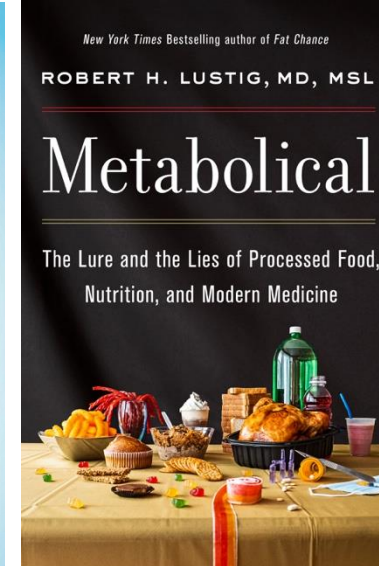
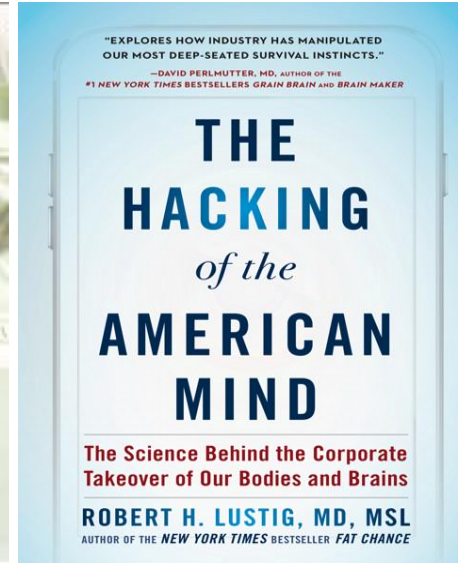
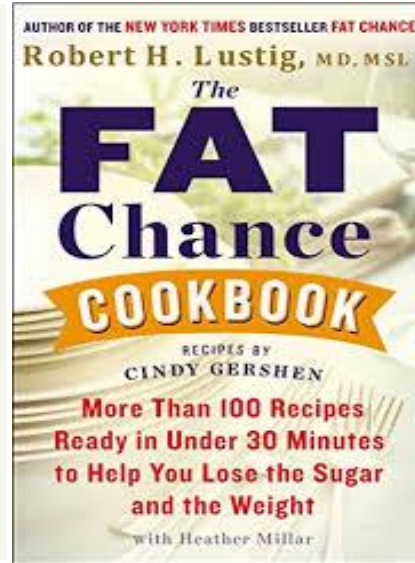
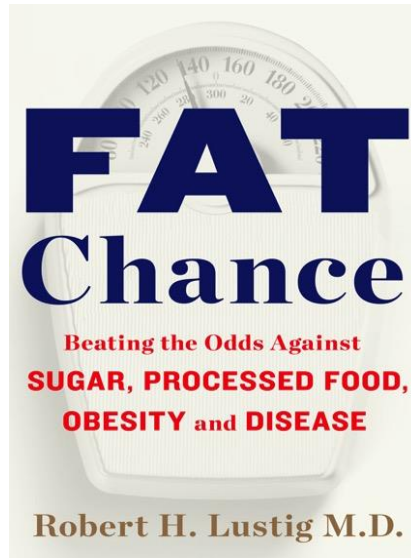


Disclosures



Chief Medical Officer:
SnapRecall
BioLumen
Perfact

Paid Advisor:
Myka Bio
TurtleTree
Levels Health

Unpaid Advisor:
Kuwaiti Danish Dairy
Blue Oak Nutraceuticals

The Global Pandemic of Chronic Metabolic Disease (75% of US Healthcare Dollars)

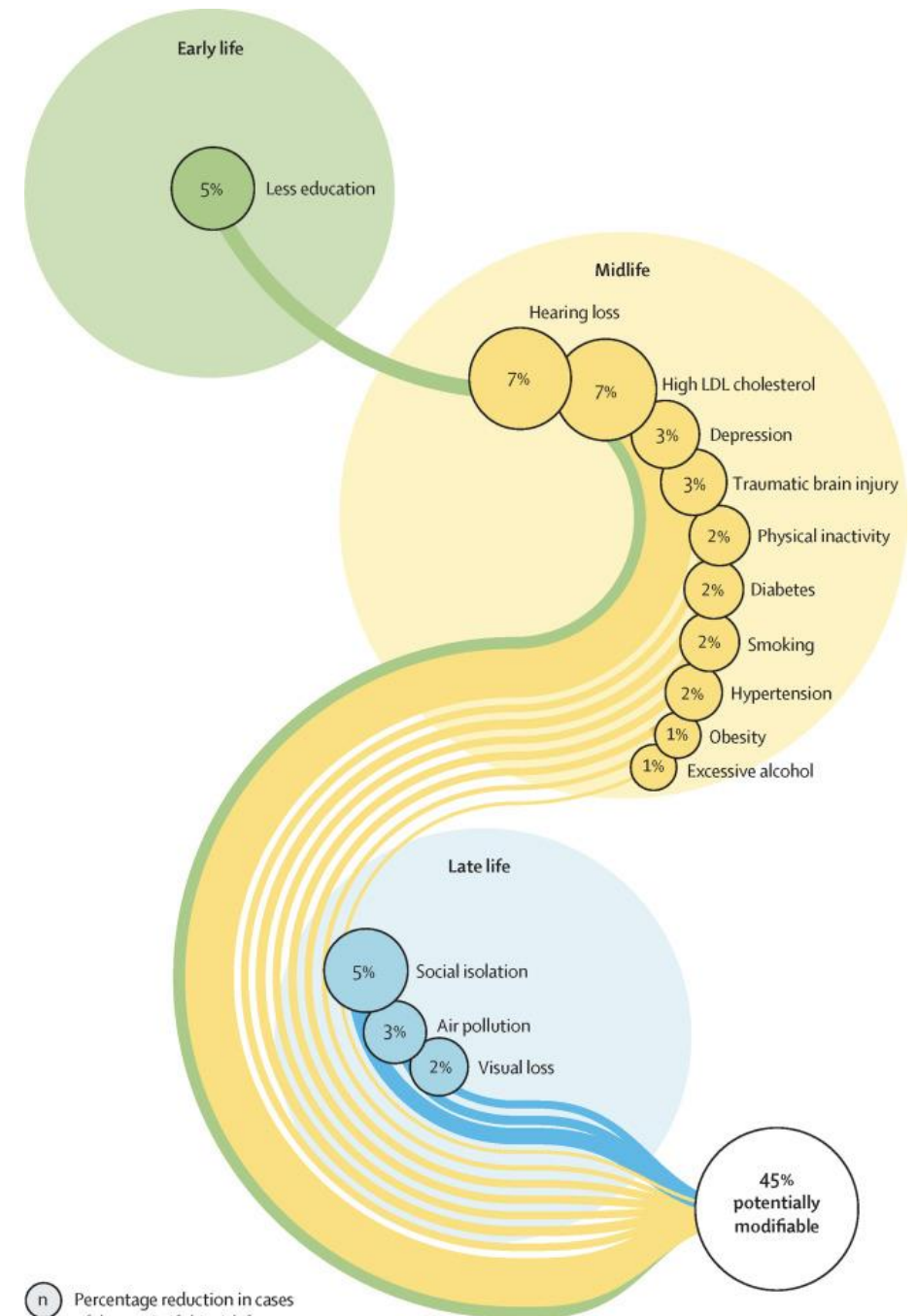
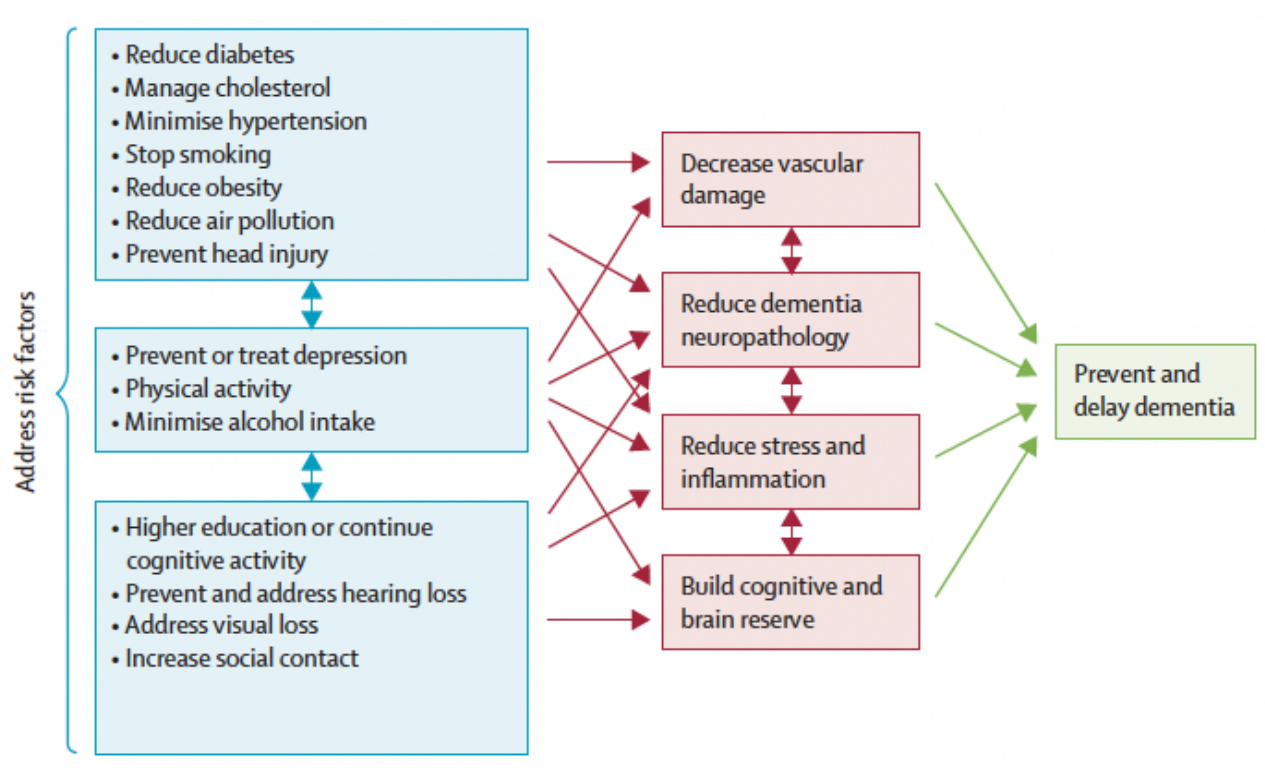
- Obesity
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- Dental Caries and Periodontitis
- Inflammatory Diseases
- Autoimmune Diseases
- Chronic Kidney Disease (CKD)
- Food Allergies and Intolerances
- Depression and Anxiety
- **Dementia and Cognitive Decline**

None of these have cures, and the treatments only treat the symptoms



Dementia prevention, intervention, and care: 2024 report of the *Lancet* standing Commission

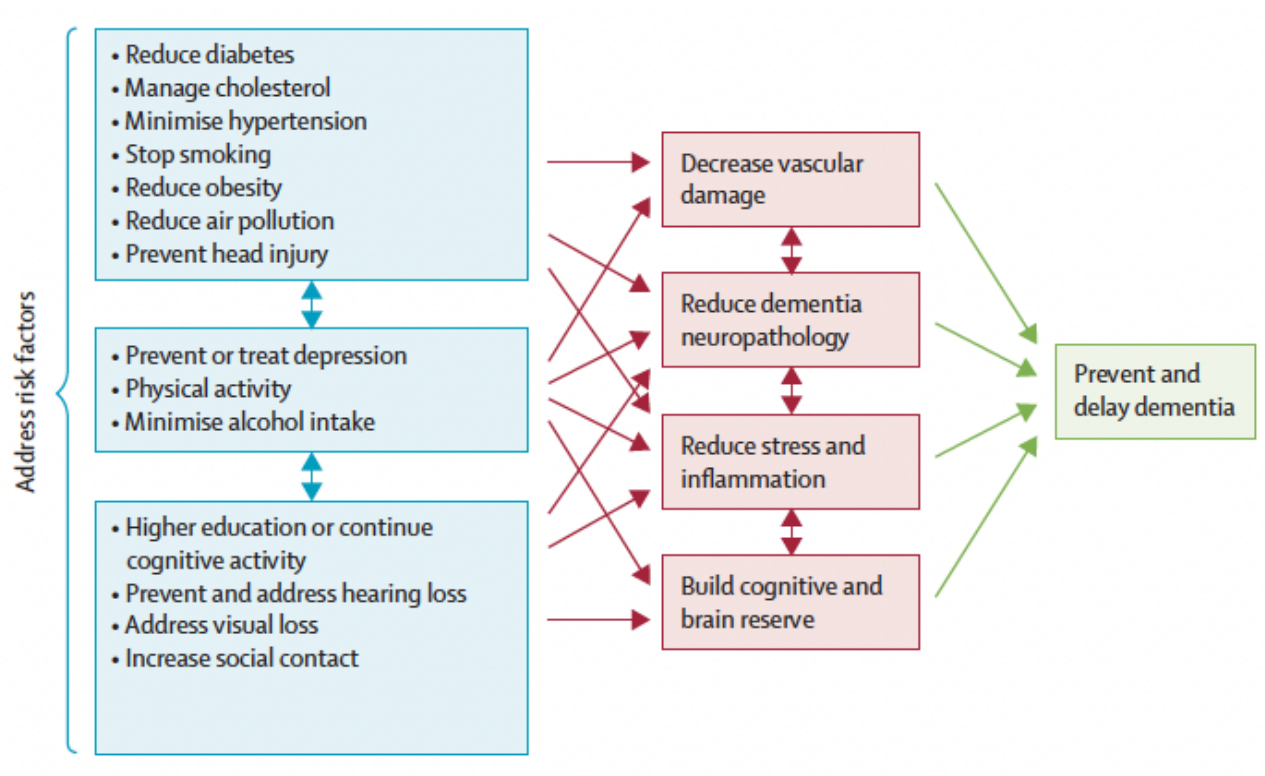
Gill Livingston, Jonathan Huntley, Kathy Y Liu, Sergi G Costafreda, Geir Selbæk, Suvarna Alladi, David Ames, Sube Banerjee, Alistair Burns, Carol Brayne, Nick C Fox, Cleusa P Ferri, Laura N Gitlin, Robert Howard, Helen C Kales, Mika Kivimäki, Eric B Larson, Noeline Nakasujja, Kenneth Rockwood, Quincy Samus, Kokoro Shirai, Archana Singh-Manoux, Lon S Schneider, Sebastian Walsh, Yao Yao, Andrew Sommerlad*, Naaheed Mukadam*



