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Fructose, Uric Acid & Metabolic Dysfunction

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AFDNP Association of Functional Diagnostic Nutrition Professionals

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Serum Uric Acid (SUA) Levels
Independent Risk Factor for All-Cause, CVD & Stroke Mortality

- 8 yr Taiwan study: 41,879 men / 48,514 women: All aged >35 yrs
  - Compared mortality relative to ***increasing SUA levels***
- Results: When SUA > 7 mg/dL, get the following increases in risk of death:
  - **16% for All-Cause, ~40% for CVD, ~35% for Ischemic Stroke**
  - **Risk of death increased 8-13% with every mg/dL of SUA above 7 mg/dL**
- **Risk of death from elevated SUA > than risk for those with CVD Hx**

JH Chen et al. 2009

Research Background

Serum Uric Acid (SUA) Levels
Independent Risk Factor for All-Cause, CVD & Stroke Mortality

Conclusion:

- **Hyperuricemia is an *independent risk factor* for All-Cause & CVD mortality, not only in pts with hypertension & DM, but also in potentially low-risk subgroups.**

What is the Underlying Cause?

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JH Chen et al. 2009

Inflammation: The Silent Killer

- Chronic Inflammation is the greatest killer of our era
- Creates a 'Cytokine Drizzle': Lack of sleep, 'Leaky Gut', etc…
  - Inflammation rise (seen with CRP, Il-6, others) mirrored by the rise in **Uric Acid**

- Uric Acid rise ***ALONE*** can cause adverse metabolic episodes, even when its levels are considered in the '**normal range**'
- ***Uric acid not only acts as a 'surrogate' marker of inflammation, but also as an AMPLIFIER of that inflammation***

Uric Acid is, therefore, at the heart of any conversation about the risk of disease*

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*Perlmutter, 2022

Obesity and Diabetes

The Insidious Role of 'Sugar'

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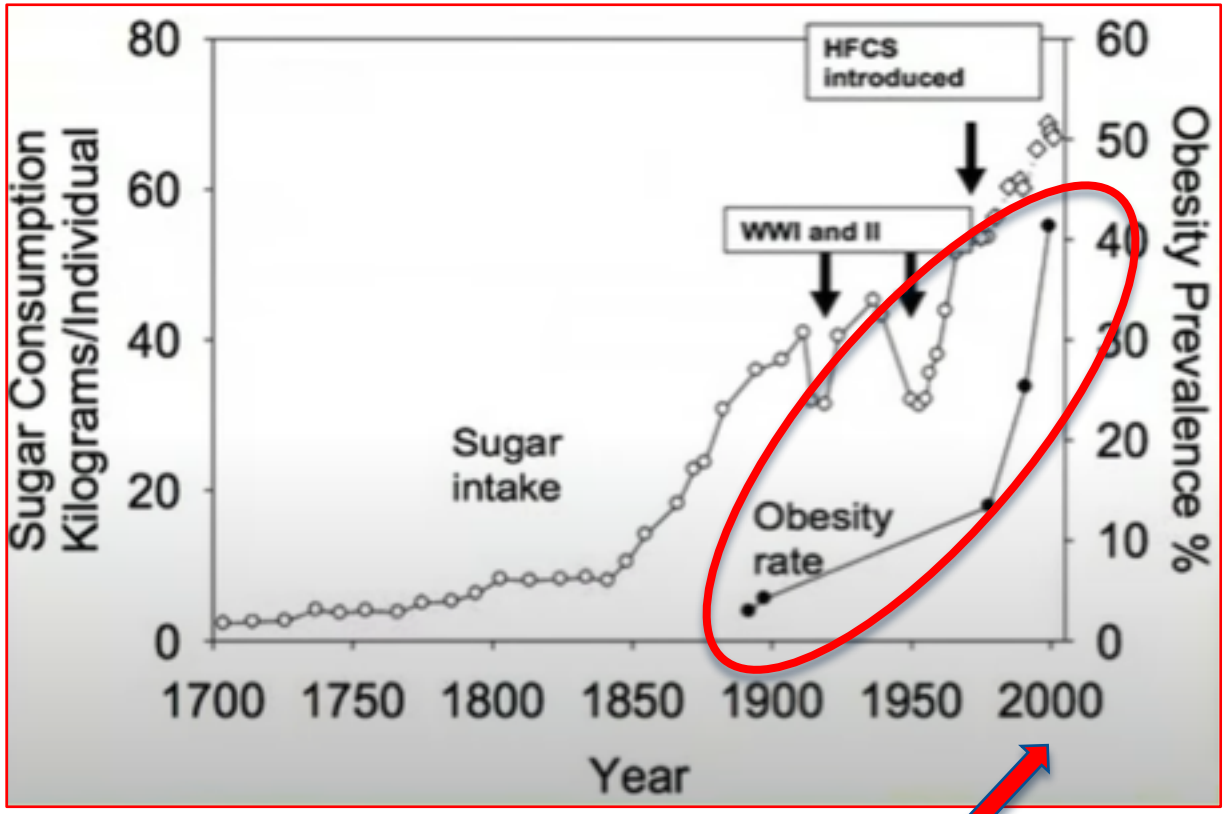
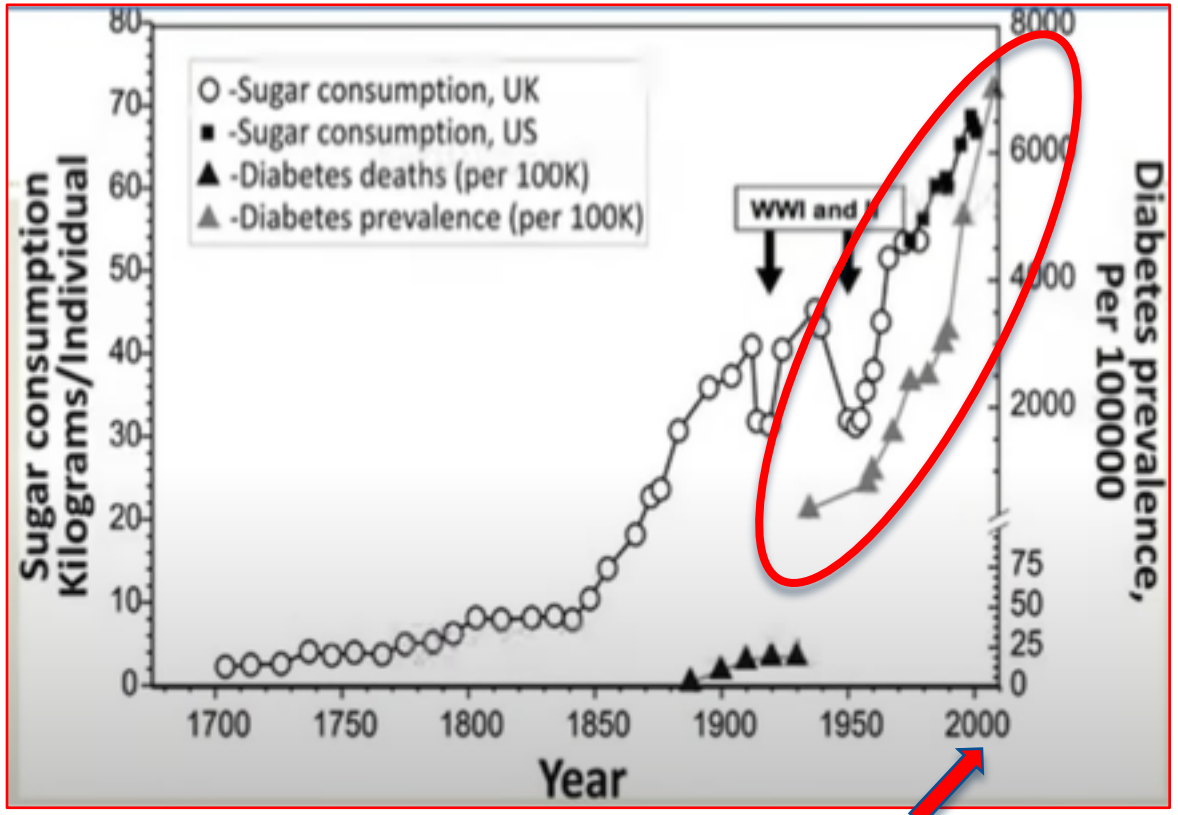
Obesity & Diabetes: The Twin Epidemics

Obesity Rates in 60-69 y.o. Men in USA



Obesity rate has reached > 40%

Diabetes / 100 thousand population



~ One in ten adults are diabetic

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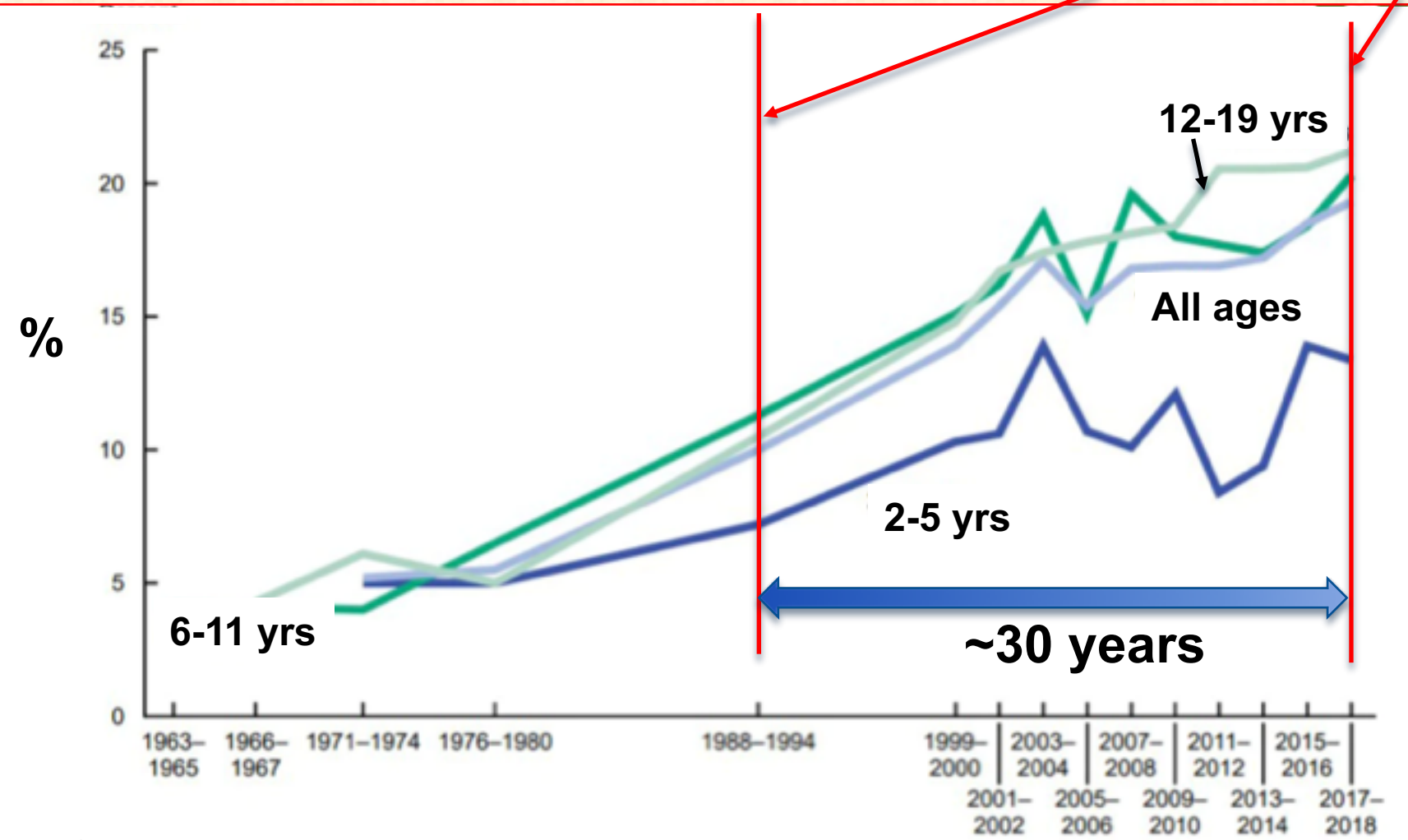
after Johnson et al, 2007

Obesity in Children in the USA

Obesity in ages 2-19: ~ **doubled** between the 1988-94 & 2017-18 periods



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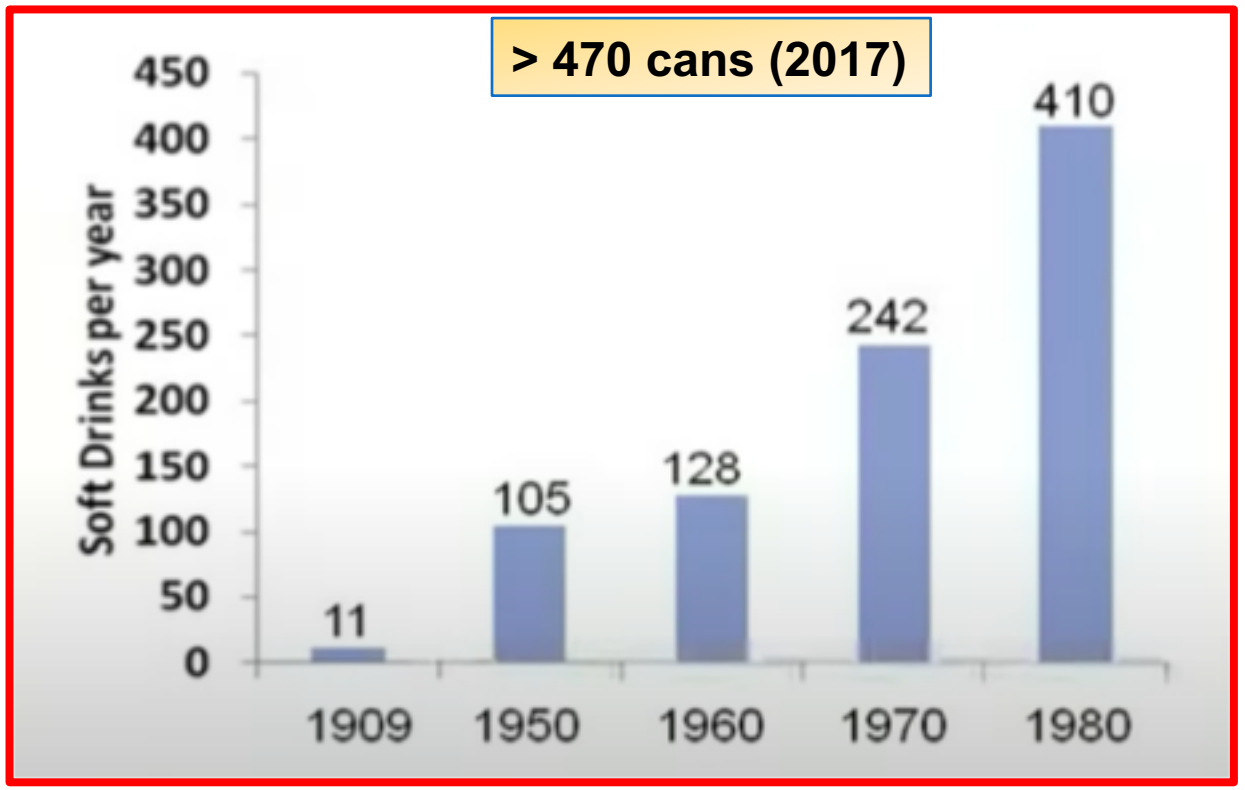
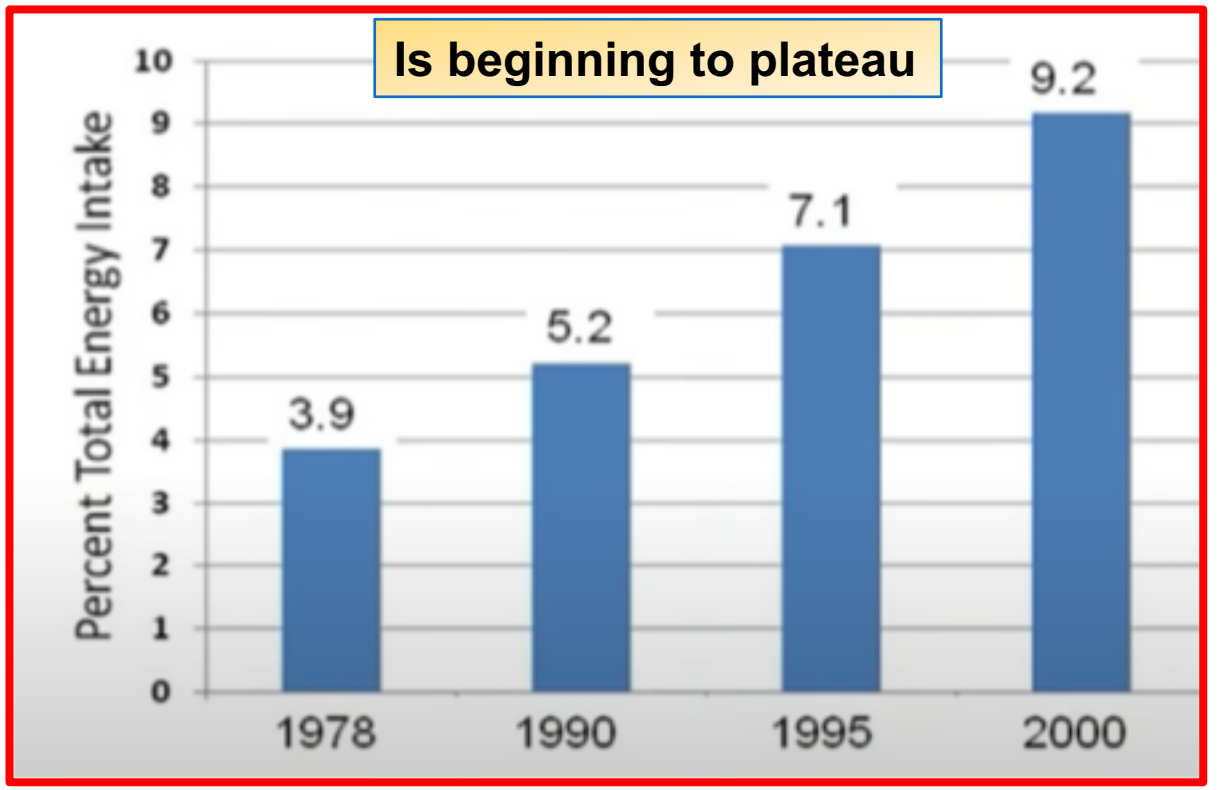
National Center for Health Statistics, National Health Examination Surveys II

