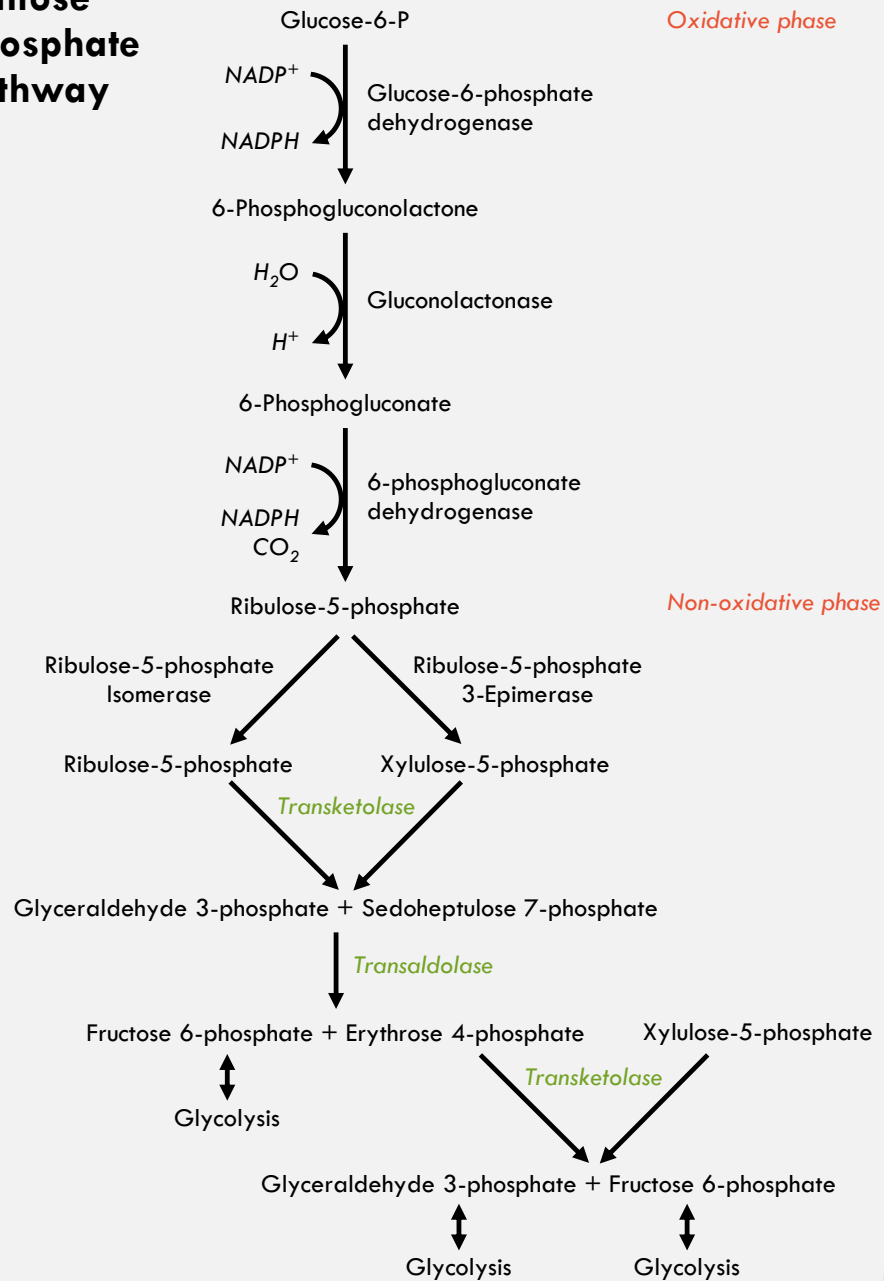
Glycolysis Pathway



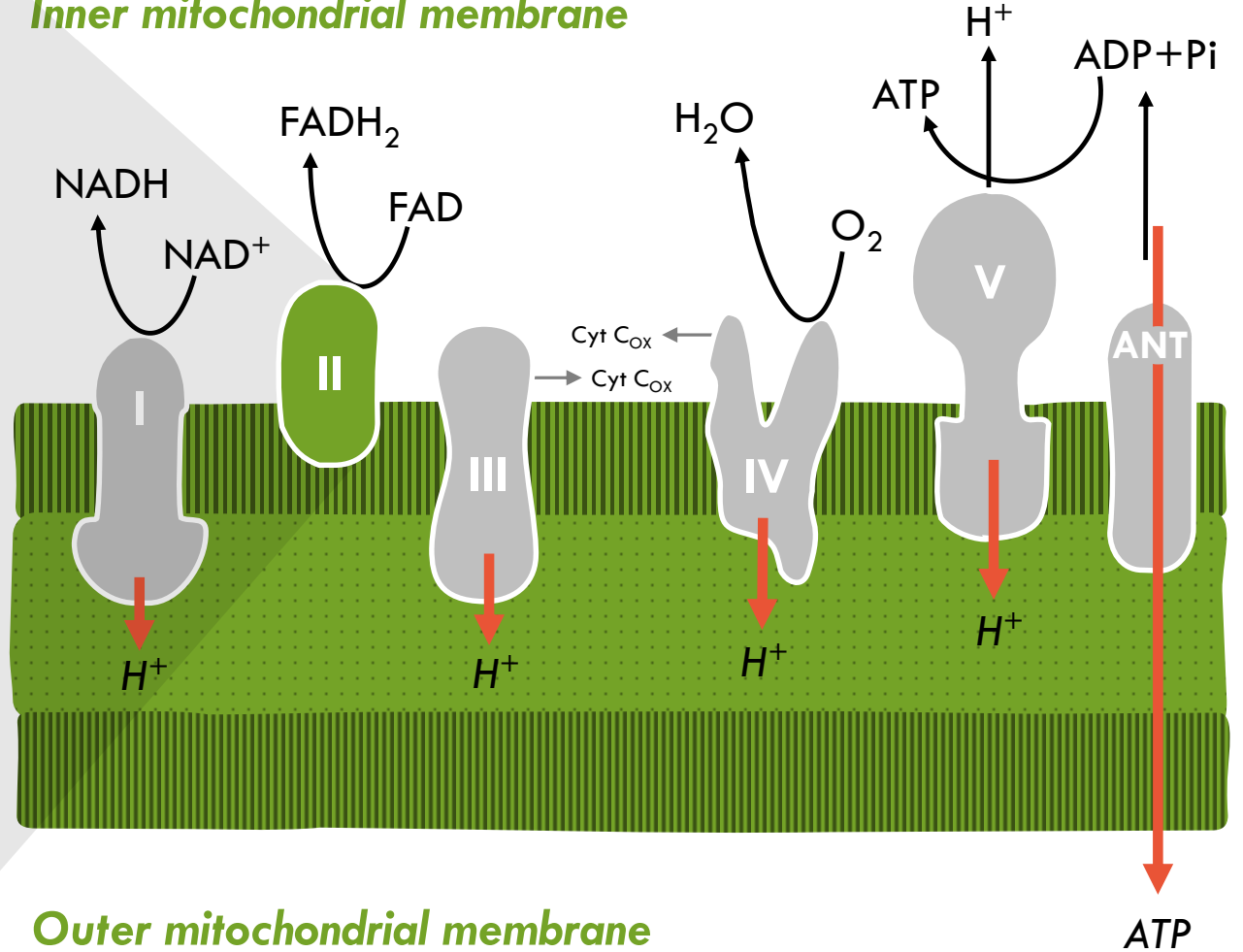
Inner mitochondrial membrane



Pentose Phosphate Pathway

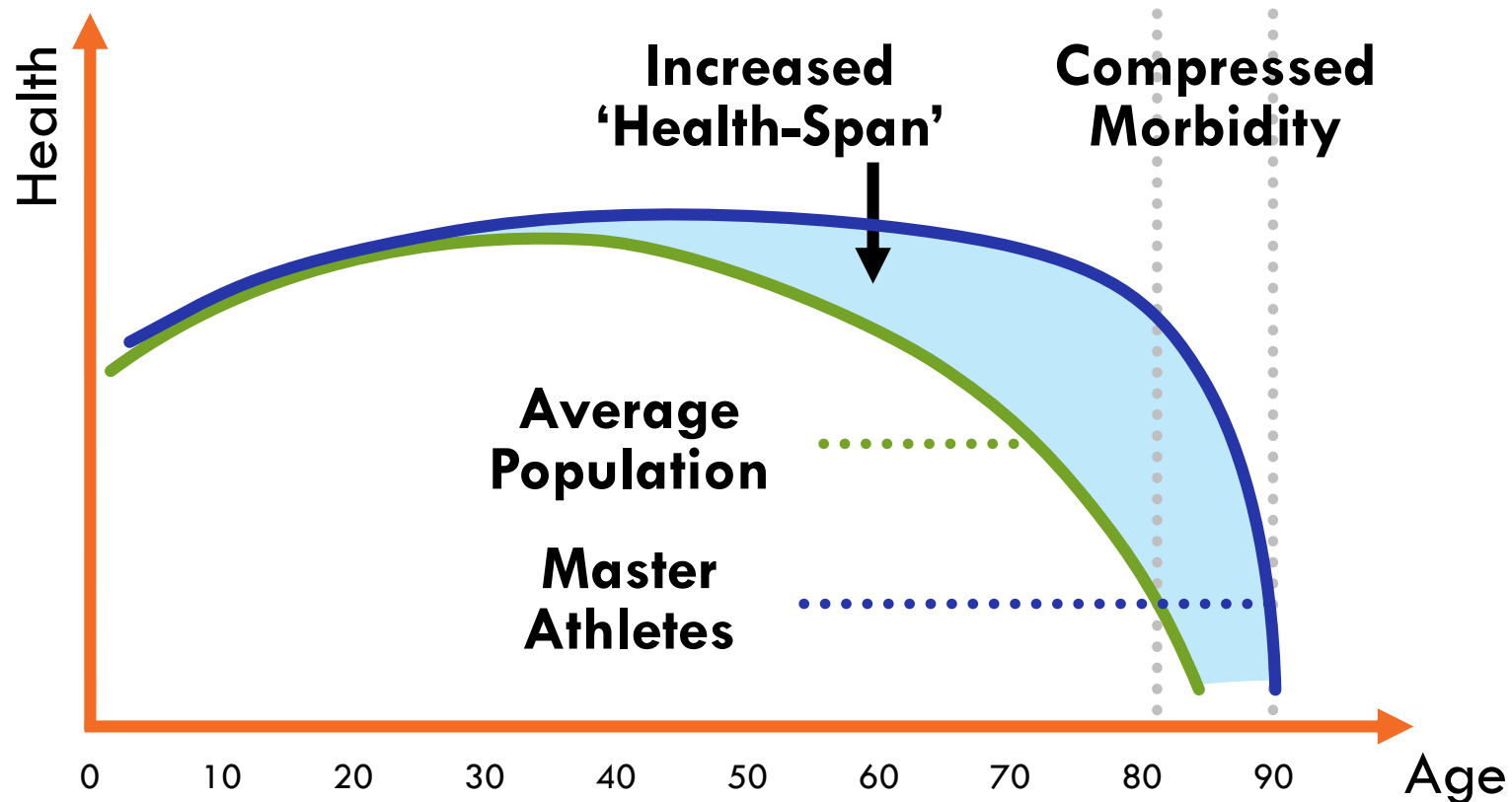


Inner mitochondrial membrane



Outer mitochondrial membrane

Complex 1 vs. Complex 2 and Health Span



The Respiratory Quotient (RQ)

The following table shows the **RQ values** for different classes of **respiratory substrate** when they are used for aerobic respiration

<i>RQ value</i>		
1.0	0.7	0.9
Glucose	Fatty acid	Protein
<i>Respiratory Substrate</i>		

If any degree of anaerobic respiration occurs RQ values significantly above a value of 1.0 are obtained

Kenyan Runners



ncbi.nlm.nih.gov

NCBI Resources How To Sign in to NCBI

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Format: Abstract Send to

Pediatr Diabetes. 2015 May;16(3):211-8. doi: 10.1111/peidi.12141. Epub 2014 Apr 23.

Metabolic inflexibility and insulin resistance in obese adolescents with non-alcoholic fatty liver disease.

Lee S¹, Rivera-Vega M, Alsayed HM, Boesch C, Libman I.

Author information

Abstract

BACKGROUND: Non-alcoholic fatty liver disease (NAFLD) is a comorbidity of childhood obesity.

OBJECTIVE: We examined whole-body substrate metabolism and metabolic characteristics in obese adolescents with vs. without NAFLD.

SUBJECTS: Twelve obese (BMI \geq 95th percentile) adolescents with and without NAFLD [intrahepatic triglyceride (IHTG) \geq 5.0% vs. $<$ 5.0%] were pair-matched for race, gender, age and % body fat.

METHODS: Insulin sensitivity (IS) was assessed by a 3-h hyperinsulinemic-euglycemic clamp and whole-body substrate oxidation by indirect calorimetry during fasting and insulin-stimulated conditions.