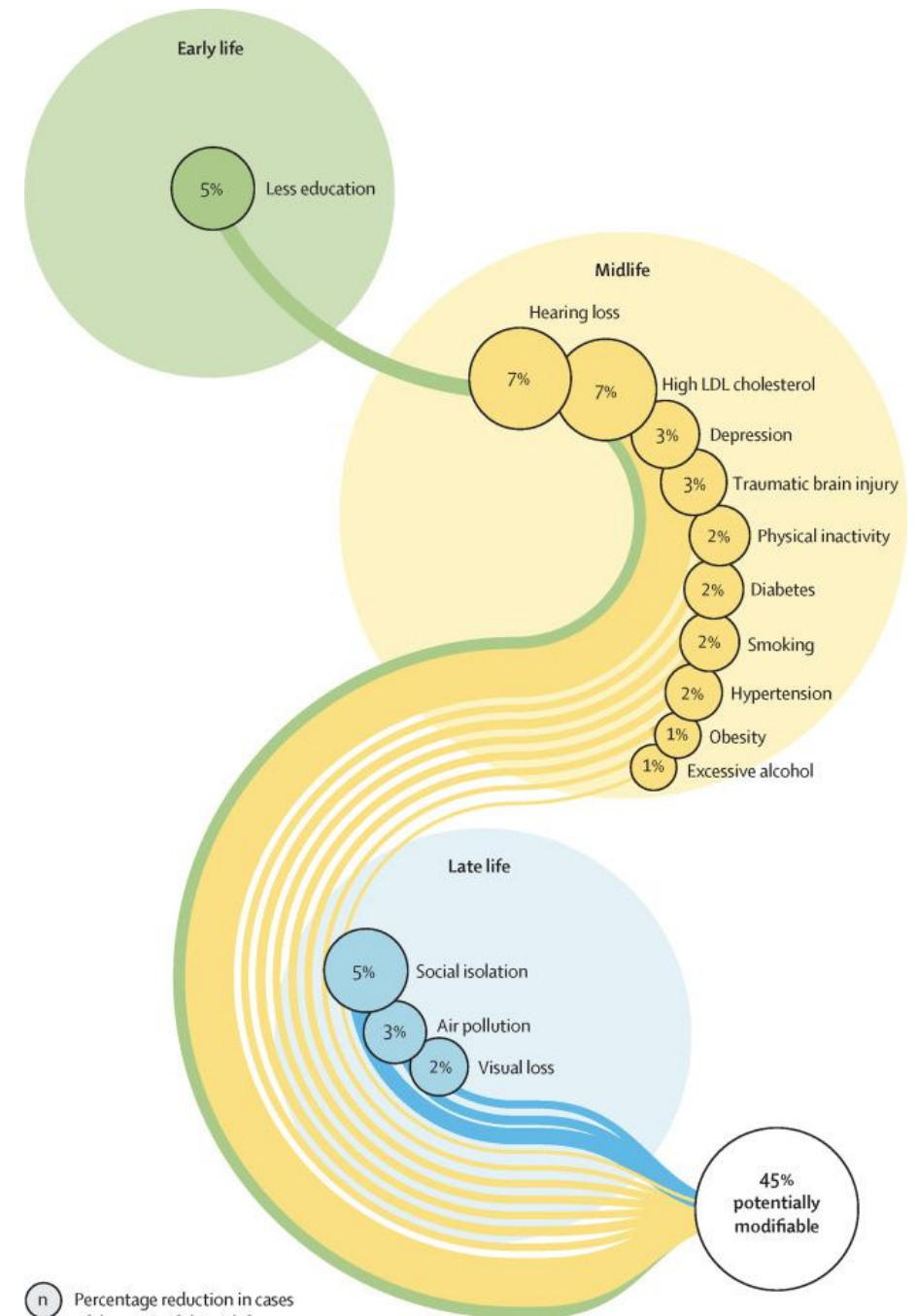


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Only 5% of Alzheimer's is genetic

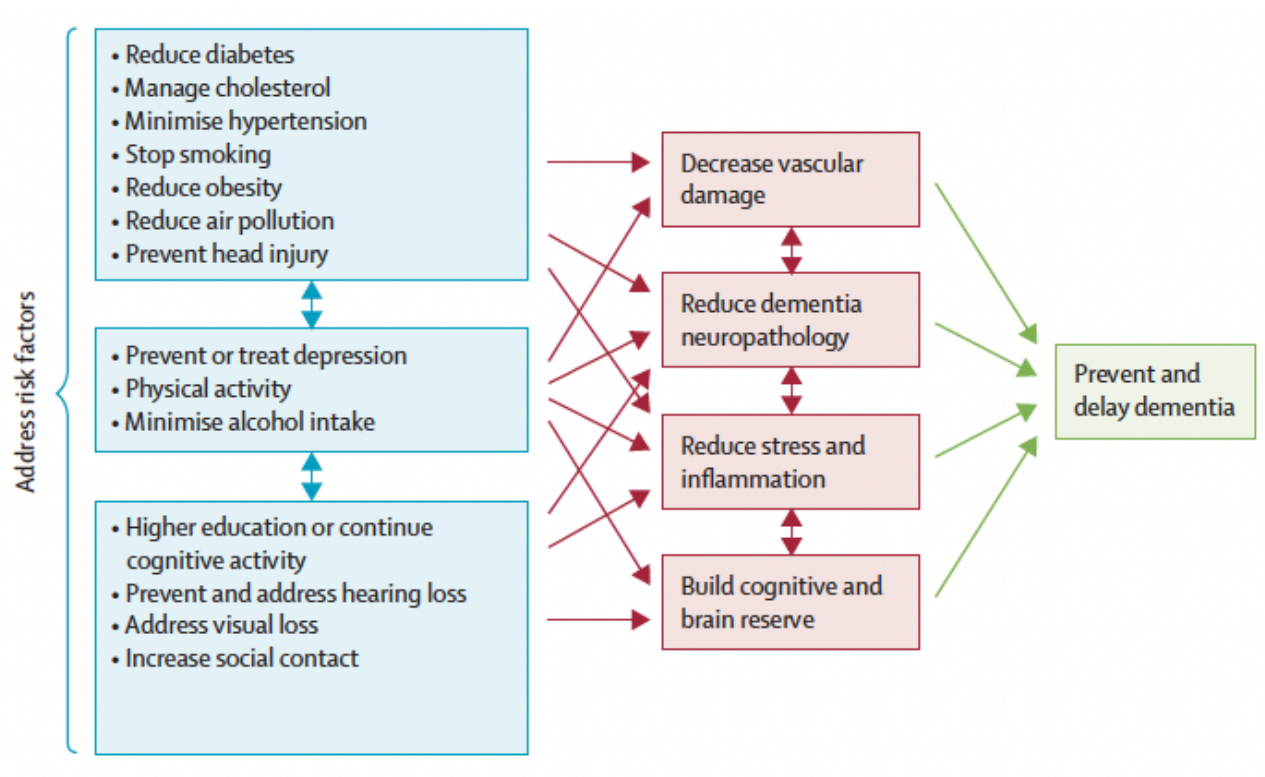


n Percentage reduction in cases of dementia if this risk factor is eliminated

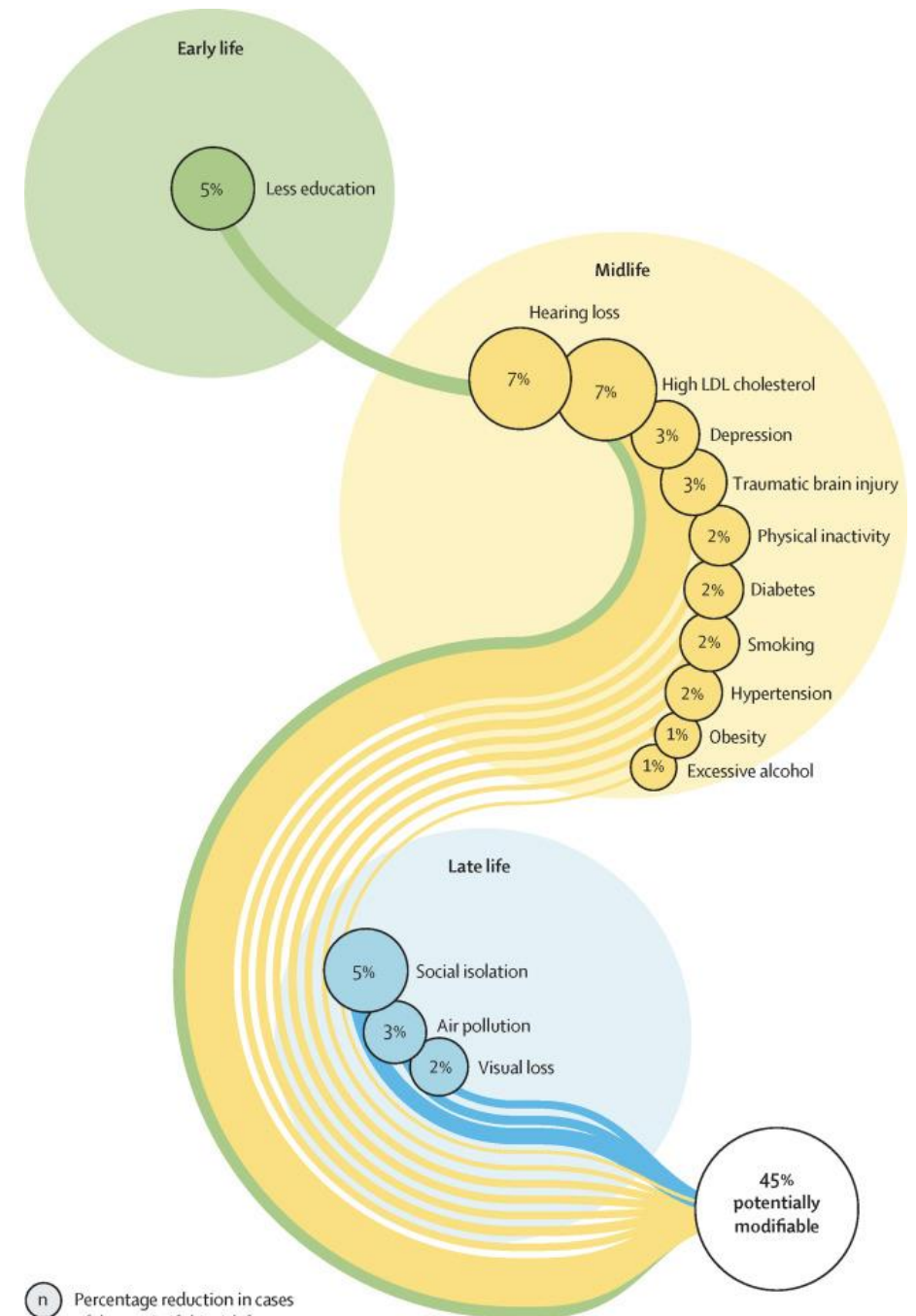


Dementia prevention, intervention, and care: 2024 report of the *Lancet* standing Commission

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Not one word about nutrition



n Percentage reduction in cases of dementia if this risk factor is eliminated

Risk Factors for Alzheimer's Disease

Conditions

- **Diabetes**
- **Obesity**
- **Hypertension**
- **Depression**

Dietary Foods

- **Sugar**
- **High Glycemic Carbohydrates**
- **High Salt Diet**
- **Ultraprocessed Foods**

E September 06, 2022; 99 (10) **RESEARCH ARTICLES**

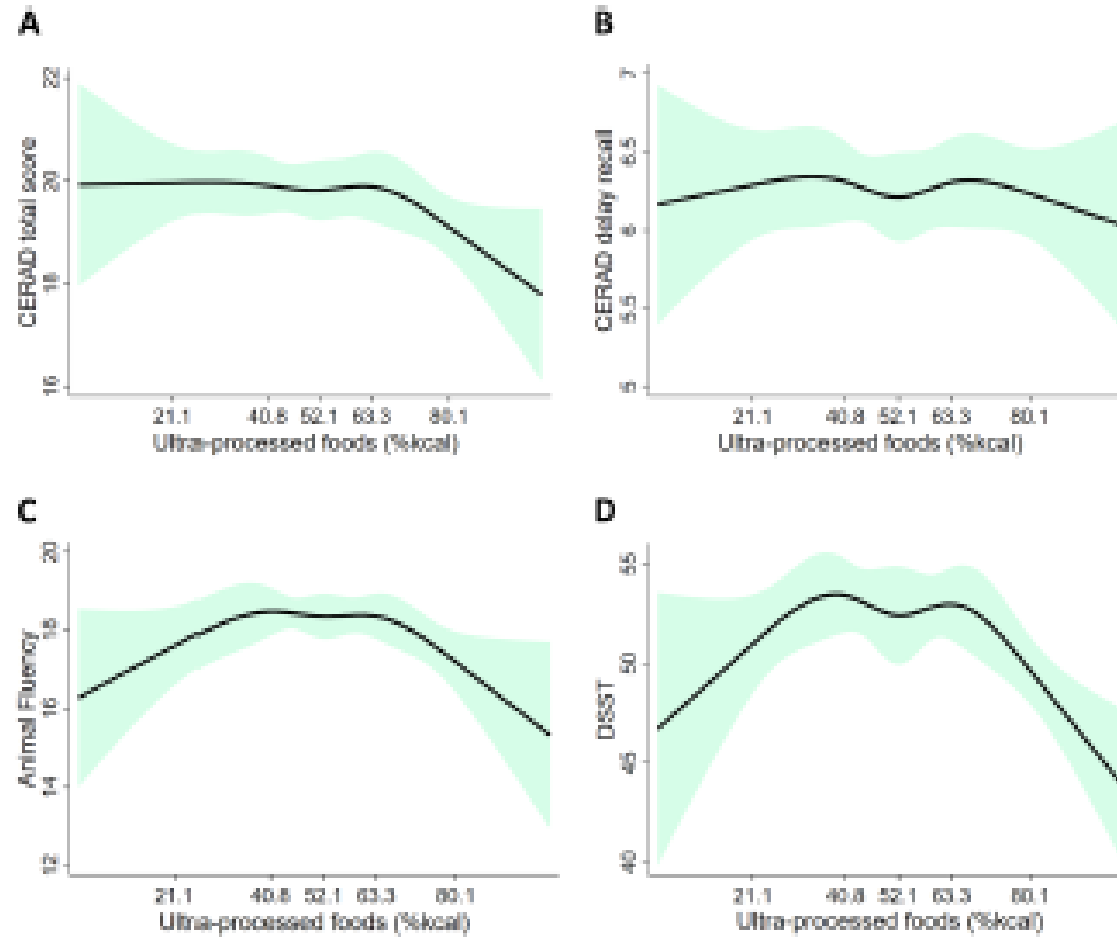
Association of Ultraprocessed Food Consumption With Risk of Dementia **A Prospective Cohort Study**

Huiping Li, Shu Li, Hongxi Yang, Yuan Zhang, Shunming Zhang, Yue Ma, Yabing Hou, Xinyu Zhang, Kaijun Niu, Yan Borné, Yaogang Wang

