

Treating Diabetes as One of Many Inflammatory Symptoms

A Native American Approach to Prevention



Presenter

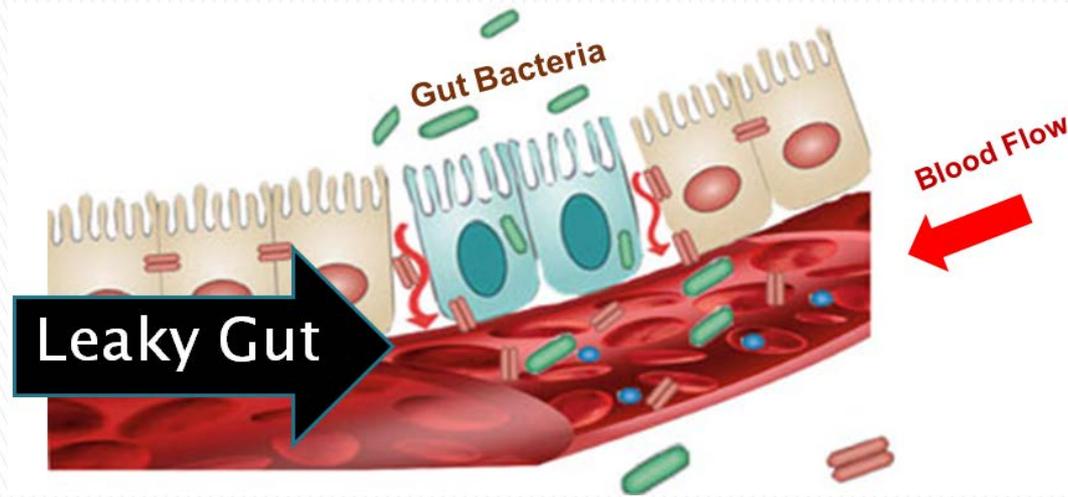
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Outline

- Increased inflammation in response to excessive endotoxin leaking from the gut and an unhealthy gut biome appears to promote diabetes, metabolic syndrome, obesity, alcoholism, and suicide.
- Many aspects of traditional Native American lifestyles reduce inflammation, including outdoor exercise and traditional foods.
- A Focused Approach on Inflammation:
 - Avoid fructose syrup sweetened drinks.
 - Avoid omega-6 fat – Promote omega-3.
 - Increase outdoor exercise/vitamin D.

Gut Bacteria give Endotoxin (LPS, Dead Bacteria Debris)



- Factors influence the leak of endotoxin from the gut into the circulation
- Circulating endotoxin causes an inflammatory reaction throughout the body that is signaled by cytokines.

Maes, Michael. "The cytokine hypothesis of depression: inflammation, oxidative & nitrosative stress (IO&NS) and leaky gut as new targets for adjunctive treatments in depression." *Neuro Endocrinol Lett* 29.3 (2008): 287–291.

Common Inflammatory Symptoms (CIS) Associate With Each Other

- Cirrhosis
- Alcoholism
- Suicide
- Diabetes
- Depression
- Impulsive Violence
- Cardio-Vascular Disease
- Metabolic Syndrome
- Obesity
- High Triglycerides
- NASH/NAFLD

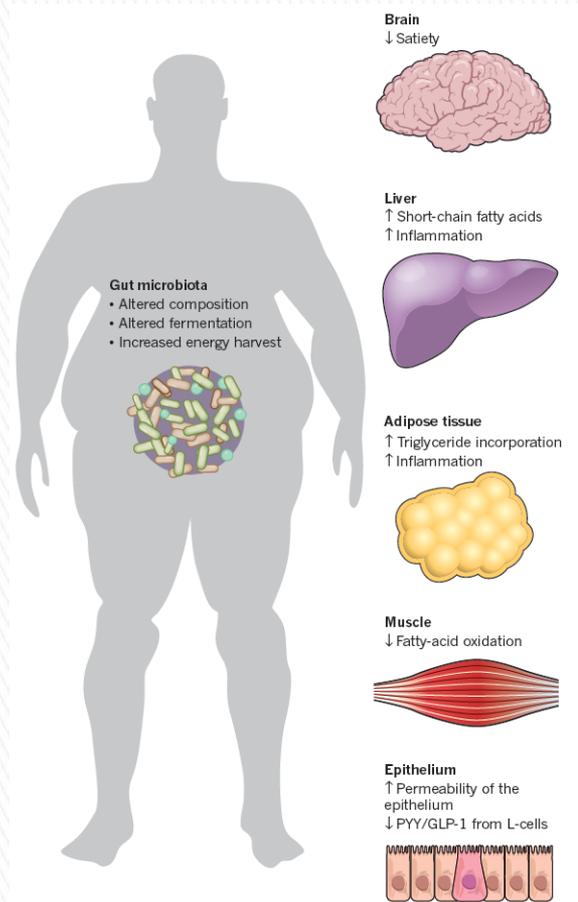
Is endotoxin the cause?

CIS Common Risk Factors

- Stress
- Smoking
- Excessive Fructose (e.g. HFC)
- Excessive Omega-6 – Lack of Omega-3 fat
- Sedentary Lifestyle
- Lack of Vitamin D (sun exposure)
- Excessive Alcohol
- Gingivitis

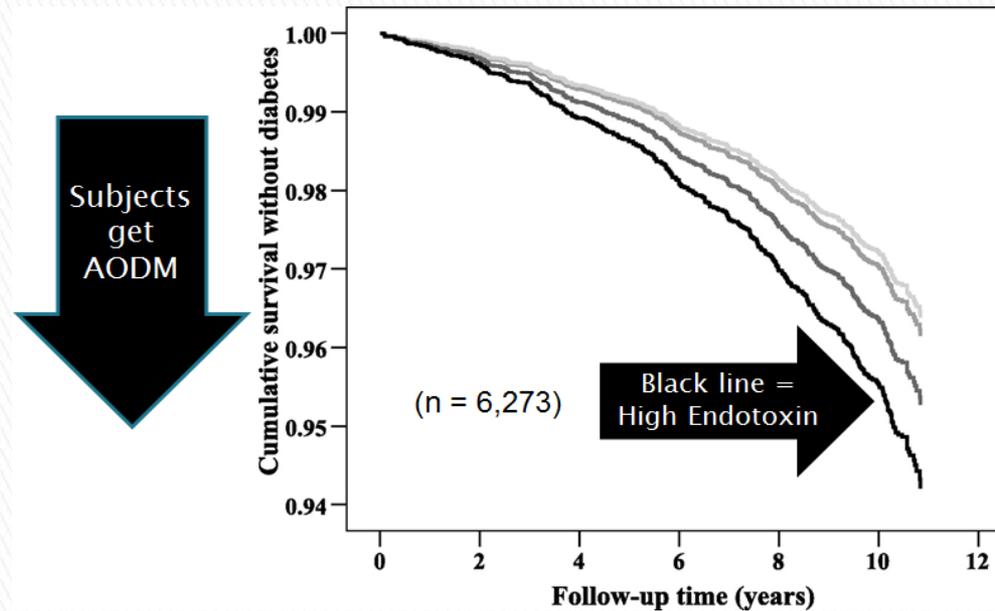
All increase the inflammatory effect of endotoxin.

Endotoxin



- Of the multiple features of the gut and microbiota which may promote CIS, endotoxin is the most studied
- To some extent, excessive endotoxin signaling has been associated with all of the diseases comprising CIS

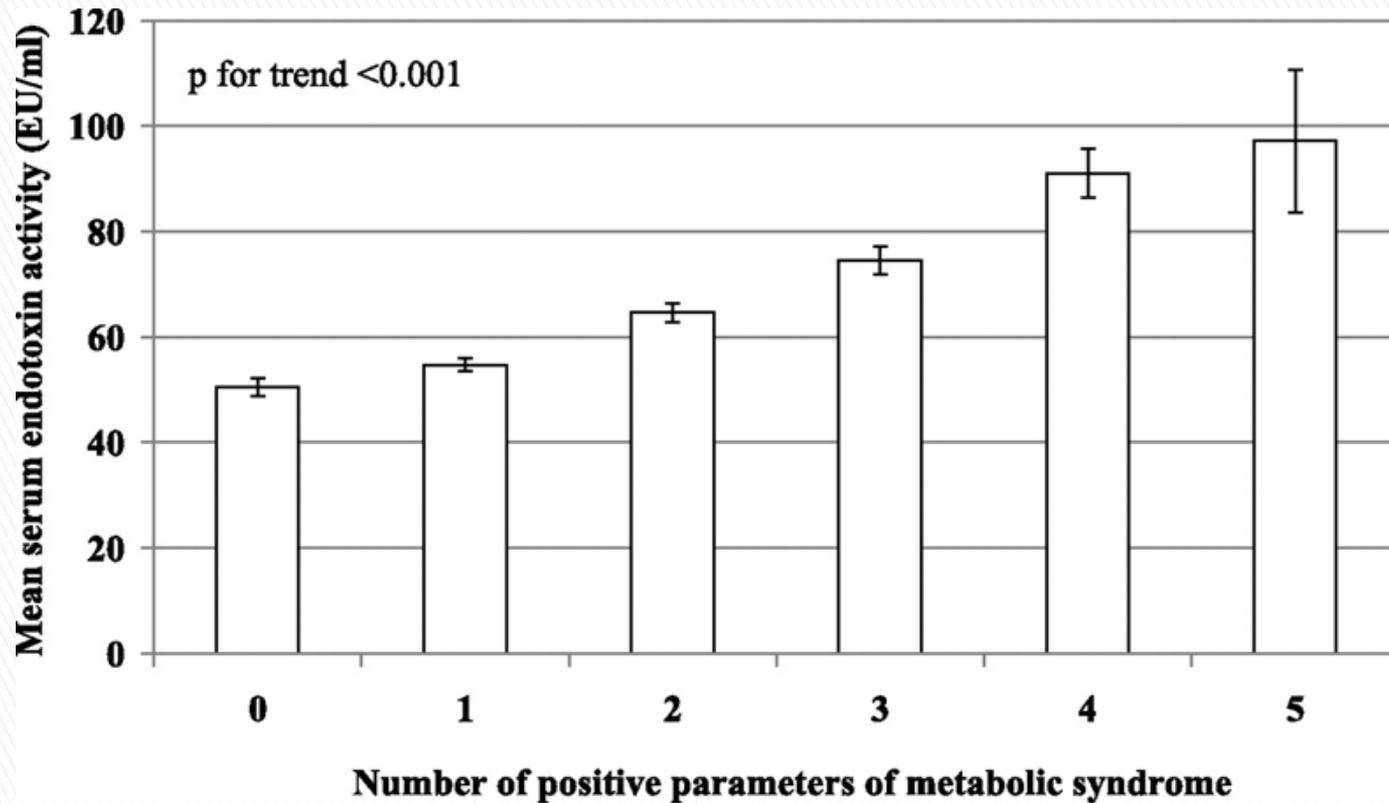
Diabetes Risk



- Subjects in Highest Quartile Group of Blood Endotoxin (Black Line) have Increased Risk of Developing Diabetes Within 10 Years.

Pussinen P J et al. Dia Care 2011;34:392–397.