The Problem: A Sugar-filled World

Soft drink intake/year/capita*



Sweetened beverage/% of total energy**



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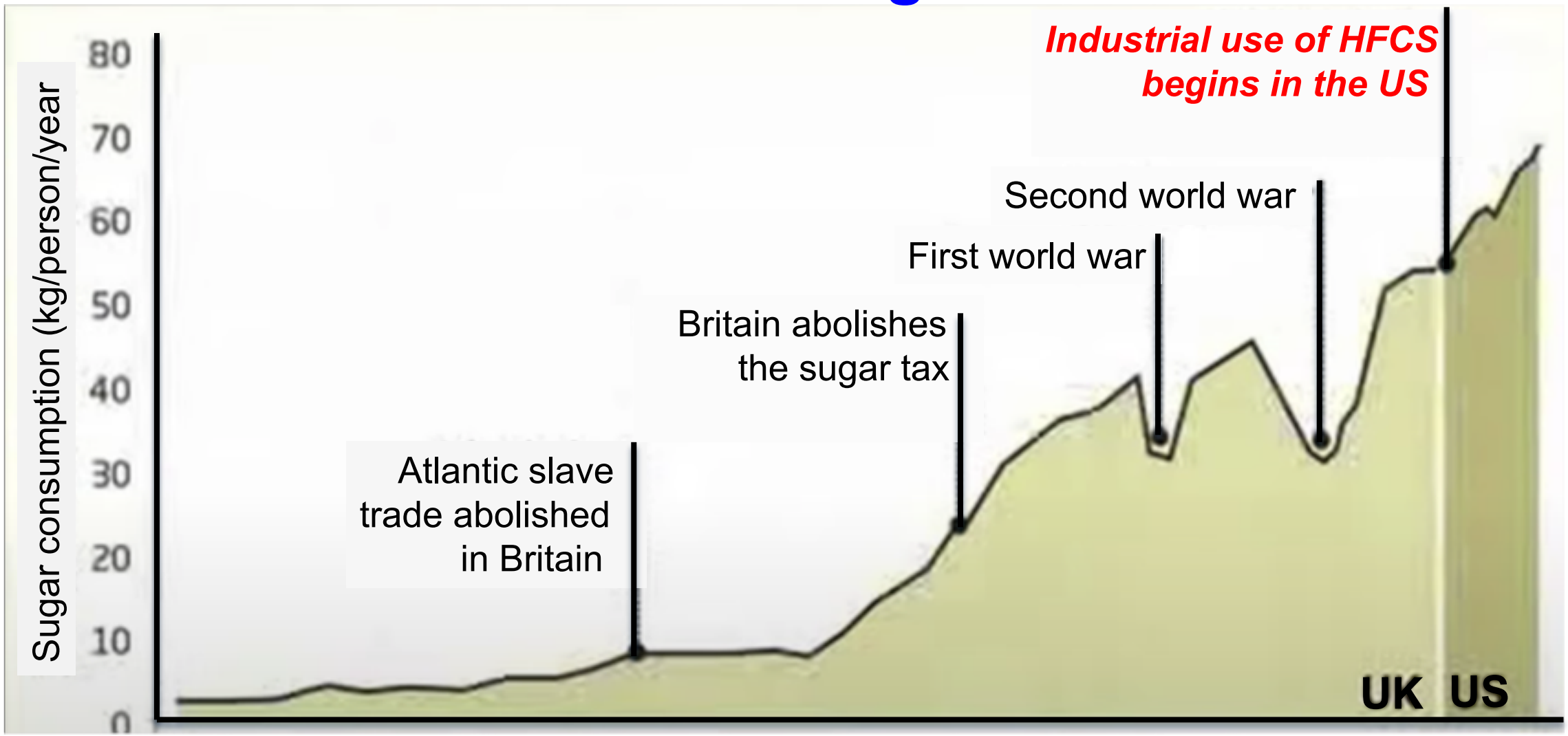
*Anderson, 1982 **Nielsen & Popkin, 2004

The Rise of Sugar Use



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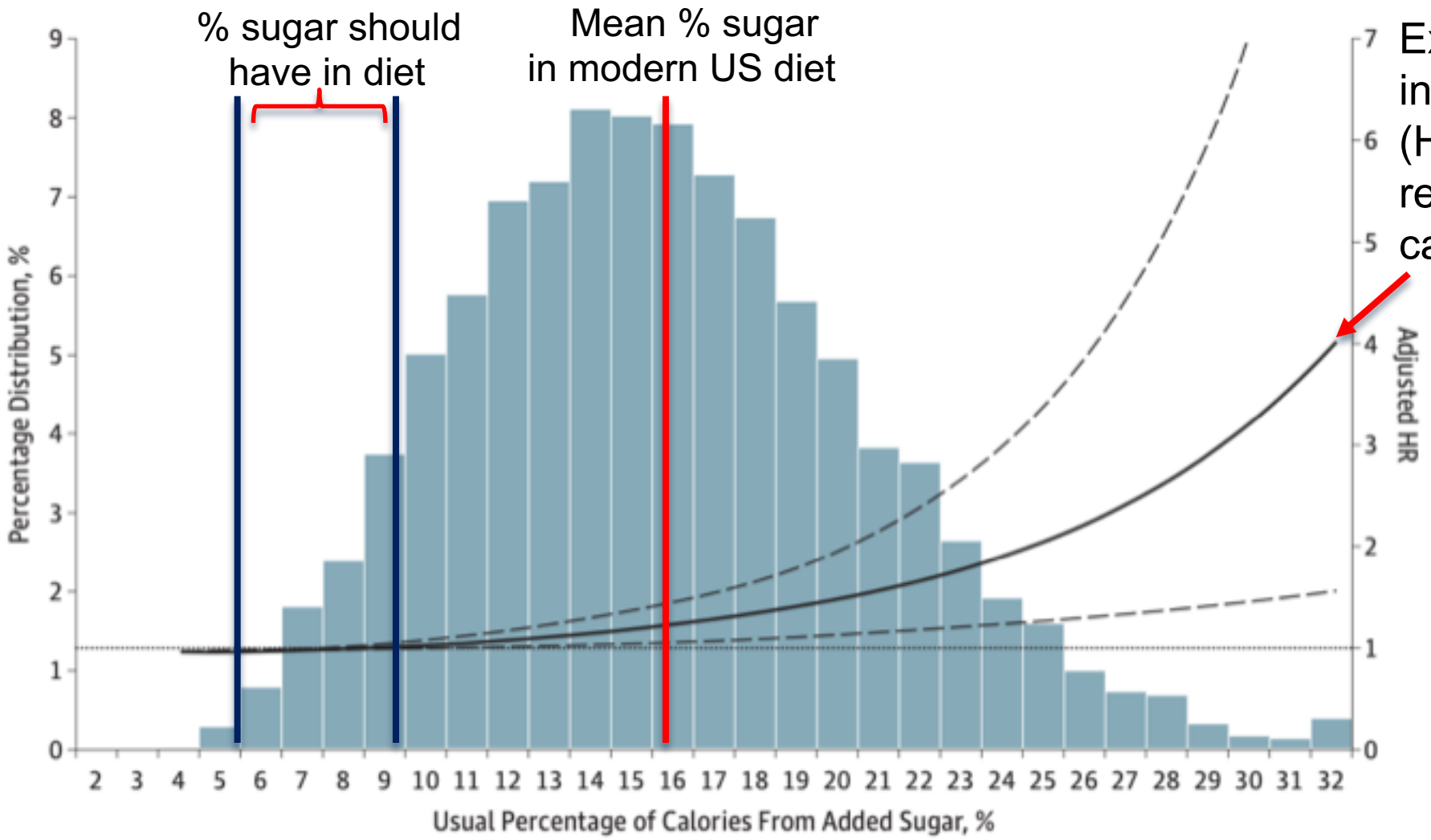
HFCS = High Fructose Corn Syrup

after Johnson et al, 2007

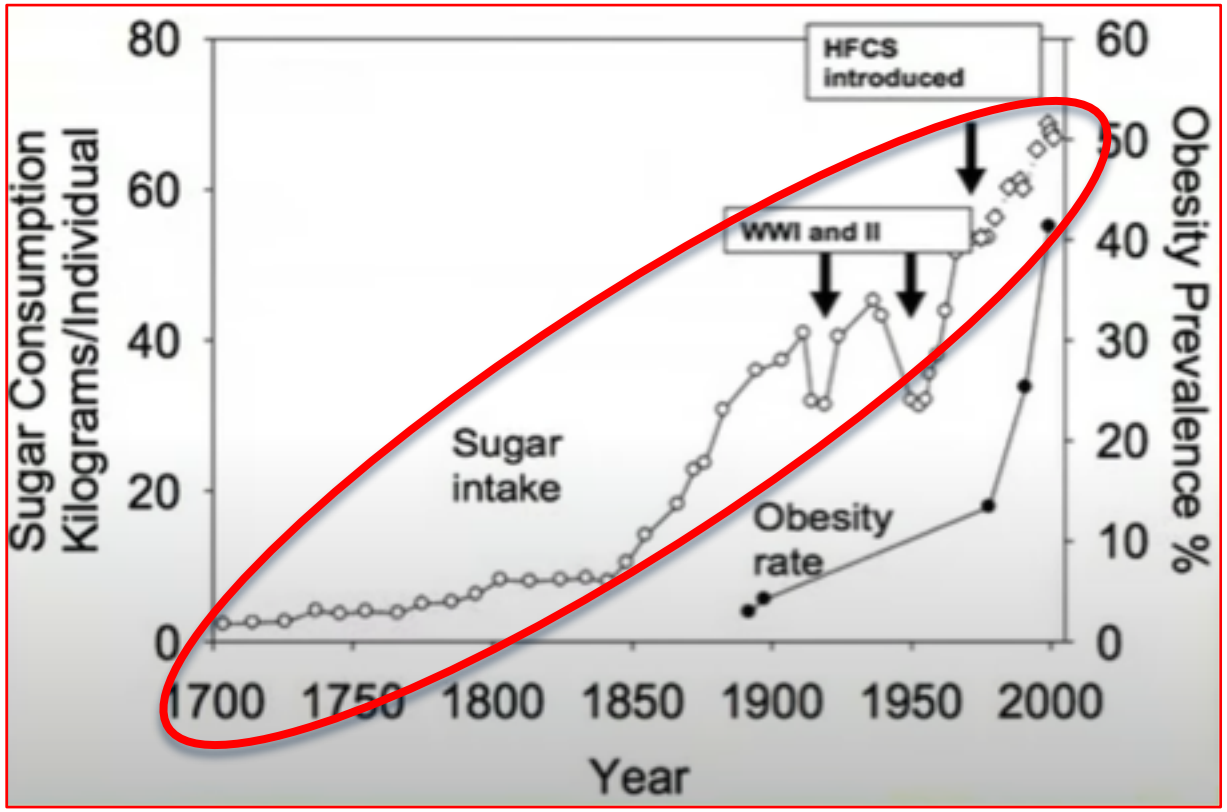
Sugar Consumption & Increase in Cardiovascular Mortality

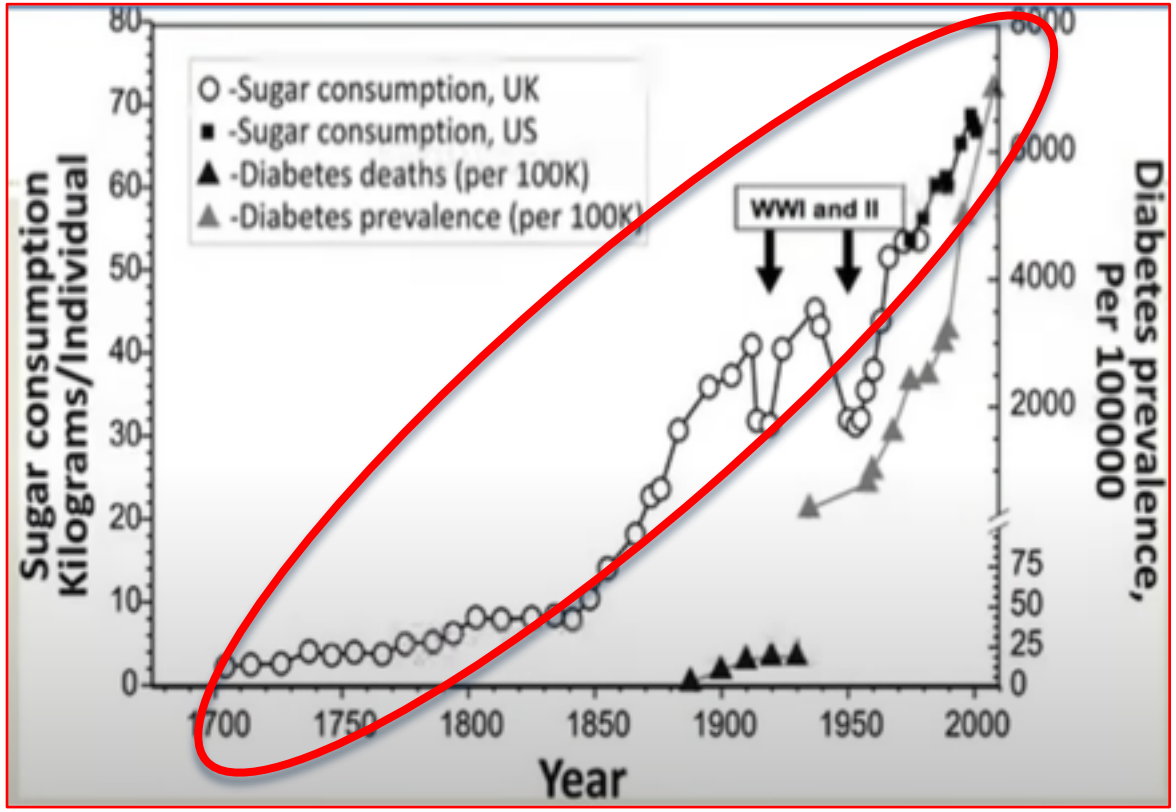


Exponential rise in Hazard Ratio (HR) for death, relative to % calories from sugar

FLUIDS iQ™ National Health and Nutrition Examination Survey Linked Mortality Files, 1988-2006 Yang et al, 2014

Sugar Intake:
The Key Factor Driving Obesity & Diabetes





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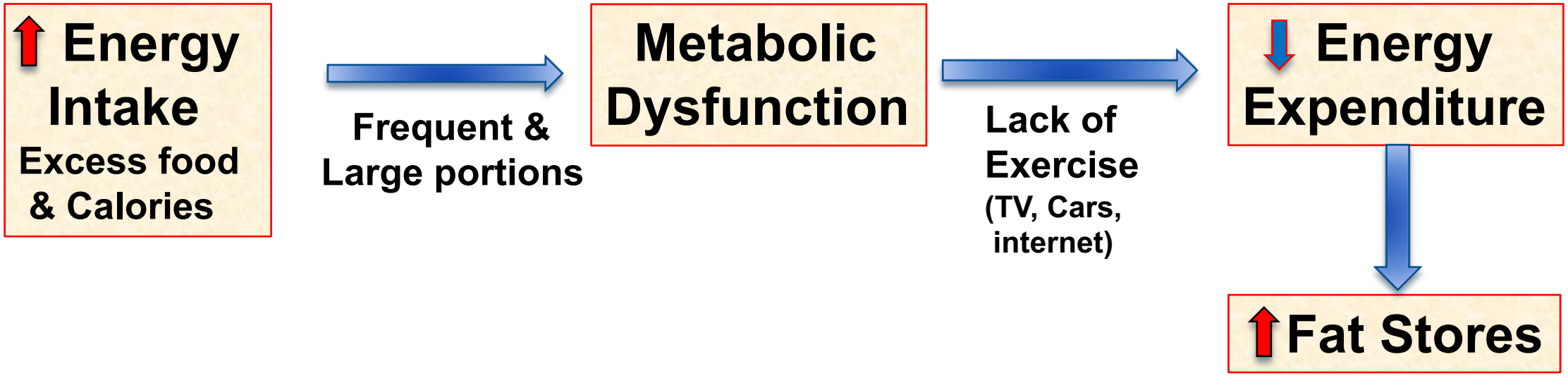
after Johnson et al, 2007

Conventional Theory of Obesity:
Excess Nutrition & Lack of Exercise



- Summary: It is modern 'Culture' that is driving Obesity & Diabetes

Is That What Is Really Happening?

Johnson, 2014

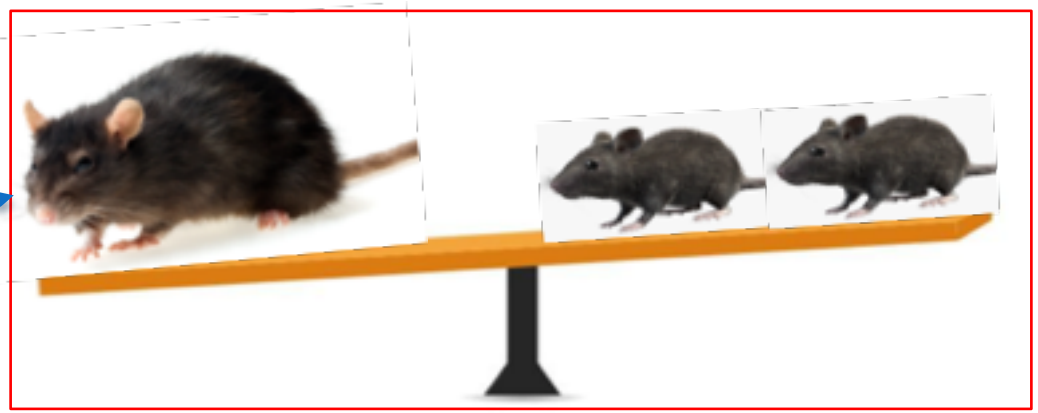
Research Background

Leptin, the 'Appetite' hormone, & the 'Obese' gene

- Leptin produced by fat cells. Regulates calories eaten & burned
  - Signals when enough fat is stored, so that stop eating & return to burning calories at a normal rate

Main role: Long-term energy regulation

Mouse lacking LEPTIN, weighs more than two control mice*



- Obese people often become **resistant to Leptin**

Appetite is a Hormonally Regulated Function

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*Yufang et al, 1995

Newest Theory of Obesity

Large portions eaten since can't control appetite (Leptin)
- Leptin Resistant & Sugar Addicted
↑ Dopamine pleasure response

Less energy produced: Have defective fat burning, d/o less ATP production in mitochondria for cell energy needs

↑ Energy Intake
Excess food & Calories

→ **Frequent & Large portions**

Metabolic Dysfunction

→ **Lack of Exercise**
(TV, Cars, internet)

↓ Energy Expenditure

↓

↑ Fat Stores

- Summary: **Biology** is driving **Culture** and not the inverse

How is this activated in Humans?