RESULTS: Adolescents with NAFLD had increased ($p < 0.05$) abdominal fat, lipids, and liver enzymes compared with those without NAFLD. Fasting glucose concentration was not different between groups, but fasting insulin concentration was higher ($p < 0.05$) in the NAFLD group compared with those without. Fasting hepatic glucose production and hepatic IS did not differ ($p > 0.1$) between groups. Adolescents with NAFLD had higher ($p < 0.05$) fasting glucose oxidation and a tendency for lower fat oxidation. Adolescents with NAFLD had lower ($p < 0.05$) insulin-stimulated glucose disposal and lower peripheral IS compared with those without NAFLD. Although respiratory quotient (RQ) increased significantly from fasting to insulin-stimulated conditions in both groups (main effect, $p < 0.001$), the increase in RQ was lower in adolescents with NAFLD vs. those without (interaction, $p = 0.037$).

CONCLUSION: NAFLD in obese adolescents is associated with adverse cardiometabolic profile, peripheral insulin resistance and metabolic inflexibility.


© 2014 John Wiley & Sons A/S. Published by John Wiley & Sons Ltd.

KEYWORDS: childhood obesity; insulin sensitivity; non-alcoholic fatty liver disease; visceral fat

PMID: 24754380 PMCID: PMC4339626 DOI: 10.1111/peidi.12141

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Review Hepatic Steatosis as a marker of Metabolic Dysfunction. [Nutrients. 2015]

Review Non-alcoholic fatty liver disease and obesity: biochemica [World J Gastroenterol. 2014]

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Nonalcoholic Fatty Liver Disease in Hispanic Youth With Dysglycemia: Ri [J Endocr Soc. 2017]

Review Targeting NAD⁺ in Metabolic Disease: New Insights Into an Old Mc [J Endocr Soc. 2017]

Visceral fat is associated with the racial differences in liver fat be [Pediatr Diabetes. 2017]

See all...

Related information

By Contrast

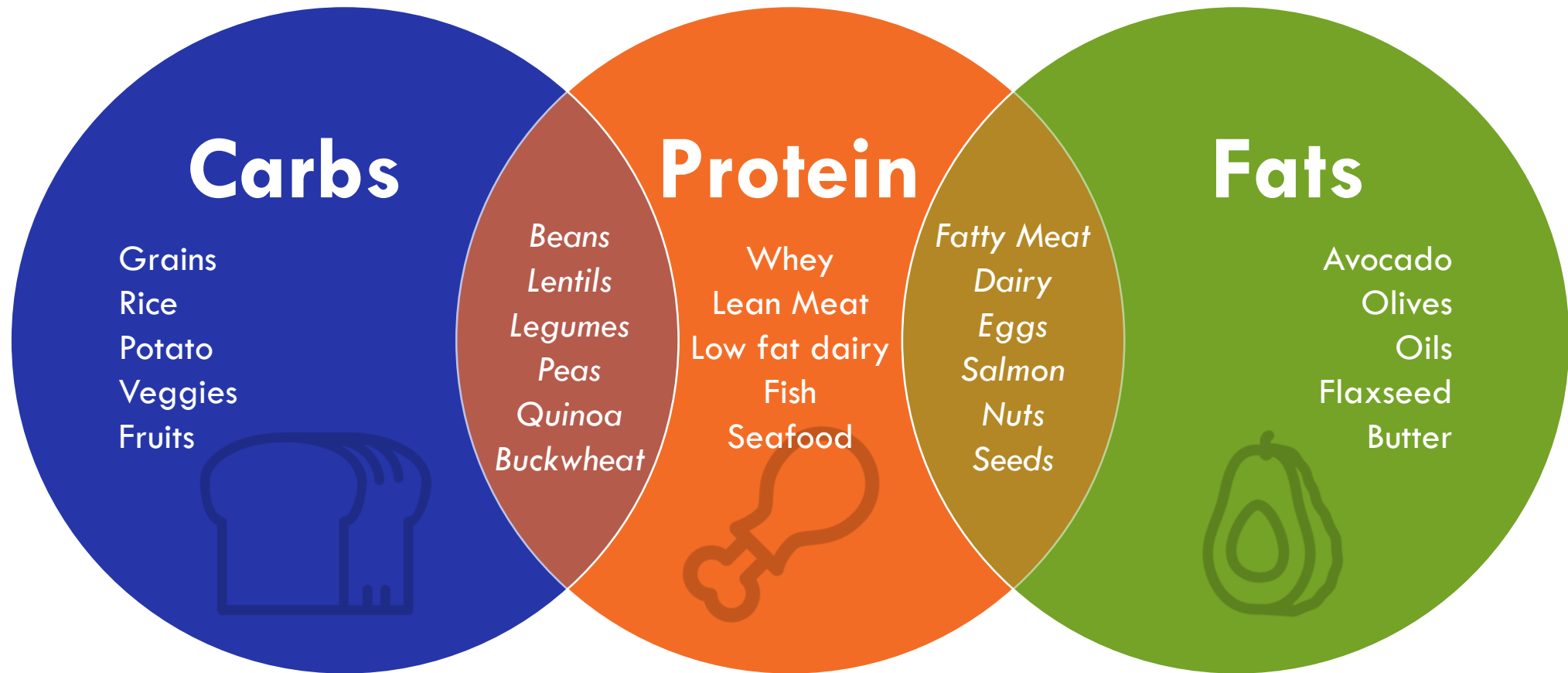
Is there
a formula
for *SUCCESS*?



The background features a dark, grid-like pattern of glowing numbers. The numbers are arranged in a grid and appear to be made of a translucent, glowing material. The numbers visible include '4', '5', '6', '7', '8', and '9'. The lighting is warm and creates a bokeh effect, with the numbers in the foreground being sharper than those in the background.