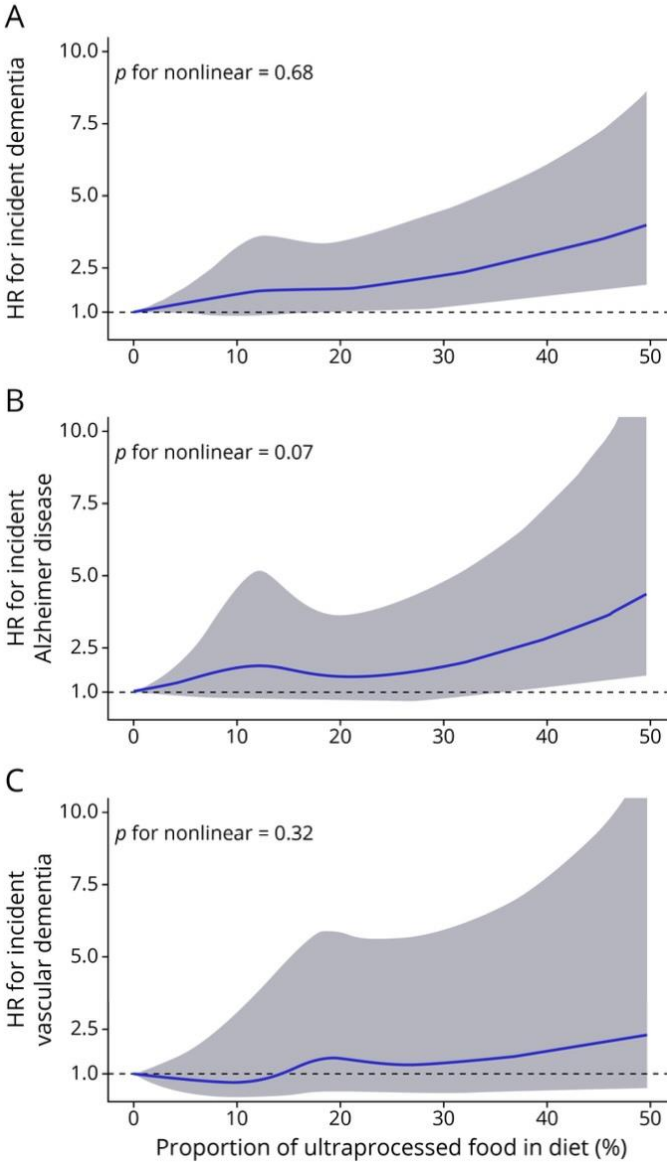
First published July 27, 2022, DOI: <https://doi.org/10.1212/WNL.000000000200871>

Ultraprocessed food inhibits cognition in older adults

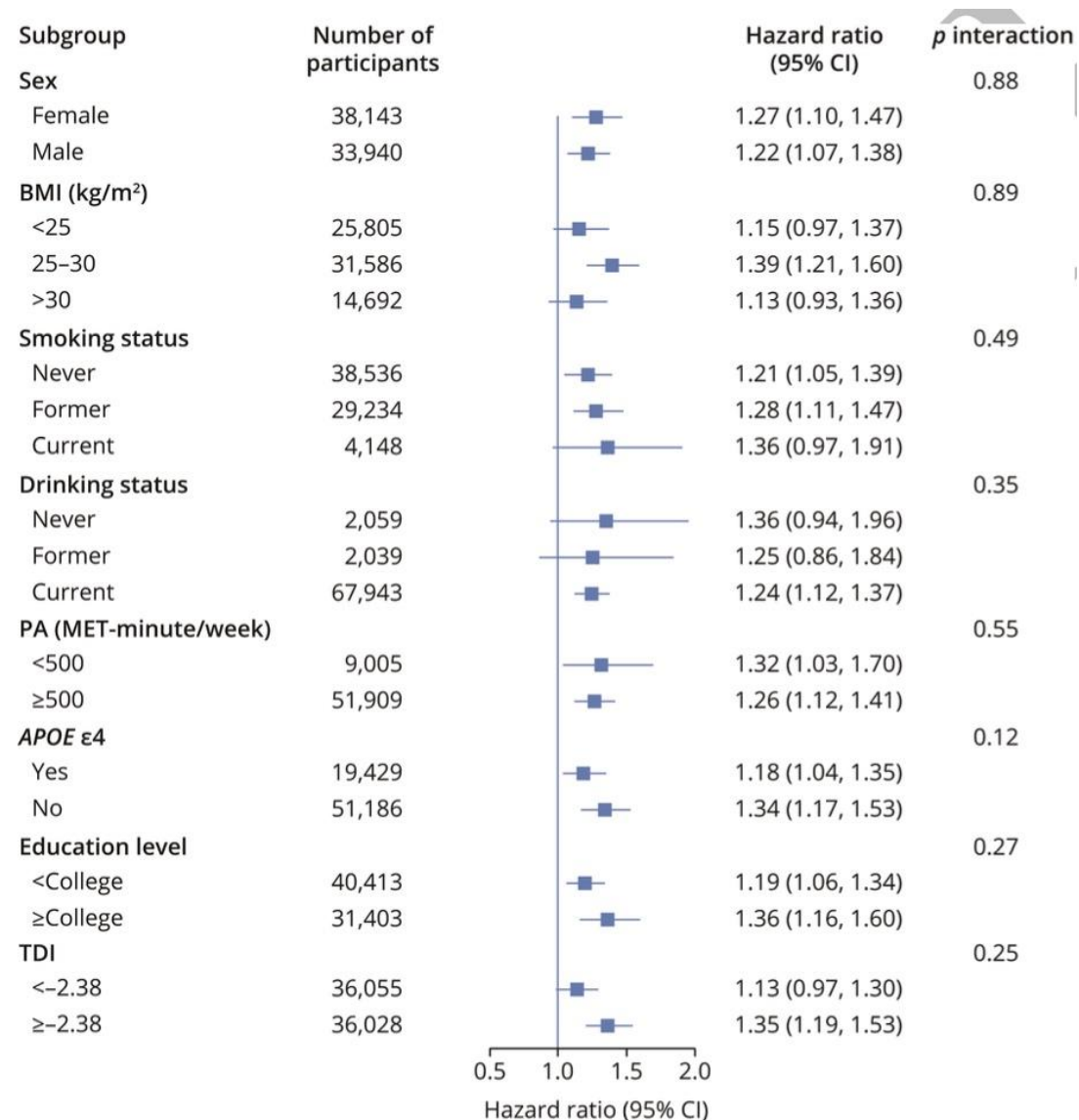
Fig. 1 The relationship between dietary UPF (as % of total energy intake) and cognitive test scores: **a** CERAD total ($P=0.308$); **b** CERAD delayed recall ($P=0.859$); **c** animal fluency ($P=0.010$); **d** digit Symbol Substitution test (DSST) ($P=0.005$). Green area represents the 95% confidence intervals. UPF ultra-processed food, %kcal % of total energy intake



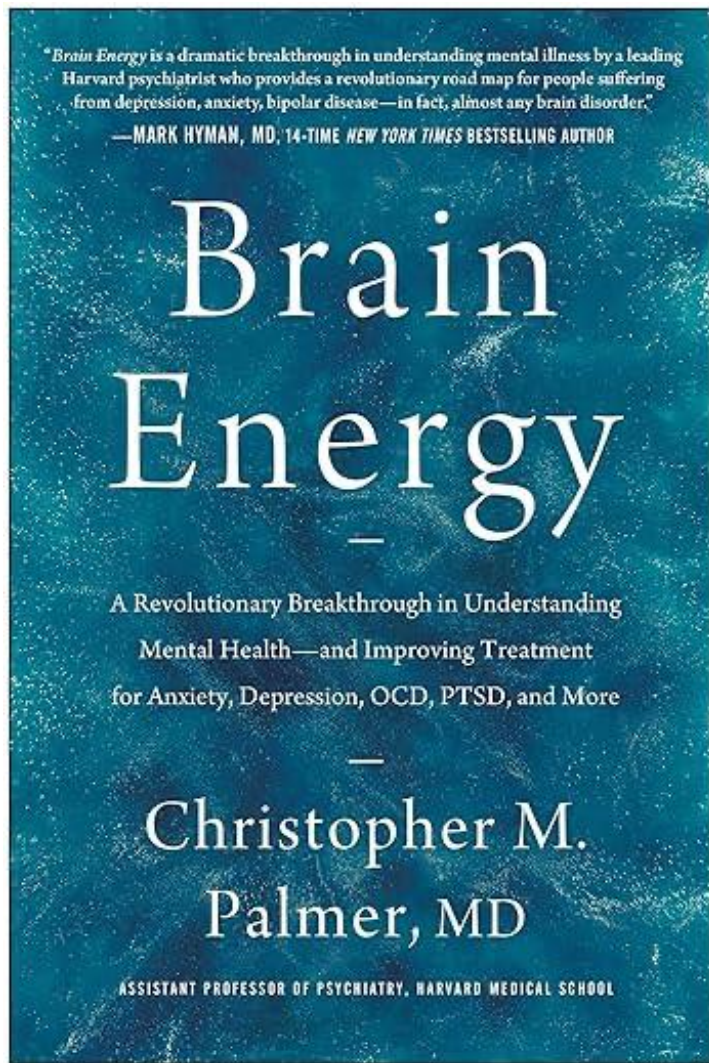
Ultraprocessed food consumption correlates with dementia



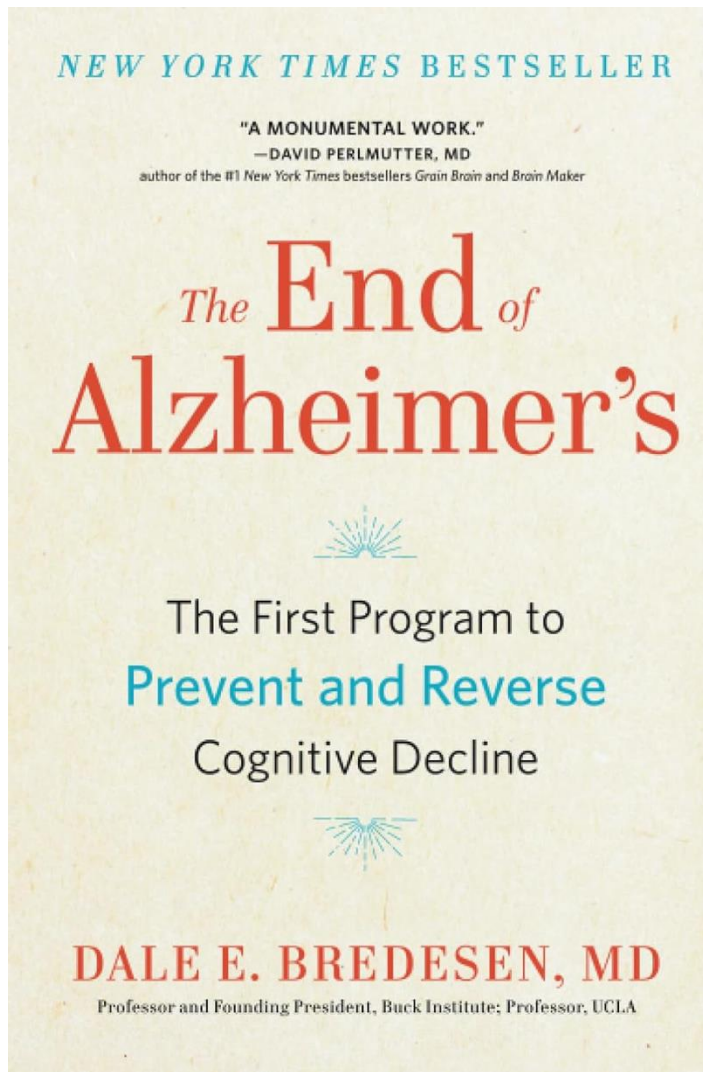
The confounders don't detract from the findings



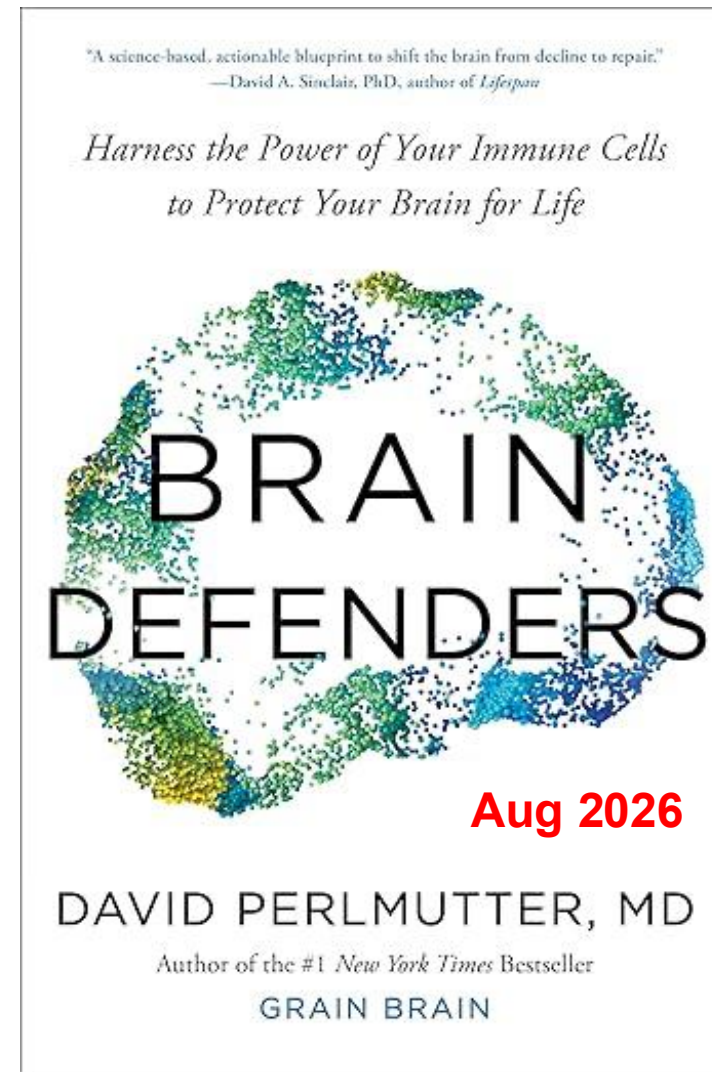
So what's with diet and dementia?