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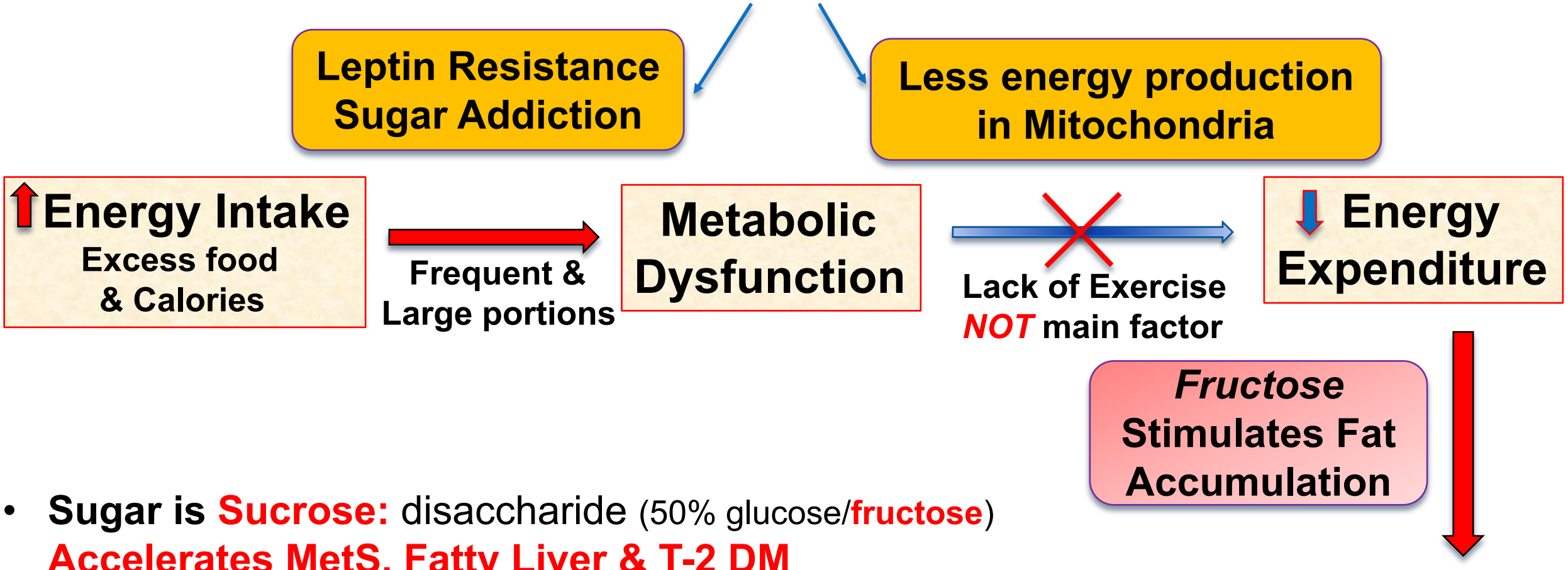
Johnson, 2014

Fructose: The Main Culprit in Weight Gain



- **Sugar is Sucrose:** disaccharide (50% glucose/**fructose**)
  Accelerates MetS, Fatty Liver & T-2 DM
- **Effects are independent of excess energy intake, or caloric restriction**

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Cox et al, 2012

Effects of Fructose on Various Organ Systems

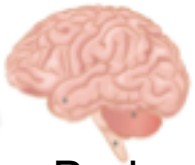
after Johnson, 2009

Sugar

HFCS**

Honey, Fruit

Fructose

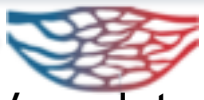


Brain

Taste center activation
Dopamine addiction
Leptin resistance
Inflammation

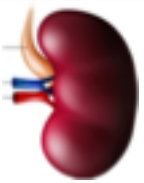
Liver

Fatty liver
Elevated triglycerides
ATP depletion
Inflammation
Uric acid generation



Vasculature

Inflammation
Endothelial dysfunction



Brain

Renal vasoconstriction
Glomerular hypertension
Renal injury
Inflammation

Adipocyte

Oxidative Stress
Inflammation
Reduced adiponectin

Metabolic Syndrome

Insulin Resistance
Elevated Blood Pressure
Dyslipidemia
Fatty Liver
Increased Glycation (AGEs*)
Inflammation
Oxidative Stress
Mitochondrial Dysfunction
Abdominal Obesity
Hyperuricemia

Type 2 Diabetes Profile

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*AGEs = Advanced Glycation End Products
**HFCS = High Fructose Corn Syrup

Obesity & Related Problems: A 'Fat Storage Condition'

The Metabolic Syndrome

- **Elevated Fasting Glucose (Insulin Resistance)**
- **Elevated Triglycerides (Hyperlipidemia)**
- **Elevated Blood Pressure**
- **Low HDL-Cholesterol (Dyslipidemia: apo A-1)**
- **Central (abdominal) Obesity**

Increased Salt Retention

Uric Acid Increase

Chronic Kidney Disease

Hypertension

Fatty Liver, Cirrhosis

T2 Diabetes

Increased risk of **Heart, Kidney & Liver Disease, Stroke, DM,** Sleep Apnea, CA & Alzheimer's

MetS in > 30% US adults, & > 50% in those over age 60 Moore et al, 2017

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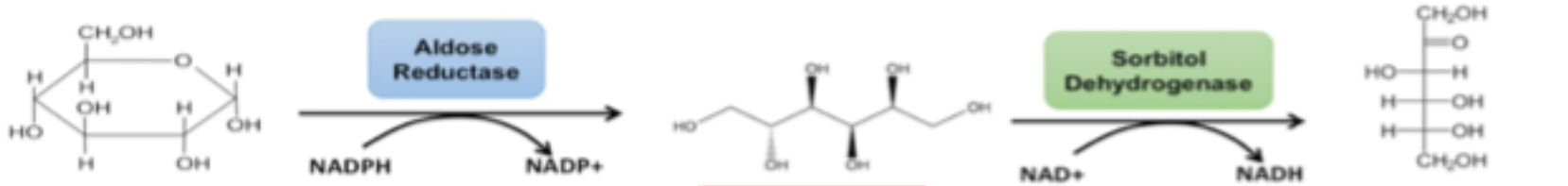
Carbohyrates (Glucose) can produce Fructose

Polyol (Sorbitol) Pathway



Glucose → Sorbitol → Fructose

- High blood Glucose stimulates Fructose creation (seen in T2 DM)
- Why does Glucose trigger this 'alarm' reaction?
  - High bl. Glucose creates sense of **dehydration**
    - >est stimulator of fructose production. Leads to fat creation
  - Why? Fat metabolism is both a source of calories & water
  - Salt activates the enzymes changing glucose to fructose

All this leads to the creation of Uric Acid

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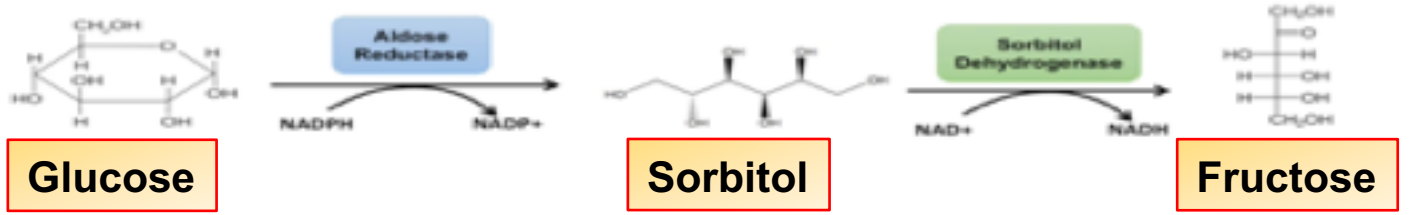
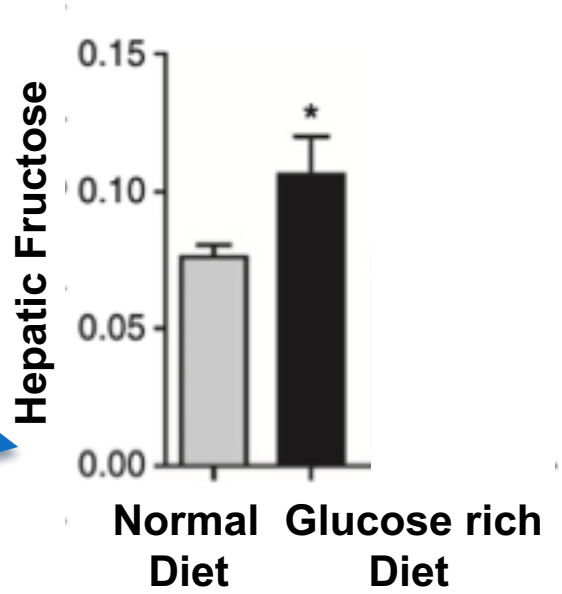
Lanaspa, Ishimoto et al, 2013

Carbohyrates (Glucose) can produce Fructose

Polyol (Sorbitol) Pathway



- **Endogenous Fructose** generation & metabolism in liver is the mechanism by which glucose promotes development of **Metabolic Syndrome**



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Lanaspa, Ishimoto et al, 2013

The ‘Sugar’ Effect: The Issue with Fruit

Fruits

Low Effect

Does the mode of Fructose delivery change its effects on the body?

Sweetened Beverages

High Effect

- **High fiber** content: Fructose delivered slowly, slowing its absorption
- **Vit C** content: which acts to increase fructose excretion
- **Antioxidants:** Flavonoids, & magnesium blunt the metabolic effects

Major Culprit:
High-Fructose Corn Syrup (HFCS)

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Summary: The Origins of Obesity

- **Fat Storage is a Biological Process**, not due to lifestyle

- Sugar contains **Fructose** which activates the fat storage process:
  - Sugar intake elevates **Body Fat**
  - Sugar intake is a prime cause of **Metabolic Syndrome** (prediabetes) increasing the risk for **Diabetes, Heart, Kidney & Liver Diseases**

- Sugar intake has increased over centuries & this intake is highest, on a % basis, in many minority populations of the world. Major culprit is **Fructose** - especially **HFCS**

HFCS = High Fructose Corn Syrup

A Key Question:

- ***Why do we choose Fructose as the main culprit, & what is it about this nutrient that causes:***

Insulin Resistance,

Diabetes

Elevated Triglycerides…..

METABOLIC SYNDROME

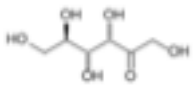
What is its mechanism of action?

Fructose Metabolism & Energy Depletion

Fructose Leads to Uric Acid formation

Fructose metabolism depletes ATP

Only nutrient to cause cell energy depletion



FRUCTOSE

KHK-A

KHK-C

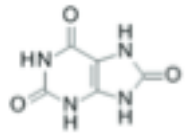
ATP

AMP

AMPD

IMP

Uric Acid



FRUCTOSE 1-P

Increases KHK-C levels

Glycogen

Glucose

Triglycerides

Large drop in cell's ATP leads to: Inflammation, Oxidative Stress, Drop in Protein Synthesis

KHK-A & C = Ketohexokinase (Fructokinase) A & C

AMPD = AMP Deaminase

after Johnson et al, 2014

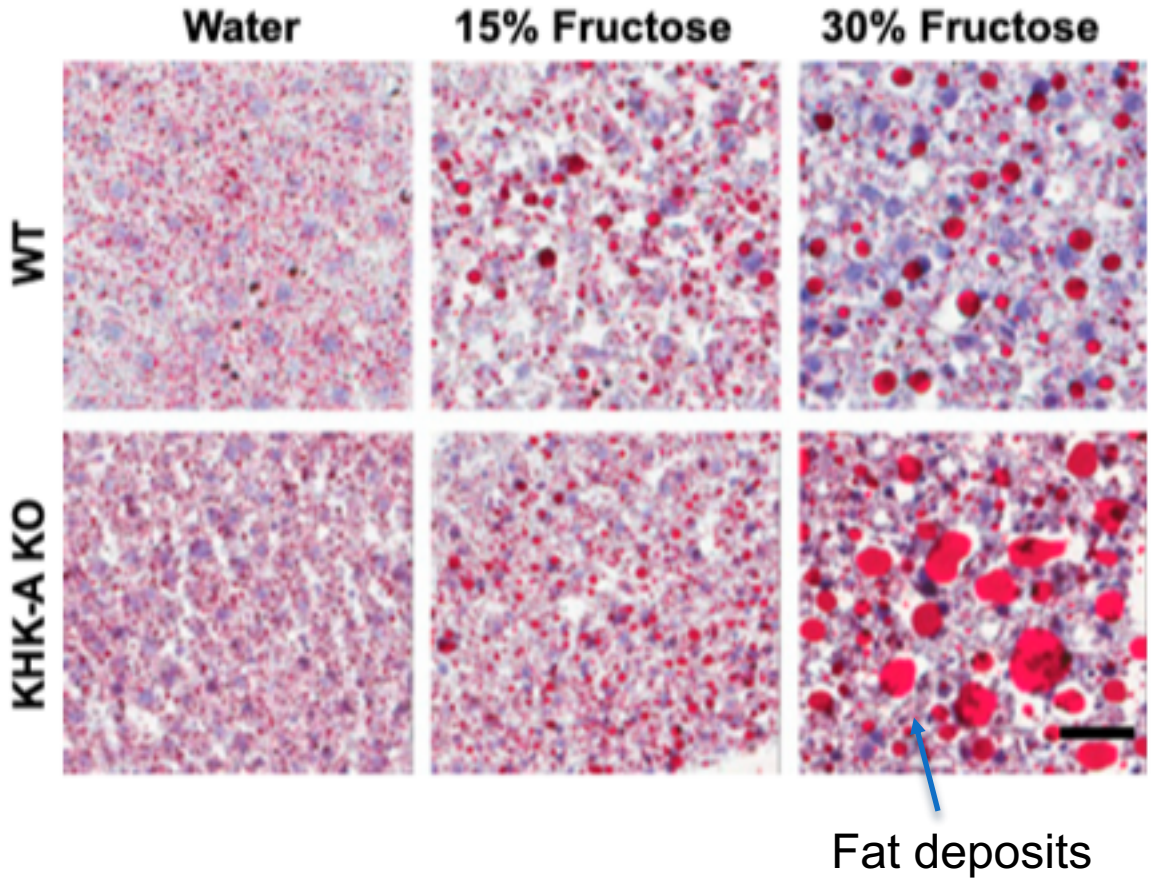
Research Background

Fructokinase importance in controlling Metabolic Pathways

Fructose metabolism starts with the enzyme Fructokinase. Exists as A & C isoforms

Fructokinase A (KHK A)
Directs fructose metabolism to glucose, glycogen & Triglyceride pathway

Fructokinase C (KHK C)
Directs fructose metabolism to **ATP depletion pathway**, leading to **fatty liver** & other signs of ***Metabolic Syndrome***
Primarily in liver, intestine, & kidney



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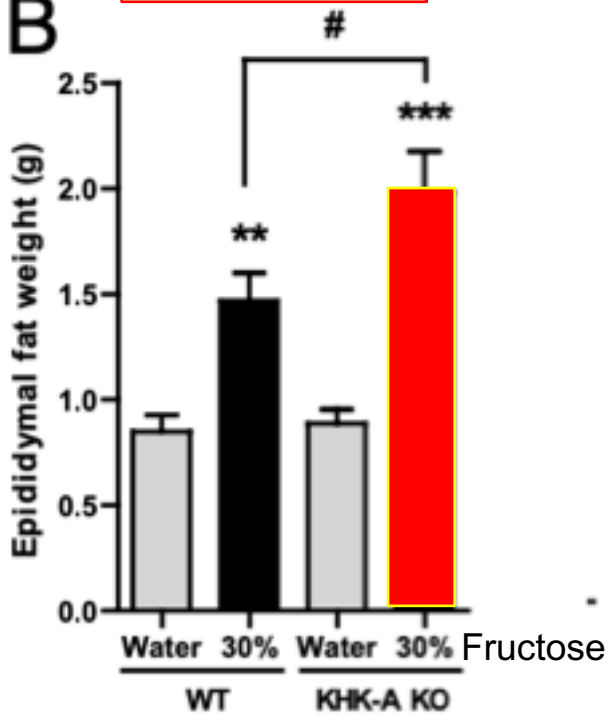
WT = Wild Type; KHK-A KO = Ketohexokinase-A (Fructokinase A) Knockout

Ishimoto et al, 2012

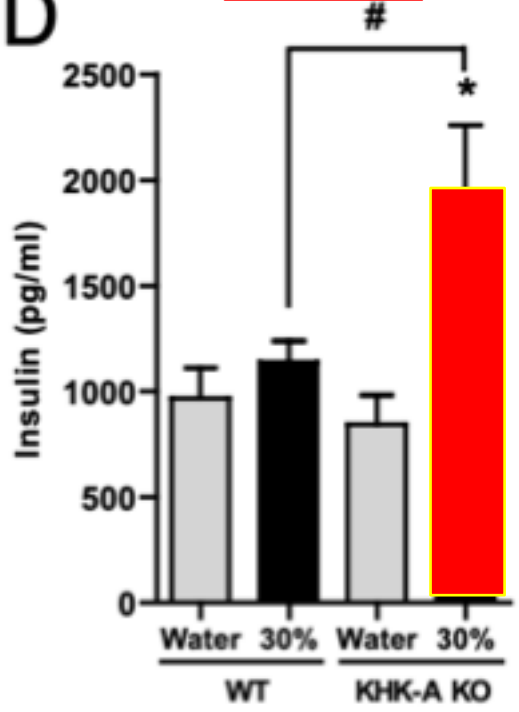
Research Background

Effect of High Fructose Consumption (in WT & KHK-A KO mice)