Higher Blood Endotoxin at Baseline Predicts Metabolic Syndrome 10 Years Later



Pussinen P J et al. Dia Care 2011;34:392-397

Endotoxin Activates TLR4, Increasing Inflammatory Cytokines

- Cytokines = Soluble proteins and peptides which function as intercellular signaling molecules.
- Cytokines have diverse functions and can act synergistically or antagonistically.
- Cytokines are secreted by almost all nucleated cells, e.g. IL-1, IL-6, and TNF- α .
- Cytokines can induce inflammation throughout the body, including the brain – e.g. can reduce serotonin levels and activate microglia.

Raison et al. “Cytokines sing the blues.” *TRENDS in Immunology*
Vol.27 No.1 January 2006

Inflammatory Cytokines Drive the Symptoms of Sickness and CIS

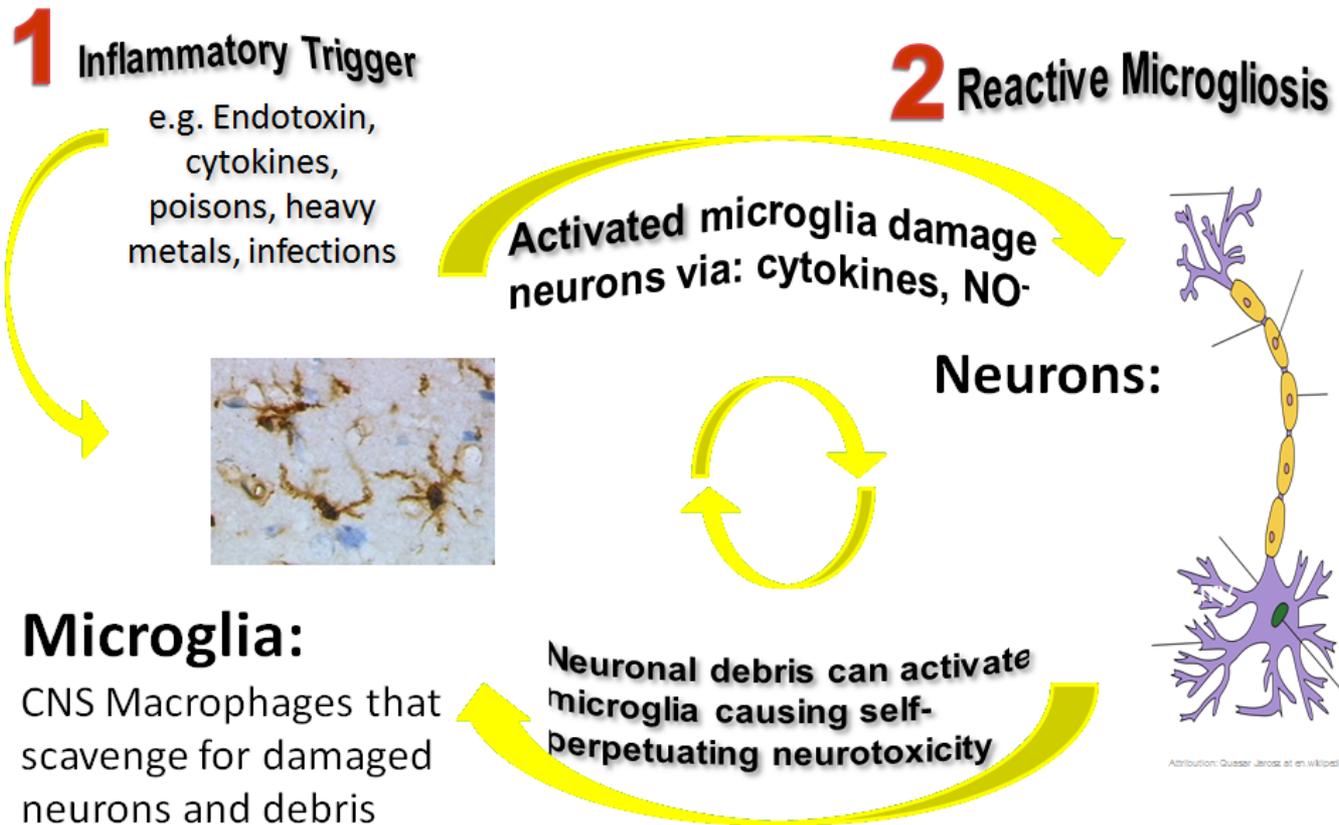
- Fever
 - Fatigue/Malaise
 - Social withdrawal
 - Suppression of appetite and libido
 - Sleep disturbances
 - Amplification of pain
 - Irritability
 - Decreased social interaction
 - Increased anxiety
 - Anhedonia
 - Poor Concentration
 - Dysphoria
-
- Symptoms correlate with peripheral IL-6
 - Acute alcohol transiently reduces IL-6 !

Inflammatory Cytokines Have a Key Role in Mood Disorders

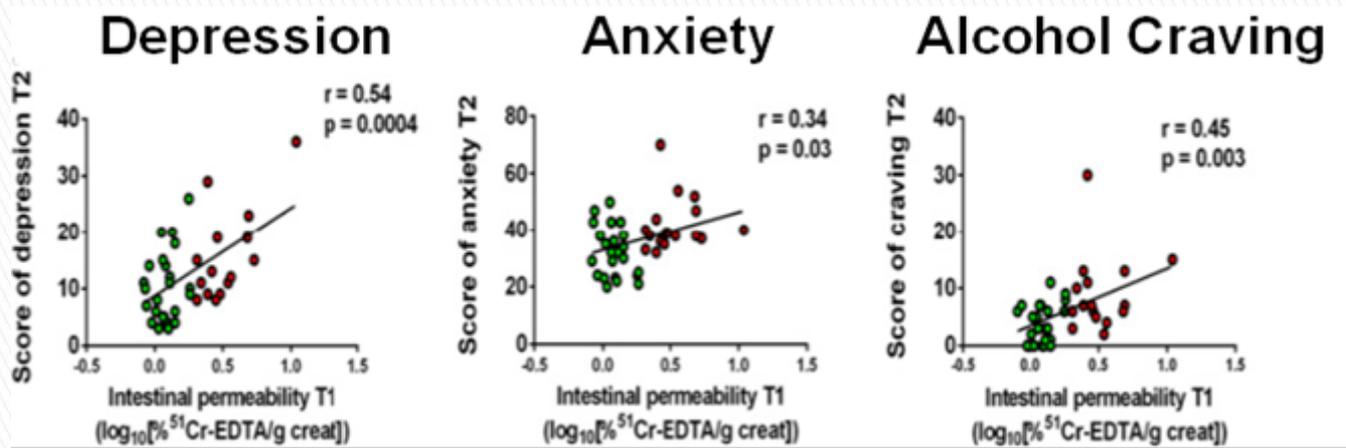
- Depression may be the body's attempt to redirect energy to fight infection
- Depression can be induced by cytokines and reduced by cytokine blocker drugs
- Neurotransmitters, e.g. Serotonin, can be modulated by cytokine activity
- Symptoms of depression correlate with levels of cytokines in the blood & brain

Maes, Michael. "The cytokine hypothesis of depression: inflammation, oxidative & nitrosative stress (IO&NS) and leaky gut as new targets for adjunctive treatments in depression." *Neuro Endocrinol Lett* 29.3 (2008): 287–291.

Cytokines Promote Neurodegeneration



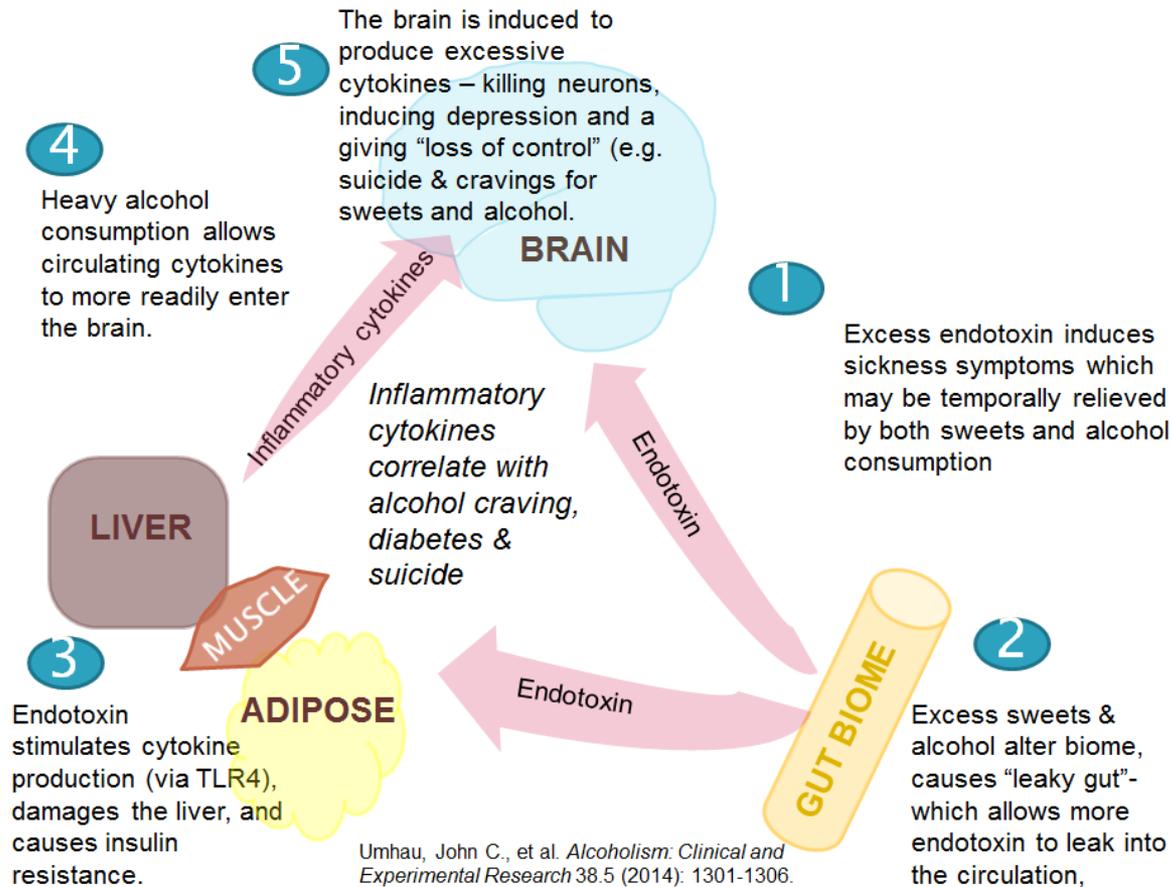
In Alcoholism



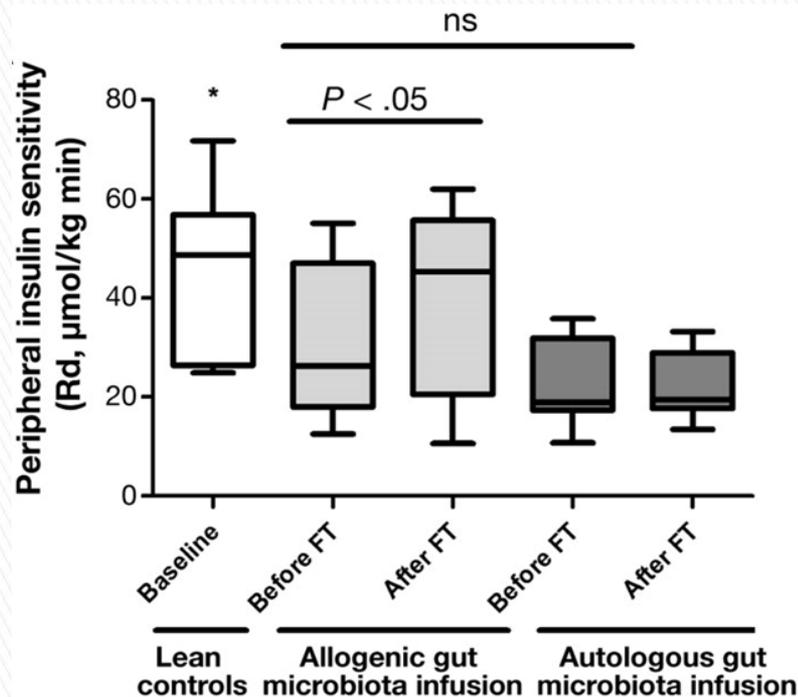
- More Gut Permeability
 - More Endotoxin
 - More Cytokines
 - More Symptoms
- More Reasons to Drink

Leclercq, Sophie, et al. "Role of intestinal permeability and inflammation in the biological and behavioral control of alcohol-dependent subjects." *Brain, behavior, and immunity* 26.6 (2012): 911–918.; Leclercq, Sophie, et al. "Intestinal permeability, gut-bacterial dysbiosis, and behavioral markers of alcohol-dependence severity." *Proceedings of the National Academy of Sciences* 111.42 (2014): E4485–E4493.