Ketogenic Diet and Improvement of Psychiatric Disease



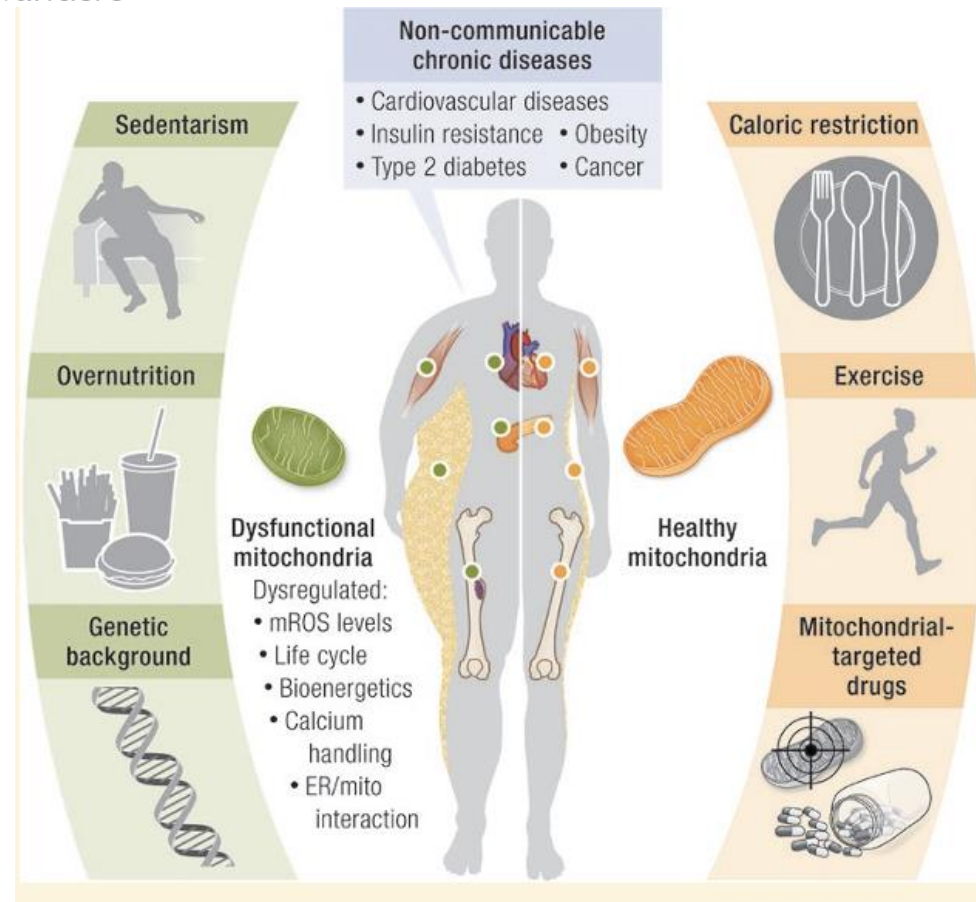
Multiple Causes of Alzheimer's, Must Attend to All of Them



Diet Changes Your Microglia, To Stop the Synapse Loss

Is Mitochondrial Dysfunction a Common Root of Noncommunicable Chronic Diseases?

Alexis Diaz-Vegas,^{1,2} Pablo Sanchez-Aguilera,¹ James R Krycer,² Pablo E Morales,¹ Matías Monsalves-Alvarez,^{1,3} Mariana Cifuentes,^{1,3,5} Beverly A Rothermel,⁴ and Sergio Lavandero^{1,4,5}



Mitochondrial dysfunction vs. a coal burning factory/mill



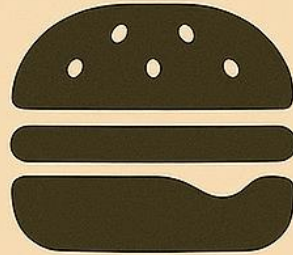
Environmental Causes Disrupting Mitochondrial Function



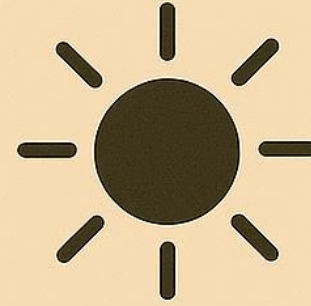
Sleep



Air Pollution



Ultra-Processed Food



Sunlight Exposure



Chronic Stress



Sedentary Behavior

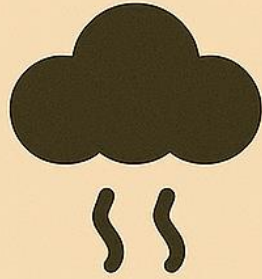


Plastics

Environmental Causes Disrupting Mitochondrial Function



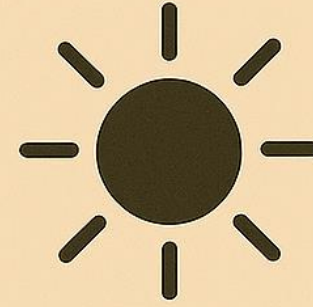
Sleep



Air Pollution



Ultra-Processed Food



Sunlight Exposure



Chronic Stress



Sedentary Behavior



Plastics

Reactive Oxygen Species (ROS):

Superoxide Anion ($O_2^{\bullet -}$)
Hydrogen Peroxide (H_2O_2)
Hydroxyl Radical (OH^{\bullet})



High Dose — Toxic ions

Low Dose — Signaling ions

ROS as a driver of mitochondrial damage is not a new idea



The Biologic Clock: The Mitochondria?

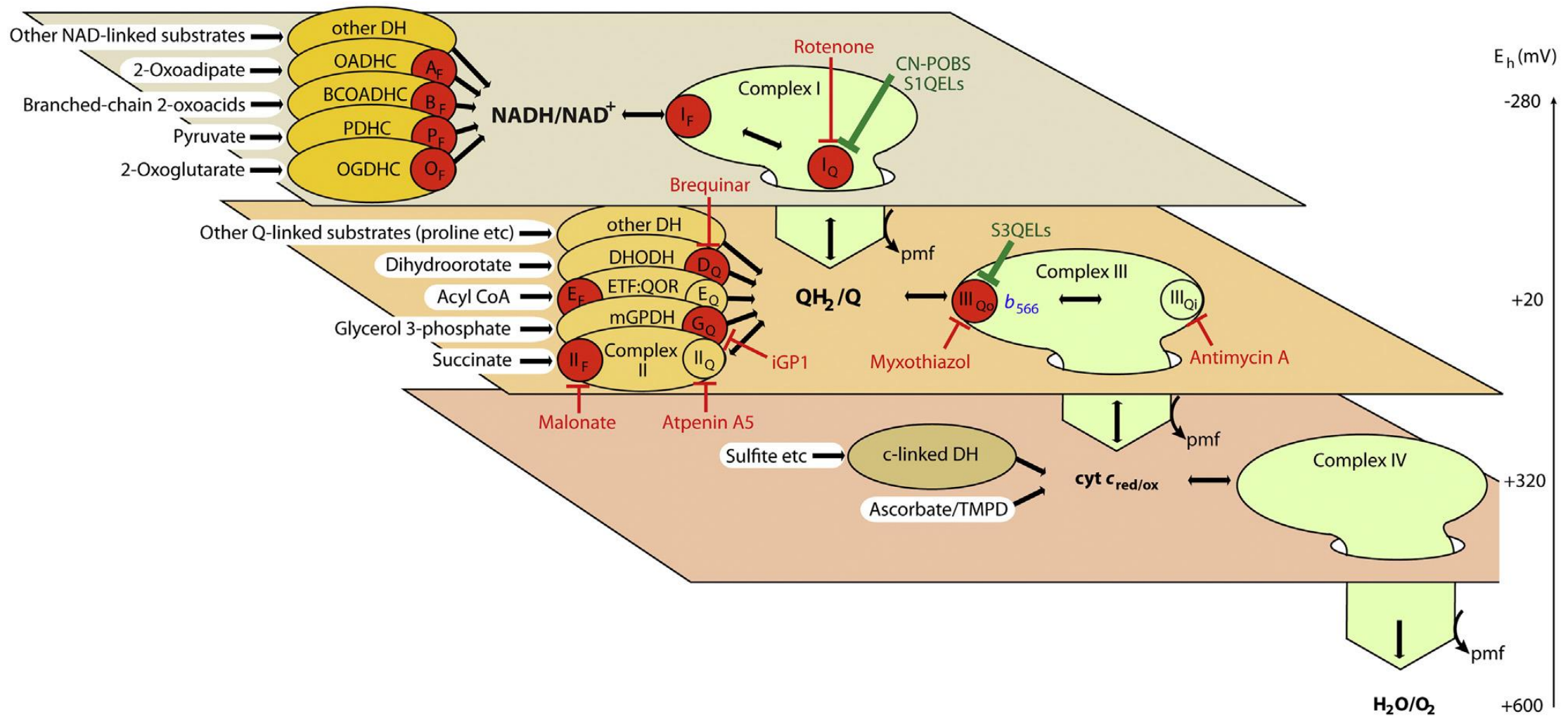
DENHAM HARMAN M.D., Ph.D.

First published: April 1972 | <https://doi.org/10.1111/j.1532-5415.1972.tb00787.x> | Citations: 1,582

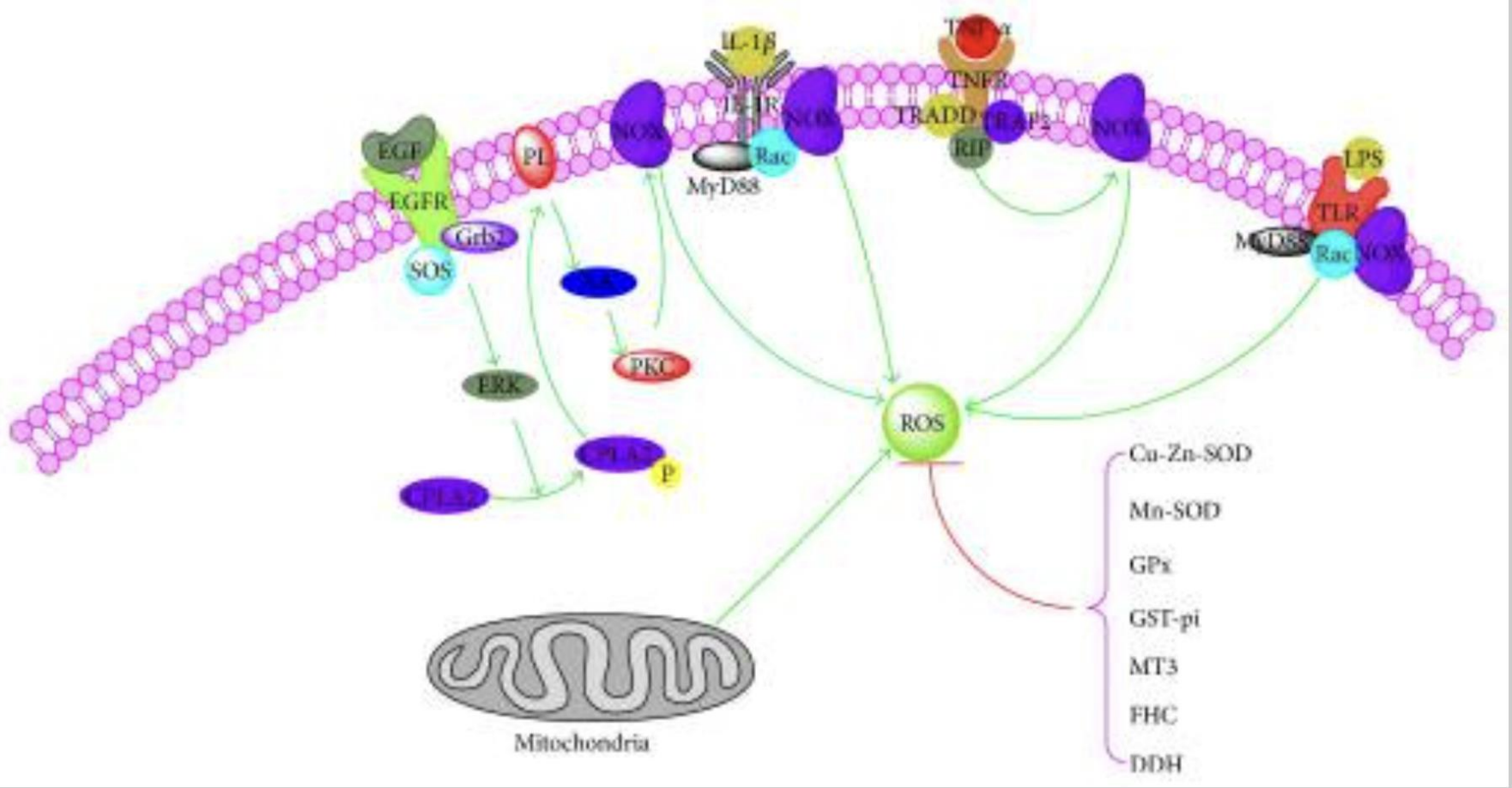
ROS is a signaling molecule, as well as a pathologic molecule

- *ROS and PI3K-Akt Signaling Pathway (metabolism)*
- *ROS and NF- κ B Signaling Pathway (inflammation)*
- *ROS and Keap1-Nrf2-ARE Signaling Pathway (growth, cancer)*
- *Cross Talk between ROS and Ca²⁺ (neurotransmission)*
- ***ROS inhibits Mitochondrial ATP production***
- *ROS without quenching (peroxisome) – oxidative damage*