Perhaps “optimum”
is **not a number.**

Perhaps “optimum” is a **SEAMLESS transition** between a wide variety of fuels.

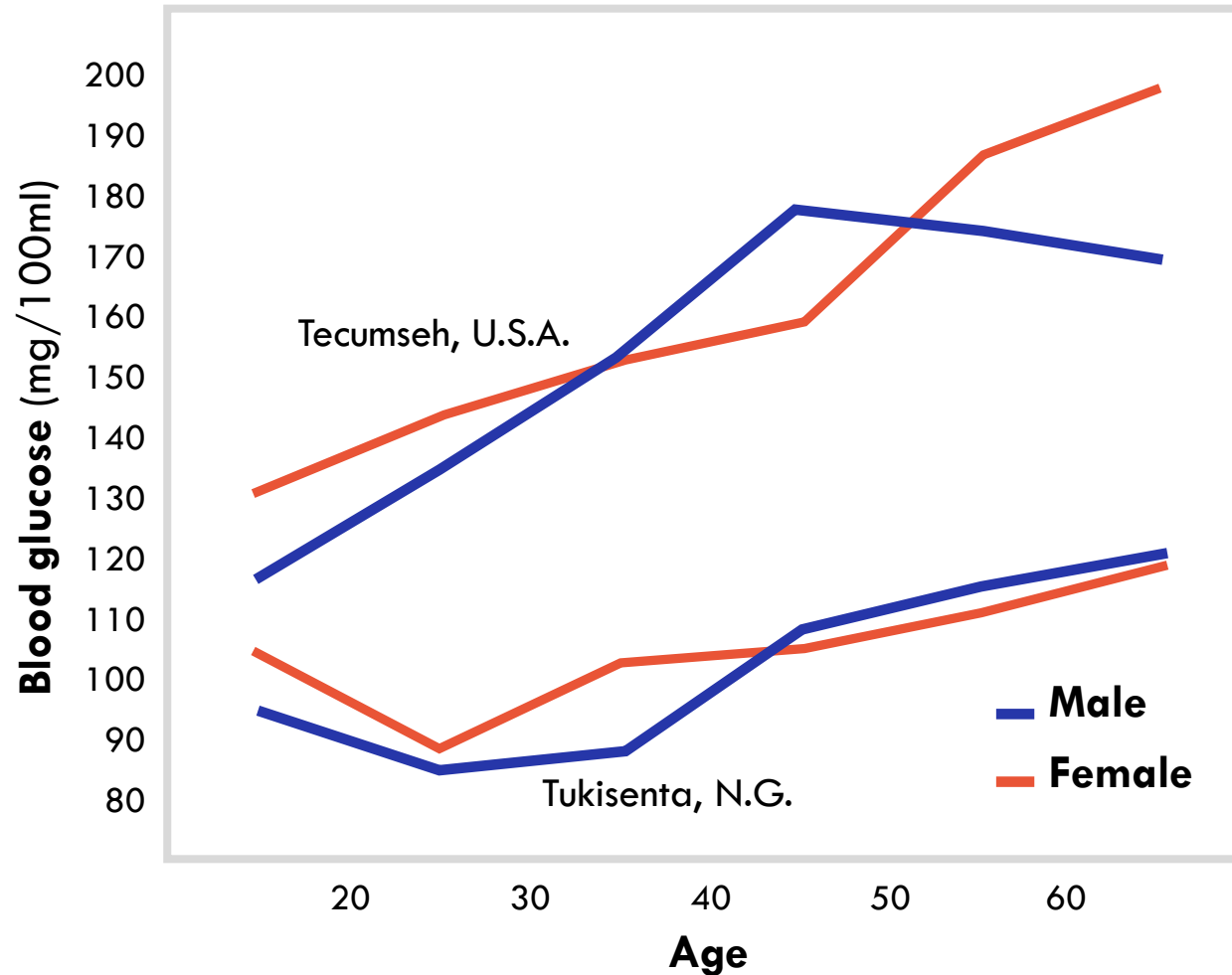


Perhaps “optimum” is a relative absence
of modern degenerative disease



The Added Problem

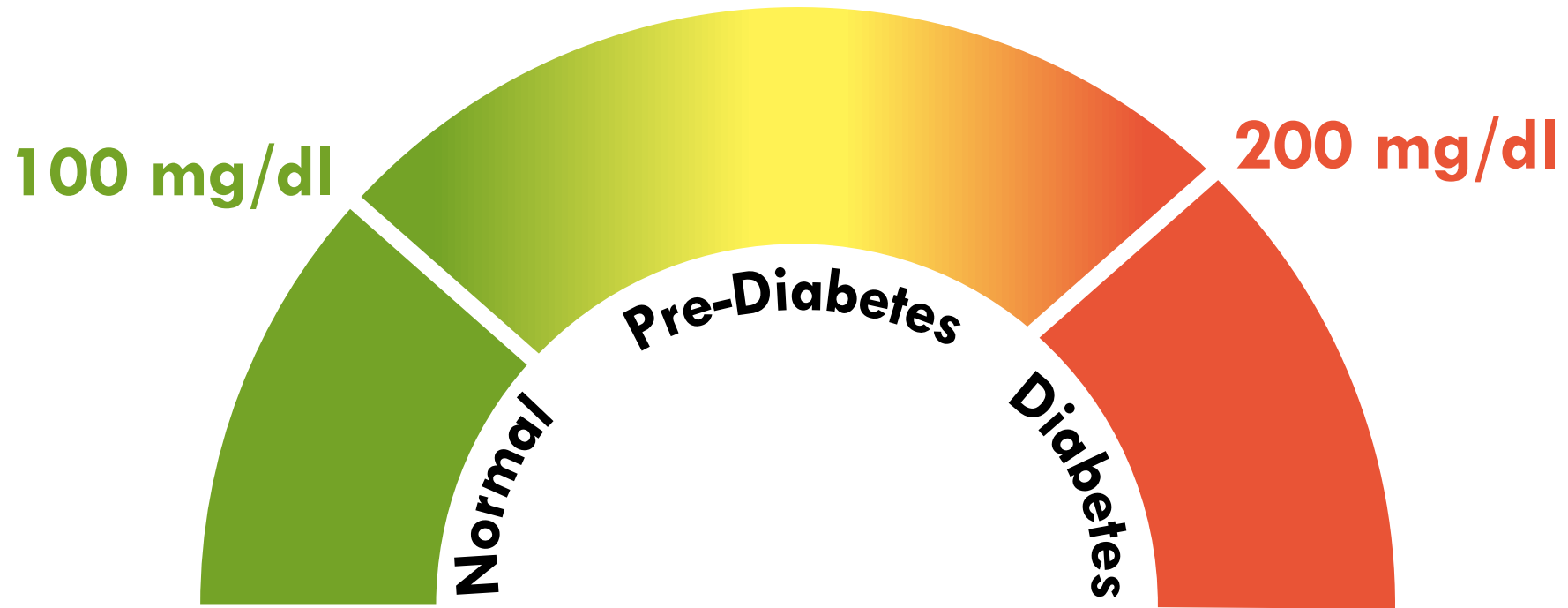
How we define “normal”



**Barely above baseline and
little decline with age!**
Also: **ONE HOUR OGTT!!!**

Our “normal”

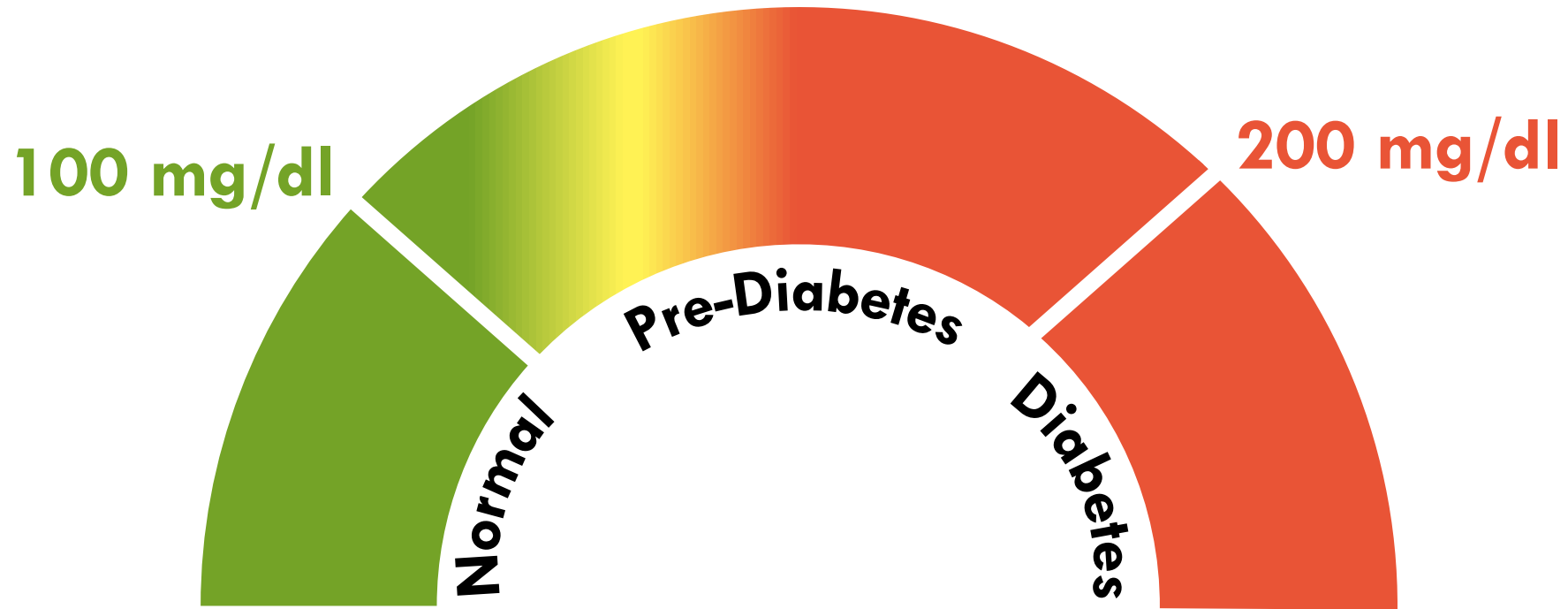
2-hour OGT test



Normal: **Not good enough**

Pre-Westernized “normal”