Excess Endotoxin Appears to be the Universal Causal Feature of CIS



“Transplant” of Gut Microbes from Lean Donors Restores Insulin Sensitivity in Metabolic Syndrome



- Replacement with “normal” gut microbiota restores normal insulin response.

Transfer of Intestinal Microbiota From Lean Donors Increases Insulin Sensitivity in Individuals With Metabolic Syndrome Anne Vrieze, et al..Gastroenterology Volume 143, Issue 4, Pages 913–916.e7 (October 2012)

The Body Interacts with Gut Microbes:

- Microbes may alter taste & change appetite.
- Microbes have genes for human neurotransmitters.
- Microbes may release toxins in absence of nutrients.
- Bacterial toxins may depress mood.
- Microbes may modulate dietary or host derived compounds that alter host metabolic pathways.
- Microbes alter cannabinoid and opioid receptors.
- Microbes may increase energy yield from food.

Alcock, Joe, Carlo C. Maley, and C. Aktipis. "Is eating behavior manipulated by the gastrointestinal microbiota? Evolutionary pressures and potential mechanisms." *Bioessays* 36.10 (2014): 940–949.

Determinants of Gut Microbiome

- Diet:
 - Type of fat?
 - Amount of fiber?
 - Type of carbohydrate?
 - Raw/processed/cooked?
 - Amount of alcohol
- Antibiotics
- Host Genotype
- Host Phenotype
- Age & Gender
- Environment
- Drugs
- Psychological Stress

Gut microbiome influences gut permeability, systemic endotoxin and inflammatory cytokines.

Therefore:

- The diet can no longer be thought of as only a source of nutrients for human cells!
- The critical function of the diet is to promote a healthy gut microbiome.

Alleviating CIS

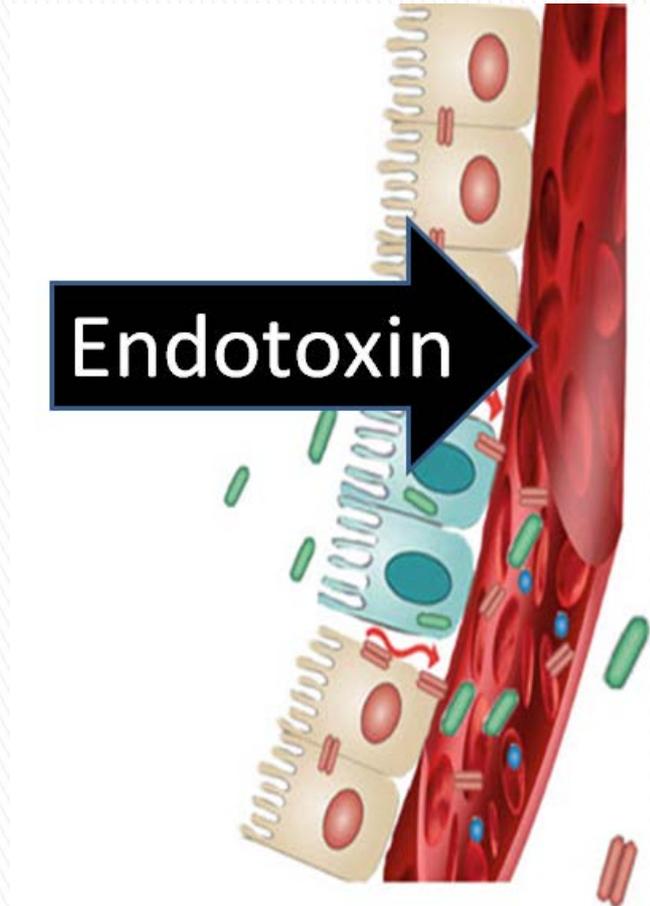
- Alcoholism, CVD, Diabetes, Obesity, may all be alleviated with:
 - Prebiotics: Non-digestible fiber compounds that may change microbiota composition and/or activity conferring benefits upon the host (e.g., fructooligosaccharides)
 - Probiotics: Live microorganisms which, when administered in adequate amounts confer a health benefit on the host

Traditional Lifestyles

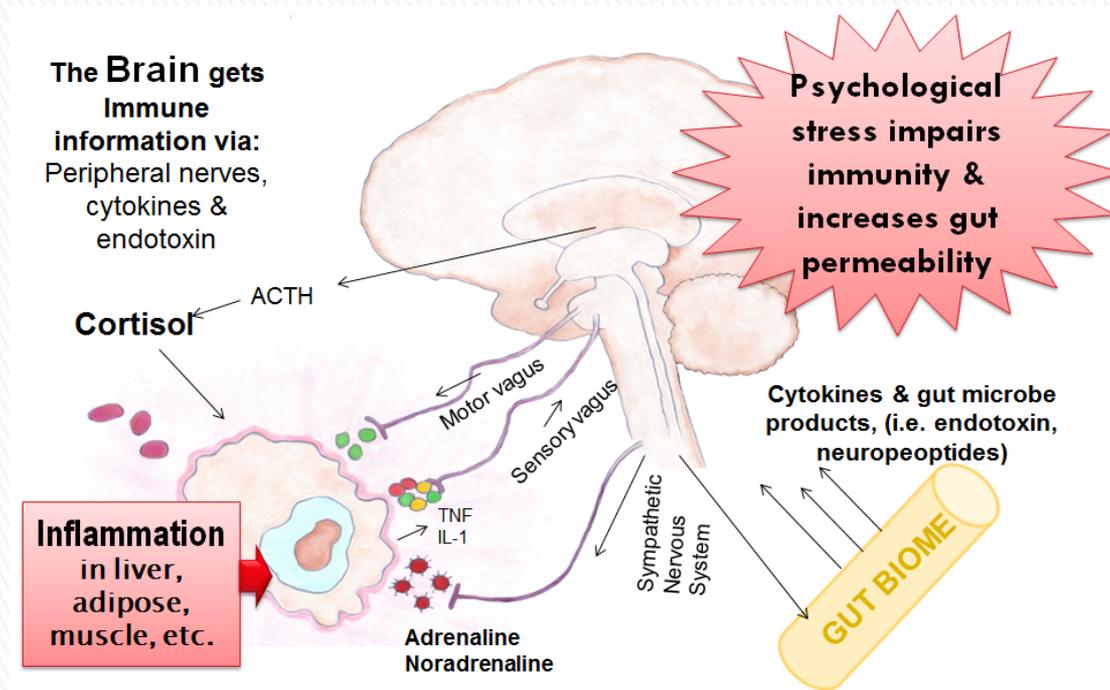
- Did a traditional lifestyle minimize inflammation due to endotoxin produced in the gut?
 - Psychological health
 - Minimal alcohol exposure
 - Physical activity
 - Outdoor living – (Vitamin D)
 - Traditional sources of dietary fat and carbohydrate

Psychological Health

- Childhood stress /Historical Trauma may cause life long epigenetic changes in gene expression which alter the inflammatory response
- Stress also increases gut permeability.



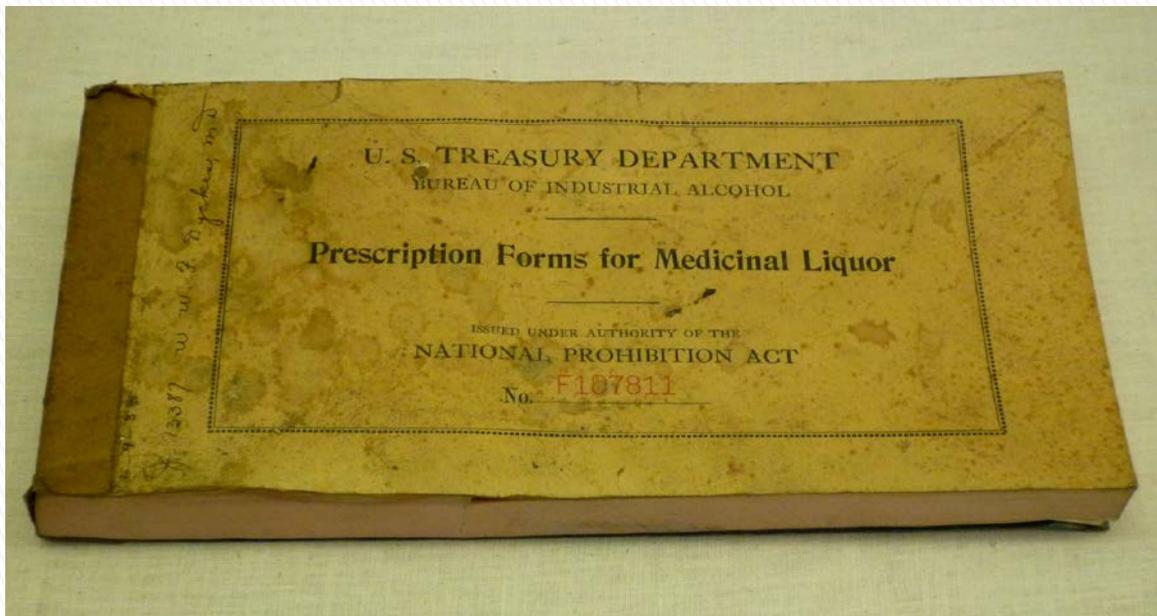
The Inflammatory Reflex



SWU 2013, Adapted by permission from Macmillan publishers Ltd., [Nature] Tracey, The Inflammatory Reflex, Volume 420, 12-19-2002.