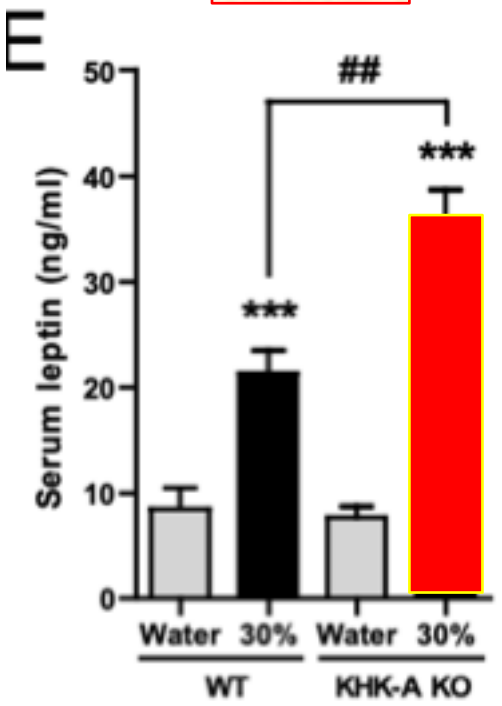
Epididymal Fat



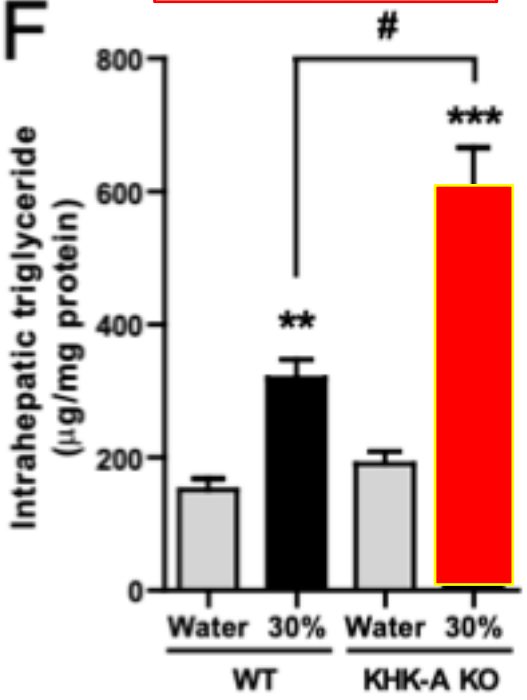
Serum Insulin



Serum Leptin



Liver Triglycerides



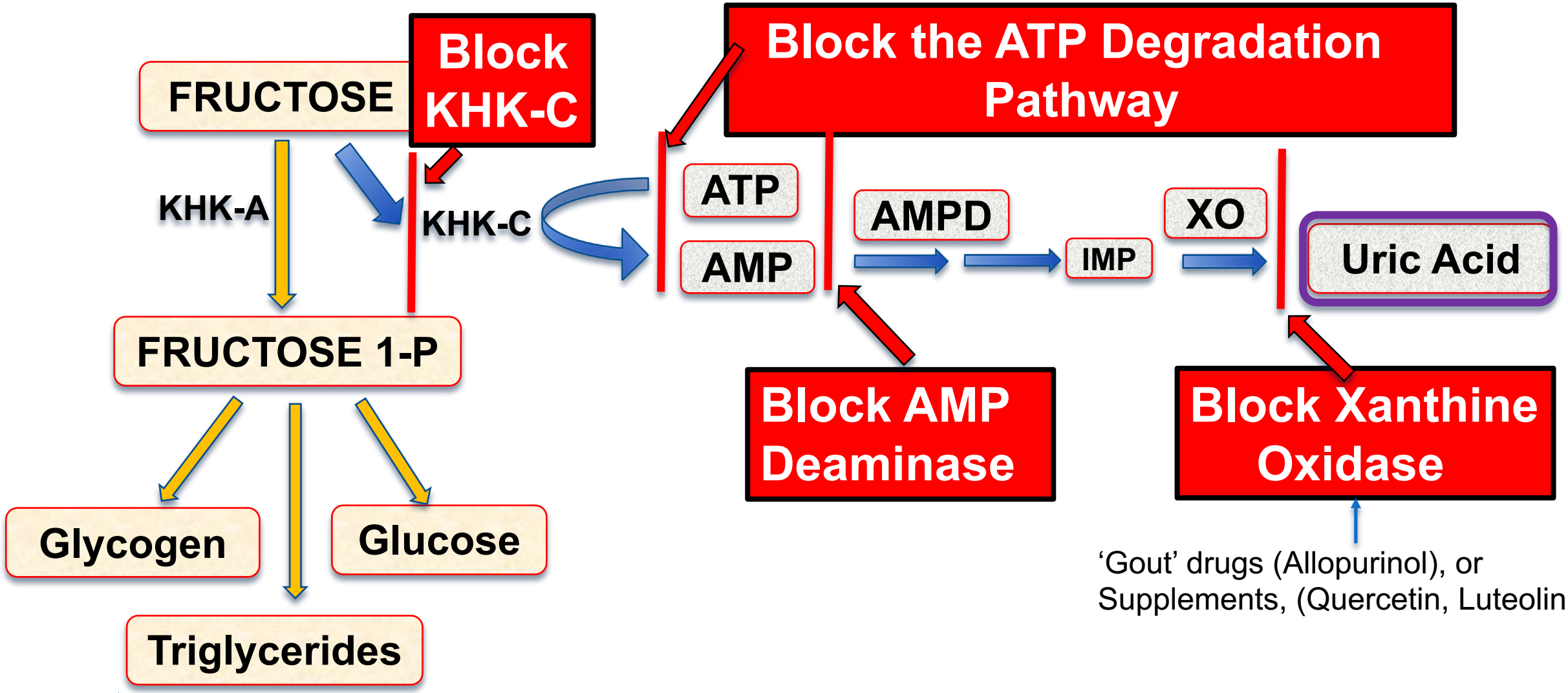
When Fructose metabolized by the energy-depleting path, Metabolic Syndrome worsens

FLUIDS iQ™

WT = Wild Type; KHK-A KO = Ketohexokinase-A (Fructokinase A) Knockout

Ishimoto et al, 2012

Controlling Fructose Metabolism & Avoiding Energy Depletion



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after Johnson et al, 2014

Key Takeaway about Fructose:

***Fructose* is the main culprit. Leads to:**

METABOLIC SYNDROME

caused by:

1. ***Eating Fructose containing foods***
2. ***Dehydration – by intention, or naturally***
3. ***Eating a high glycemic diet (high glucose)***

Commonality: Dehydration (real, or perceived)

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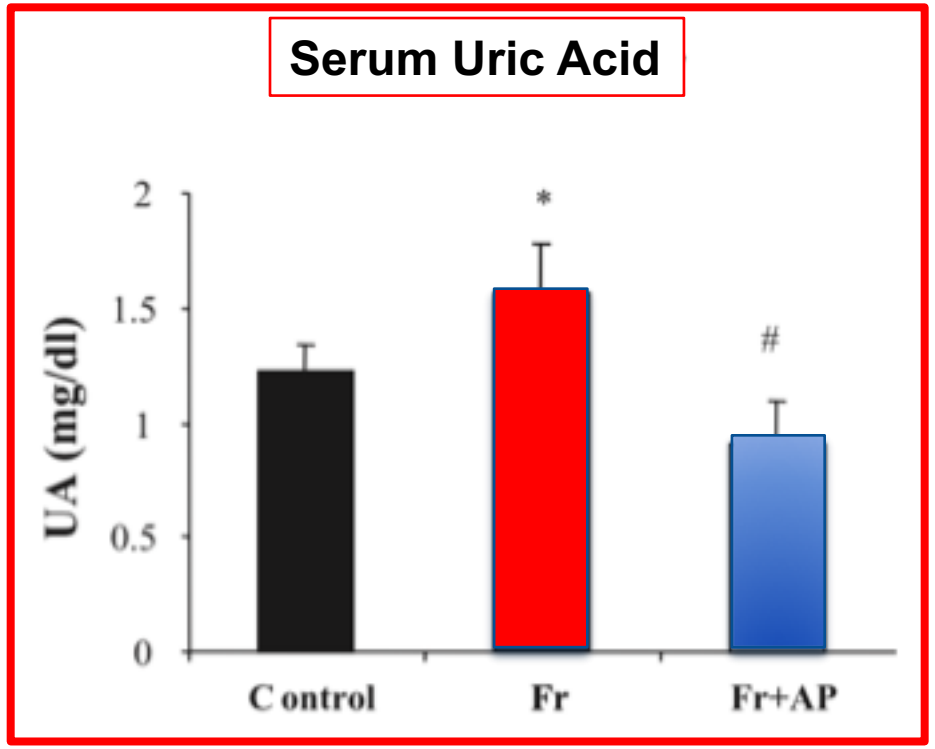
Question:

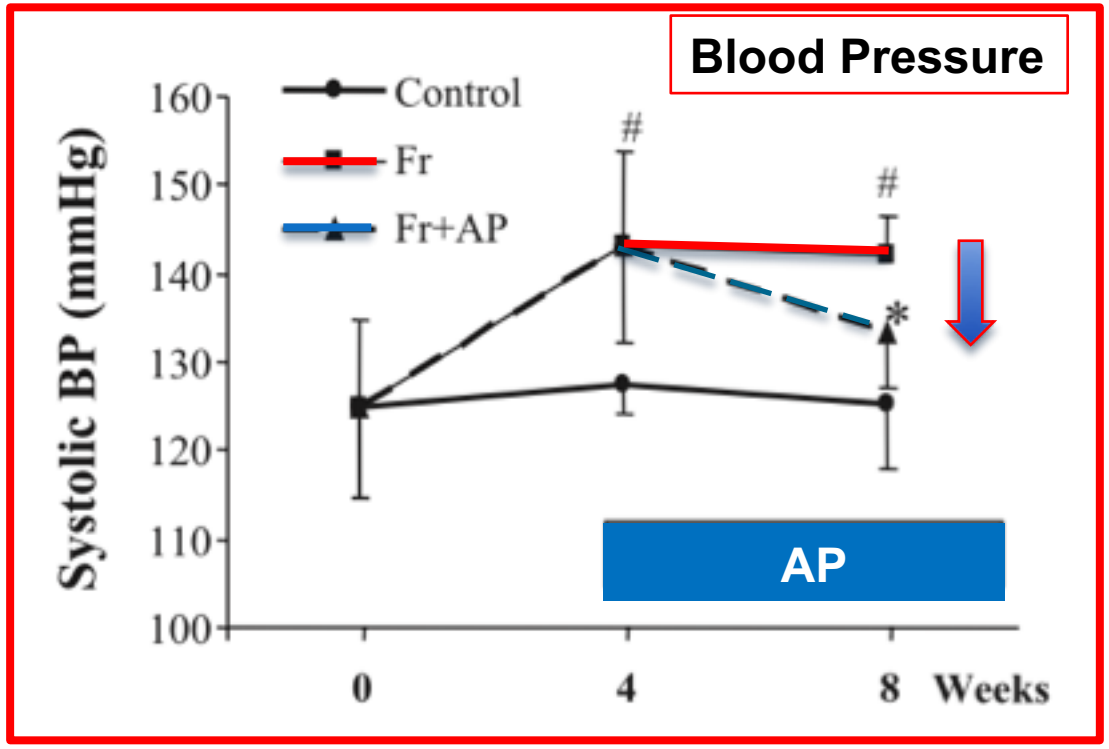
How does the use of Fructose relate to Uric Acid?

What is the mechanism of Uric Acid action & its importance as both a culprit & biomarker?

Causal Role for Uric Acid in Fructose-induced Met. Syndrome

- **Fructose-induced hypertension is Uric Acid dependent**





- Allopurinol reduces both amount of uric acid made by body cells & urate in blood

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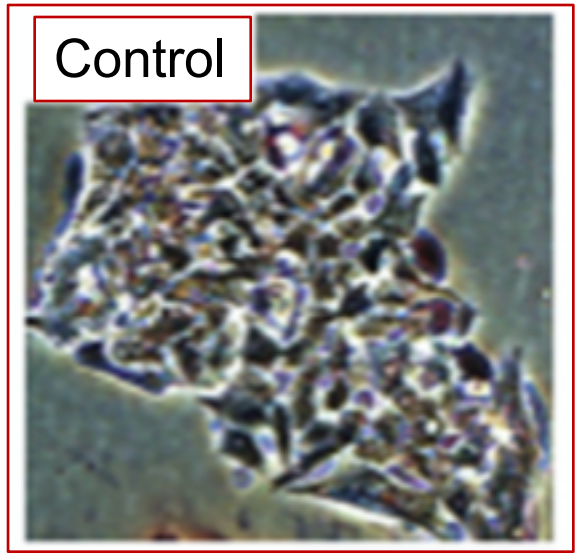
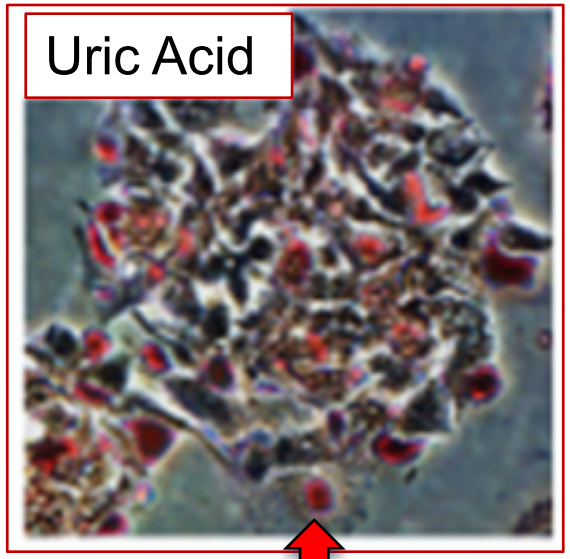
AP = Allopurinol

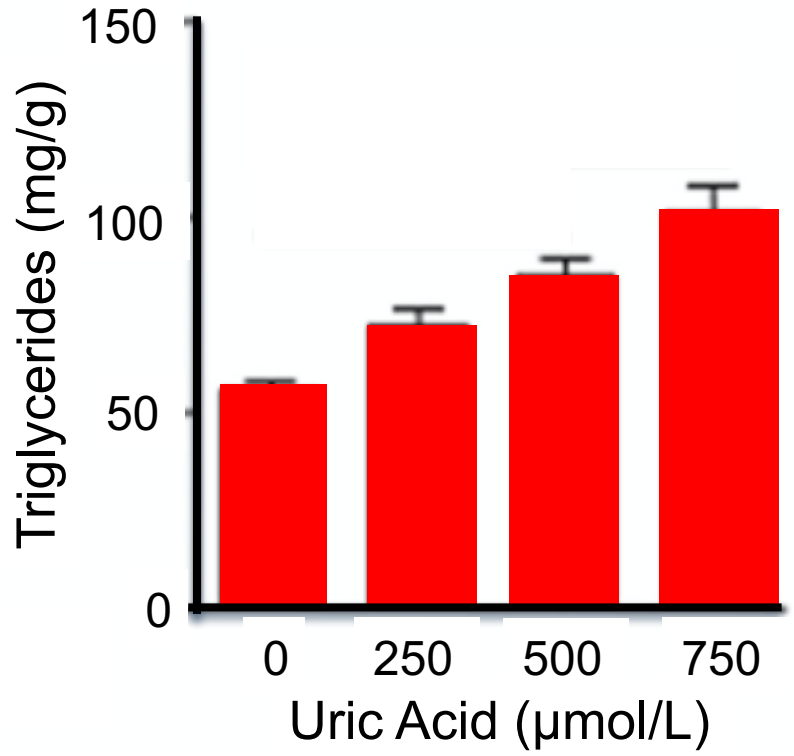
Nakagawa et al, 2006

Research Background

Uric Acid induces fat accumulation in liver cells independently of fructose metabolism







Increase in Triglyceride content:
Associated with accumulation of lipid-containing vacuoles (Oil Red-O staining)

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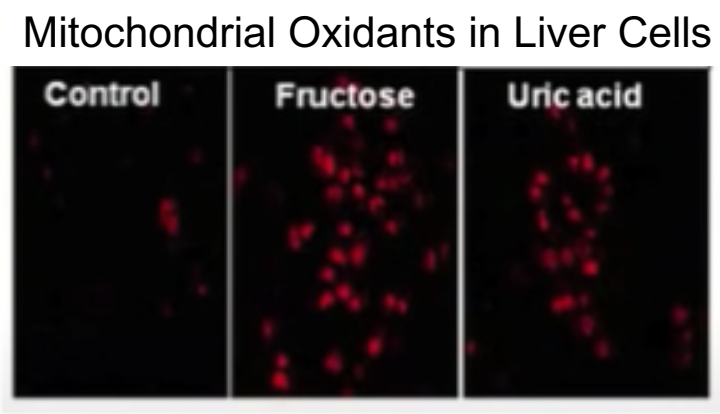
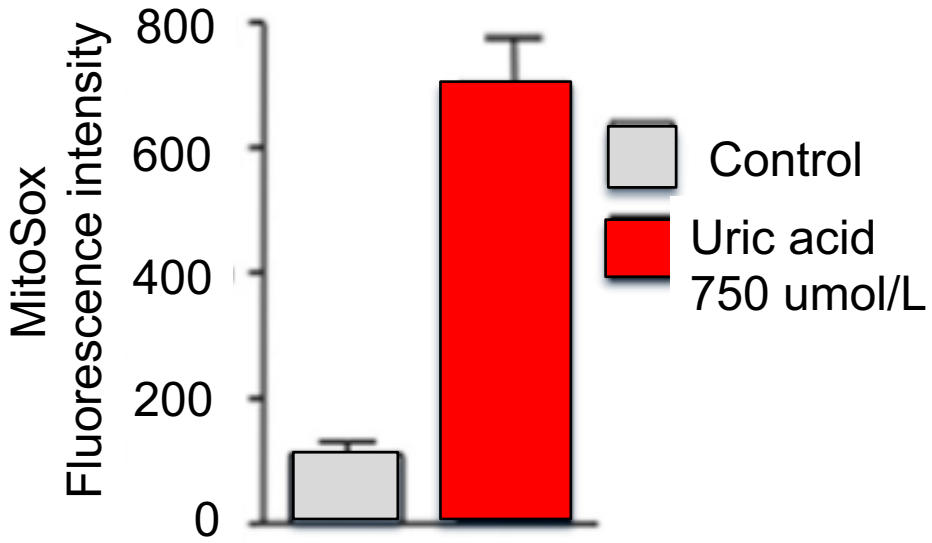
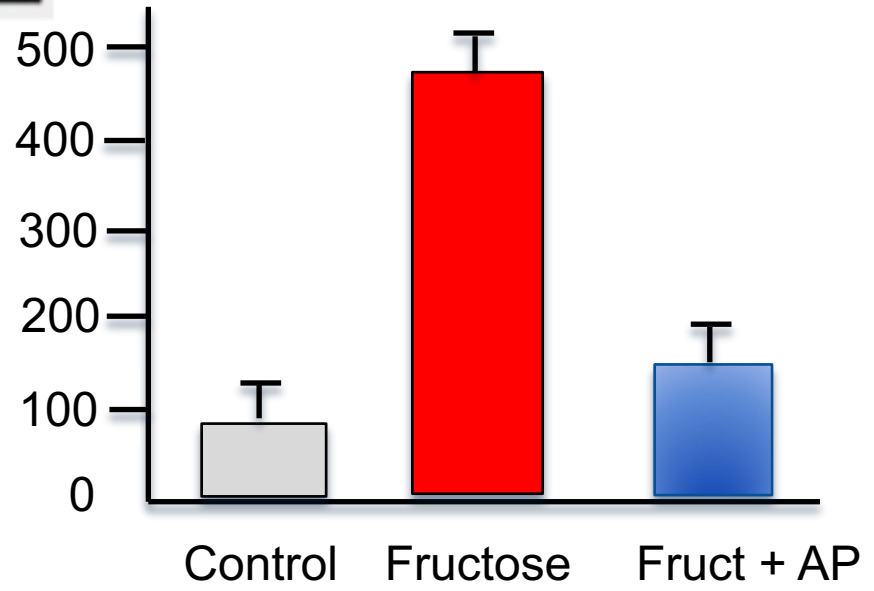
Lanaspra et al, 2012