1-hour OGT test



Establishing Physiologic norms:
The best of Ancestral Health

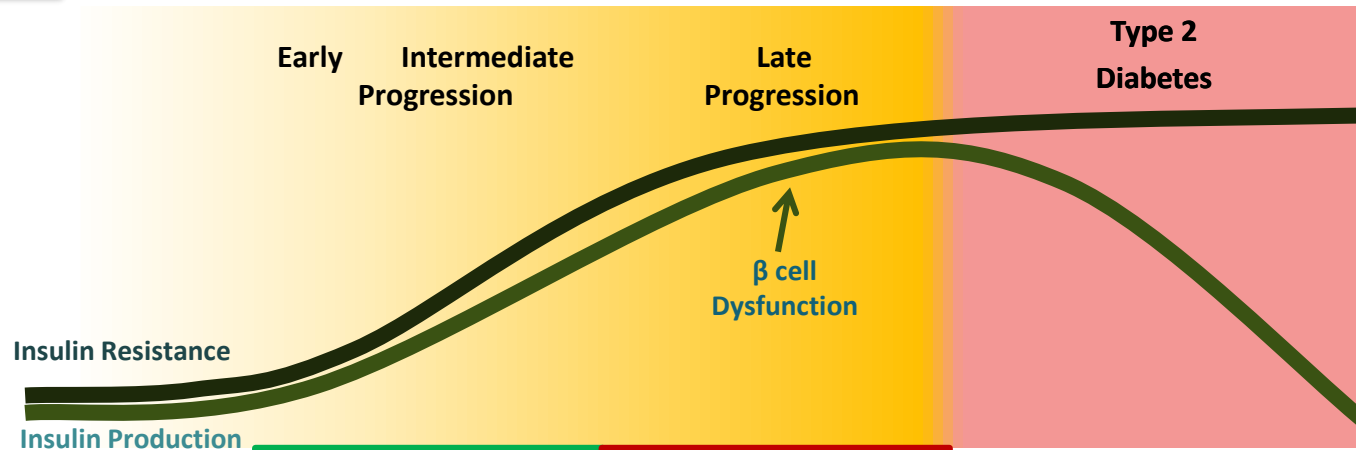
“Prediabetes” is Inadequate Marker of DM Risk

DIAGNOSTIC DILEMMA

Risk of diabetic progression is assessed by glucose measures that are the “response”, not the “cause” of worsening glucose metabolism.

< 100 mg/dL			100-125 mg/dL					≥ 125 mg/dL			
“Normal” Glucose					Pre-Diabetes					Diabetes	
80	85	90	95	100	105	110	115	120	125	>125	Plasma Glucose, mg/dL
5.5			5.7		6.0			6.4		>6.4	HbA1c %

Continuum of Type 2 Diabetes Progression



UNMET DIAGNOSTIC NEED

“Diagnostic tests should be developed to better distinguish patients who will progress to diabetes from those who will not.”¹

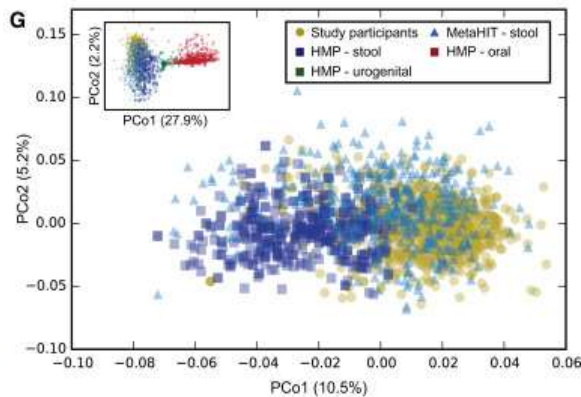
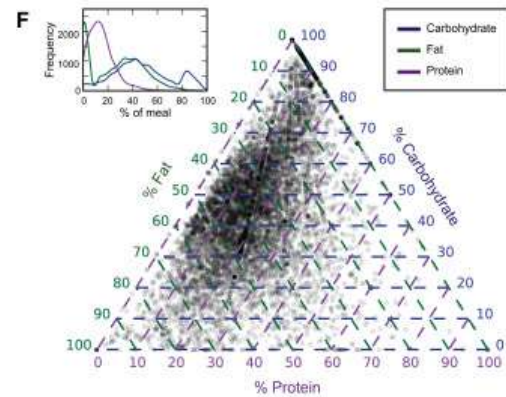
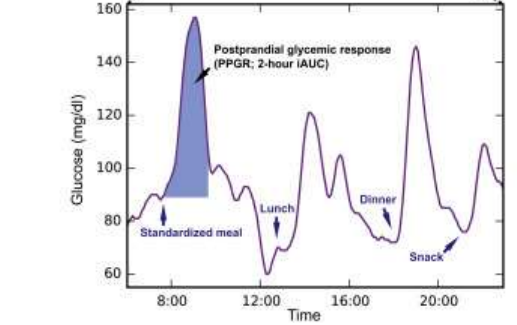
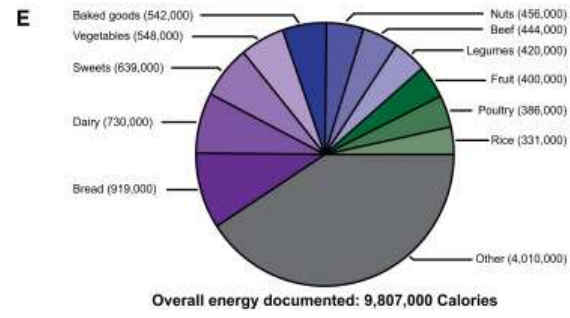
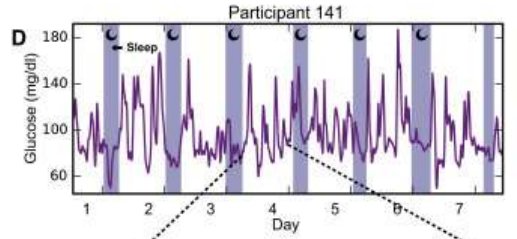
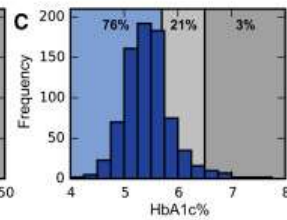
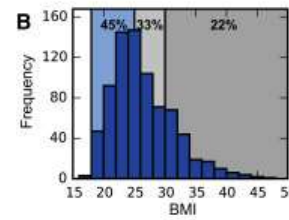
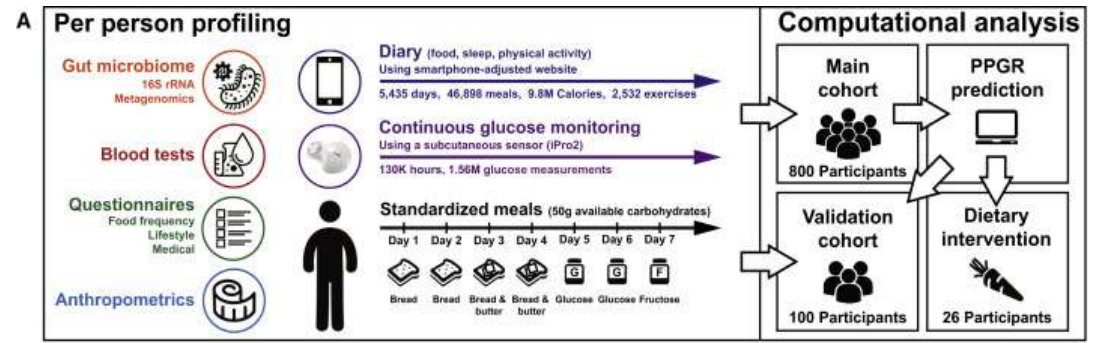
Many with glucose 100-110 mg/dL do not progress to T2DM/

Others with glucose 90-99 mg/dL develop diabetes in <5 years

Those with late stage progression (e.g. FPG > 110) frequently have vascular complications and increased pancreatic dysfunction with high risk of progression to Type 2 diabetes