11 separate mitochondrial enzymes give off ROS's

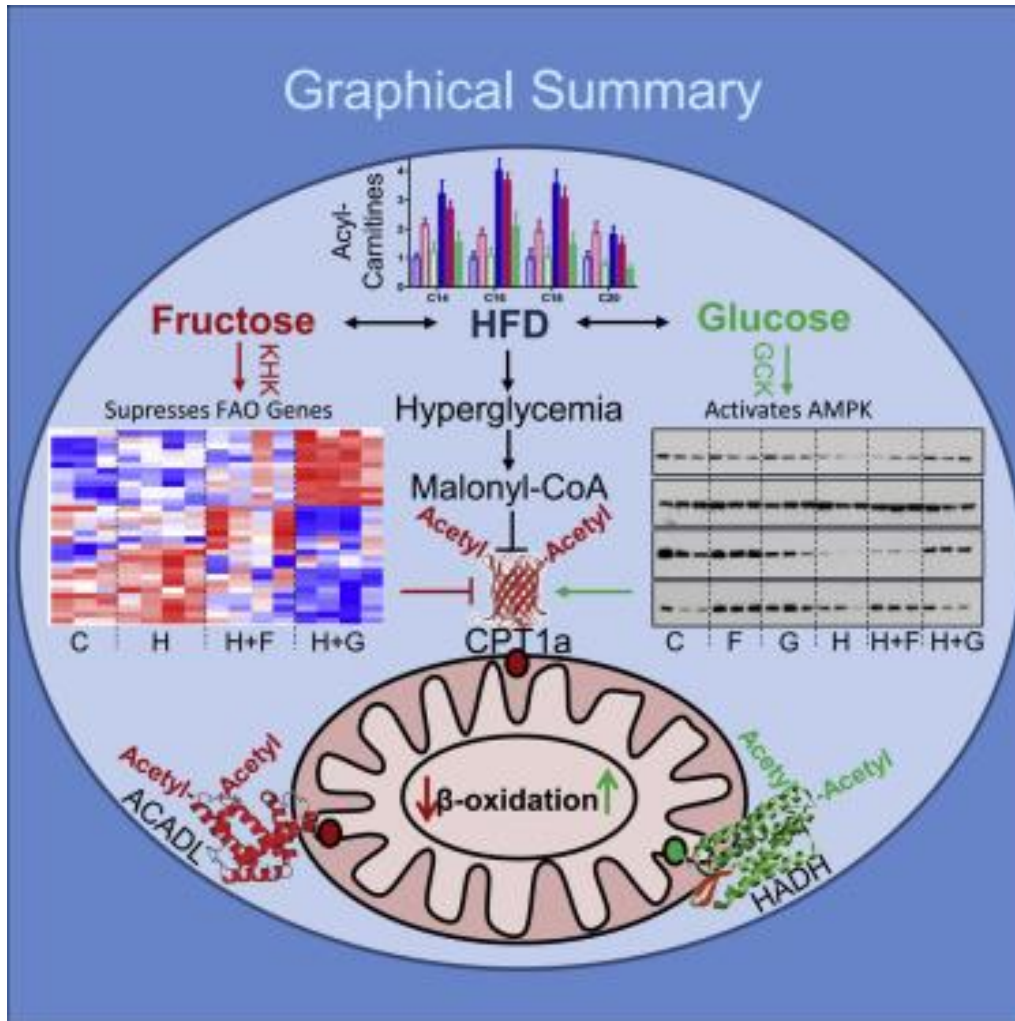


Mitochondria and other exposures make ROS's



Fructose

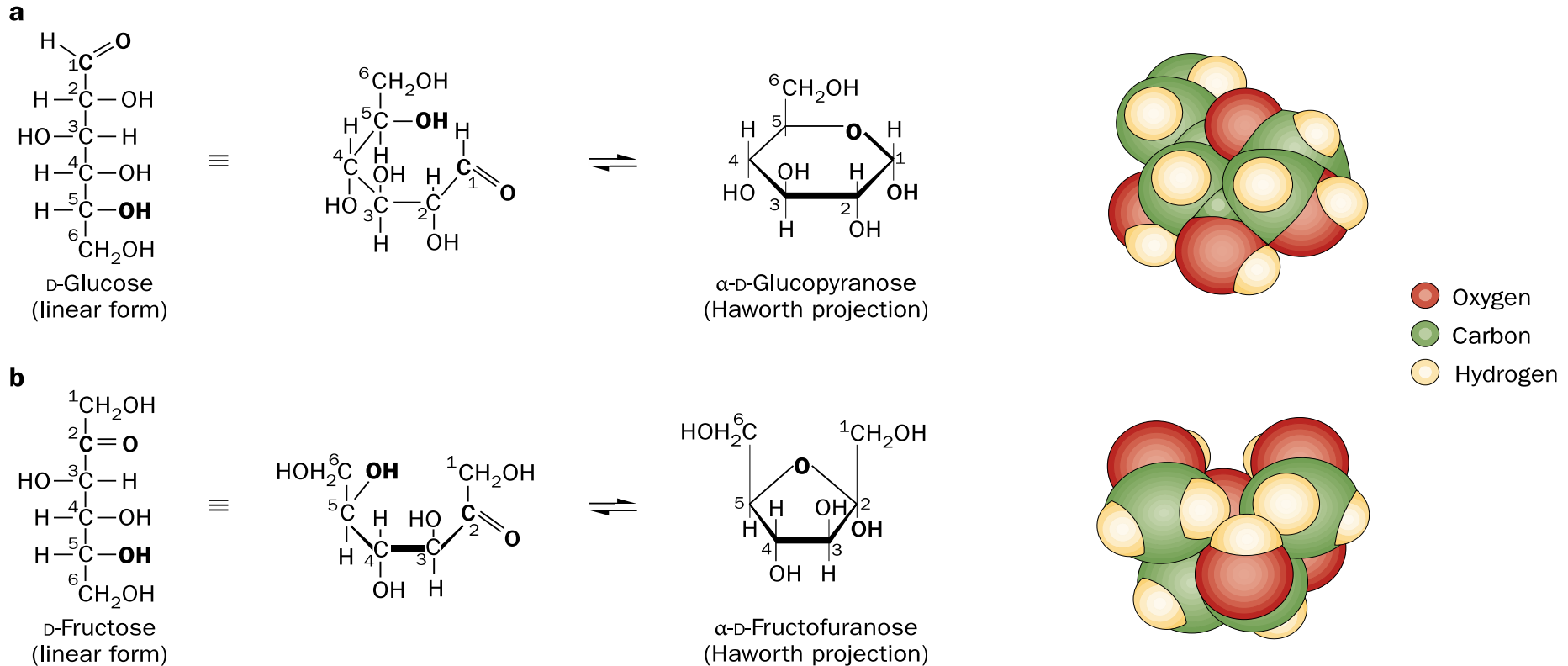
Fructose reduces liver mitochondrial function, while glucose stimulates it



"The most important takeaway of this study is that high fructose in the diet is bad," says Dr. Kahn. "It's not bad because it's more calories, but because it has effects on liver metabolism to make it worse at burning fat. As a result, adding fructose to the diet makes the liver store more fat, and this is bad for the liver and bad for whole body metabolism."

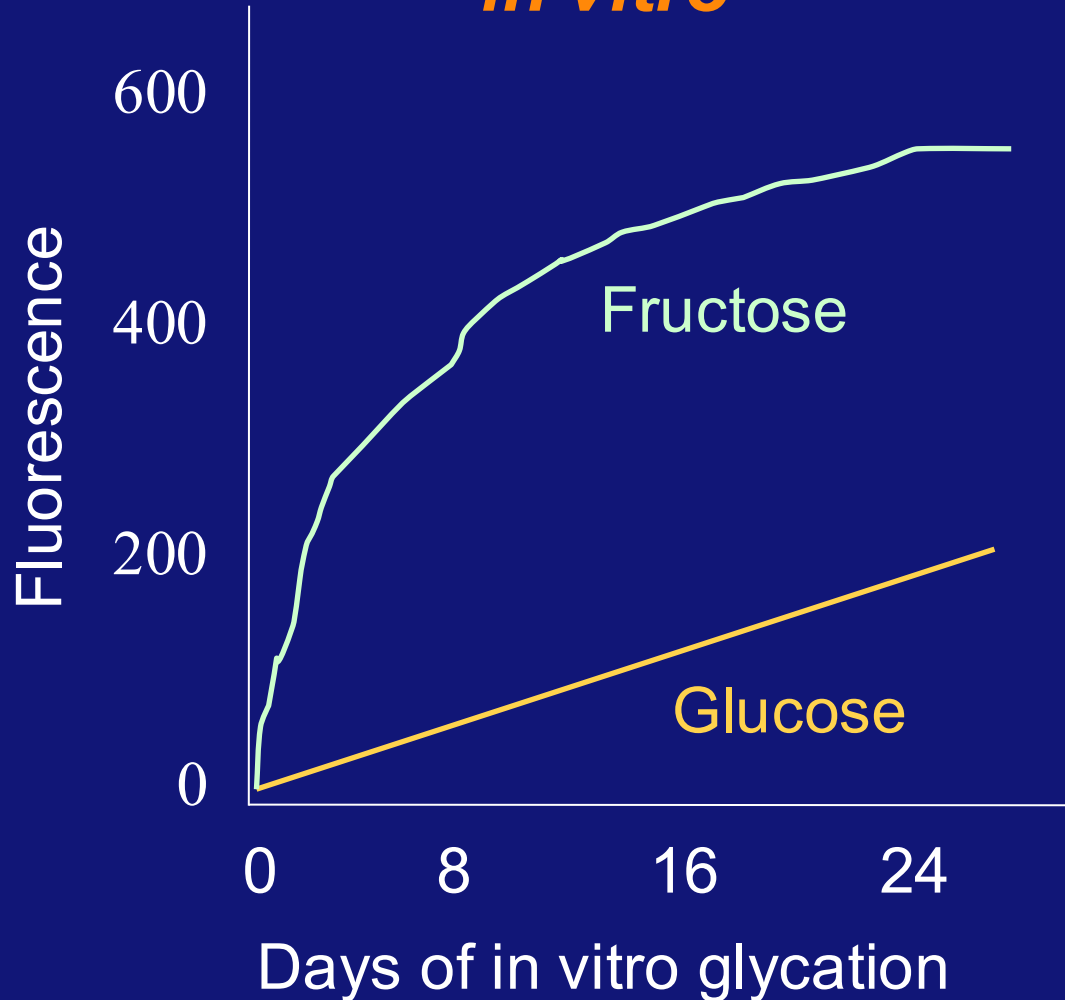
Dr. C. Ronald Kahn,
CEO, Joslin Diabetes Center

The furan ring of fructose is more unstable, so at equilibrium, fructose exists in the linear form



Non-enzymatic glycation: fructose >> glucose

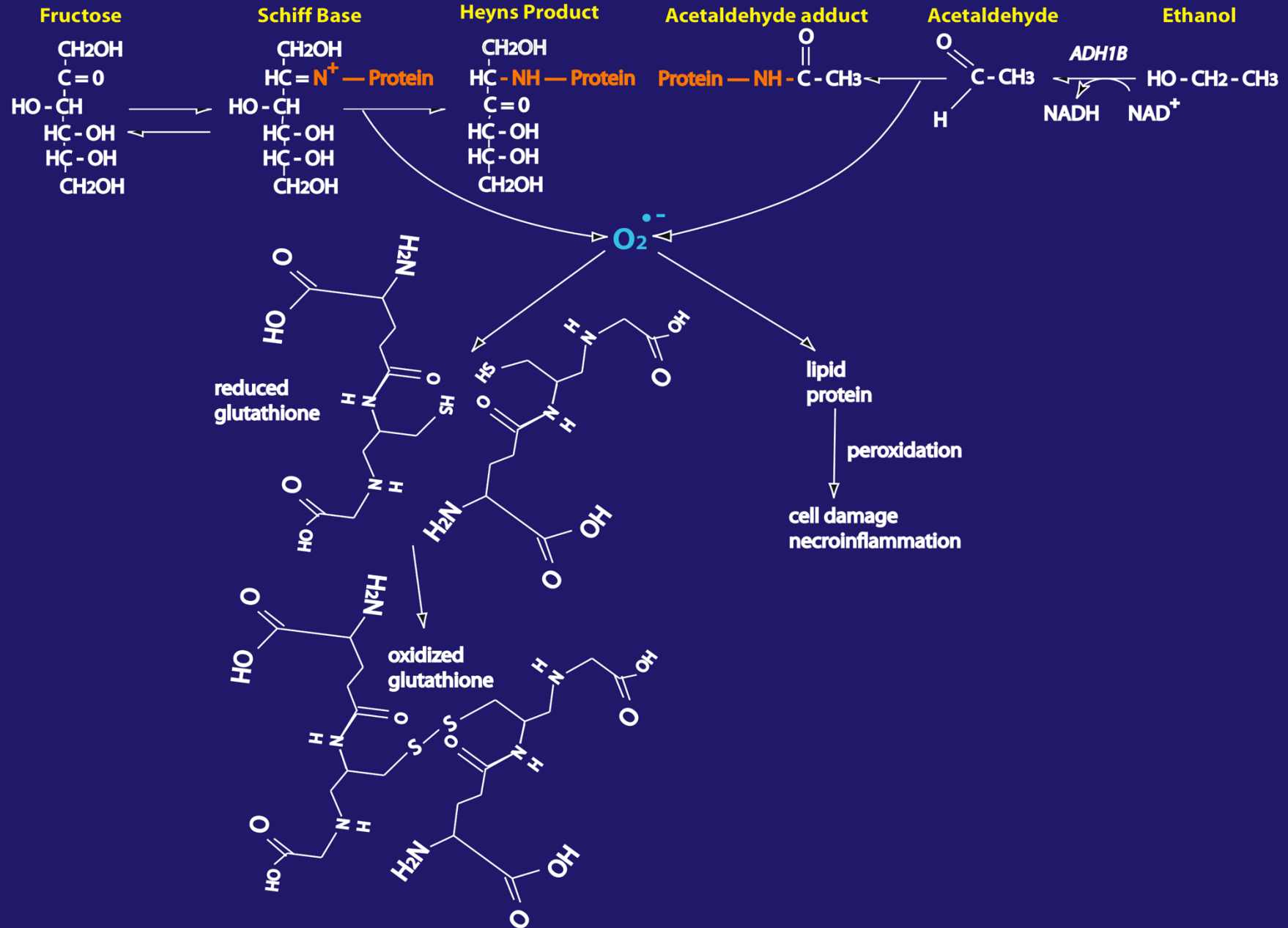
Fructose and glycation *in vitro*



Rates of reactivity

	Rate (/mM/hr)	Carbonyl (ROS) %
Glucose	0.6	0.002
Galactose	2.8	0.02
Fructose	4.5	0.7

ROS formation from aldehydes and ketals



Hepatocyte death *in vitro* upon fructose exposure (after generation of H₂O₂)

Treatment	ED ₅₀
Fructose	1.5 ± 0.13 M
Glucose	>1.5 M
Glycoaldehyde	20 ± 2 mM
Glyoxal	5 ± 0.5 mM

Hepatocyte death *in vitro* upon fructose exposure (after generation of H₂O₂)

Treatment	ED ₅₀	ED ₅₀ (with H ₂ O ₂)
Fructose	1.5 ± 0.13 M	12 ± 2 mM
Glucose	>1.5 M	1.5 M
Glycoaldehyde	20 ± 2 mM	0.5 ± 0.1 mM
Glyoxal	5 ± 0.5 mM	0.02 ± 0.002 mM

Prevented by addition of:

antioxidant vitamins (VitB₁, VitB₆, VitC)