Lanaspa et al, 2012

Uric Acid causes Mitochondrial Oxidative Stress in Hepatic Cells





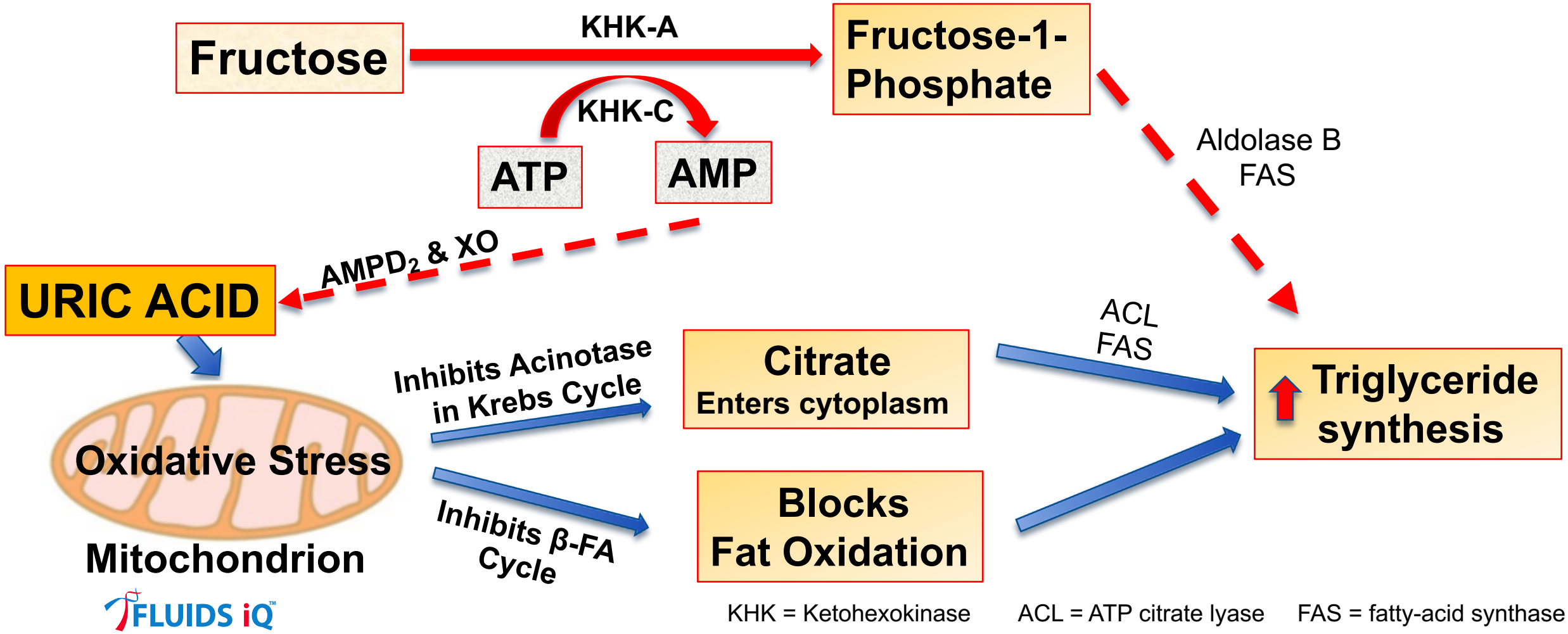


AP = Allopurinol

Lanaspa et al, 2012

Uric Acid mediates fat accumulation in hepatocytes

- UA increases Liver Fat through Mitochondrial Oxidative Stress



Uric Acid as an Independent Risk Factor

- **Uric Acid has its own 'taste - Umami': One of the 5 major tastes**

Sweet → Triggers Seeking Fructose

Salty → Triggers Fructose Production

Umami → Cured & Organ Meats, Beer, Tomatoes, Blue Cheese (caesar salad), Anchovies → Activated by Glutamate (MSG) → ***Creates Uric Acid***

Bitter / **Sour** → Signal not to eat the Fructose creating foods

- **Umami taste stimulates UA creation - *independent* of Fructose**
  - **Gm for gm, MSG is more potent than sugar. However, we eat very little MSG**
- **Real-life Potency for Uric Acid creation:**
  #1- Sugar, #2 - High Glycemic Carbs, #3 - Salty Foods, #4 - MSG (Umami)

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Lanaspa, Ishimoto et al, 2013

Summary:
The Slippery Slope to Metabolic Syndrome

- **Fructose causes cell energy depletion due to ATP degradation**

  The only nutrient to create this depletion in cell metabolism

- **HOW?**
  - **This metabolic pathway, of ATP degradation & energy depletion, leads to the creation of elevated Uric Acid levels**
  - **Elevated UA levels, in turn, lead to very high sensitivity to glucose and these degradation pathways**

Increased levels of URIC ACID become an Independent Risk Factor for Metabolic Syndrome

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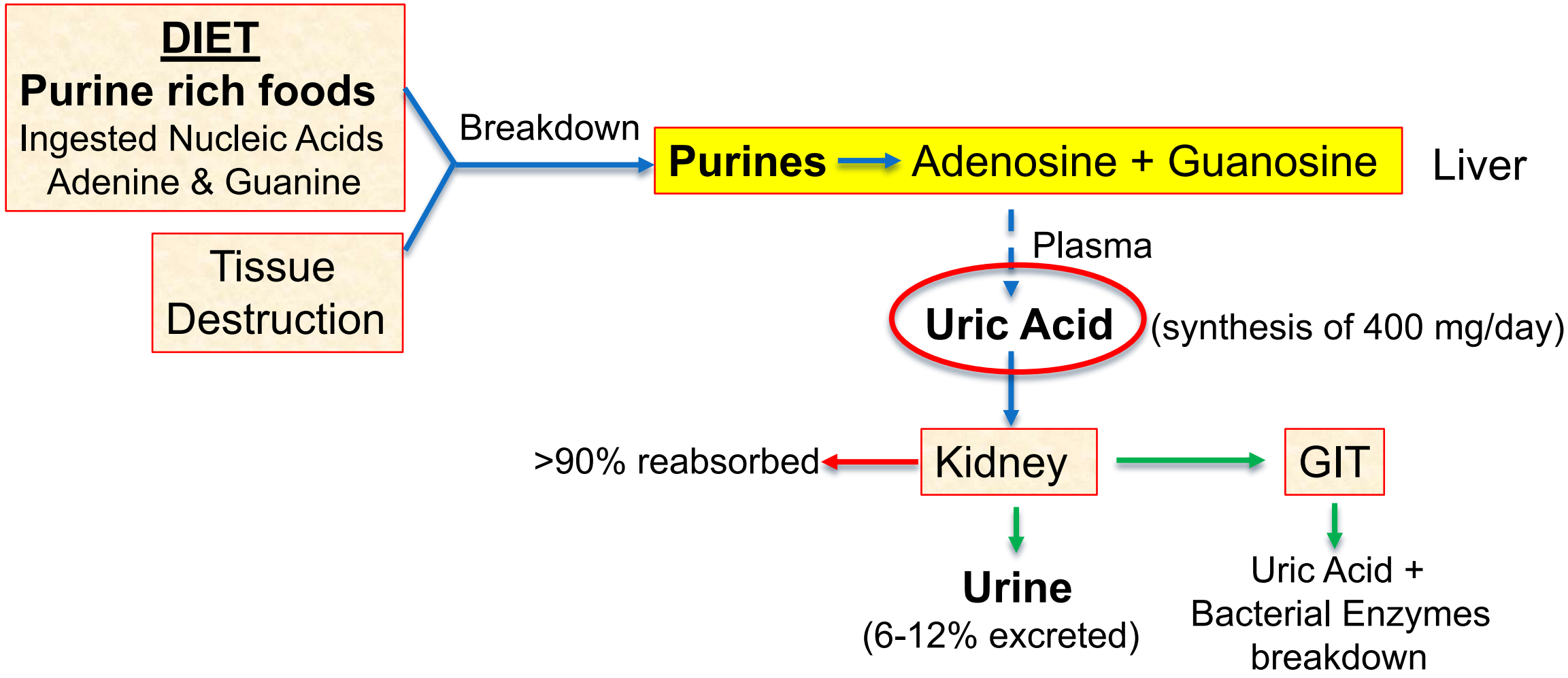
Purine & Uric Acid Metabolism



GIT = Gastrointestinal Tract

Uric Acid-Nitric Oxide (N_2O) Connection

- Fructose
- Purines
- Alcohol

→ ⇧ Uric Acid → ⇩ Nitric Oxide →

- Insulin Resistance
- Hypertension
- Reduced blood flow to organs

- **Nitric Oxide**: Important regulator of **Cardiovascular Syste**m
  - **Vasodilates** vascular inner muscles, increasing circulation & Insulin's move from blood into cells

- Uric Acid ⇩es N_2O action by: 1) ⇩ N_2O production & 2) Jeopardizing N_2O function

  This compromises insulin function & CV health
- N_2O deficiency & damaged functionality, is associated with CVD, T2 DM & triggers hypertension & loss of vascular compliance. Associated with erectile dysfunction.

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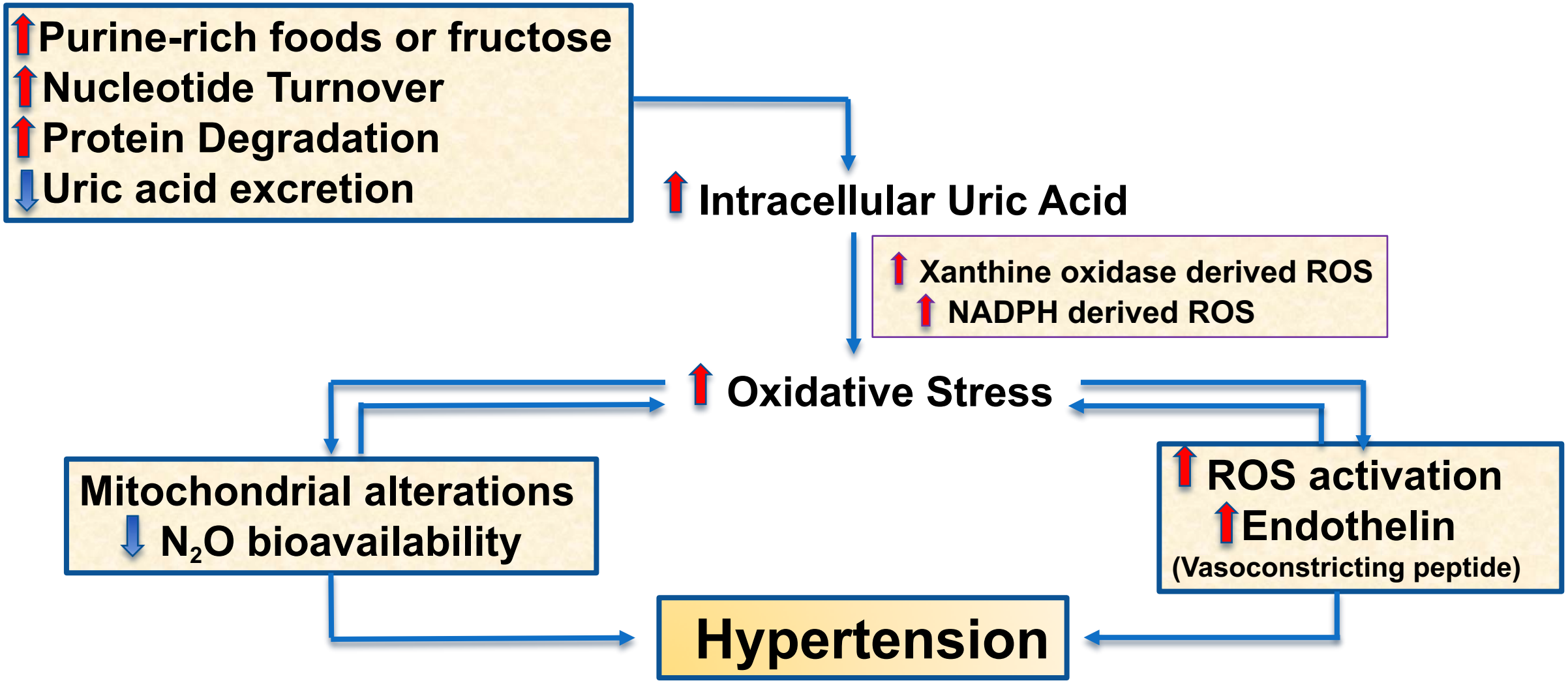
Mechanism: How Uric Acid may Cause Hypertension



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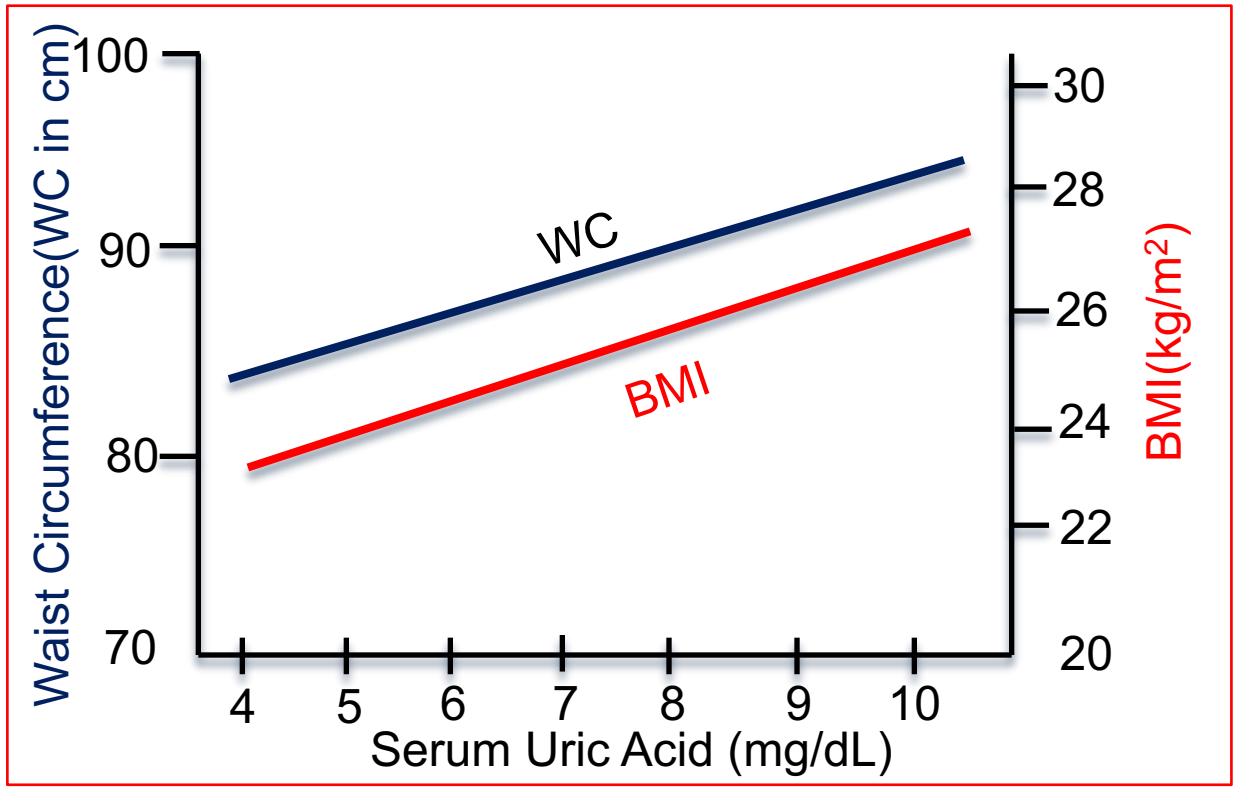
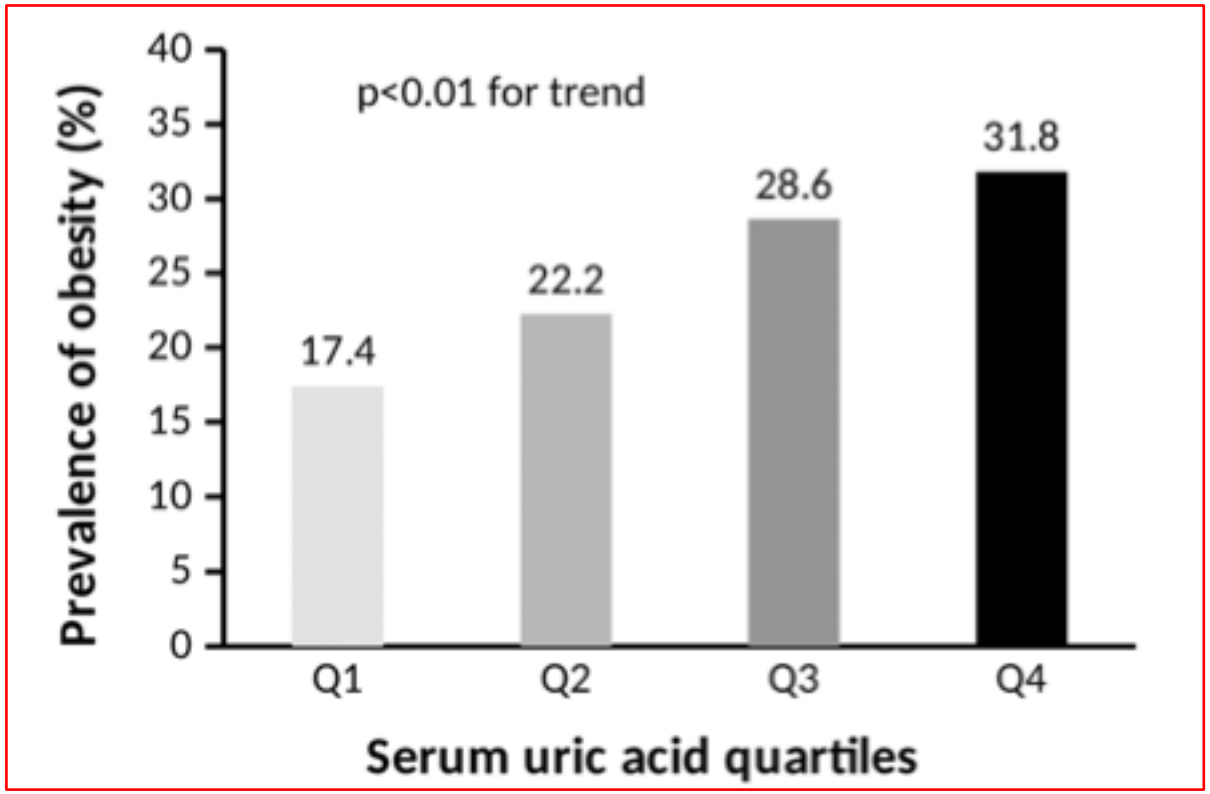
Johnson RJ. Hypertension. What Are the Key Arguments Against Uric Acid as a True Risk Factor for Hypertension?, 2013, 61, 948-951

Research Background

Serum Uric Acid (SUA): Obesity, BMI & Waist Circumference





Significant association between SUA & obesity (Bangladeshi adults). Recommendation: "Routine SUA measurement in obese to prevent hyperuricemia & related complications."