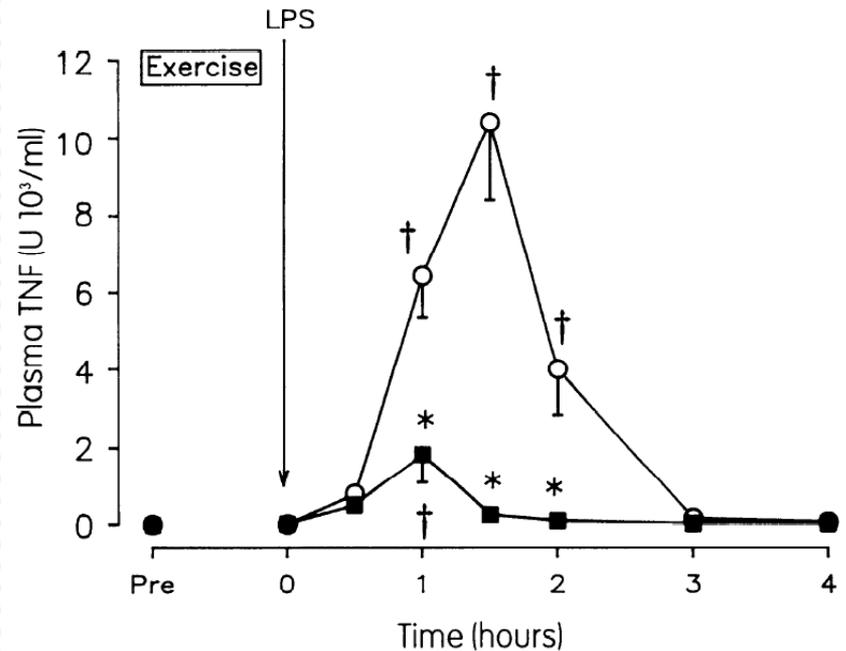
Minimal Alcohol Exposure

- Excessive alcohol increases inflammation.
- Moderate alcohol reduces inflammation.
 - Was used medicinally to treat “sickness.”



Physical Activity

- Exercise reduces the inflammation caused by endotoxin.

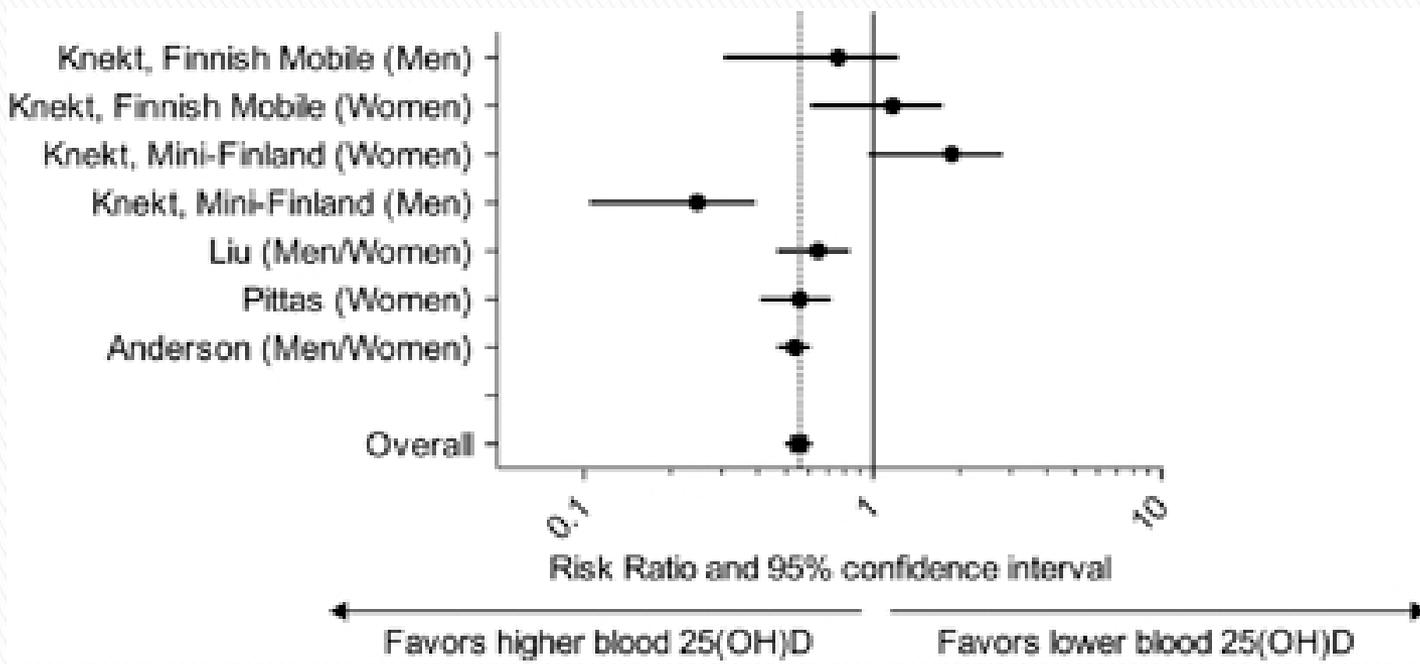


“Prior exercise suppresses the plasma tumor necrosis factor response to bacterial lipopolysaccharide,” Bagby, G. J. et. al., J Appl Physiol 77:1542–1547, 1994

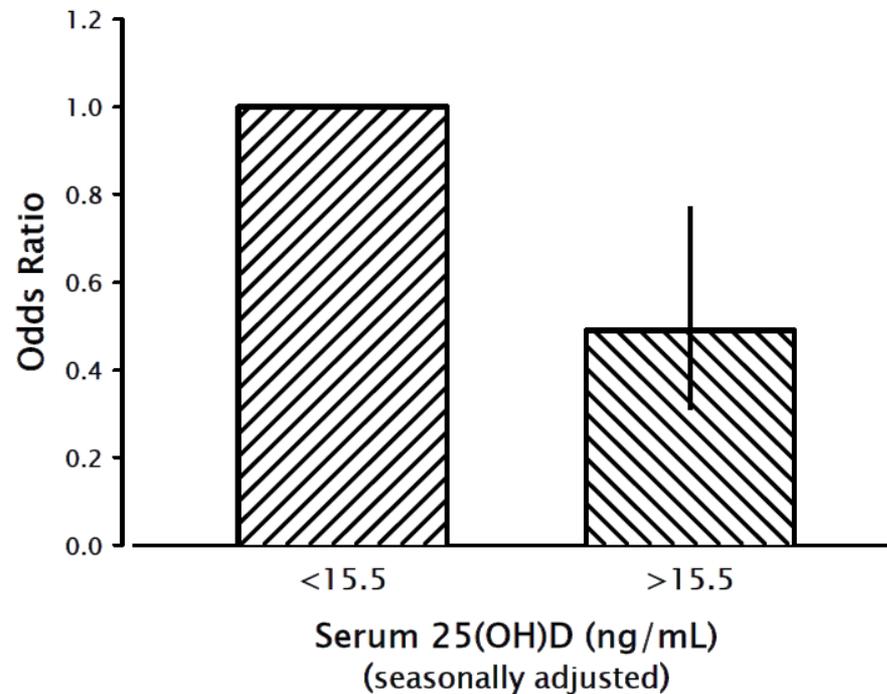
Outdoor Living – (Vitamin D)

- Baseline blood 25(OH)D levels predict the incidence of type 2 diabetes.

Mitri, J., M. D. Muraru, and A. G. Pittas. "Vitamin D and type 2 diabetes: a systematic review." *European journal of clinical nutrition* 65.9 (2011): 1005–1015.

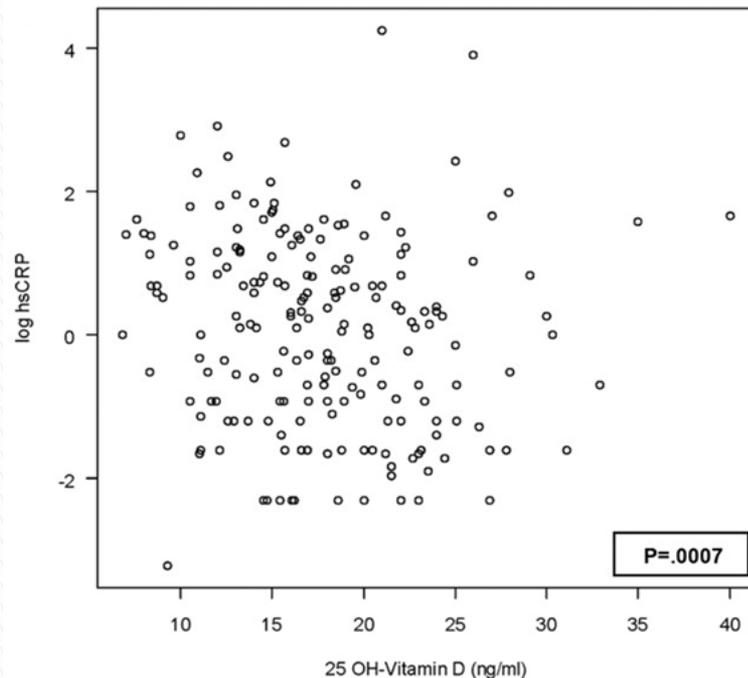


Low Vitamin D Levels Associated with ~Twice the Risk of Suicide



Umhau JC, George, DT., Heaney, RP.... & Schwandt, ML. Low Vitamin D Status and Suicide: A Case-Control Study of Active Duty Military Service Members. PloS one, 2013, 8(1), e51543.

Vitamin D Deficiency in Native American Children



- Vitamin D deficiency is common in Native American children, and correlates with CRP, a marker of inflammation.
- Low levels of Vitamin D increase suicide risk.

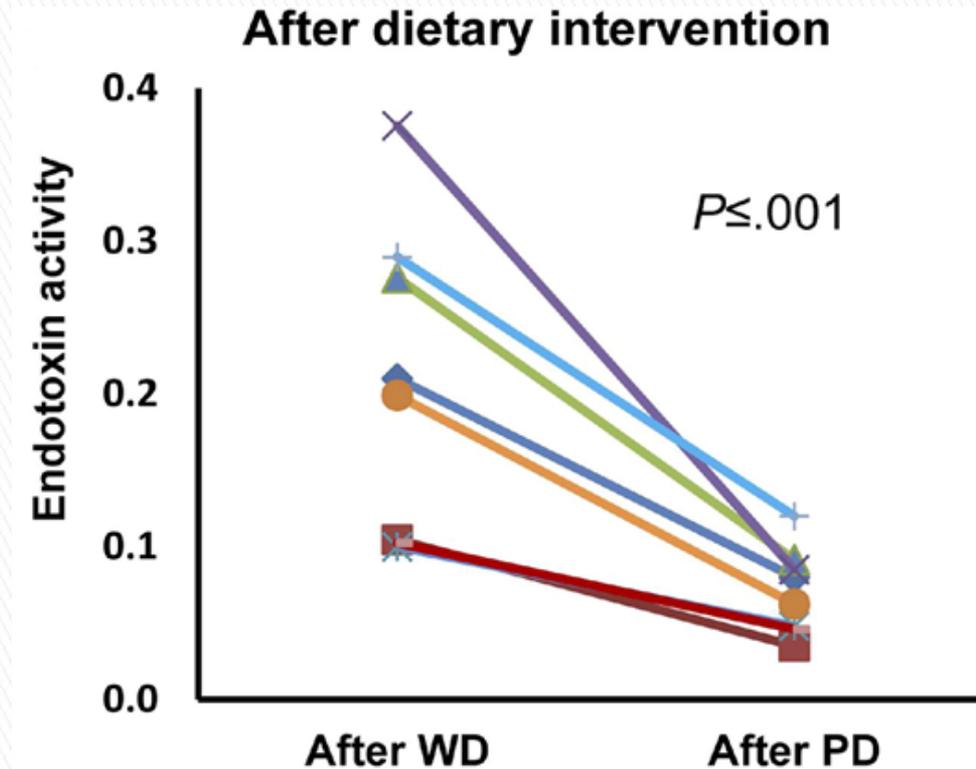
Vitamin D Insufficiency is Associated With Diabetes Risk in Native American Children; Nsiah-Kumi P A et al. CLIN PEDIATR 2011;51:146-153

Traditional Sources of Dietary Fat and Carbohydrate

Did a diet of wild game and the “three sisters” minimize inflammation due to endotoxin produced in the gut?