1. AACE Prediabetes Consensus Statement, Endocr Pract. 2008;14(No. 7) 941

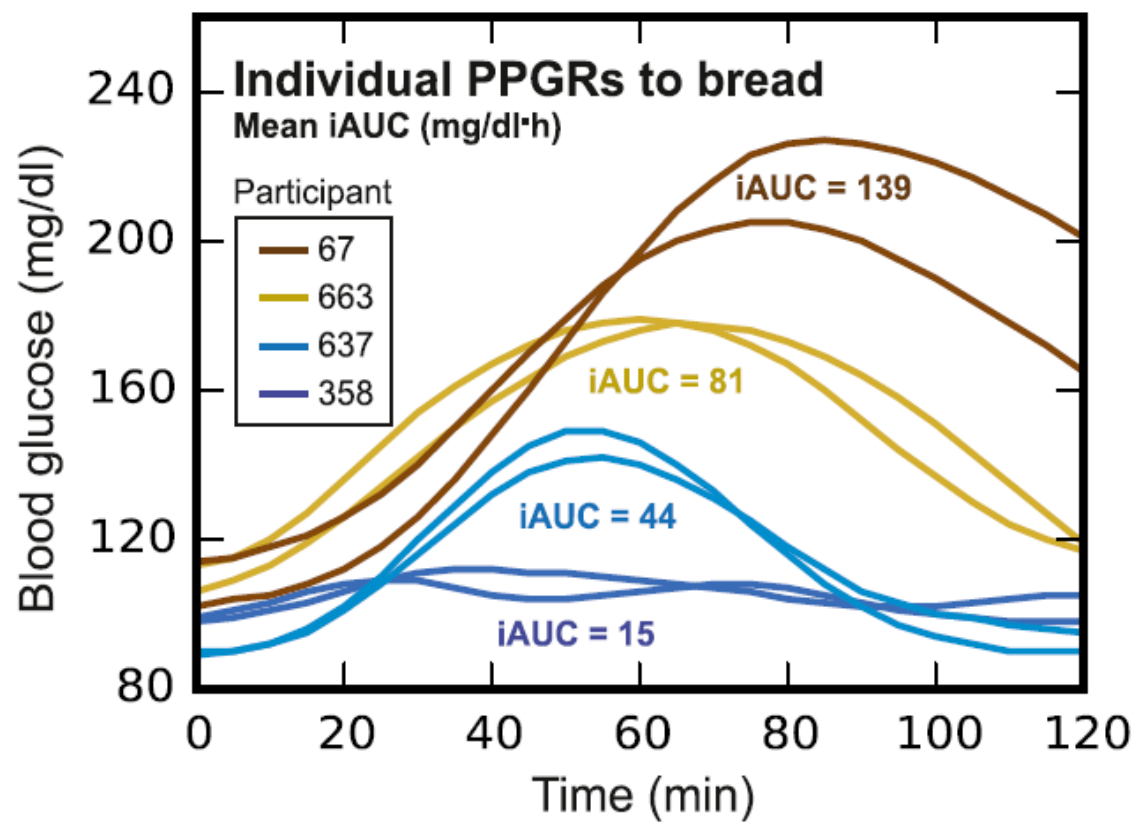
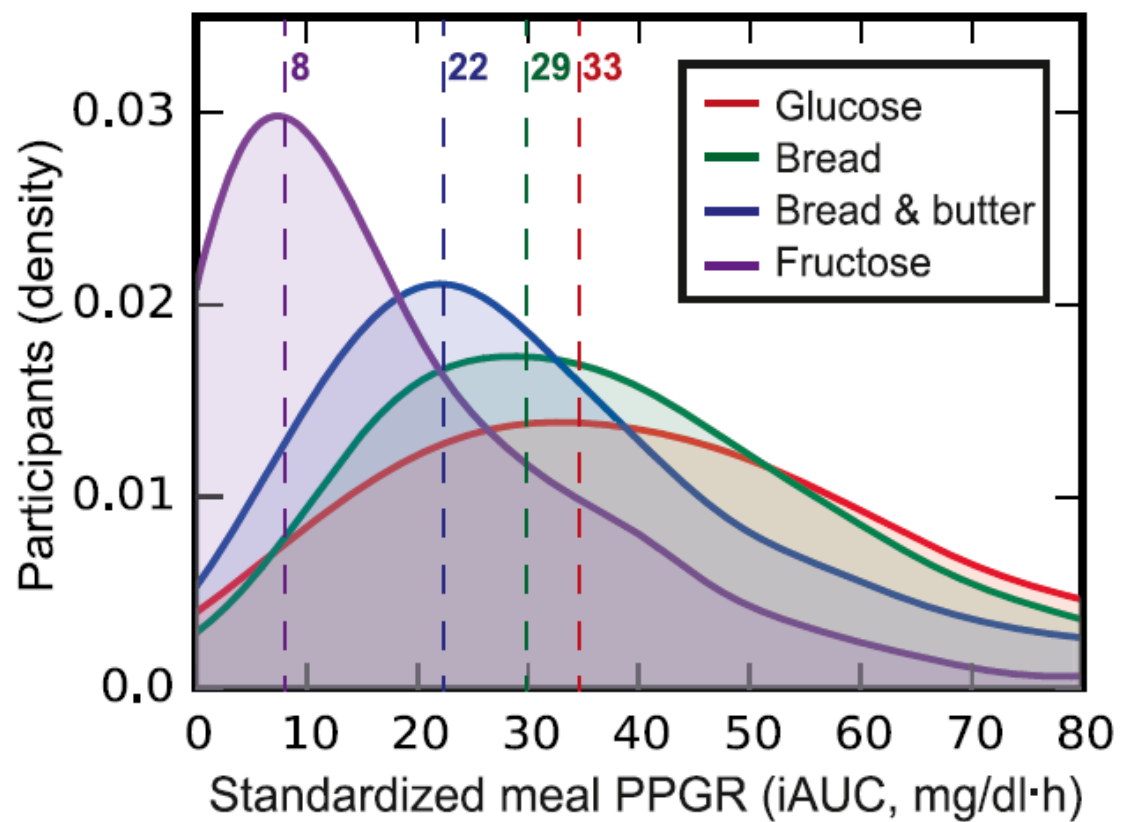
Insulin load/glycemic response important due to individual variations