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Ali et al, Pone, 2018

Serum Uric Acid predicts development of Diabetes

Location	Population	End point	F/U	Independent	Year	First Author
Israel	10,000 men	diabetes	5 years	Yes	1975	Medalie
U.S.	5,209 adults	diabetes	26 years	Men	1985	Brand
Naura	266 adults	diabetes	6 years	Women	1985	Balkau
Sweden	766 men	type 2 diabetes	13.5 years	Yes	1988	Ohlson
Britain	7,735 men	NIDDM	12.8 years	Yes	1995	Perry
Kinmen (China)	654 high risk	diabetes	3 years	Yes	1998	Chou
Mauritius	2,605 adults	IGT or diabetes	5 years	Yes	2000	Boyko
Japan	6,356 men	type 2 diabetes	9 years	No	2001	Taniguchi
Germany	6,166 adults	type 2 diabetes	3–14 years	Women	2002	Meisinger
U.S.	9,020 adults	↑insulin	11 years	Yes	2003	Carnethon
Japan	2,310 men	IFG or diabetes	6 years	Yes	2003	Nakanishi
Kinmen (China)	641 adults	IFG or diabetes	7 years	Women	2004	Lin
U.S.	60 adults with MI	↑insulin	6 months	Yes	2005	Nakagawa
Finland	522 high risk	type 2 diabetes	4.1 years	No	2006	Niskanen
Netherlands	4,536 adults	type 2 diabetes	10 years	Yes	2008	Dehghan
Mauritius	4,259 adults	diabetes	5 years	Men	2008	Nan
China	2,609 adults	type 2 diabetes	9 years	Yes	2008	Chien
U.S.	9,689 adults	met syn	5.7 years	Yes	2008	Sui
U.S.	566 high risk	type 2 diabetes	13 years	Yes	2009	Kramer
U.S.	9,175 adults	type 2 diabetes	26–28 years	Yes	2010	Bhole
Korea	4,779 men	met syn	3 years	Yes	2011	Ryu
Japan	12,643 adults	IFG and diabetes	5 years	Women	2011	Yamada
China	924 adults	type 2 diabetes	3.5 years	Yes	2011	Wang
Italy	758 adults/BP	type 2 diabetes	3 years	Yes	2011	Viazzi

Johnson, Diabetes,2013

Elevated Serum Uric Acid predicts Hypertension

Study	Population	F/U	Independent	Year	Author
Israeli Heart Study	10,000 males	5 YRS	Not done	1972	Kahn
Kaiser Permanente	2,062 subjects	6 YRS	Yes	1990	Selby
Univ of Utah	1482 adults	7 YRS	Yes	1991	Hunt
Olivetti Heart Study	619 males	12 YRS	Yes	1994	Jossa
CARDIA study	5,115 adults	10 YRS	Yes	1999	Dyer
Osaka Health Survey	6,356 males	10 YRS	Yes	2001	Taniguchi
Hawaii-Los Angeles-Hiroshima	140 males	15 YRS	Yes	2001	Imazu
Osaka Factory Study	433 males	5 YRS	Yes	2003	Masuo
Osaka Health Survey	2310 males	6 YRS	Yes	2003	Naganishi
Okinawa	4,489 adults	13YRS	Yes	2004	Nagahama
Bogalusa Heart	679 children	11 YRS	Yes	2005	Alper
Framingham	3,329 adults	4 YRS	Yes	2005	Sundstrom
Normative Aging Study	2062 males	21 YRS	Yes	2006	Perlstein
ARIC	9,104 adults	9 YRS	Yes	2006	Mellen
Beaver Dam	2,520 adults	10 YRS	Yes	2006	Shankar
MRFIT	3,073 men	6 YRS	Yes	2007	Krishnan
Health Professional Followup	750 men	18 YRS	No	2007	Forman
Nurse Health Study	1,500 women	5 YRS	Yes	2009	Forman
China	7,220 adults	4 YRS	Yes	2009	Zhang

- 18 of 19 studies found that Uric Acid **independently** predicts the development of hypertension

Johnson,2014

Uric Acid (UA) & Gut Health

- Intestines exposed to UA. Elevations change bacterial composition
- **Hyperuricemia characterized by dysregulated intestinal immunity, systemic inflammation & *compromised intestinal barrier****
- ⬆ UA levels select for inflammatory bacteria & results in ⬆ ed blood LPS
- Disrupts the Gut Barrier Lining and ***Increases Permeability***
- Leads to ⬆ frequency & duration of gout
  - 17 'gout'-related bacteria levels predict gout diagnosis with 90% accuracy**
  - **These 'Gout Bacteria' quite similar to those found in people with T-2 DM & other features of Metabolic Syndrome**

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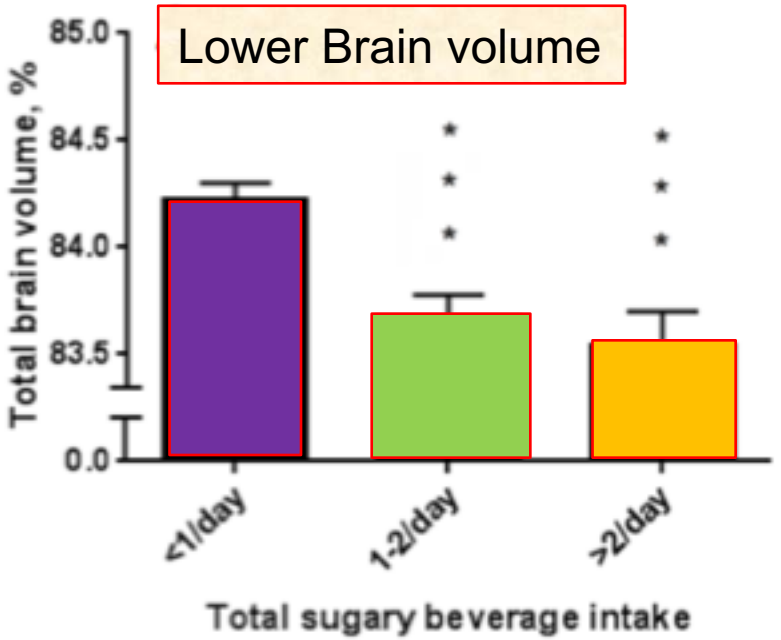
*Qiulin Lv et al, 2020; **Zhuang et al, 2016

Sugary Beverage Intake & Pre-clinical Alzheimer's



Equivalent to 1.5-2.6 yrs of brain aging for brain volume, & 3.5-13 yrs of brain aging for episodic memory*

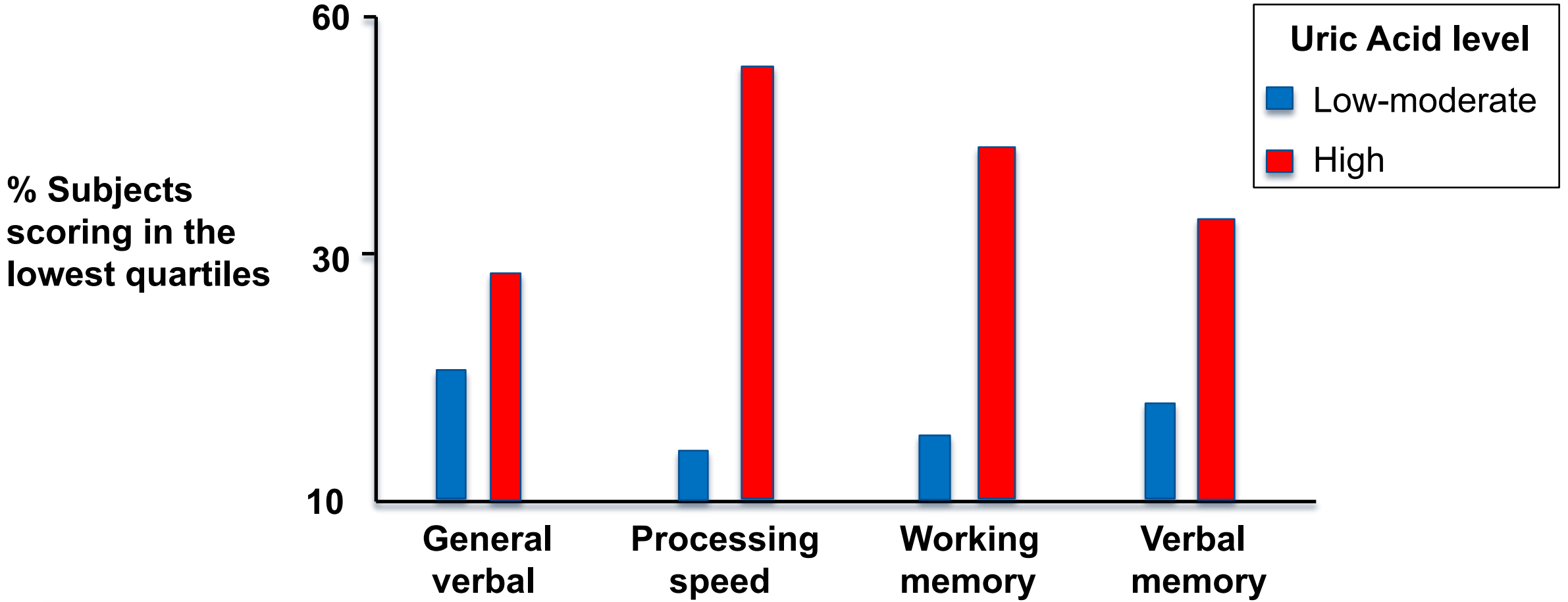
What are UA's roles in this phenomenon?

- **Bioenergetics:** Fructose raises UA levels & lowers insulin signaling. Cells lose ability to use glucose: ie; they become **Insulin Resistance****
- **Nitric Oxide**: ⬆ UA creates ⬆ **Oxidative Stress** (increases free radicals) & ⬇ N_2O synthesis***
  - Compromises blood flow, including to brain
  - Decreases N_2O synthase (Makes N_2O in brain) Reduces synaptic transmission & memory

FLUIDS iQ™ *Pase et al, 2017

**Johnson et al, 2011; ***Blossom, 2011

Uric Acid & Cognitive Impairment



Even mild elevations in UA levels (Low-Mod & High - but still 'normal range') increase the risk of cognitive decline in elderly

Johns Hopkins study: Schretlen, 2007

What led to the situation where Fructose & Uric Acid are now central players in these modern severe problems?

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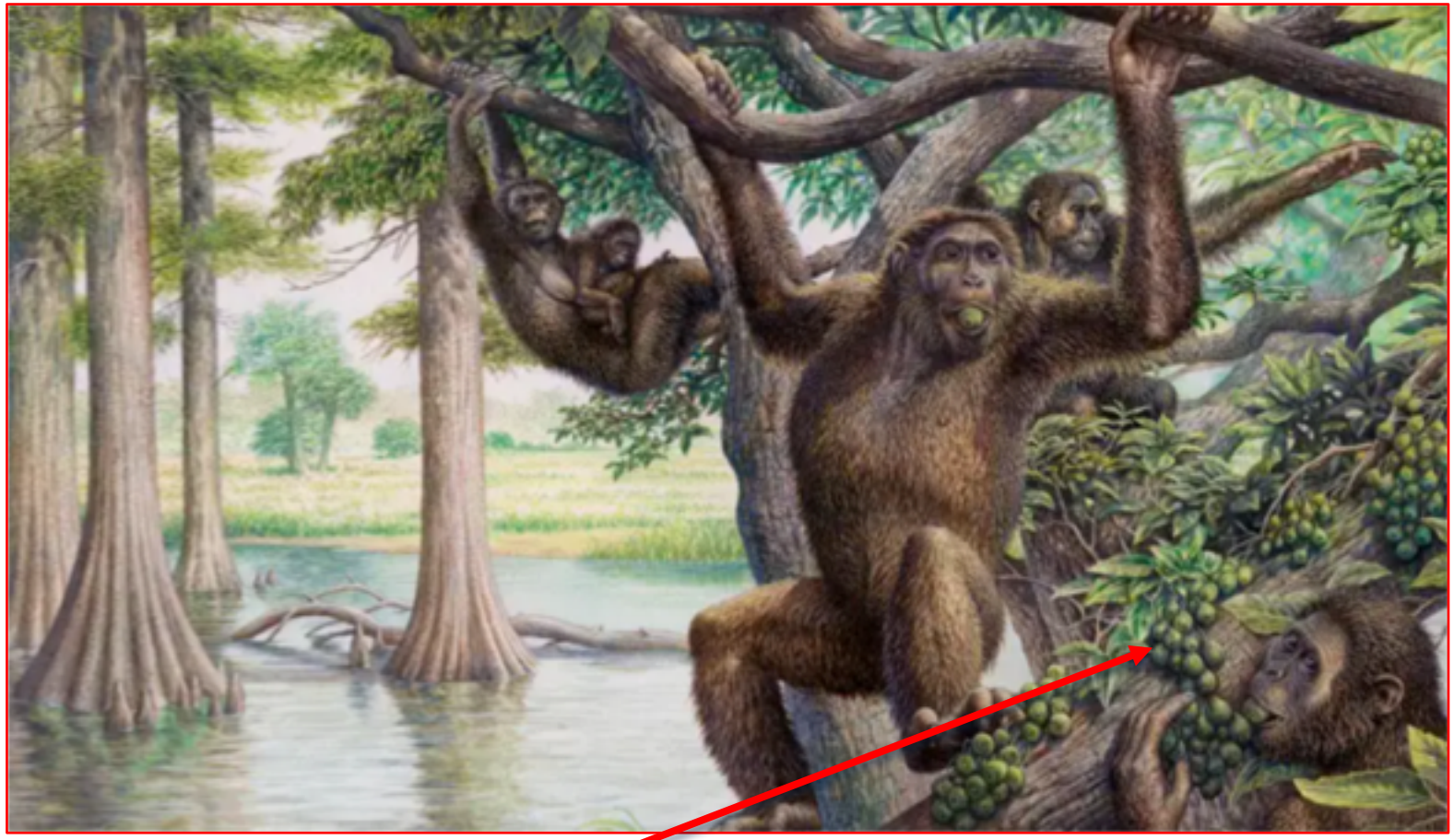
Early Miocenean Apes: 22 – 17 million years ago



1. Fruit eating – high fructose content
2. Living in tropical rain forests of Africa

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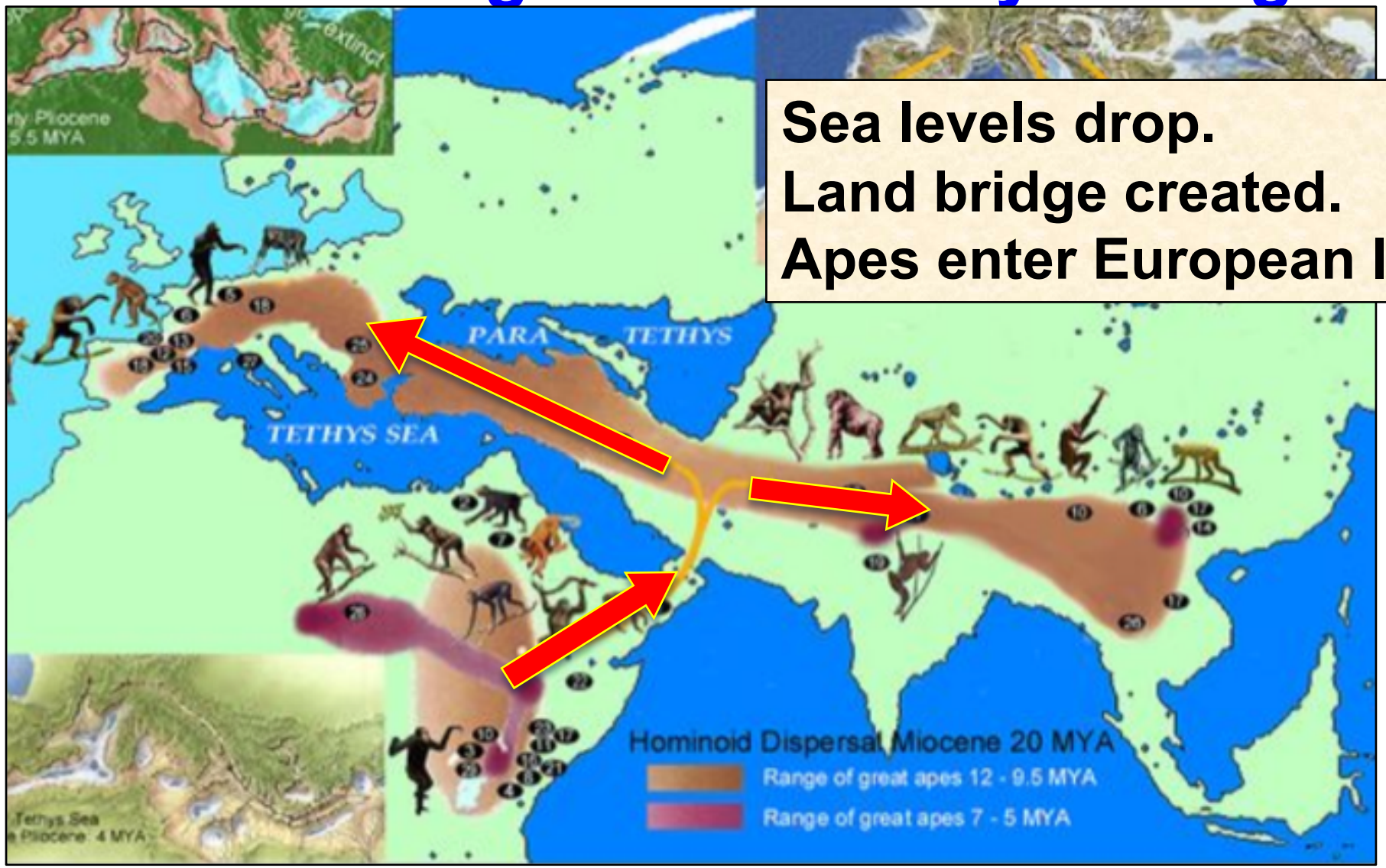
after Perlmuter, 2022