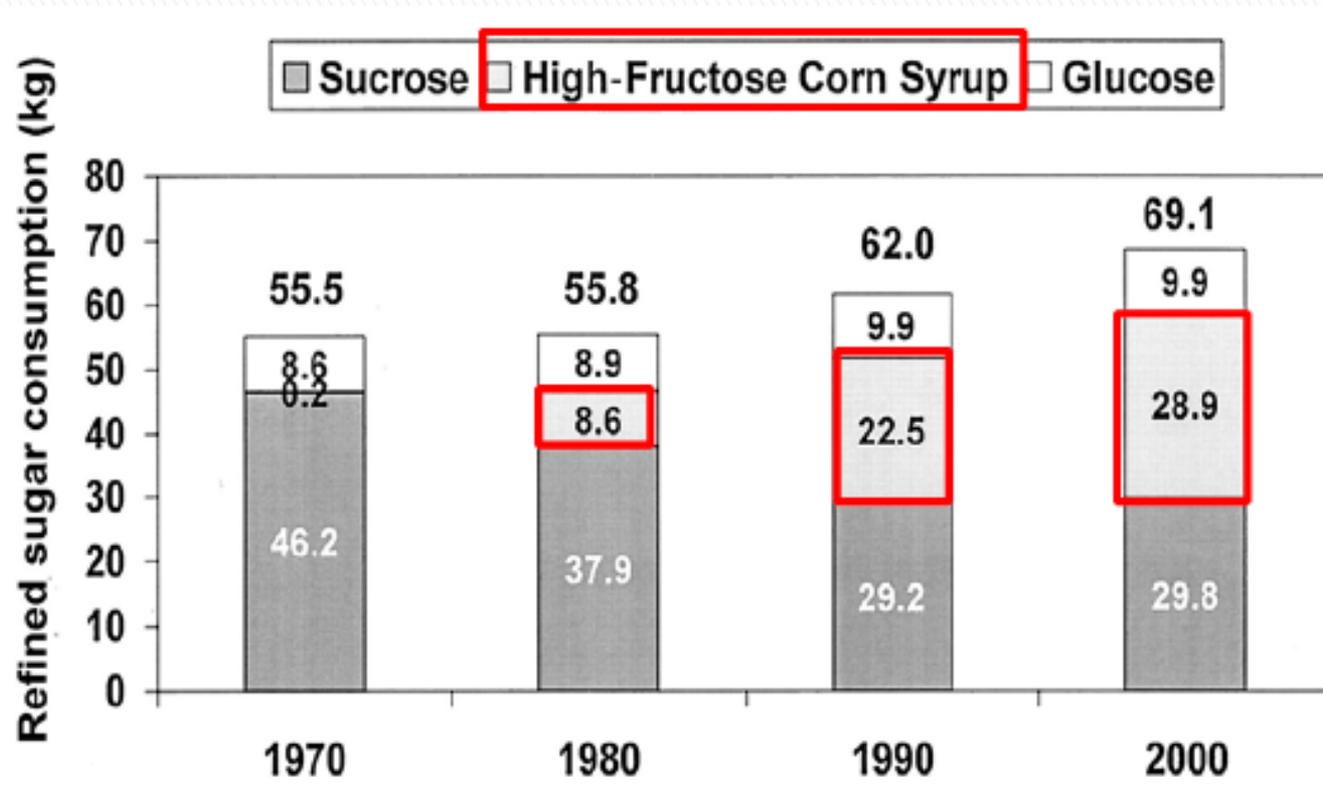


A Prudent Diet (PD, high fiber) gives less Blood Endotoxin than a Western Diet (WD)



Swaroop Pendyala, Jeanne M. Walker, Peter R. Holt Gastroenterology Volume 142, Issue 5, Pages 1100-1101.e2 (May 2012)

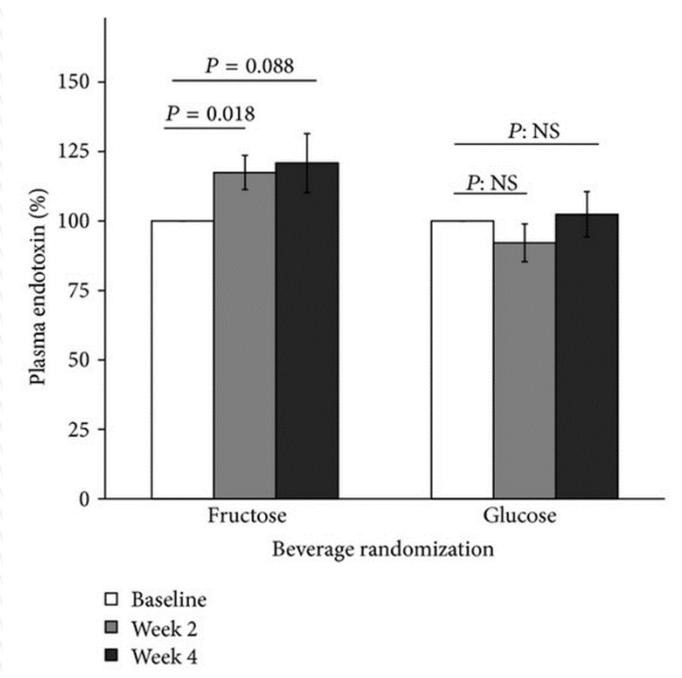
High Fructose Corn Syrup: a Major Source of Calories in Modern Diets



Cordain L et al. Am J Clin Nutr 2005;81:341-354, Adapted from the US Department of Agriculture, Irina Kirpich

Fructose Drinks Raise Endotoxin

Percentage change of plasma endotoxin level in adolescents with NAFLD after 2- and 4-week ingestion of study-provided fructose or glucose-only beverages. Baseline values were set as reference (100%). Error bars stand for SE.



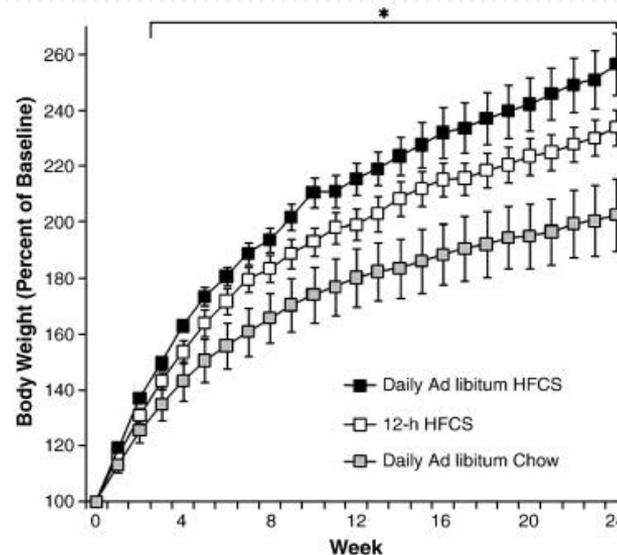
Int J Hepatol. 2014; 2014: 560620. Published online 2014 Sep 28. doi: 10.1155/2014/560620; Fructose ingestion is associated with intestinal bacterial dysbiosis and increased gut permeability. Yilmaz, Y. Aliment Pharmacol Ther. 2012; 35: 1135-1144

High Fructose Corn Syrup Sweetened Soft Drinks – Associated With:

- Obesity
- Depression
- Metabolic Syndrome
- Adult Onset Diabetes
- Non-Alcoholic Fatty Liver Disease
- Aggression and suicidal behavior in high school students

Int J Inj Contr Saf Promot. 2013 Jul 8. Soft drinks, aggression and suicidal behaviour in US high school students. Solnick SJ, Hemenway D. Tappy, Luc, and Kim-Anne Lê. "Metabolic effects of fructose and the worldwide increase in obesity." *Physiological reviews* 90.1 (2010): 23–46. De Koning, Lawrence, et al. "Sugar-sweetened and artificially sweetened beverage consumption and risk of type 2 diabetes in men." *The American journal of clinical nutrition* 93.6 (2011): 1321–1327. ; Nseir, William, Fares Nassar, and Nimer Assy. "Soft drinks consumption and nonalcoholic fatty liver disease." *World journal of gastroenterology: WJG* 16.21 (2010): 2579. ; Shi, Zumin, et al. "Soft drink consumption and mental health problems among adults in Australia." *Public health nutrition* 13.07 (2010): 1073–1079.; Dhingra, Ravi, et al. "Soft drink consumption and risk of developing cardiometabolic risk factors and the metabolic syndrome in middle-aged adults in the community." *Circulation* 116.5 (2007): 480–488.

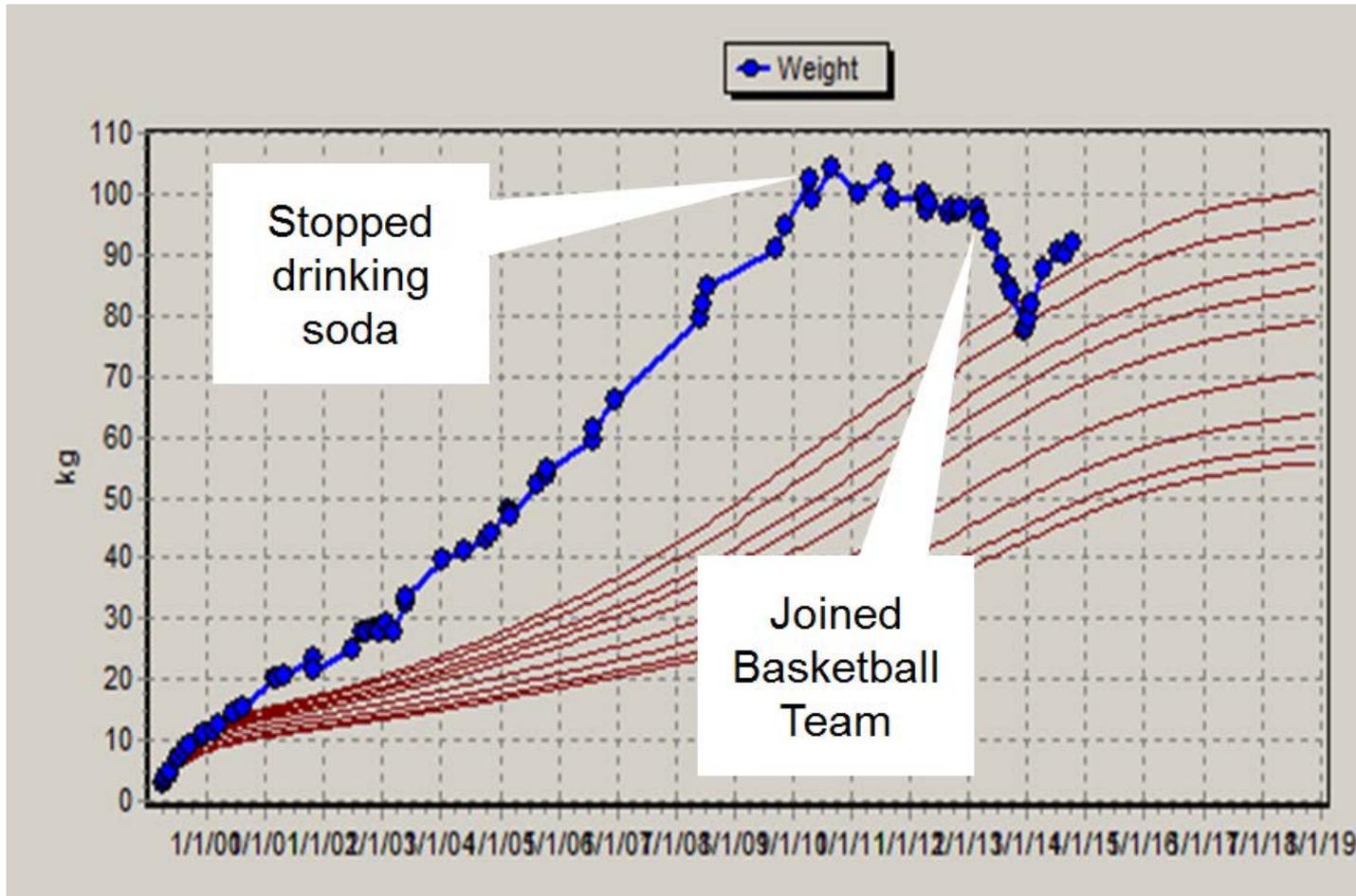
High Fructose Corn Syrup Causes Leaky Gut and Altered Biome, Giving Obesity and Liver Inflammation



- But Coffee is anti-inflammatory and reduces the risk of suicide and AODM.