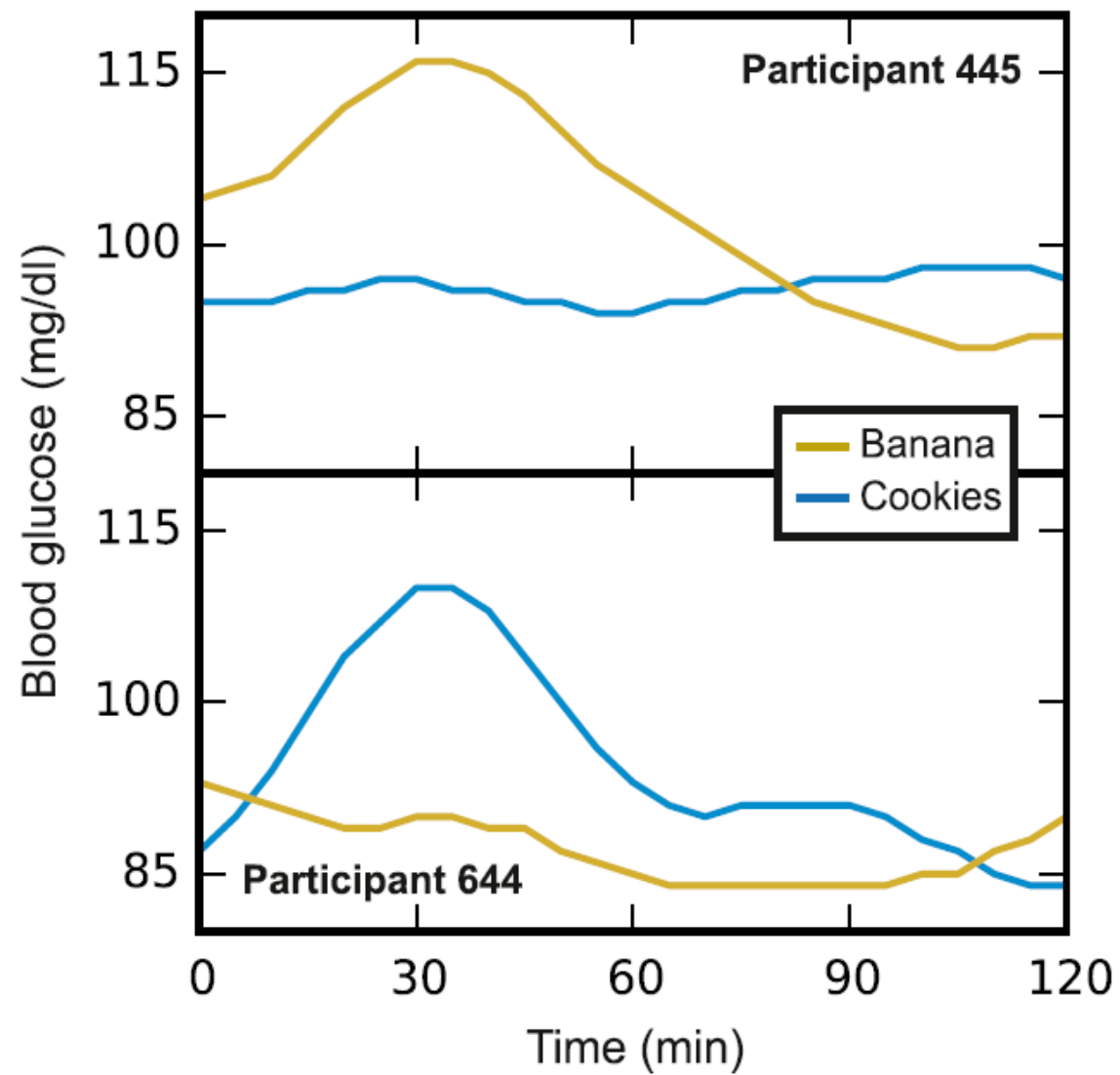
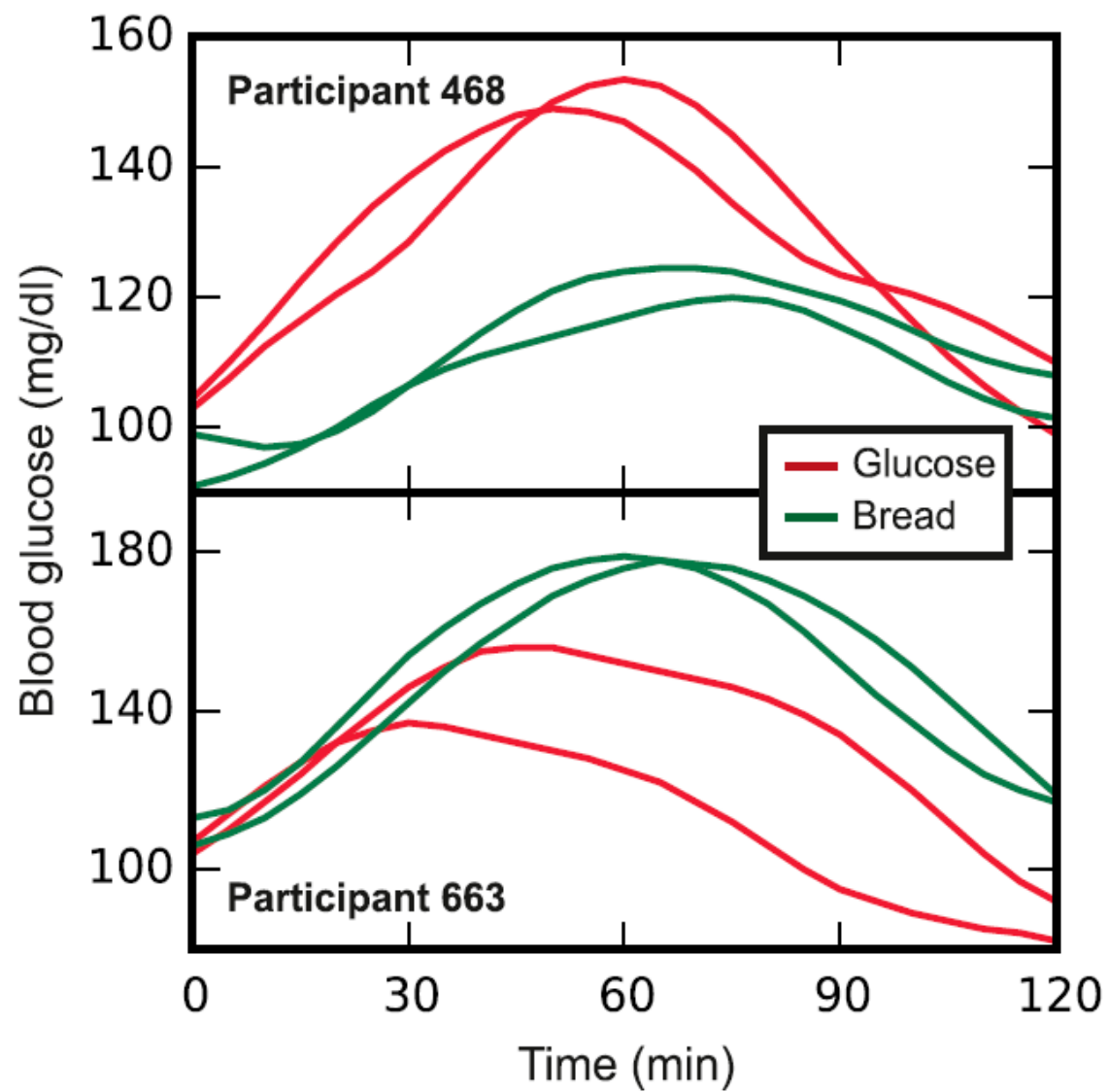


Weitzman inst.

Brain hates glucose deltas (Remember Hysteresis!!)

Overeating





Real World Example:
7 Day Carb Test



My
Blood Glucose



Nicki's
Blood Glucose

US
Quantified



Real World Example #2:


**Is the LC flu a symptom
of problems or normal?**

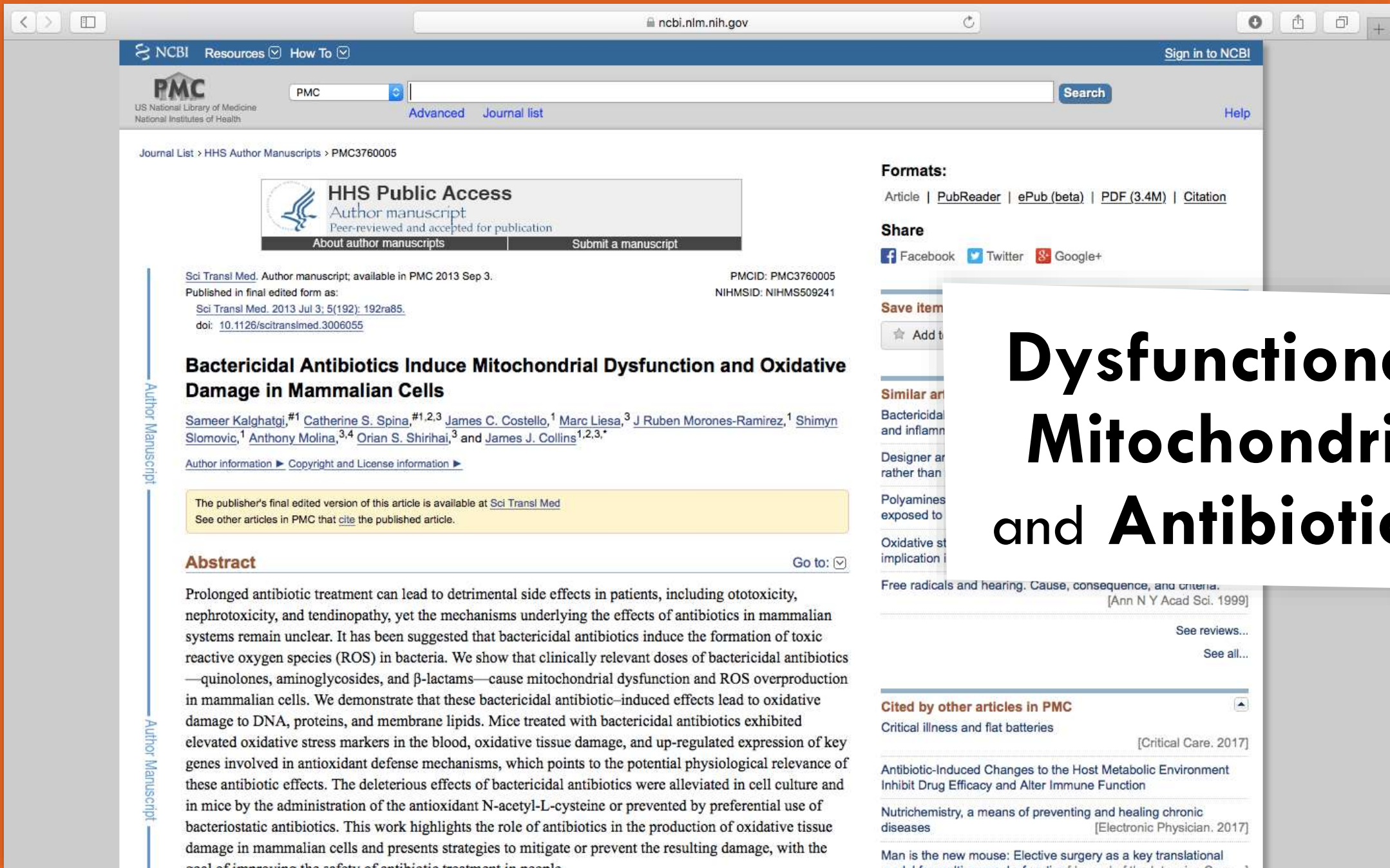
SEAMLESS

Transition to Ketosis



OK,
why can't we
transition
seamlessly?