P450 inhibitors

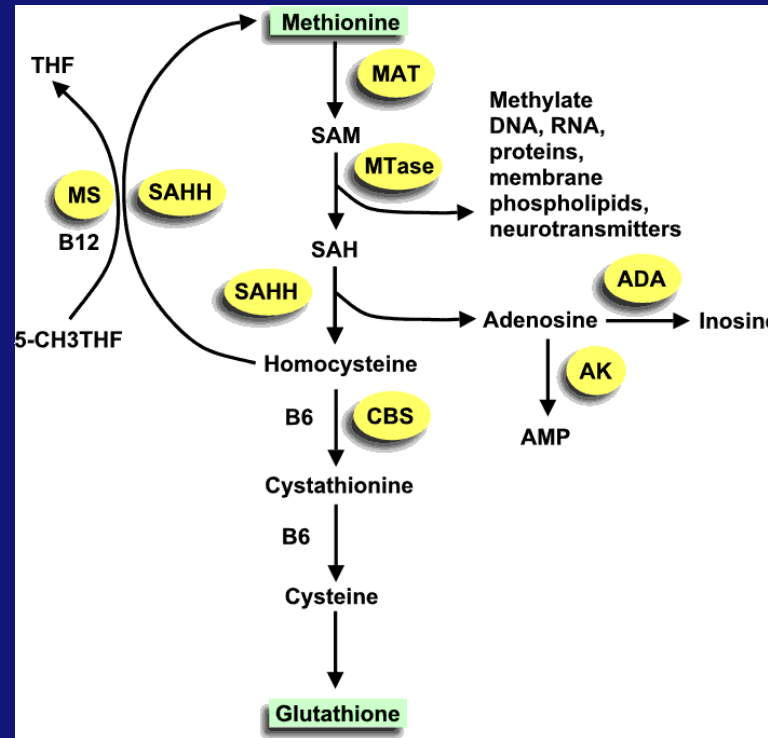
hydroxyl radical and carbonyl scavengers

heavy metal chelators

The Methionine-Choline Deficient Diet

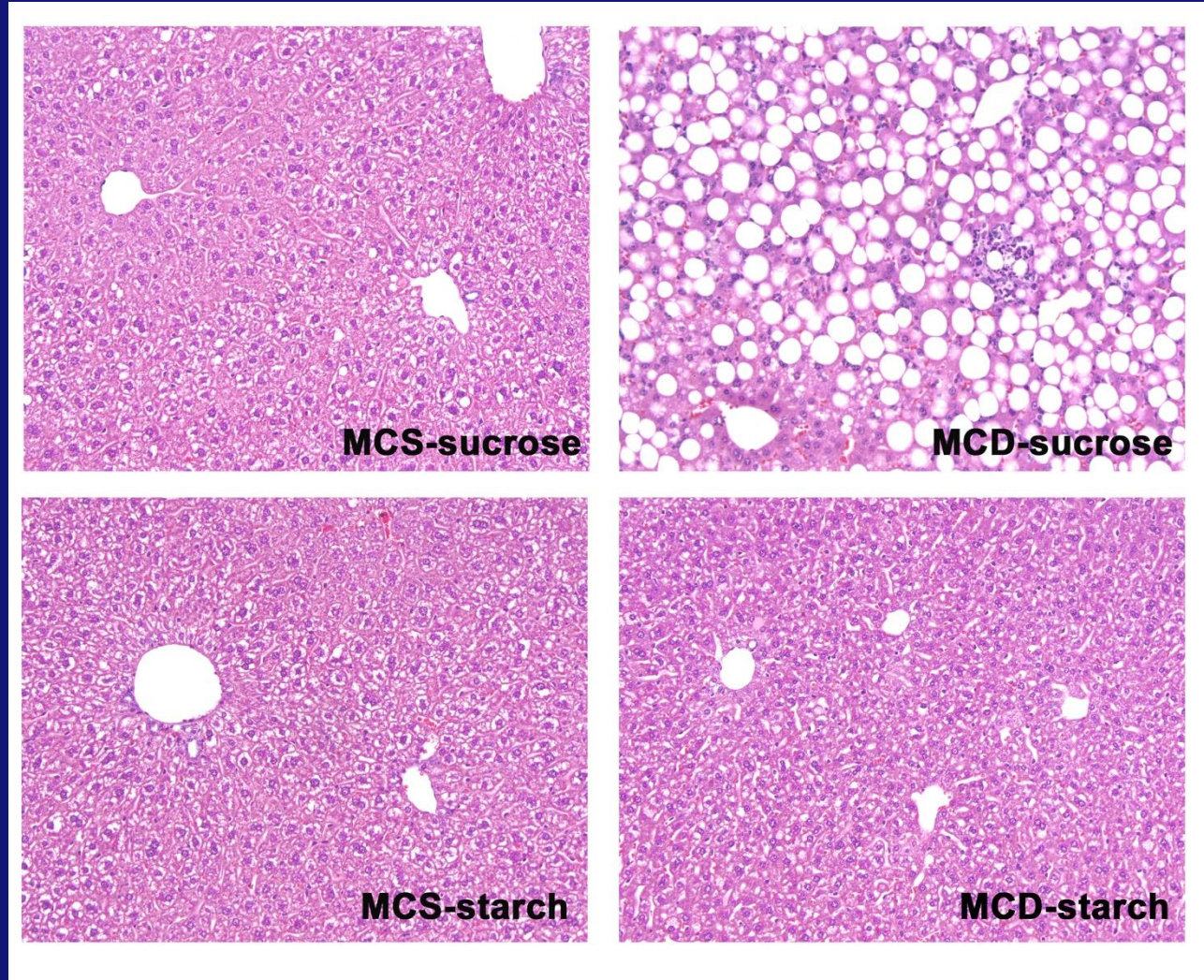
Fastest animal model of NASH

- sucrose necessary to provide the substrate for steatosis
- methionine deficiency reduces glutathione, the hepatic hydroxyl radical scavenger

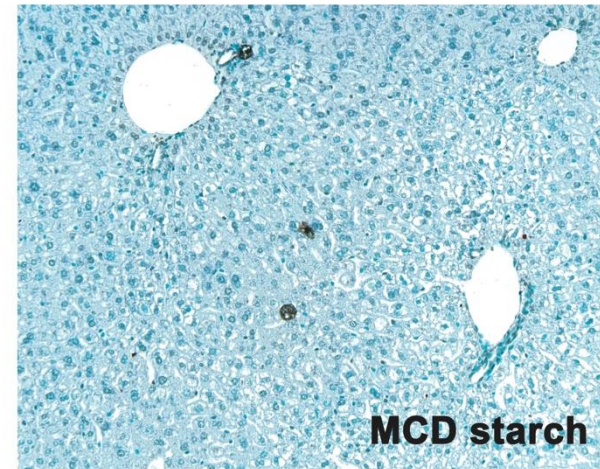
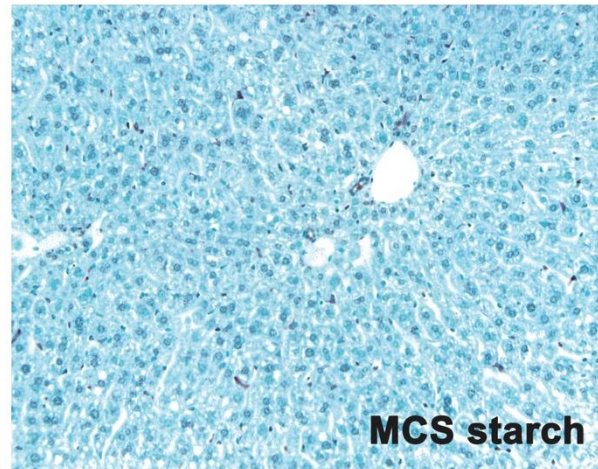
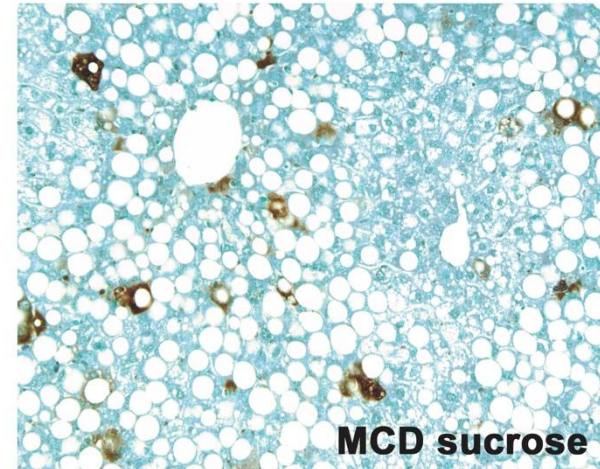
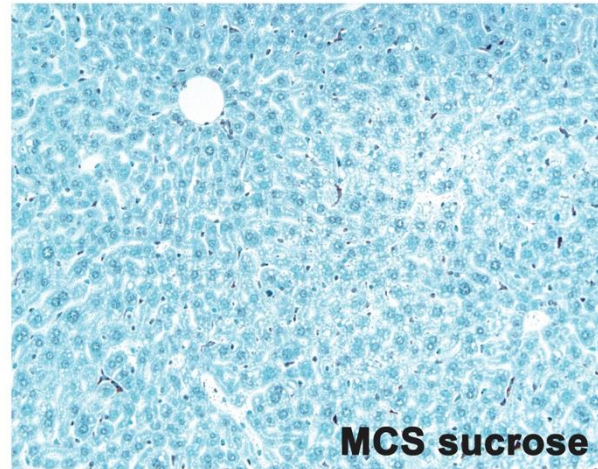


- choline deficiency reduces phosphatidyl choline, another mechanism of hepatic lipid export

Sucrose is necessary for NAFLD in the Methionine-Choline deficient diet



TUNEL staining in the Methionine-Choline deficient diet



The Global Pandemic of Chronic Metabolic Disease (75% of US Healthcare Dollars)

- Obesity — SUGAR!
- Type 2 Diabetes — SUGAR!
- Cardiovascular Diseases (CVD) — SUGAR!
- Hypertension (High Blood Pressure) — SUGAR!
- Fatty Liver Disease — SUGAR!
- Cancer — SUGAR!
- Osteoporosis — SUGAR!
- Gastrointestinal Disorders — SUGAR!
- Dental Caries and Periodontitis — SUGAR!
- Inflammatory Diseases — SUGAR!
- Autoimmune Diseases — SUGAR!
- Chronic Kidney Disease (CKD) — SUGAR!
- Food Allergies and Intolerances — SUGAR!
- Depression and Anxiety — SUGAR!
- **Dementia and Cognitive Decline ???**



Does sugar cause dementia?

Obesity is associated with dementia

Luchsinger et al. *J Alz Dis Assoc Dis* 2011

Obesity is associated with altered neural projections c/w dementia

Bouret et al. *Cell Metab* 7:179, 2008

Sugar generates insulin resistance and hyperinsulinemia

Seneff et al. *Eur J Int Med* 22:134, 2011

Insulin resistance and high insulin levels are associated with dementia

Craft et al. *Nat Rev Neurol* 8:360, 2012

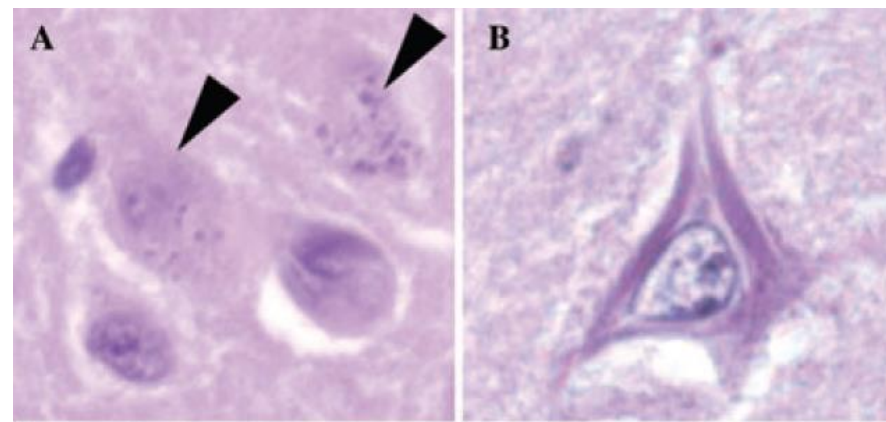
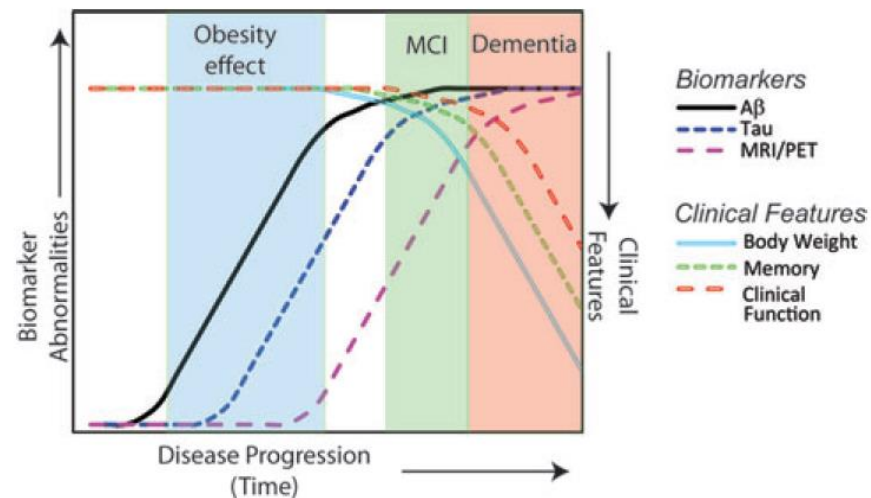
Western Diet correlates with dementia

Barberger-Gateau et al. *Neurology* 69:1921, 2007

Fat or sugar both cause obesity in rats, but only sugar caused cognitive decline

Jurdak et al. *Nutr Neurosci* 11:48, 2008

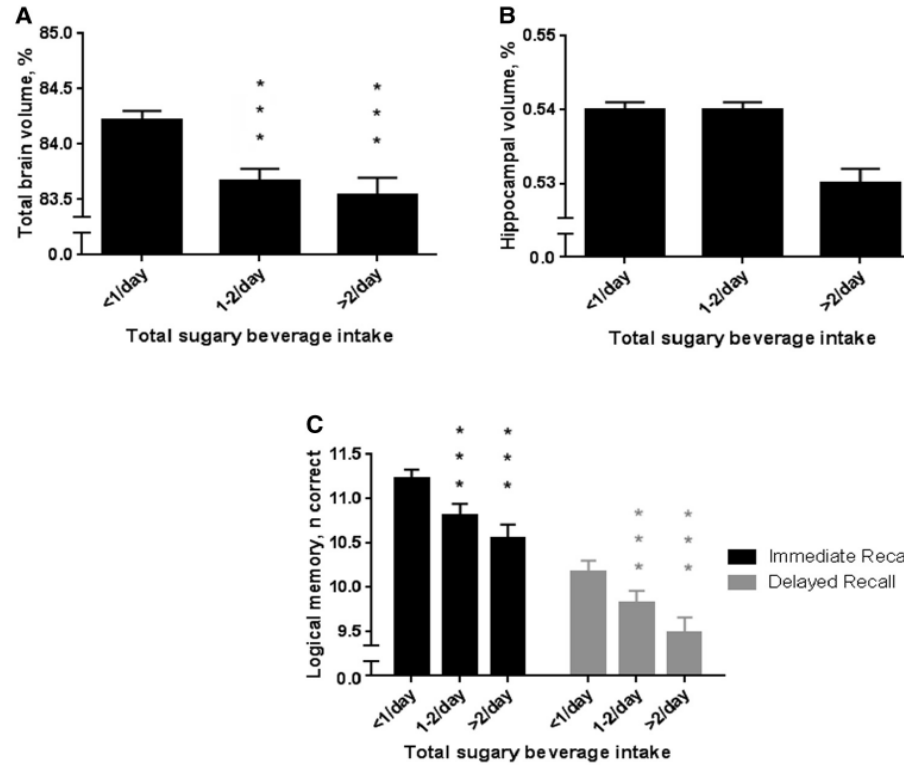
**Causative data in animals;
Associative data in humans**



Featured Article

Sugary beverage intake and preclinical Alzheimer's disease in the community

Matthew P. Pase^{a,b,c,*}, Jayandra J. Himali^{a,b,d}, Paul F. Jacques^{b,e}, Charles DeCarli^{b,f},
Claudia L. Satizabal^{a,b}, Hugo Aparicio^{a,b}, Ramachandran S. Vasan^{b,g,h}, Alexa S. Beiser^{a,b,d},
Sudha Seshadri^{a,b}