Miriam E. Bocarsly, Elyse S. Powell, Nicole M. Avena, Bartley G. Hoebel, High-fructose corn syrup causes characteristics of obesity in rats: Increased body weight, body fat and triglyceride levels, *Pharmacology Biochemistry and Behavior*, Volume 97, Issue 1, November 2010, Pages 101–106, Yilmaz, Y. *Aliment Pharmacol Ther.* 2012; 35: 1135–1144

Successful Intervention with a 15 Year Old Boy



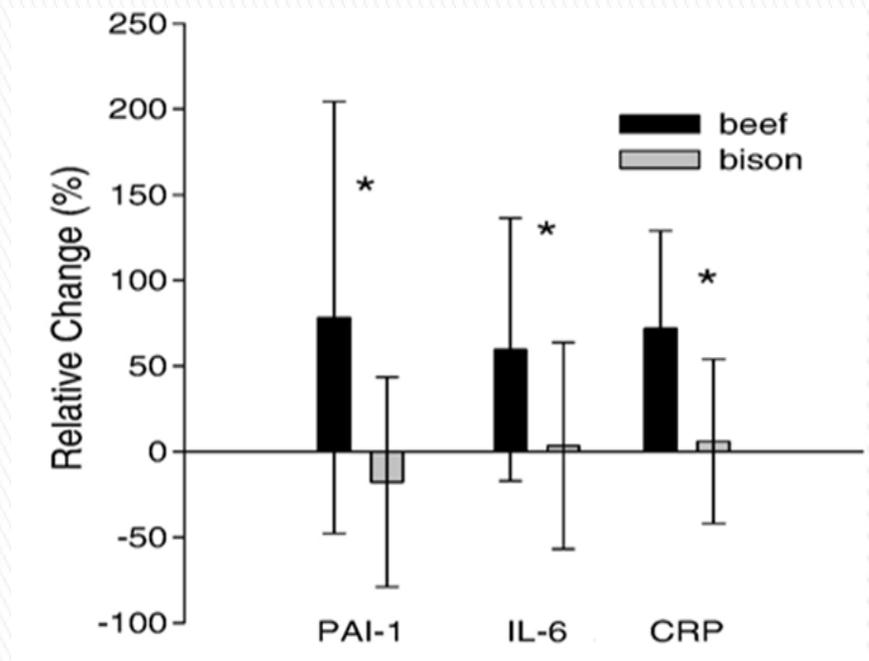
Traditional Native American Diets

- Included omega-3 fat from fish and wild game.



Traditional Diets Contained Healthy Fat

- A seven-week Bison diet reduced inflammatory markers (IL-6, CRP)



John McDaniel et al. Bison meat has a lower atherogenic risk than beef in healthy men
Nutrition Research 2013

Liver Inflammation in Alcoholism is Influenced by the Type of Dietary Fat

- **GOOD:**
 - Saturated fat
 - Lard (from game)
 - Butter
 - Coconut oil
- **BAD:**
 - Polyunsaturated fat (Linoleic Acid – Omega 6)
 - Corn oil
 - Soybean oil
 - Safflower oil
 - Peanut oil

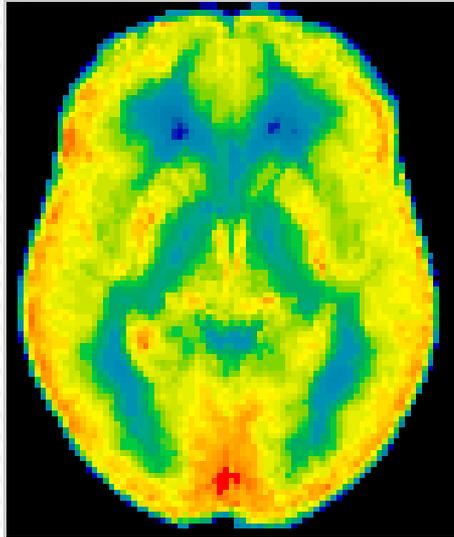
Kirpich, Irina A., et al. "The Type of Dietary Fat Modulates Intestinal Tight Junction Integrity, Gut Permeability, and Hepatic Toll-Like Receptor Expression in a Mouse Model of Alcoholic Liver Disease." *Alcoholism: Clinical and Experimental Research* 36.5 (2012): 835–846.

Polyunsaturated fats include omega-6 and omega-3 fatty acids

- The American = a high omega-6 fat diet
- Omega-3 & 6 fats are similar long molecules, but can not be inter-converted
- Like vitamins, omega-3 & 6 fats are essential.
- Dietary omega 3 & 6 are important for signaling molecules like prostaglandins.
- Stored in all our fat & tissue membranes.

Umhau, John C., and Karl M. Dauphinais. "Omega-3 polyunsaturated fatty acids and health." *Low-Cost Approaches to Promote Physical and Mental Health*. Springer New York, 2007. 87-101.;

The Effect of Diet Lasts for Years



PET scan image of C¹¹
DHA uptake in the
human brain.

Umhau et al. PloS One, 2013

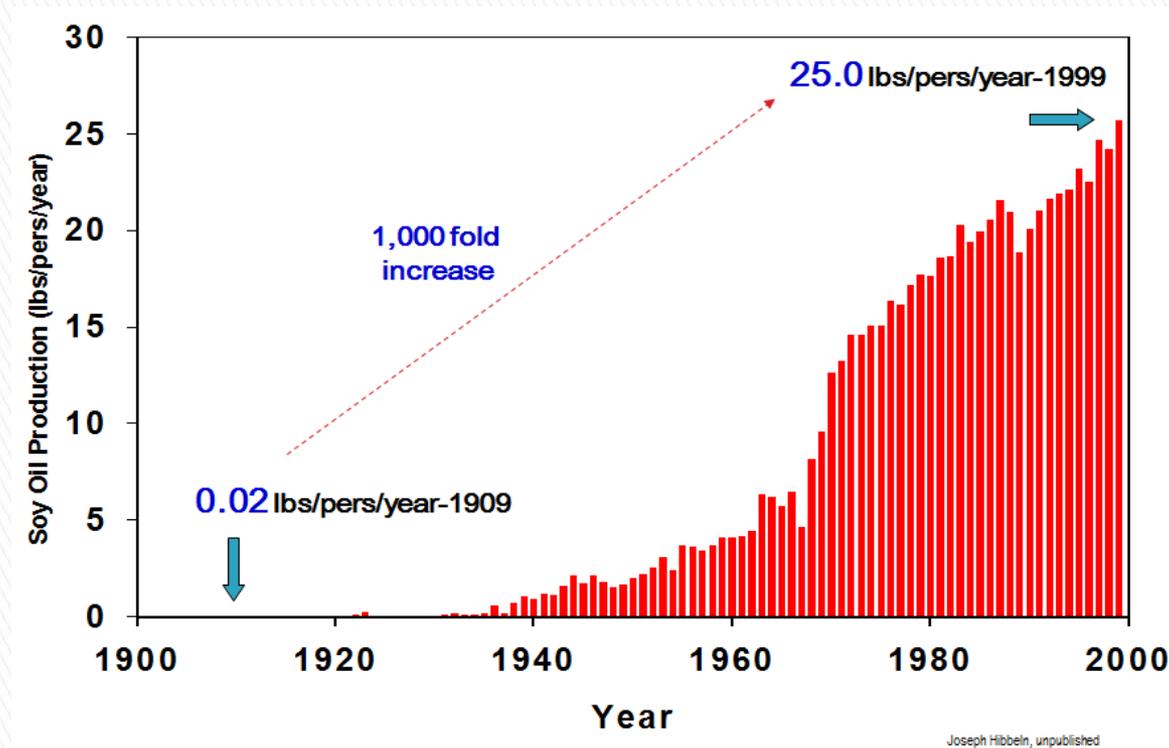
Omega-3 fat (DHA) is stored in all membranes: half
life = 2.5 years

Dietary Omega-6 Fatty acid content influences health

- Polyunsaturated Omega-6 fatty acids may promote cardiovascular disease, and death
- Excessive omega-6 fat can promote many inflammation related disorders
- The modern American diet is abundant in omega-6 fat, present in oil from corn, peanuts, and soy as well as in poultry, beef, and pork fattened on these commodities.

Blasbalg, Tanya L., et al. "Changes in consumption of omega-3 and omega-6 fatty acids in the United States during the 20th century." *The American journal of clinical nutrition* 93.5 (2011): 950-962. Ramsden, Christopher E., et al. *Bmj* 346 (2013): e8707.

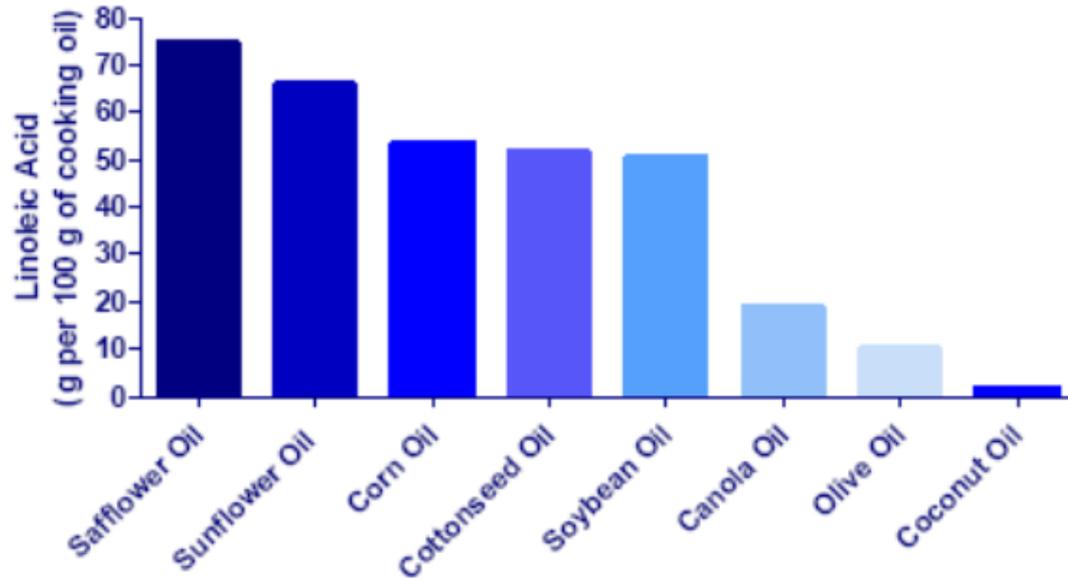
Soy Oil Production 1909–1999



Blasbalg, Tanya L., et al. "Changes in consumption of omega-3 and omega-6 fatty acids in the United States during the 20th century." *The American journal of clinical nutrition* 93.5 (2011): 950–962.