Dysfunctional Mitochondria and Antibiotics

Sci Transl Med. Author manuscript; available in PMC 2013 Sep 3.
Published in final edited form as:
Sci Transl Med. 2013 Jul 3; 5(192): 192ra85.
doi: [10.1126/scitranslmed.3006055](https://doi.org/10.1126/scitranslmed.3006055)

PMCID: PMC3760005
NIHMSID: NIHMS509241

Bactericidal Antibiotics Induce Mitochondrial Dysfunction and Oxidative Damage in Mammalian Cells

Sameer Kalghatgi,^{#1} Catherine S. Spina,^{#1,2,3} James C. Costello,¹ Marc Liesa,³ J Ruben Morones-Ramirez,¹ Shimyn Slomovic,¹ Anthony Molina,^{3,4} Orian S. Shirihai,³ and James J. Collins^{1,2,3,*}

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Abstract

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Prolonged antibiotic treatment can lead to detrimental side effects in patients, including ototoxicity, nephrotoxicity, and tendinopathy, yet the mechanisms underlying the effects of antibiotics in mammalian systems remain unclear. It has been suggested that bactericidal antibiotics induce the formation of toxic reactive oxygen species (ROS) in bacteria. We show that clinically relevant doses of bactericidal antibiotics—quinolones, aminoglycosides, and β -lactams—cause mitochondrial dysfunction and ROS overproduction in mammalian cells. We demonstrate that these bactericidal antibiotic-induced effects lead to oxidative damage to DNA, proteins, and membrane lipids. Mice treated with bactericidal antibiotics exhibited elevated oxidative stress markers in the blood, oxidative tissue damage, and up-regulated expression of key genes involved in antioxidant defense mechanisms, which points to the potential physiological relevance of these antibiotic effects. The deleterious effects of bactericidal antibiotics were alleviated in cell culture and in mice by the administration of the antioxidant N-acetyl-L-cysteine or prevented by preferential use of bacteriostatic antibiotics. This work highlights the role of antibiotics in the production of oxidative tissue damage in mammalian cells and presents strategies to mitigate or prevent the resulting damage, with the goal of improving the safety of antibiotic treatment in people.

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[Critical Care. 2017]

Antibiotic-Induced Changes to the Host Metabolic Environment Inhibit Drug Efficacy and Alter Immune Function

Nutrichemistry, a means of preventing and healing chronic diseases
[Electronic Physician. 2017]

Man is the new mouse: Elective surgery as a key translational model for multi-organ dysfunction [Journal of the Intensive Care Society]

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Curr Opin Endocrinol Diabetes Obes. 2010 Oct;17(5):446-52. doi: 10.1097/MED.0b013e32833c3026.

Mitochondrial dysfunction in obesity.

Bournat JC¹, Brown CW.

Author information

Abstract

PURPOSE OF REVIEW: The review highlights recent findings regarding the functions of mitochondria in adipocytes, providing an understanding of their central roles in regulating substrate metabolism, energy expenditure, disposal of reactive oxygen species (ROS), and in the pathophysiology of obesity and insulin resistance, as well as roles in the mechanisms that affect adipogenesis and mature adipocyte function.

RECENT FINDINGS: Nutrient excess leads to mitochondrial dysfunction, which in turn leads to obesity-related pathologies, in part due to the harmful effects of ROS. The recent recognition of 'ectopic' brown adipose in humans suggests that this tissue may play an underappreciated role in the control of energy expenditure. Transcription factors, PGC-1alpha and PRDM16, which regulate brown adipogenesis, and members of the TGF-beta superfamily that modulate this process may be important new targets for antiobesity drugs.

SUMMARY: Mitochondria play central roles in ATP production, energy expenditure, and disposal of ROS. Excessive energy substrates lead to mitochondrial dysfunction with consequential effects on lipid and glucose metabolism. Adipocytes help to maintain the appropriate balance between energy storage and expenditure and maintaining this balance requires normal mitochondrial function. Many adipokines, including members of the TGF-beta superfamily, and transcriptional coactivators, PGC-1alpha and PRDM16, are important regulators of this process.

PMID: 20585248 PMCID: PMC5001554 DOI: 10.1097/MED.0b013e32833c3026

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“Excessive energy substrates lead to mitochondrial dysfunction with consequential effects on lipid and glucose metabolism... maintaining this balance requires normal mitochondrial function.”

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Free Radic Biol Med. 2010 Aug 1;49(3):401-7. doi: 10.1016/j.freeradbiomed.2010.04.033. Epub 2010 May 5.

Mitochondrial dysfunction may explain the cardiomyopathy of chronic iron overload.

Gao X¹, Qian M, Campian JL, Marshall J, Zhou Z, Roberts AM, Kang YJ, Prabhu SD, Sun XF, Eaton JW.

Author information

Abstract
In patients with hemochromatosis, cardiac dysfunction may appear years after they have reached a state of iron overload. We hypothesized that cumulative iron-catalyzed oxidant damage to mitochondrial DNA (mtDNA) might explain the cardiomyopathy of chronic iron overload. Mice were given repetitive injections of iron dextran for a total of 4 weeks after which the iron-loaded mice had elevated cardiac iron, modest cardiac hypertrophy, and cardiac dysfunction. qPCR amplification of near-full-length (approximately 16 kb) mtDNA revealed >50% loss of full-length product, whereas amounts of a qPCR product of a nuclear gene (13 kb region of beta globin) were unaffected. Quantitative rtPCR analyses revealed 60-70% loss of mRNA for proteins encoded by mtDNA with no change in mRNA abundance for nuclear-encoded respiratory subunits. These changes coincided with proportionate reductions in complex I and IV activities and decreased respiration of isolated cardiac mitochondria. We conclude that chronic iron overload leads to cumulative iron-mediated damage to mtDNA and impaired synthesis of mitochondrial respiratory chain subunits. The resulting respiratory dysfunction may explain the slow development of cardiomyopathy in chronic iron overload and similar accumulation of damage to mtDNA may also explain the mitochondrial dysfunction observed in slowly progressing diseases such as neurodegenerative disorders.

PMID: 20450972 PMCID: PMC2900522 DOI: 10.1016/j.freeradbiomed.2010.04.033

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- Restoring the impaired cardiac calcium homeostasis and cardiac function [Sci Rep. 2017]
- Increased mitochondrial DNA deletions and copy number in transfusion-dependent [JCI Insight. 2016]
- Combined Iron Chelator and Antioxidant Exerted Greater Efficacy on Cardioprot [PLoS One. 2016]

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Mitochondrial Dysfunction and Iron Overload

Mitochondrial Dysfunction and Sleep

The screenshot shows the website for the Journal of Clinical Sleep Medicine. At the top, there is a search bar and navigation links for 'All Volumes', 'All Issues', and 'All Words'. The journal's title and subtitle, 'Official Publication of the American Academy of Sleep Medicine', are prominently displayed. Below this, the current issue information is shown: 'Current Issue: Volume: 14 Number: 01'. There are buttons for 'View Current Issue', 'SUBSCRIBE', and 'LOGIN'. The article being viewed is 'Sleep Disorders Associated with Primary Mitochondrial Diseases' by Ryan J. Ramezani, B.S.¹; Peter W. Stacpoole, Ph.D., M.D.^{1,2}. The article is categorized as a 'Review Article' and has a DOI of <http://dx.doi.org/10.5664/jcsm.4212>. Navigation options for the article include 'Abstract', 'Full Text', 'Purchase Article', 'Share', 'PDF', 'Slides', and 'Print'. The abstract section is titled 'ABSTRACT' and contains the following text: 'Study Objectives Primary mitochondrial diseases are caused by heritable or spontaneous mutations in nuclear DNA or mitochondrial DNA. Such pathological mutations are relatively common in humans and may lead to neurological and neuromuscular complication that could compromise normal sleep behavior. To gain insight into the potential impact of primary mitochondrial disease and sleep pathology, we reviewed the relevant English language literature in which abnormal sleep was reported in association with a mitochondrial disease. Design We examined publications reported in Web of Science and PubMed from February 1976 through January 2014, and identified 54 patients with a proven or suspected primary mitochondrial disorder who were evaluated for sleep disturbances. Measurements and Results Both nuclear DNA and mitochondrial DNA mutations were associated with abnormal sleep patterns. Most subjects who underwent polysomnography had central sleep apnea, and only 5 patients had obstructive sleep apnea. Twenty-four patients showed decreased ventilatory drive in response to hypoxia and/or hypercapnia that was not considered due to weakness of the intrinsic'. On the left side of the page, there is a sidebar with a 'Primary Mitochondrial Diseases' section containing links for 'Sleep Medicine Pearls', 'Letters to the Editor', and 'Journal Club'. Below this are buttons for 'EARN CME', 'ACCEPTED PAPERS', and 'CLASSIFIEDS'.

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Sleep Disorders Associated with Primary Mitochondrial Diseases

Ryan J. Ramezani, B.S.¹; Peter W. Stacpoole, Ph.D., M.D.^{1,2}

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ABSTRACT

Study Objectives

Primary mitochondrial diseases are caused by heritable or spontaneous mutations in nuclear DNA or mitochondrial DNA. Such pathological mutations are relatively common in humans and may lead to neurological and neuromuscular complication that could compromise normal sleep behavior. To gain insight into the potential impact of primary mitochondrial disease and sleep pathology, we reviewed the relevant English language literature in which abnormal sleep was reported in association with a mitochondrial disease.

Design

We examined publications reported in Web of Science and PubMed from February 1976 through January 2014, and identified 54 patients with a proven or suspected primary mitochondrial disorder who were evaluated for sleep disturbances.