Global Cooling: ~ 17 million years ago



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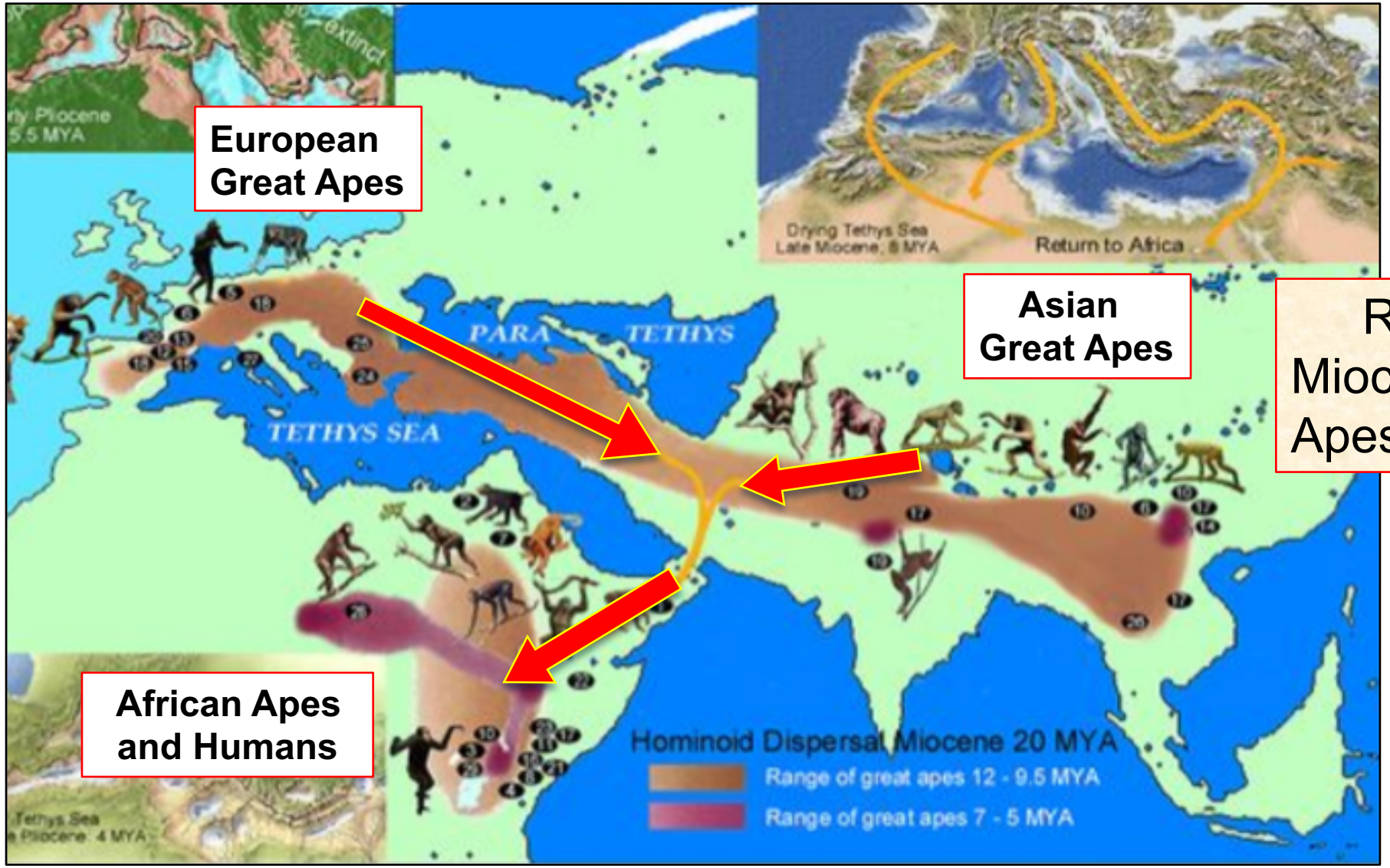
Continued Global Cooling: 13-8 million years ago



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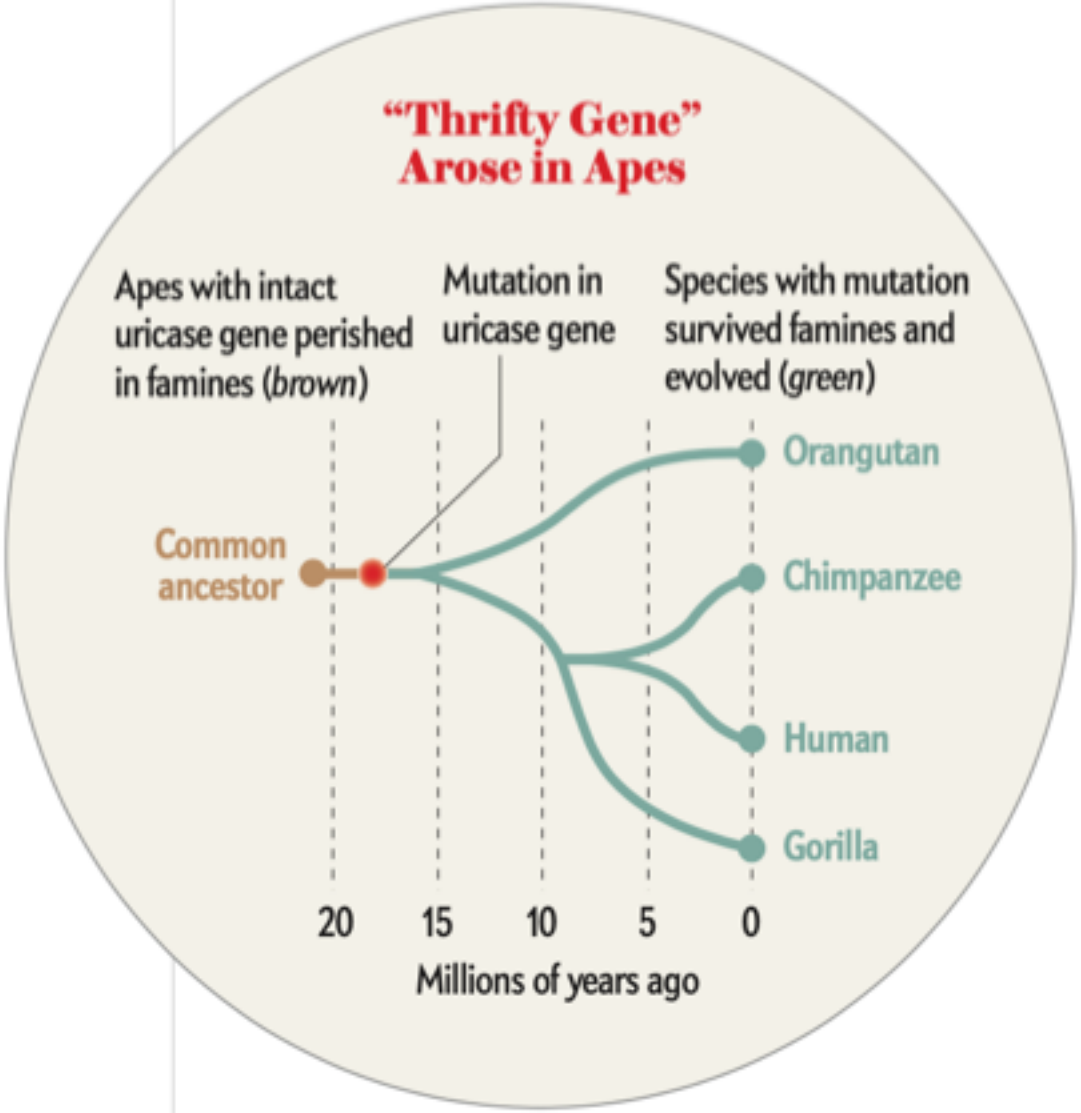
after Begun, Science, 2000 & evolution-involution.org

The Uricase Mutation

Johnson & Andrews, Sci Amer, 2015

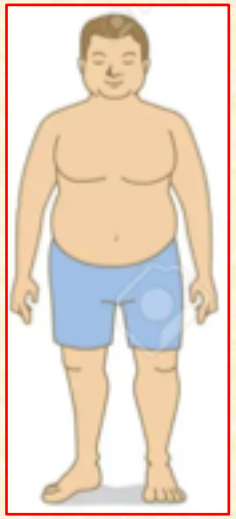


- Apes ~16 million yrs ago in subtropical Europe. Global cooling changed forest. Fruit scarce. **Mutation occurs in gene coding for uricase** (Helps convert fruit sugar (fructose) into fat calorie stores, rather than immediate burn)
- Enabled apes to survive food shortages. Same mutation in all **modern apes & humans**
- **The uricase mutation predisposes modern humans to obesity & diabetes.**

The Uricase Mutation: Then & Now

Increased Uric Acid
(food scarcity)

→ Survival



Increased Uric Acid
(food abundance)

→ Health threatened

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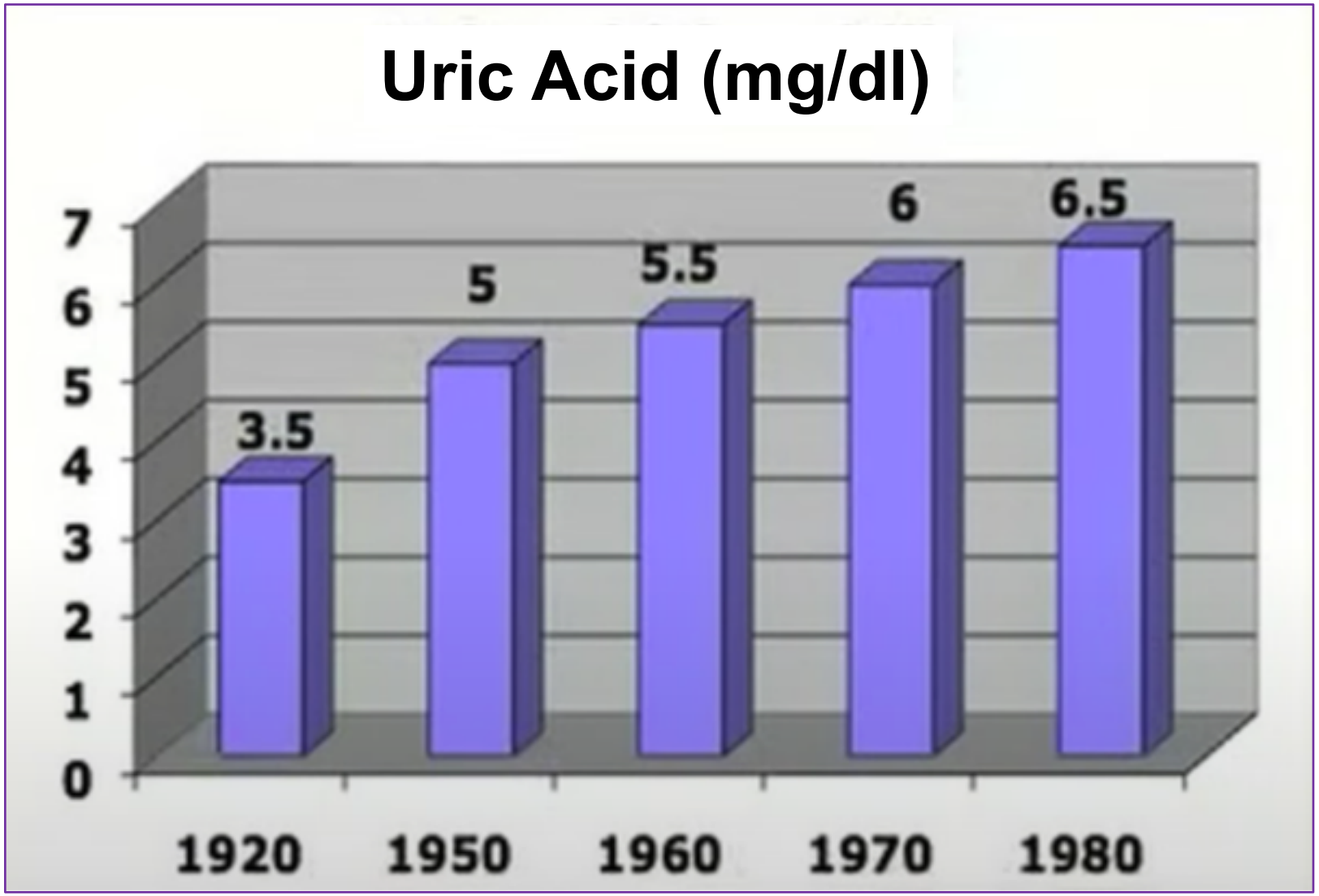
Uric Acid rise in the USA in Twentieth Century



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Johnson, 2014

Obesity, Metabolic Syndrome & the 'Survival Switch'

- Ancient 'Survival Switch': ↑ food intake & fat accumulation, ↓ exercise
  - Survival mechanism in the wild. Store fat to make it through the winter famine
  - Store in fat cells, & in liver. ↑ fats in blood: triglycerides & cholesterol

- Become **Insulin Resistant**: ↓ glucose uptake by muscles, so can ↑ to brain
- Become **Leptin Resistant** (eat & don't feel full - keep eating)
  - Associated with eating ripe fruit – high **Fructose** levels.

- Create a ↓ed resting energy metabolism: **Metabolic Syndrome**

  In nature - a **Survival Tool**. To modern humans - **Pathophysiologic Problem**

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What can be done to Effectively Lower Levels of Uric Acid?

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Laboratory Testing

- Prior to starting a dietary program, should get the following lab tests, with supervision of an appropriate health professional

Test	Ideal Level
Fasting blood glucose	< 95 mg/dL
Fasting insulin	< 8 IU/ml (ideally < 3 IU/ml)
Hemoglobin A1c	4.8 to 5.4%
C-Reactive Protein (CRP)	0 to 3.0 mg/L (ideally < 1.0 mg/L)
Uric Acid	**5.5 mg/dL or less**

Uric Acid Reference Ranges in Blood and Urine*

- Blood: 'Normal' Serum UA levels, as opposed to ↘
  - Adult Male: 2.5-7.0 mg/dL (rise after puberty)
  - Adult Female: 1.5-6.0 mg/dL (Low until menopause)

  } ***Optimal: < 5.5 mg/dL***

  due to ↓ Estrogen (helps rid body of UA)
  - Elderly: Values may be slightly increased
  - Child: 2.5-5.5 mg/dL; Newborn: 2.0-6.2 mg/dL
  - Therapeutic target for gout: < 6-7 mg/dL. Hyperuricemia: UA level > 6 mg/dL
  - Critical Values: > 12 mg/dL

- Urine: Optimal UA range is 250-750 mg/24 hr (SI units)

*American College of Rheumatology

Uric Acid Reference Ranges in Blood*

- Serum uric acid (SUA) levels categorized into mg/dL quartiles:

Baseline characteristics of participants

Uric acid, mean ± SD mg/dl	6.8 ± 1.6	5.4 ± 1.4
Serum uric acid level by age group, mean ± SD mg/dl (no.)		
35–44 years	6.90 ± 1.49 (9,135)	4.95 ± 1.19 (9,532)
45–54 years	6.85 ± 1.49 (11,355)	5.11 ± 1.27 (13,670)
55–64 years	6.68 ± 1.67 (9,667)	5.56 ± 1.43 (13,981)
≥65 years	6.72 ± 1.66 (11,722)	5.79 ± 1.59 (11,331)
Serum uric acid level, mg/dl		
≤5	4,619 (11.0)	22,116 (45.6)
5.1–7	20,638 (49.3)	20,934 (43.2)
7.1–9	13,399 (32.0)	4,657 (9.6)
>9	3,223 (7.7)	807 (1.7)
Hyperuricemia (serum uric acid level >7 mg/dl)	16,622 (39.7)	5,464 (11.3)

- Note: > 90% males above 5.5. Lower levels in females

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*Chen et al, 2009

Sources that are High in Purine

- **Alcoholic beverages**: Mostly liquor and beer (due to the yeast)
- **Fish**: Seafood & shellfish - includes anchovies, sardines, herring, mussels, codfish, scallops, trout, tuna and haddock
- **Meats**: Mostly organ meats, such as liver & kidney, sweetbreads Others; bacon, turkey & veal
- **Vegetables**: Mushrooms, green peas, spinach, asparagus, broccoli & cauliflower

Drugs that Increase Uric Acid

- **ASA** ('Aspirin' – doses of 60-300 mg/d)
- **Omeprazole** ('Prilosec' for acid reflux)
- **Diuretics** (in Tx of CHF)
- **β -blockers** ('Propranolol')
- **Testosterone**
- **Sildenafil** ('Viagra')
- **Niacin** (Vit B3)
- **Levodopa** (for Parkinson's)

Strategies for Lowering Uric Acid Levels

- 1. Dietary
- 2. Time-Restricted Eating (TRE)
- 3. Supplements
- 4. Lifestyle Protocols
  - A) Sleep
  - B) Exercise

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1. Dietary Choices

- 1. **Adopt the eating of foods that will not activate the 'Fat Switch'**
  - Gluten free & mostly plant-based meals, containing vegetables
  - White meats, fish, nuts & seeds, organic eggs, extra virgin olive oil
  - Add fiber to diet: Beans, broccoli, berries, avocados, apples, whole grains
  - UA-lowering alternatives: Cherries, broccoli sprouts, coffee
- 2. **Avoid or Limit high glycemic foods** – bread, rice, cereals, chips
  - If eating them, drink water – 6-8 glasses/day. This decreases **salt** levels
  - Limit or eliminate: Refined carbs, liquid sugar (soft drinks or most fruit juices) added sugar or artificial sweeteners
- 3. **Limit purine-heavy organ meats & fish**: eg; Liver, kidney, anchovies
- 4. **Limit alcohol, especially beer**

Johnson, 2022; Perlmutter, 2022

2. Time-Restricted Eating (TRE)

- **Limit meals** (caloric consumption) to 8-12 (10) hr window:
  - Improves insulin sensitivity, BP, fat metabolism
  - Improves function of kidney, liver, pancreas, brain & gut*
- **Prolong fasting state**: Triggers Autophagy**
  - Cellular process that cleanses & detoxifies
  - Triggered by AMPK – fat burning molecule that removes internal pollutants
- **TRE lowers Inflammation & long term UA levels:**
  - **Beneficial for weight management & metabolism**

AMPK = AMP-activated protein kinase

*Manoogian et al, 2021; **Jamshed et al, 2019

3. Supplements

- **Quercetin**
- **Luteolin**
- **Docosahexaenoic Acid (DHA)**
- **Vitamin C**

Quercetin

- **Dietary polyphenol:** Potent antioxidant & anti-inflammatory
- **Lowers UA**: In both healthy & those with above-normal UA (Dose: I mo. of 500 mg/day*)
  - Individuals at high risk of CV events have shown lowered BP & & LDL**
- **Inhibits enzyme Xanthine Oxidase (XO):**
  - XO required in final step of UA creation (similar to how the drug Allopurinol works)

Luteolin

- **Inhibits enzyme Xanthine Oxidase:**
  - In mild hyperuricemia, shown to lower UA levels*** (Dose: 100 mg/day)
- **Prevents dysfunction of insulin-creating β cells in pancreas**
- **Sources:** Fruits, vegetables & herbs
  - Green peppers, celery, citrus, broccoli, herbs (thyme, rosemary, oregano)

*Yuanlu et al, 2016; **Seban et al, 2016; ***Imran et al, 2019

Docosahexaenoic Acid (DHA)

- **Omega-3 Fatty Acid**. Building block for brain cell membranes
  - Reduces brain inflammation & increases BDNF.
- Reduces Gut inflammation. **Blocks effects of fructose**
- Diet creates 25% of optimal needs. Suppl[t:] Fish oil or DHA direct (~1000mg/d)*

Vitamin C

- Supplementation **lowers Serum UA****, & in those susceptible to gout*****
- Increases UA urinary **excretion** & decreases reabsorption in kidney
- **Antioxidant**: Reduces tissue damage that could lead to UA production