The Major Omega-6 Fatty Acid in Western Diet is Linoleic Acid

- Has increased with modern agriculture and has pro-inflammatory metabolites.



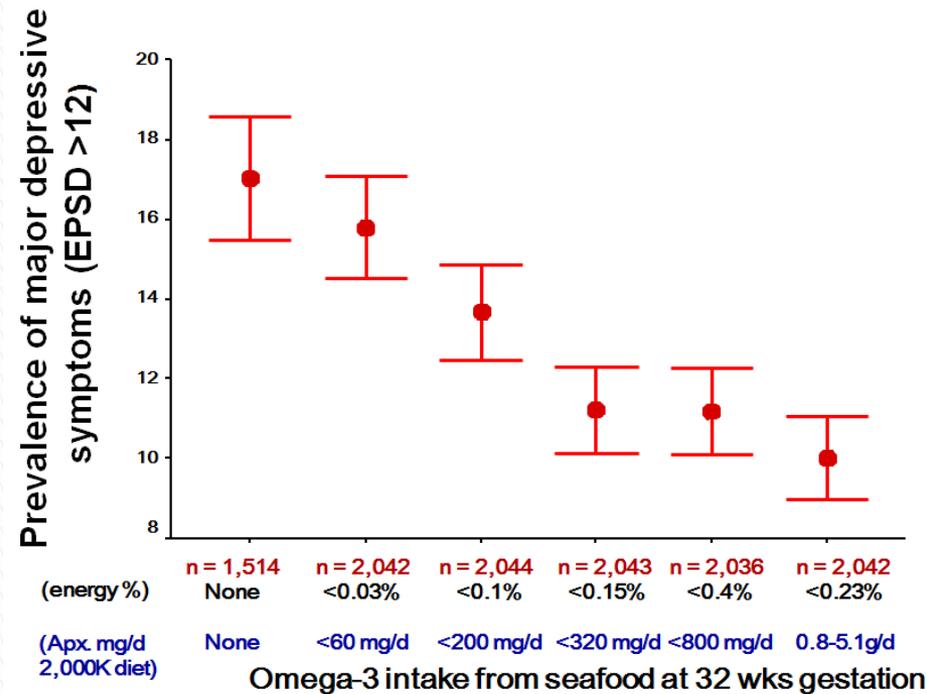
Blasbalg T L et al. Am J Clin Nutr 2011;93:950-962
Cordain L et al. Am J Clin Nutr 2005;81:341-354, Gerrior S,
Bente L. Nutrient content of the U.S. food supply, 1909-99: a
summary report

Dietary Omega-3 Fatty acid influences health

- Although once abundant in our diet, omega-3 is often limited to seafood or mother's milk, also in walnuts, leafy plants
- Omega-3 fat reduces inflammation & cytokines
- Omega-3 fat is critical for brain function
- Multiple studies suggest that omega-3 fat can improve mood and cognitive function, reduce cardiovascular disease, stroke, arthritis etc.

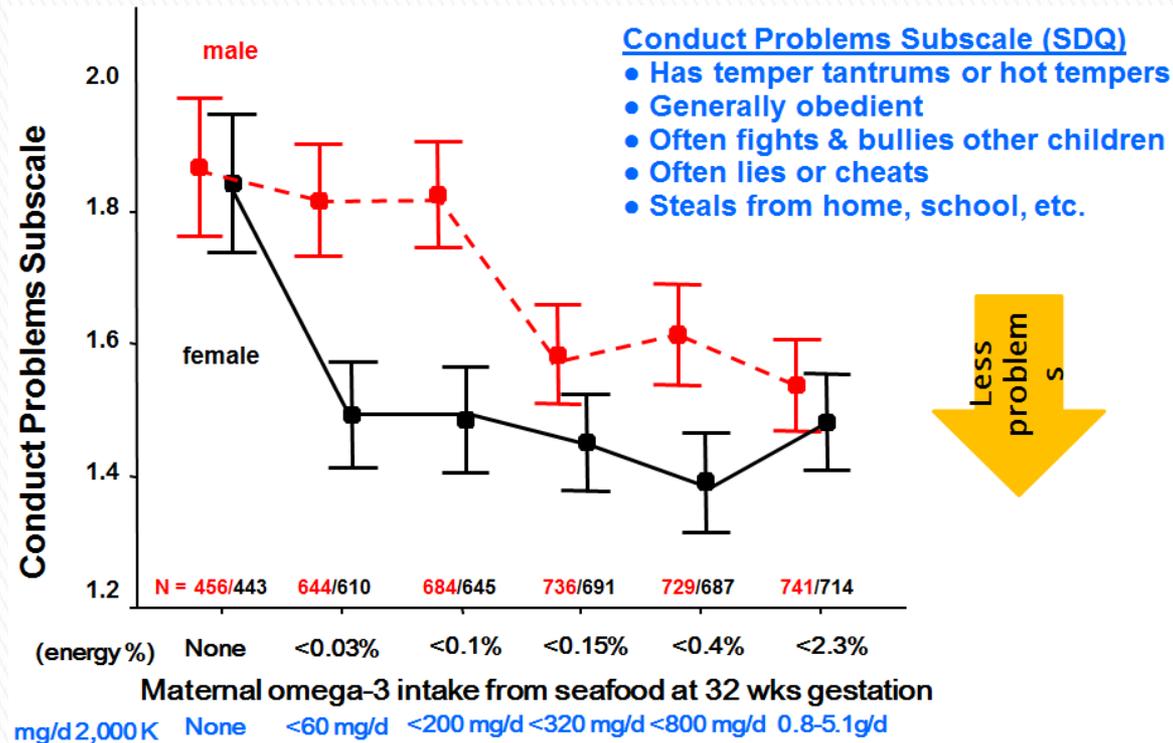
Umhau, John C., and Karl M. Dauphinais. "Omega-3 polyunsaturated fatty acids and health." *Low-Cost Approaches to Promote Physical and Mental Health*. Springer New York, 2007. 87-101.; Mori, Trevor A., and Lawrence J. Beilin. "Omega-3 fatty acids and inflammation." *Current atherosclerosis reports* 6.6 (2004): 461-467.

Maternal Intake of Fish During Pregnancy and Prevalence of Major Depressive Symptoms



Golding, Jean, et al. "High levels of depressive symptoms in pregnancy with low omega-3 fatty acid intake from fish." *Epidemiology* 20.4 (2009): 598-603.

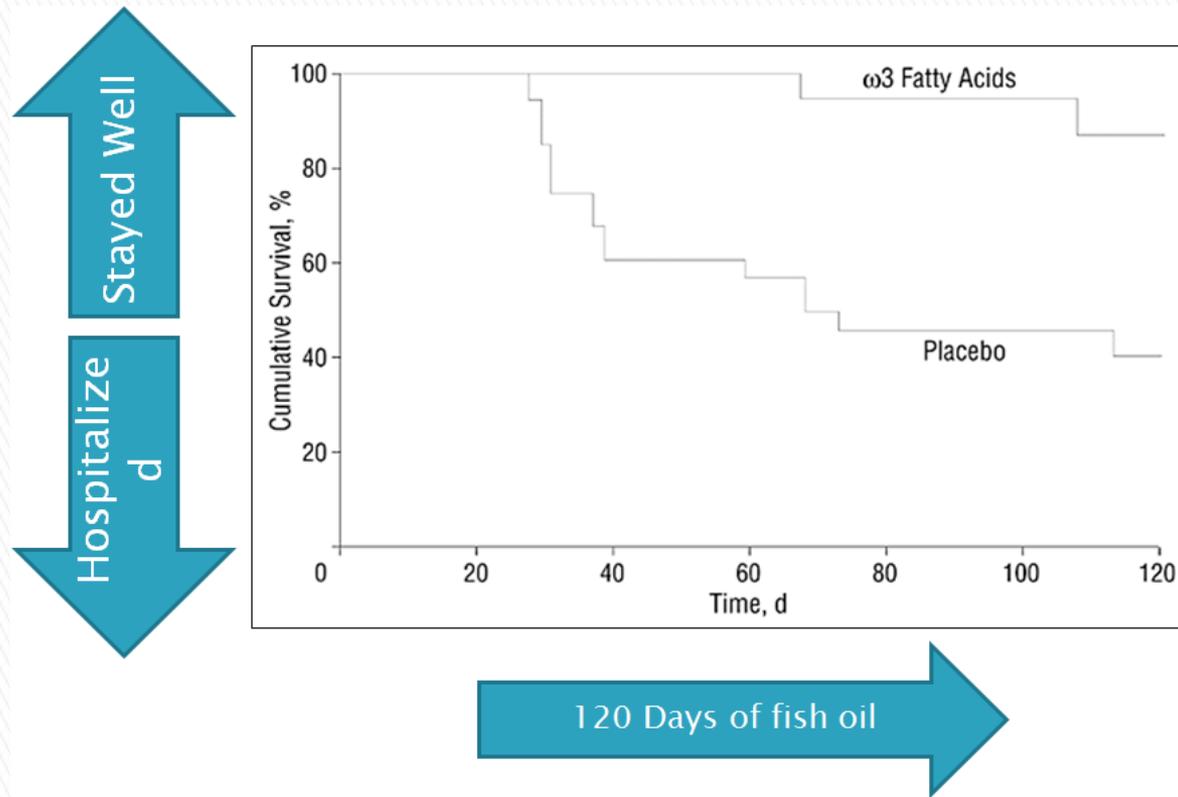
Eating Less Fish During Pregnancy Increases Conduct Disorder Symptoms in Children at 7 Years of Age



Hibbeln, Joseph R., et al. "Maternal seafood consumption in pregnancy and neurodevelopmental outcomes in childhood (ALSPAC study): an observational cohort study." *The Lancet* 369.9561 (2007): 578–585.