Sugar consumption correlates with dementia, as well as other systemic diseases

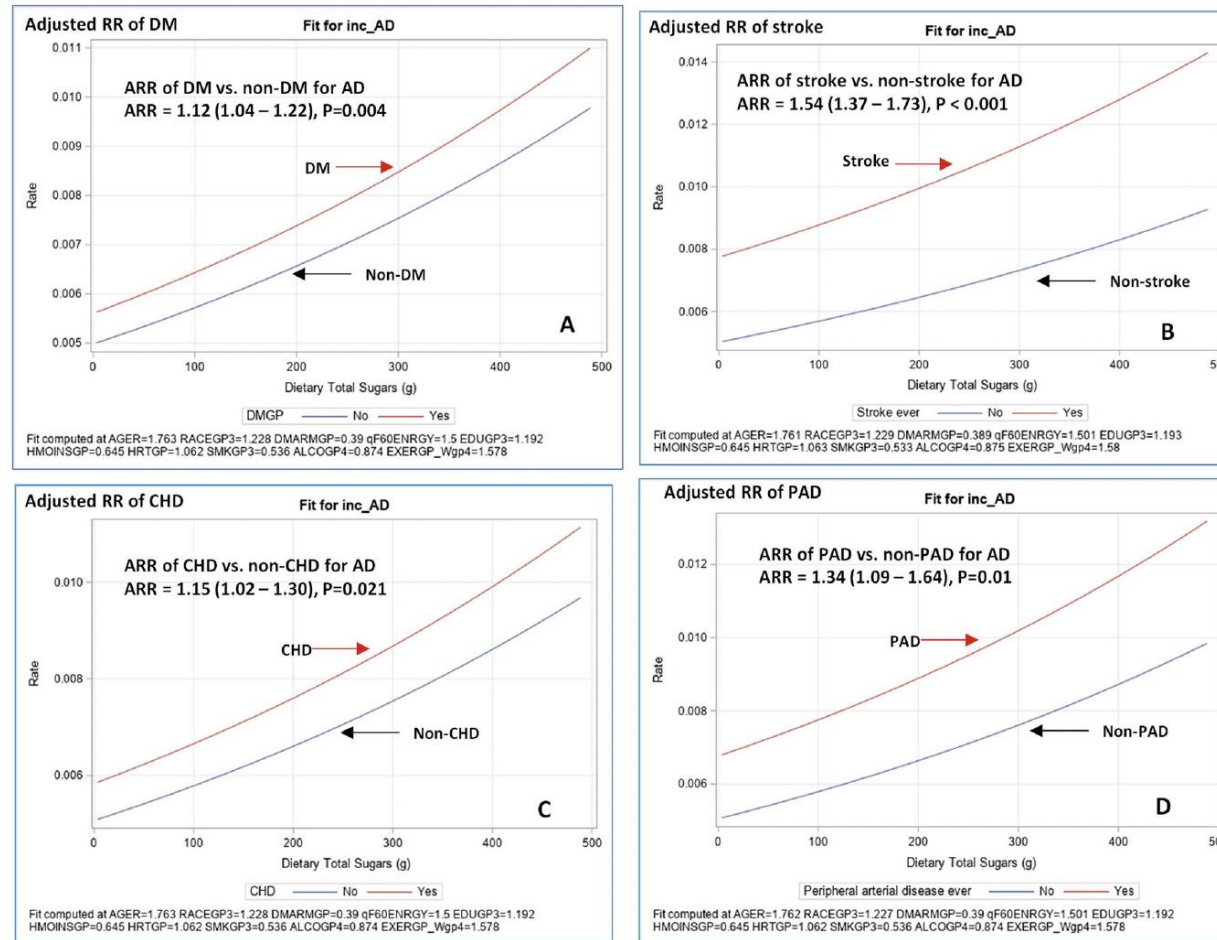
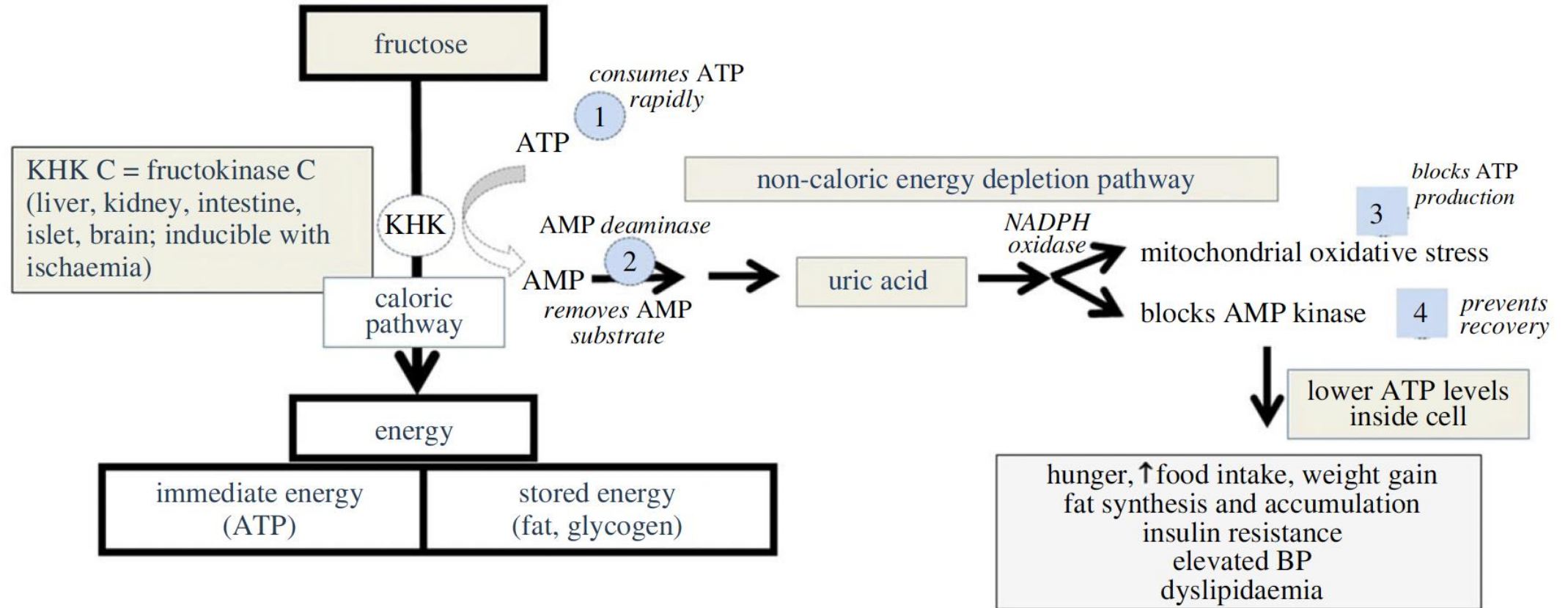
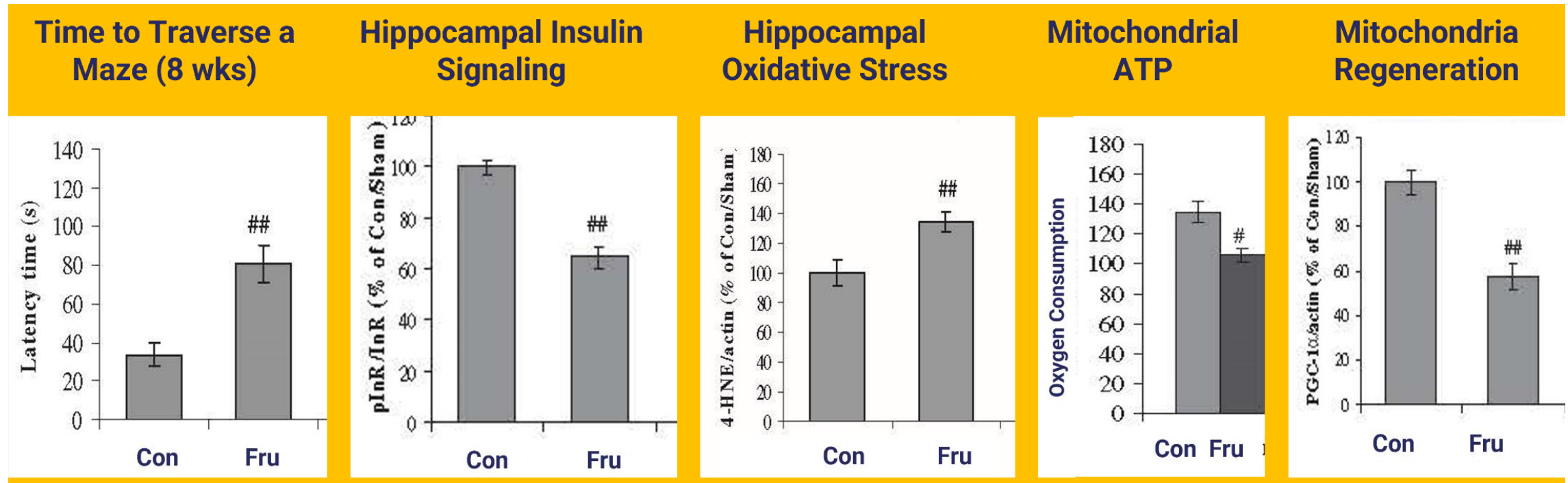


Figure 1. Participants with chronic conditions of diabetes mellitus (DM, Figure 1A), stroke (Figure 1B), coronary heart disease (CHD, Figure 1C), and peripheral arterial disease (PAD, Figure 1D) (red lines) had a significantly higher risk of AD than those without these conditions (black lines). There was an increasing trend of sugar intake (as indicated by x-axis) associated with an increase in incident AD rate (as indicated by y-axis) among those with (red line) and without these conditions (black line). Relative risk (RR) was adjusted for the same covariates in Model 3 of Table 4.

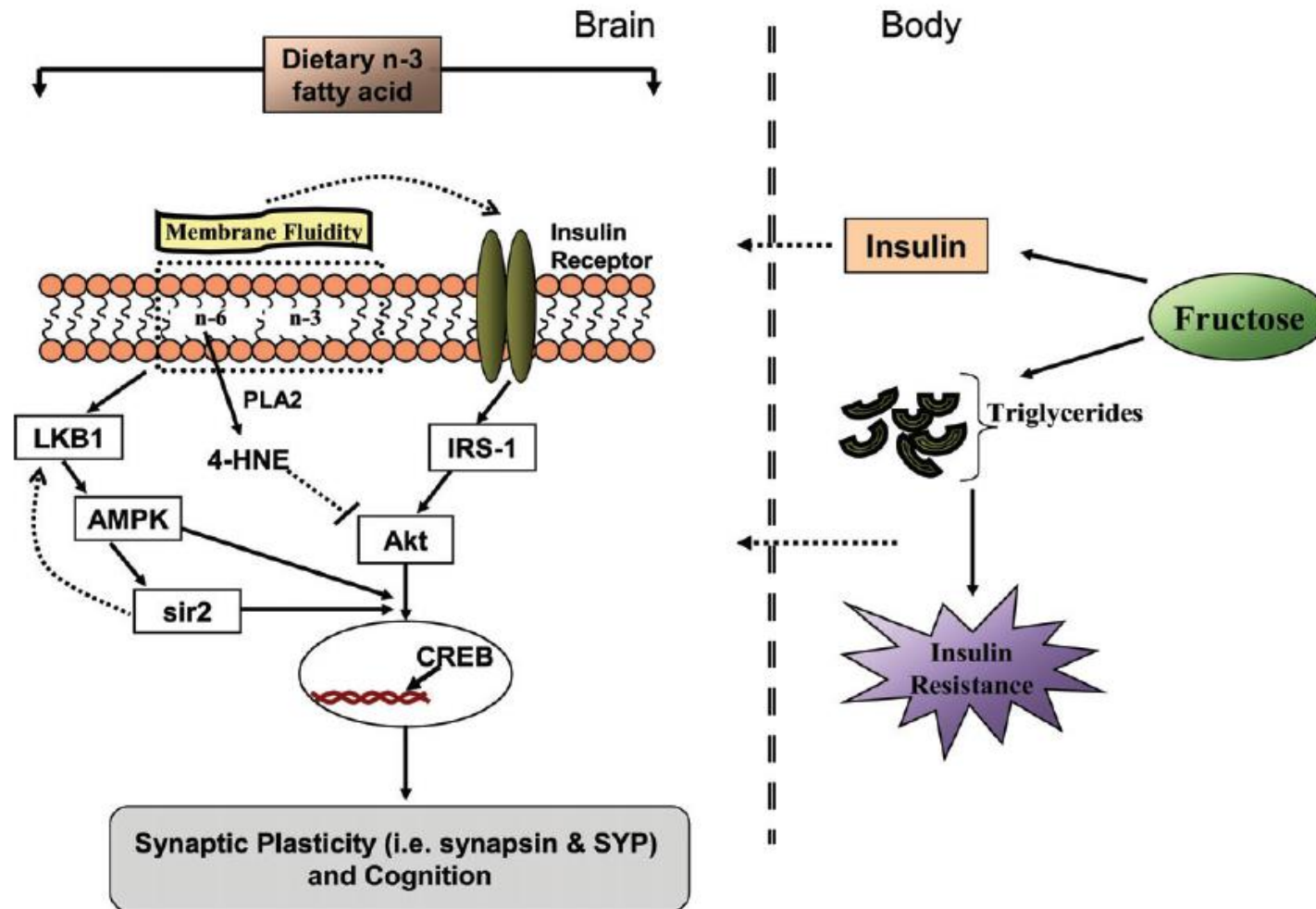
Fructose and inhibition of ATP generation



Effect of Dietary Fructose on the Rat Brain



Insulin resistance, especially in the absence of omega-3's, means lack of neuron signaling



A close-up photograph of a hand holding a slice of whole-grain toast. A bite has been taken out of the bottom right corner, revealing the porous interior of the bread. The toast is golden-brown with some darker spots, possibly from toasting. The background is a plain, light-colored surface.

INGESTED DIETARY

ADVANCED GLYCATION END PRODUCTS

Extruders operate at 200° C



DING RUN

CE CNAS IAF ISO 14001 SGS

DINGRUN MACHINERY
TradeKey.com

The advertisement features a central image of a stainless steel extruder machine with a hopper on top and a control panel on the side. To the left of the machine is a long, black, spiral-shaped extruder tube. Above the machine are several certification logos: CE, CNAS, IAF (Member of Multilateral Recognition Arrangement), and ISO 14001 SGS. Below the machine are four small, rounded square images showing different types of extruded products: puffed yellow snacks, orange fried sticks, white puffed snacks, and orange fried sticks. The entire advertisement is framed by a blue border.