BDNF = Brain Derived Neurotrophic Factor

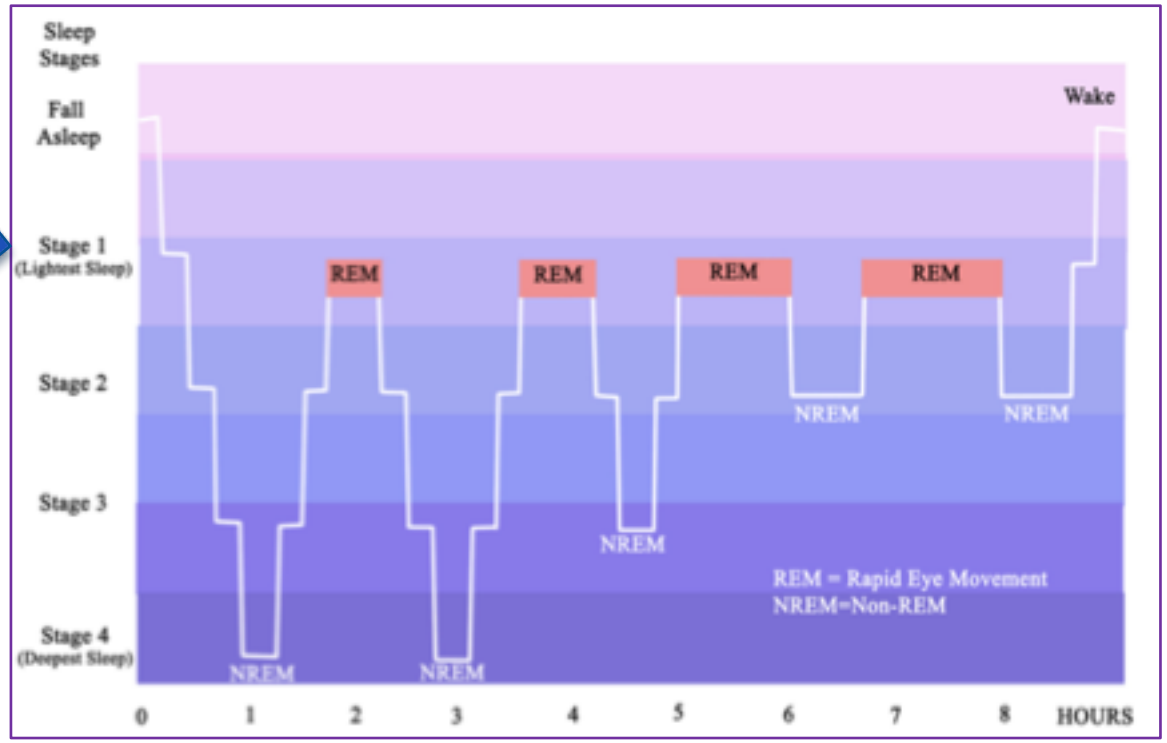
*Allaire et al, 2016; **Hyon et al, 2008; ***Jurachek et al, 2011

4. Sleep:

Essential for Metabolic Health

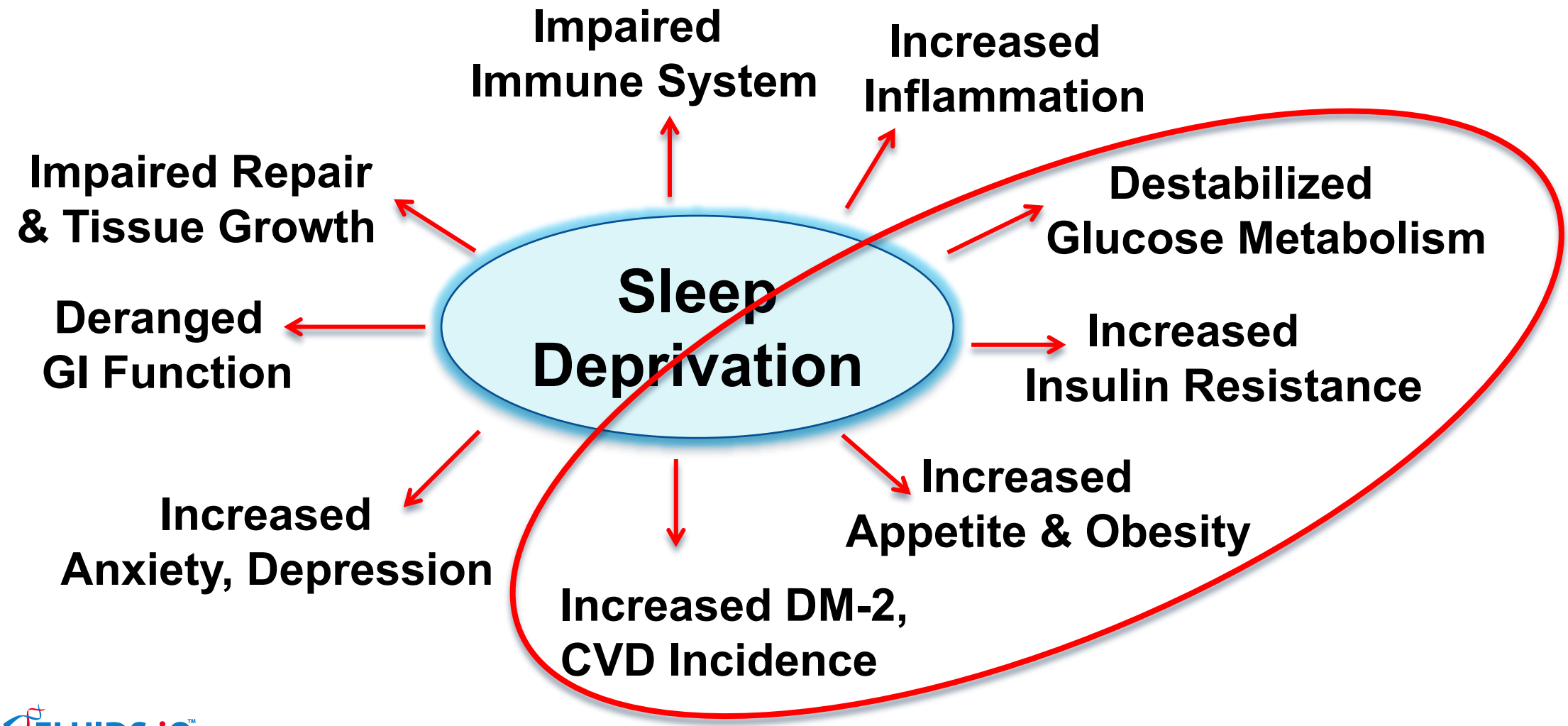
REM Sleep
- ~25% of sleep time in adults
- > in infants (up to ~50%)
- Increased length with each cycle

Non-REM Sleep
- ~75% sleep time in adults
- 4-5 Cycles/ night
- First 2 Cycles longer & deeper



- Important time for restoration & repair of body at cellular level
  - Includes maintenance of the immune system & metabolic functions
  - Stages 3 & 4 (deep, slow-wave) important for insulin use to regulate blood sugar

Effects of Insufficient Sleep



Sleep and the Microbiome: Two Way Street

- Microbiota effect how we sleep
- Sleep & circadian rhythms affect microbial diversity & overall health

'The Gut-Brain Axis'

- 2 nights of **Insufficient** or disrupted sleep:
  - Rapid negative effect on microbiome health*
  - **Significant decrease in commensal bacterial species**
  - **Increase in species linked *specifically* to obesity and T-2 DM**
  - **Significant decrease in insulin sensitivity**

*Benedict et al, MM, 2016

Sleep and Diabetes

- Poor Sleep: Affects **Diabetes** directly & indirectly
  - Triggers changes to hormones: Contributes to weight gain & obesity
  - Causes changes to behavior and lifestyle.

- Sleep disruption increases risks for T-2 DM
  - T-2 DM much more likely to have OSA & other sleep disorders
  - The more severe the sleep problems, the more severe & less controlled the DM

- **'Short Sleep'** and its risks in older adulthood:
  - If insufficient sleep, ~ 2x more likely to be diagnosed with T-2 DM*

OSA = Obstructive Sleep Apnea

* Mesarwi, 2013

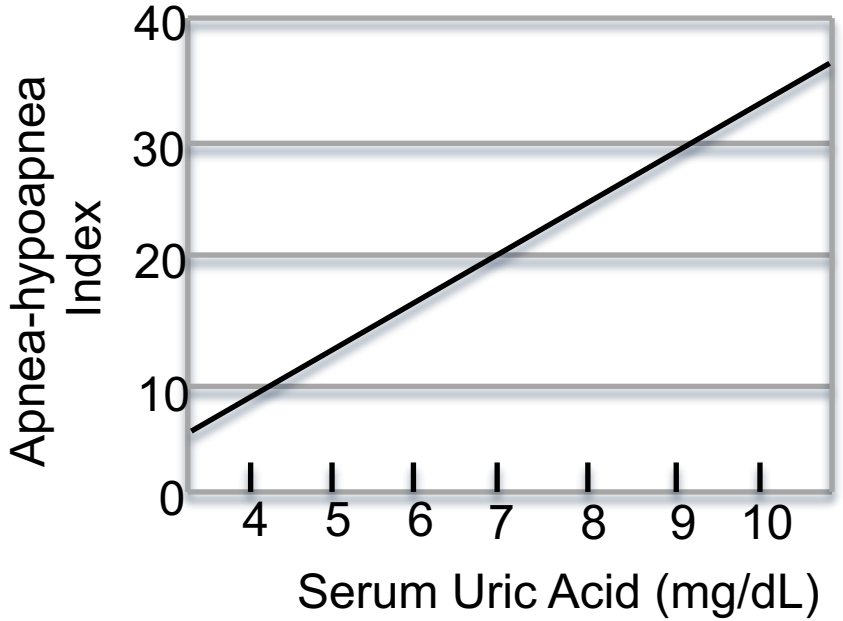
*Papendreou, 2019; **Zheng, 2019 (adapted Perlmutter, 2022)

Uric Acid and Obstructive Sleep Apnea (OSA)

- Sufficient sleep equates with low UA levels*

- UA Rise seen with increased sleep disruption, due to increased OSA
  - Note: Subjects had T-2 DM, with overweight BMI**
- Common connecting element of increased UA, OSA & T-2 DM

Metabolic Syndrome



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Effect of Exercise

Main Purpose:

Not to lose weight, but to **stimulate mitochondrial function** & decrease the risk of weight gain

Best Exercise Mode - Zone 2:

Jogging (or similar modality), that creates 60-70% of maximum heart rate

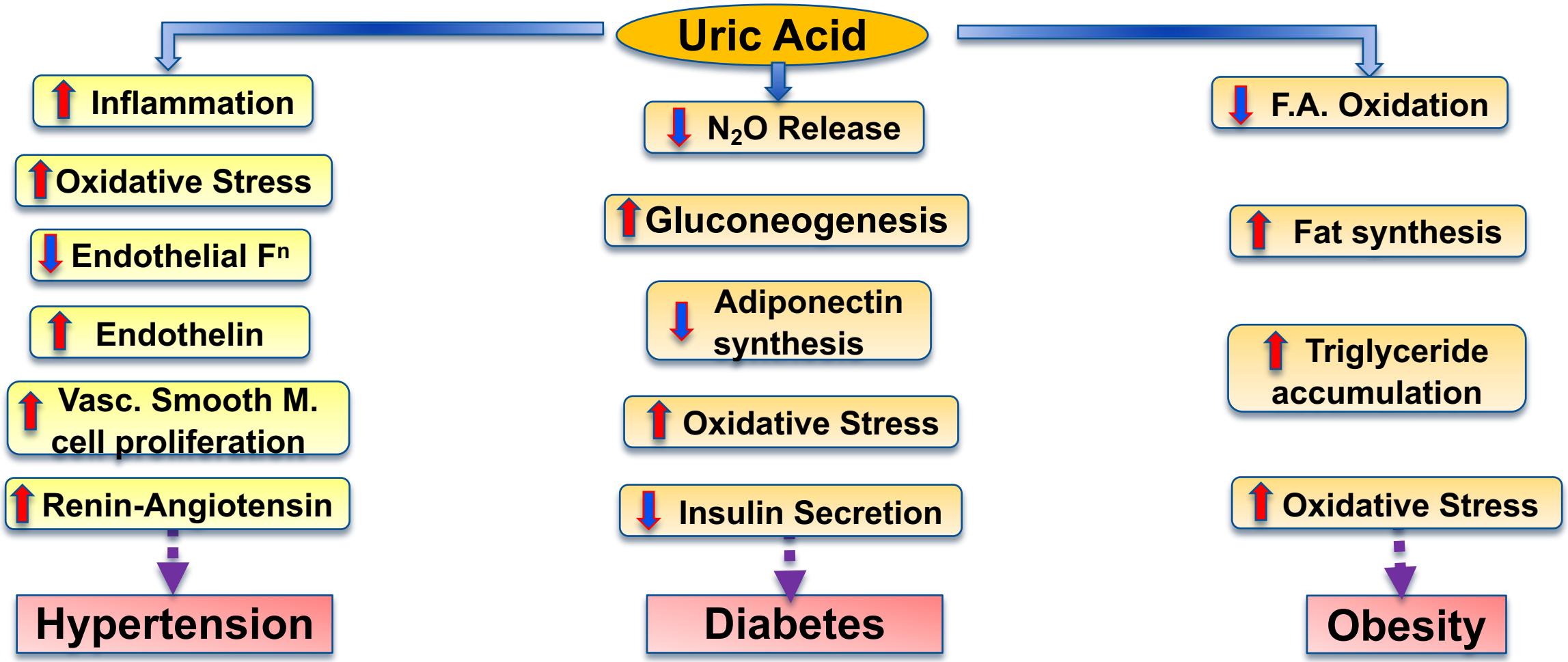
Purpose: Enables the sustaining of a pace just below the aerobic threshold, for ~ 30 min

Uric acid in Metabolic Syndrome: From an innocent bystander to a central player

"Summary:
We have entered a new exciting period in the history of **uric acid**. While uric acid was once the lonely dinner conversation for those suffering from **gout or kidney stones**, it is now being evaluated as a potential **master conductor in the worldwide symphony of obesity, diabetes, and cardiorenal disease.**
It is time to..determine whether lowering uric acid can be beneficial in the prevention and **treatment of hypertension, insulin resistance, obesity, fatty liver, and cardiovascular disease**."

Kanbay M et al. Eur J Intern Med. 2016; 29: 3–8

Uric Acid Induced Effects:
Role in Pathogenesis of Hypertension, DM, & Obesity



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after Kanbay M et al, 2016

Uric Acid (UA):
The Critical Strategic Metabolic Biomarker

- Conventional Knowledge:
  - High UA causes 'Gout' – crystals in toes &/or kidney ⟹ pain

- New Knowledge: UA a powerful trigger of '**Metabolic Storage Mode**'
  An ancient response to compromised food resources, whose intention was to make & store fat, raise BP & Blood glucose, in order to get nutrients to the brain

- **Ancient SURVIVAL mechanism: Now a major METABOLIC problem**

- **In modern societies, Metabolic Dysfunction is the greatest danger to achieving a healthy and long life**

Uric Acid (UA): Strategic Metabolic Biomarker

- UA comes from 3 main sources: Purines, Alcohol (beer), **FRUCTOSE**
- In humans, UA levels are 4-5 x that of other mammals
  - It accumulates & signals to prepare for caloric scarcity
- Leads to **Metabolic Syndrome**: **#1 Cause of deaths on planet** (Much > COVID)
- Often leads to DM, CVD, Kidney & Liver Diseases and Alzheimer's
- Reason: Increases in BP, Insulin Resistance, Inflammation, Oxidative Stress:
  All influence Brain function
- ***Uric Acid*** ***levels an important new tool and a key*** ***Independent Risk Factor***
  that, on its own, corresponds to injury or harm to the body

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Summary:
What is the Most Important Takeaway Message?*

<u>Nutrition matters & food is the most important asset</u>

- Poor, or suboptimal diet, is responsible for 1 in 5 global deaths
- *Results in* ***Uric Acid Dysregulation & Metabolic Dysfunction***
- ***Uric Acid now shown to be "Master Conductor" of chronic Disease***

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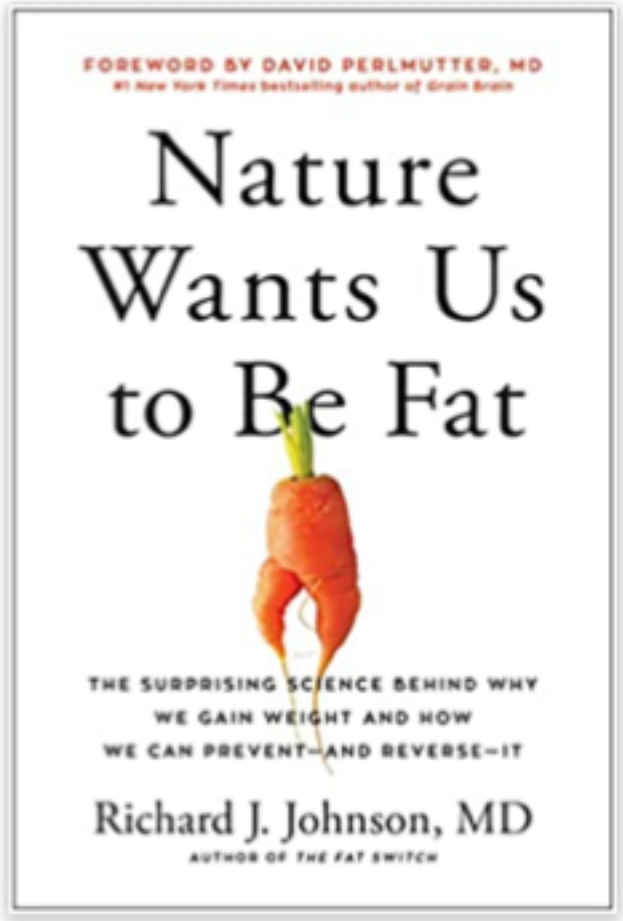
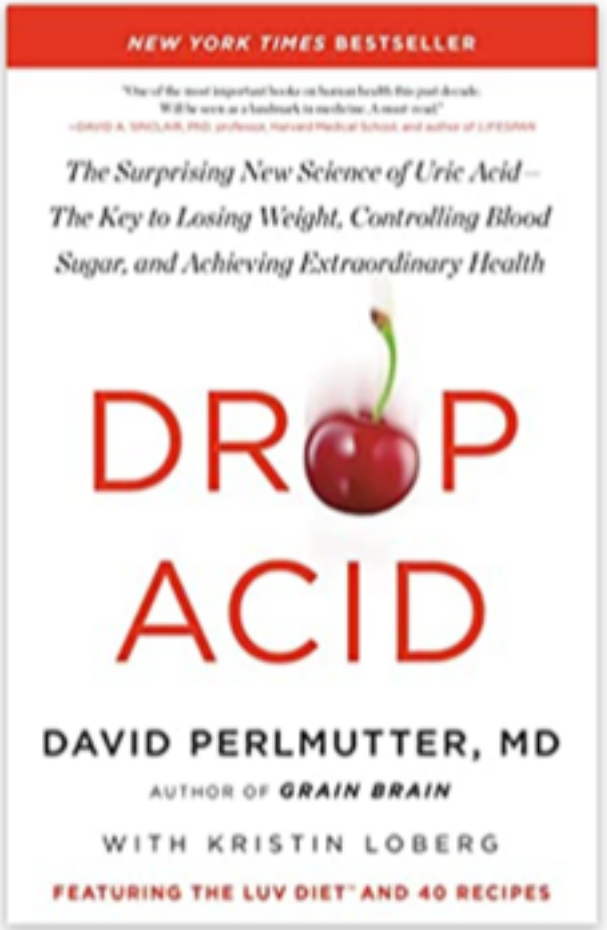
*adapted Perlmutter, 2022

Reading References





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Fructose, Uric Acid & Metabolic Dysfunction

Thank You

Dr Aron Gonshor: PhD, DDS, FRCD(C), FAO

June 1, 2022

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