Measurements and Results

Both nuclear DNA and mitochondrial DNA mutations were associated with abnormal sleep patterns. Most subjects who underwent polysomnography had central sleep apnea, and only 5 patients had obstructive sleep apnea. Twenty-four patients showed decreased ventilatory drive in response to hypoxia and/or hypercapnia that was not considered due to weakness of the intrinsic

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Microbial Ecology in Health and Disease Taylor & Francis Taylor & Francis Group

Microb Ecol Health Dis. 2015; 26: 10.3402/mehd.v26.27458. PMID: PMC4425813
Published online 2015 May 7. doi: 10.3402/mehd.v26.27458

Gastrointestinal dysfunction in autism spectrum disorder: the role of the mitochondria and the enteric microbiome

Richard E. Frye,^{1,2,*} Shannon Rose,^{1,2} John Slattery,^{1,2} and Derrick F. MacFabe³

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Autism spectrum disorder (ASD) affects a significant number of individuals worldwide with the prevalence continuing to grow. It is becoming clear that a large subgroup of individuals with ASD demonstrate abnormalities in mitochondrial function as well as gastrointestinal (GI) symptoms. Interestingly, GI disturbances are common in individuals with mitochondrial disorders and have been reported to be highly prevalent in individuals with co-occurring ASD and mitochondrial disease. The majority of individuals with ASD and mitochondrial disorders do not manifest a primary genetic mutation, raising the possibility that their mitochondrial disorder is acquired or, at least, results from a combination of genetic susceptibility interacting with a wide range of environmental triggers. Mitochondria are very sensitive to both endogenous and exogenous environmental stressors such as toxicants, iatrogenic medications, immune activation, and metabolic disturbances. Many of these same environmental stressors have been associated with ASD, suggesting that the mitochondria could be the biological link between environmental stressors and neurometabolic abnormalities associated with ASD. This paper reviews the possible links between GI abnormalities, mitochondria, and ASD. First, we review the link between GI symptoms and abnormalities in mitochondrial function. Second, we review the evidence supporting the notion that environmental stressors linked to ASD can also adversely affect both mitochondria and GI function. Third, we review the evidence that enteric bacteria that are overrepresented in children with ASD, particularly *Clostridia* spp., produce short-chain fatty acid metabolites that are potentially toxic to the

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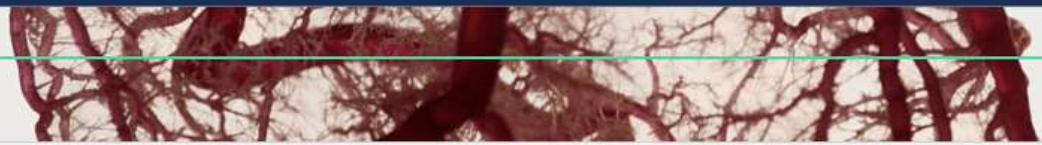
Modulation of Immunological Pathways in Autistic and Neurotypical Lymphoblastoid Cell [Frontiers in Immunology. 2017]

Hypothesis: Brain carnitine deficiency causes nonsyndromic autism with an extreme male bi [BioEssays : news and reviews i...]

Mitochondrial dysfunction in the gastrointestinal mucosa of children with autism: A blinded case-control stu [PLoS ONE. 2017]

Tryptophan status in autism spectrum disorder and the influence of supplementation on its levels [Metabolic Brain Disease. 2017]

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The many roads to mitochondrial dysfunction in neuroimmune and neuropsychiatric disorders

Gerwyn Morris and Michael Berk

BMC Medicine 2015 13:68

<https://doi.org/10.1186/s12916-015-0310-y> | © Berk and Morris; licensee BioMed Central. 2015

Received: 23 December 2014 | Accepted: 4 March 2015 | Published: 1 April 2015

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Abstract

Background

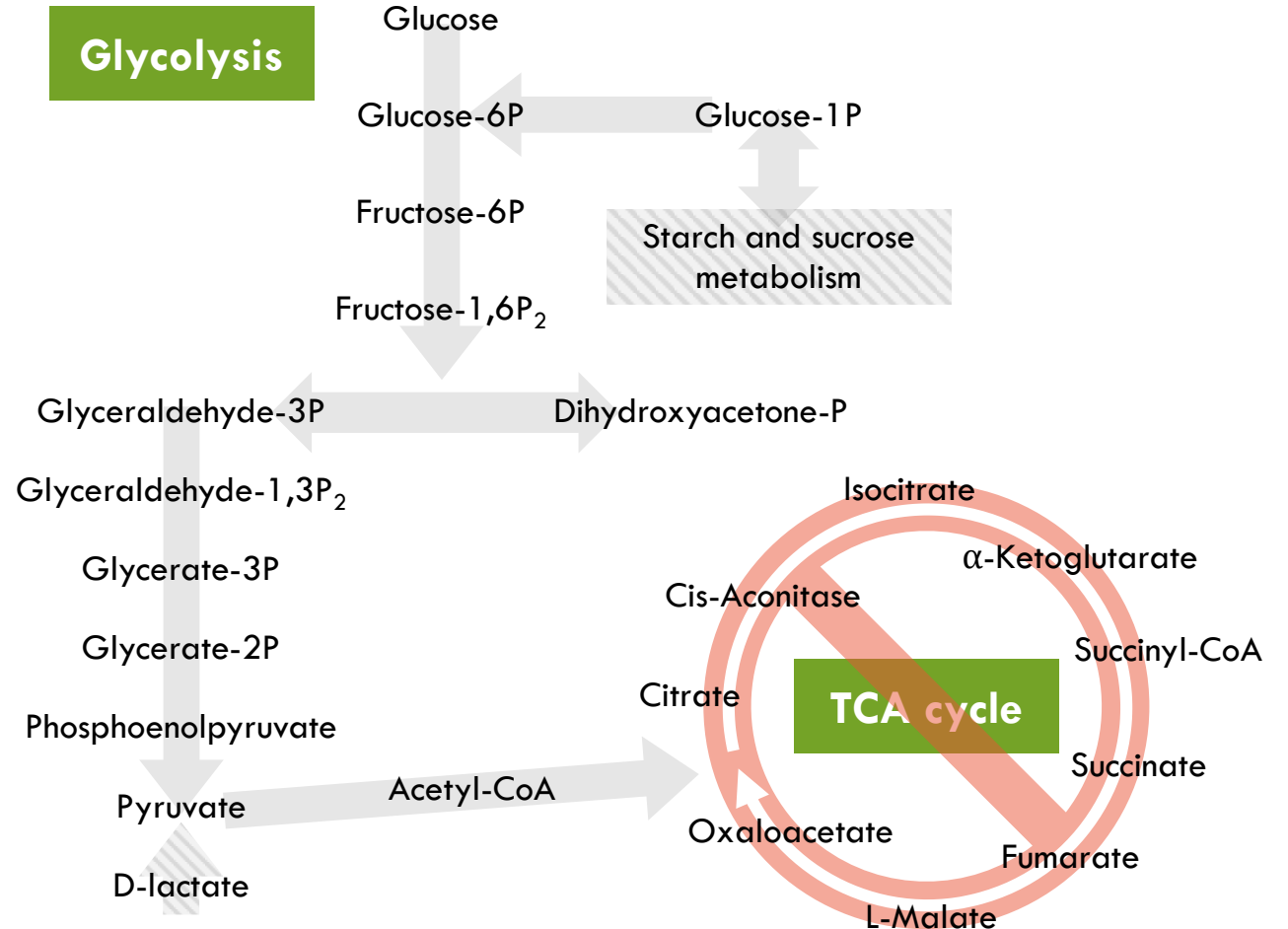
Mitochondrial dysfunction and defects in oxidative metabolism are a characteristic feature of many chronic illnesses not currently classified as mitochondrial diseases. Examples of such illnesses include bipolar disorder, multiple sclerosis, Parkinson's disease, schizophrenia, depression, autism, and chronic fatigue syndrome.

Discussion

While the majority of patients with multiple sclerosis appear to have widespread

Your Metabolism = your Mitochondria

If your mitochondria are broken, only thing left is Glycolysis. Complexes 1, 3, 4, etc.



What about multi-generational epigenetic changes??

**MATERNAL
SOCIAL
TRANSMISSION**

F0-F1
Mother-infant
interactions

F1-F2
Mother-infant
interactions

F2-F3
Mother-infant
interactions

Epigenetic
Variation

F0
Environmental
exposure

F1 Offspring
development

F2 Offspring
development

F3 Offspring
development

**PATERNAL
GERMLINE
TRANSMISSION**

Epigenetic
variation in
F0 sperm

Epigenetic
variation in
F1 sperm

Epigenetic
variation in
F2 sperm

The screenshot shows a web browser window displaying a Cambridge University Press article. The page title is "Development and Psychopathology". The article title is "Epigenetic legacy of parental experiences: Dynamic and interactive pathways to inheritance" by Frances A. Champagne. The article is cited by 2 others and was published online on 30 September 2016. The abstract is partially visible at the bottom of the page.



ENOUGH TALK!

OK Propeller Head,
that sounds great ?
but *what* to **DO** ●



Reclaiming and maintaining **our metabolic flexibility** (ie. *mitochondrial health*)



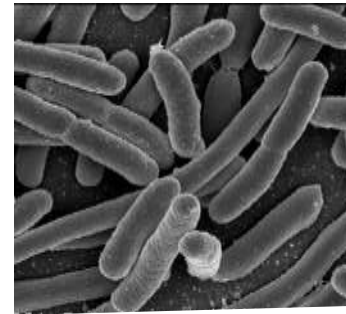
Circadian rhythm



Sleep



Light exposure



Gut health



Meaningful relationships



Lift weights



Go fast



Go slow



Novel experiences

Regarding Food



Test and track
BG response
(*WTE-7 Day Carb Test*)



Be aware of
immunogenic
foods



Eat with the
seasons



Get **as much variety**
as possible without
getting in trouble -
hyperpalatability

Our consistent and fatal mistake:

The “Procrustean Bed” of the Macronutrient Wars



Make your bed fit you!



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