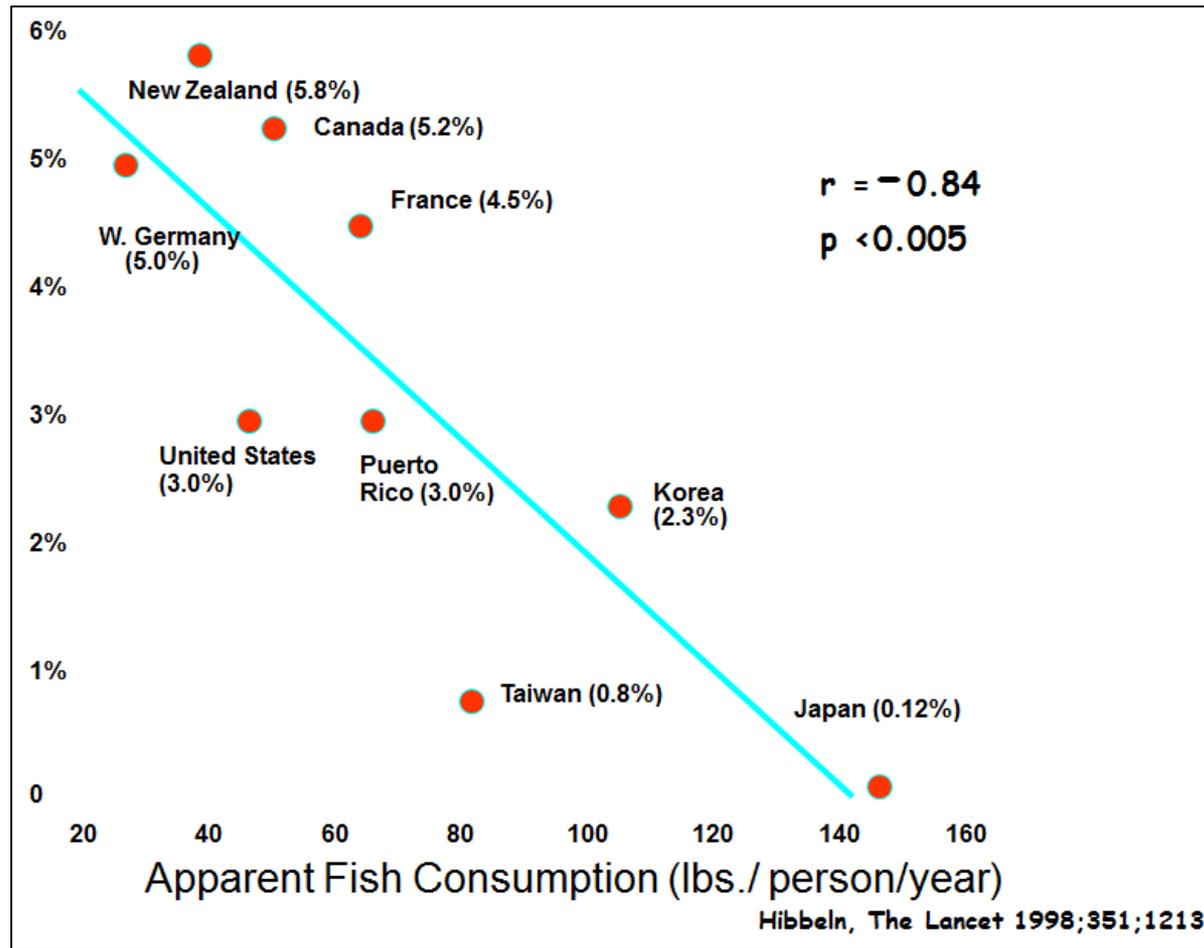


Bipolar Subjects Received 14 Capsules Daily, Either Placebo or Fish Oil (6.2 g EPA & 3.4 g DHA)



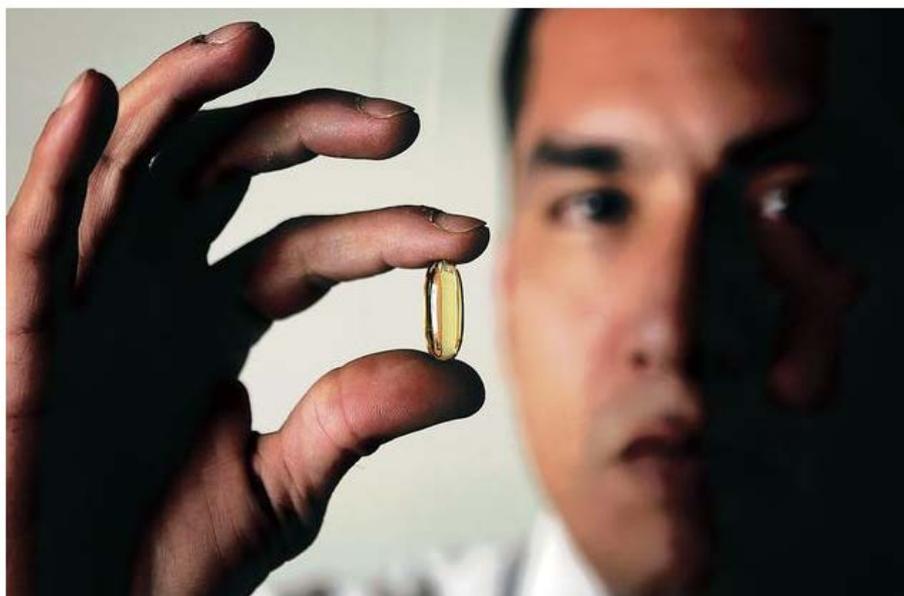
Stoll, A. L. et al. Arch Gen Psychiatry 1999;56:407-412.

Major Depression, Annual Prevalence, (rate per 100 Persons)



Fish oil Unhooks Meth Head – Ex-addict Says it Cleared his Addled Mind

Arizona Daily Star
www.dailystar.com @www.azstar.net.com



By Carla McClain
Tucson, Arizona; Published: 09.07.2005

Fish oil Unhooks Meth Head

...Fired from his job, rejected by his family, John Palma bounced in and out of jails and hospitals as he sank into severe, suicidal depression, returning always to the drug that destroyed him.

"I just did not want to talk to anyone, see anyone, have anything to do with people and their insults. My mind was so scattered, I couldn't really grasp what anyone was saying," said Palma, 30...

Flagged as an addict least likely to succeed in his drug recovery program at the Salvation Army, Palma joined a small, unscientific medical experiment there, when counselors began slipping little pills in his food.

Today, five months after taking daily high doses of omega-3 supplements, Palma has emerged from his depression to rejoin the world, his head clear, his brain back in operation. The fog has lifted, as he puts it.

Ex-addict Says it Cleared his Addled Mind

... Palma and his counselors are firmly convinced the omega-3s are the key to his unexpected success.

"I just think more clearly now," Palma said. "Before, I couldn't read the AA book. It was very hard for me – I would have to read it over and over just to get it. And I can honestly pay attention to what people are saying. My family has noticed it – everyone has."

Around the Rehab Center, the staff joked about Palma, so dramatic were the changes in him after about six weeks of taking the fish oil supplements.

"It was – oh my God – who is this new person?" said Paulina Castillo, the center's director of rehabilitation services.

Palma was one of three meth addicts with especially difficult mental health histories who have tried the omega-3s in the Salvation Army experiment.

"In all three, the omegas have made such a difference," said Castillo, noting that two, including Palma, have graduated.

Dietary Recommendations for Omega-3 Consumption

- The American Psychiatric Association: patients with mood and impulse control disorders take 1 gm /day of EPA + DHA.
- The American Heart Association : people with CHD risk to eat about 1 gm /day EPA + DHA, preferably from oily fish.
- Mercury in fish is a minimal issue.
- Lowering dietary omega-6 may give even more of the same effect!

Freeman, Marlene P., et al. "Omega-3 fatty acids: evidence basis for treatment and future research in psychiatry." *Journal of Clinical Psychiatry* 67.12 (2006); *Child Neuropsychol* 2014;20(5):527-38. . doi: 10.1080/09297049.2013.824955. Epub 2013 Aug 25

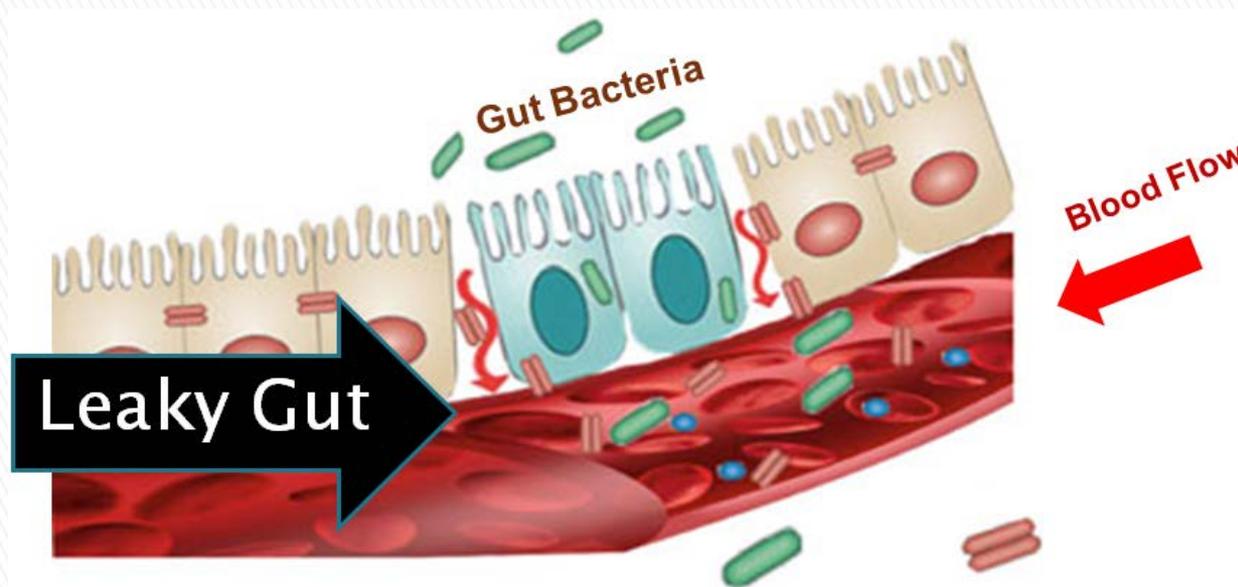
Fish or Other Food Source: Grams of Omega-3 in a 4-ounce Serving

- Chinook Salmon 3.6
- Albacore tuna 2.6
- Mackerel 1.8–2.6
- Rainbow trout 1.0
- Whiting 0.9
- Shrimp 0.5
- Cod 0.3
- Spinach 0.9
- English Walnuts 6.8
- Wheat & oat germ 0.7–1.4
- Farm raised tilapia or catfish None!



Gut bacteria → Endotoxin

- Diet, genetics, stress, inflammation & biome influence the leak of endotoxin from the gut into the circulation.
- Circulating endotoxin causes an inflammatory reaction throughout the body that is signaled by cytokines.



Summary

- Diseases found in modern western society occur together and can be thought of as Common Inflammatory Symptoms (CIS).
- Risk factors associated with CIS all increase inflammation associated with excessive bacterial debris (Endotoxin) in the circulation.
- Through inflammatory mechanisms endotoxin from microbes in the gut has been associated with all the symptoms of CIS.
- The diet has two essential functions:
 - Provide nutrients for human cells
 - Provide a substrate for gut microbes.
- The extent which gut microbes influence appetite, metabolism, endocrine function, and behavior is unknown but likely to be significant.
- Many aspects of pre-modern/traditional American Indian lifestyles reduce inflammation, including exercise, sun exposure (Vitamin D), and consuming traditional dietary fat and carbohydrate.
- A New Approach to Nutrition Will:
 - Recommend foods based on their pre-biotic effect as well as their caloric effect.
 - Replace fructose syrup sweetened drinks (with coffee?)
 - Reduce omega 6/3 ratio by eliminating “high omega-6” vegetable oils and the consumption of animals and fish raised on such foods.

Questions?