Foods that generate dietary AGE's

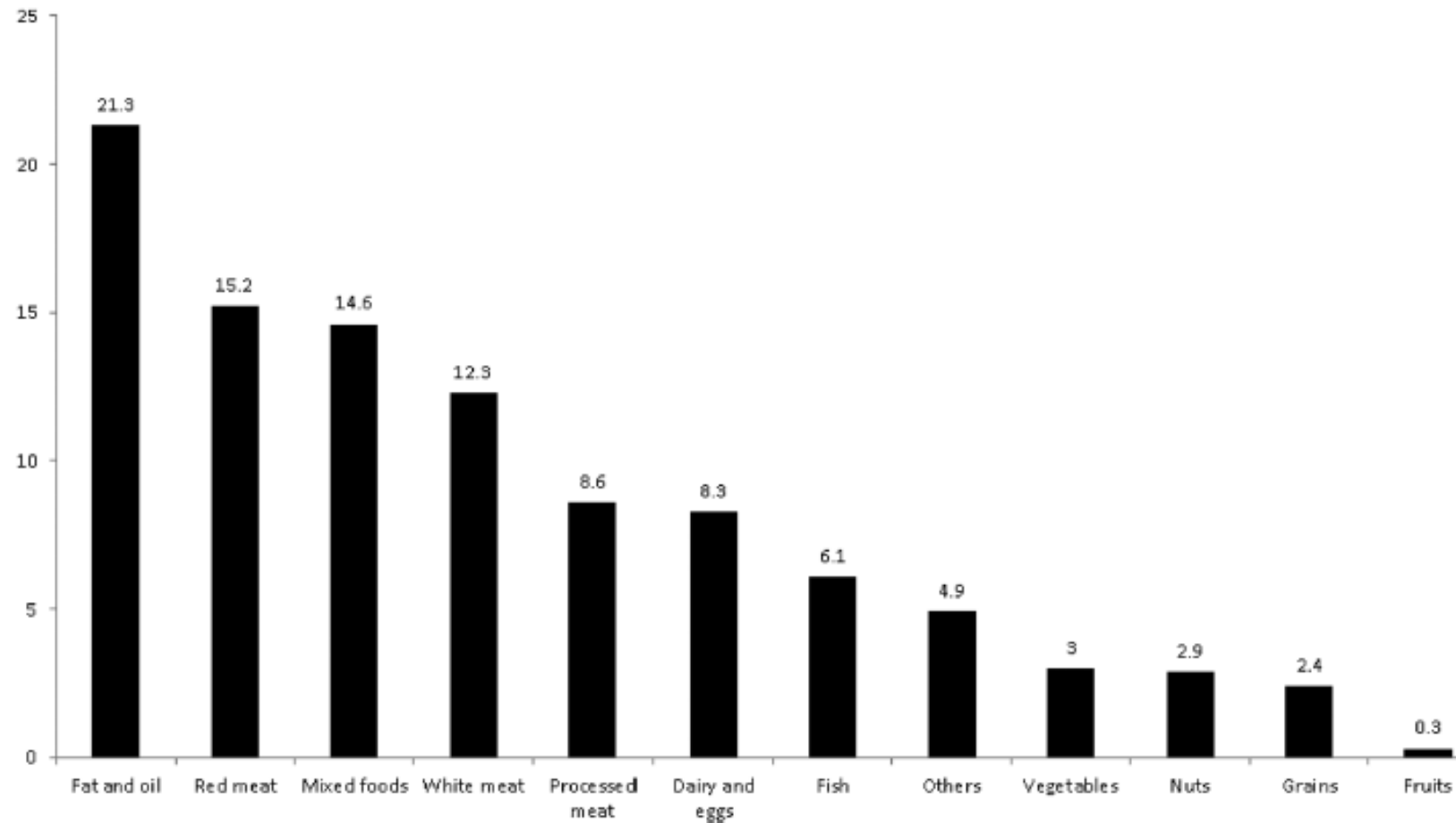
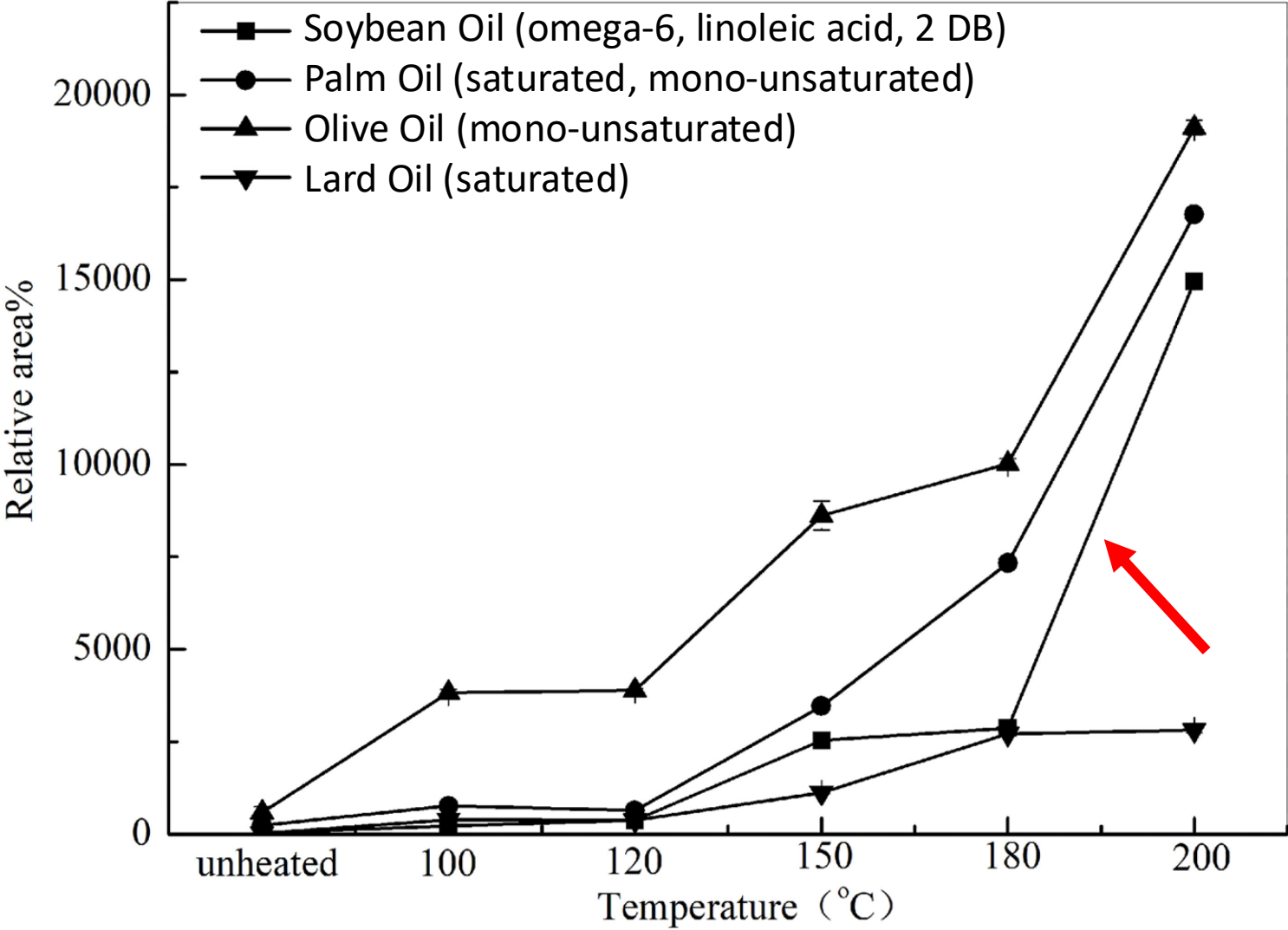


Figure 2.

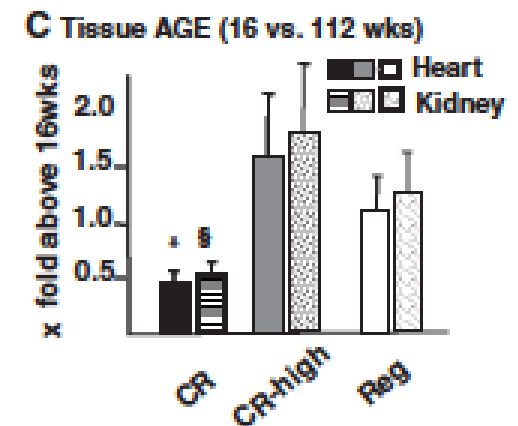
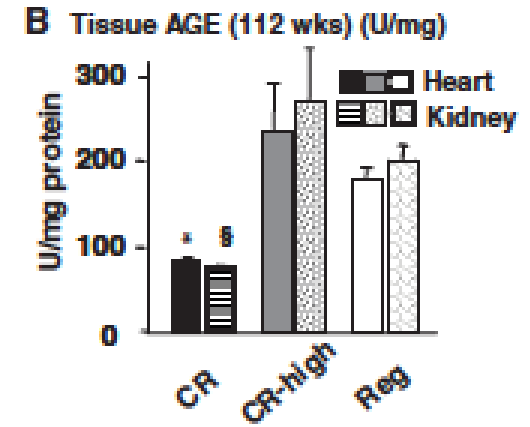
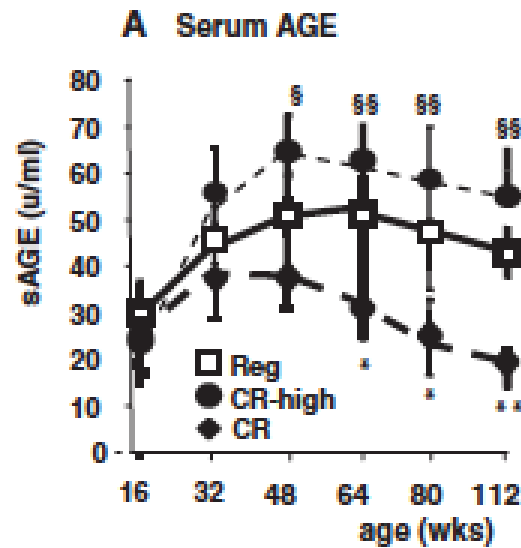
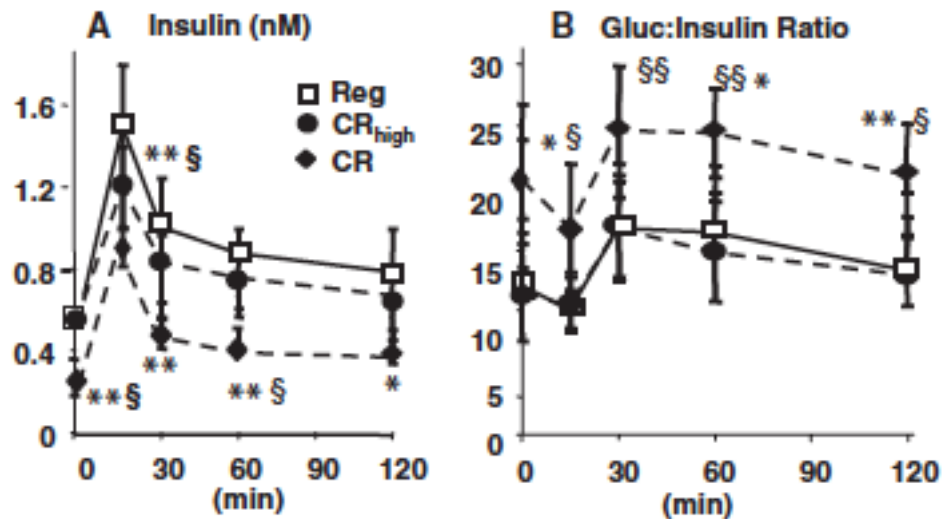
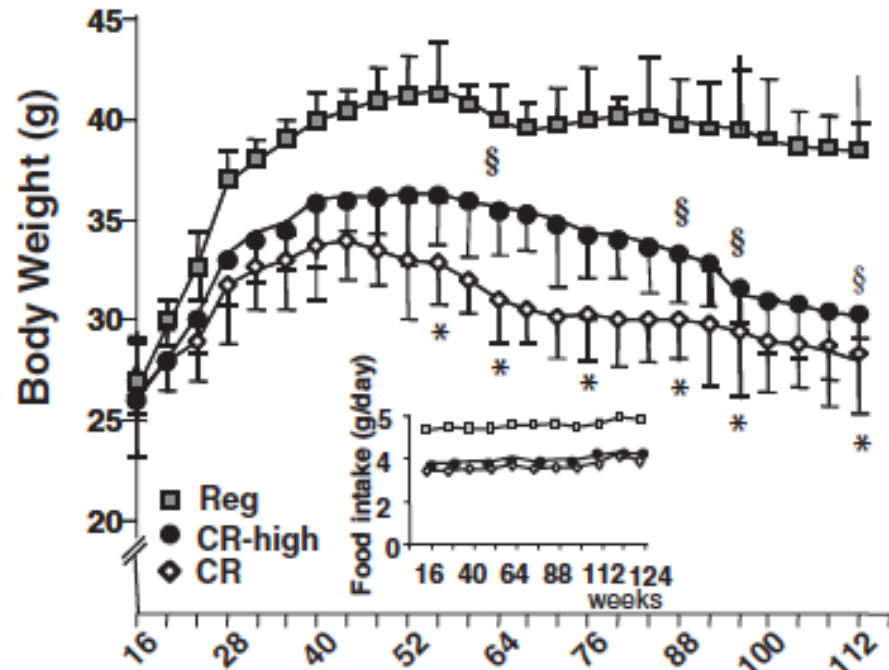
Percentage contribution of food groups to total CML-AGE intake. **Fat and oil:** Butter, margarine, white sauce, cheese sauce, sour cream, sweet cream, salad dressing, and gravy; **Red meat:** Beef roast, pork chop, pork roast, hamburger, liver, meat loaf, and steak; **Mixed foods:** Mixed dish, pizza, spaghetti, lasagna, and potpie; **White meat:** Chicken or turkey; **Processed meat:** Cold cut, ham, sausage, bacon, and hotdog; **Dairy and eggs:** Ice cream, cheese, cottage cheese, milk, yogurt, and eggs; **Fish:** Fish, shellfish, and tuna; **Others:** Cake, candy, donut, pie, biscuit, beer, coffee, liquor, soda, tea, wine, chip, cracker, sugar, fruit punch, juice, tomato juice, apple juice, ketchup, jelly, and pancake; **Vegetables:** Broccoli, Brussel sprout, cabbage, carrots, cauliflower, celery, cucumber, greens, green pepper, lettuce, pea, spinach, squash, tomato, tomato sauce, mixed vegetables, beet, beans, chili, onion, garlic, potatoes, sweet potatoes, soup, and tofu; **Nuts:** Peanut and peanut butter; **Grains:** Grains, brown rice, white rice, corn, bread, cereal, and cookie; **Fruits:** Apple, applesauce, apricot, banana, cantaloupe, grapefruit, grapes, orange, peach, plum, prune, raisin, strawberry, pineapple, watermelon, and fruit mixtures.

Cooking oils generate aldehydes and ROS's at different temperatures depending on number of double-bonds



Do Dietary AGE's Lead to Disease?

Animal Model of Caloric Restriction + Heating Oils



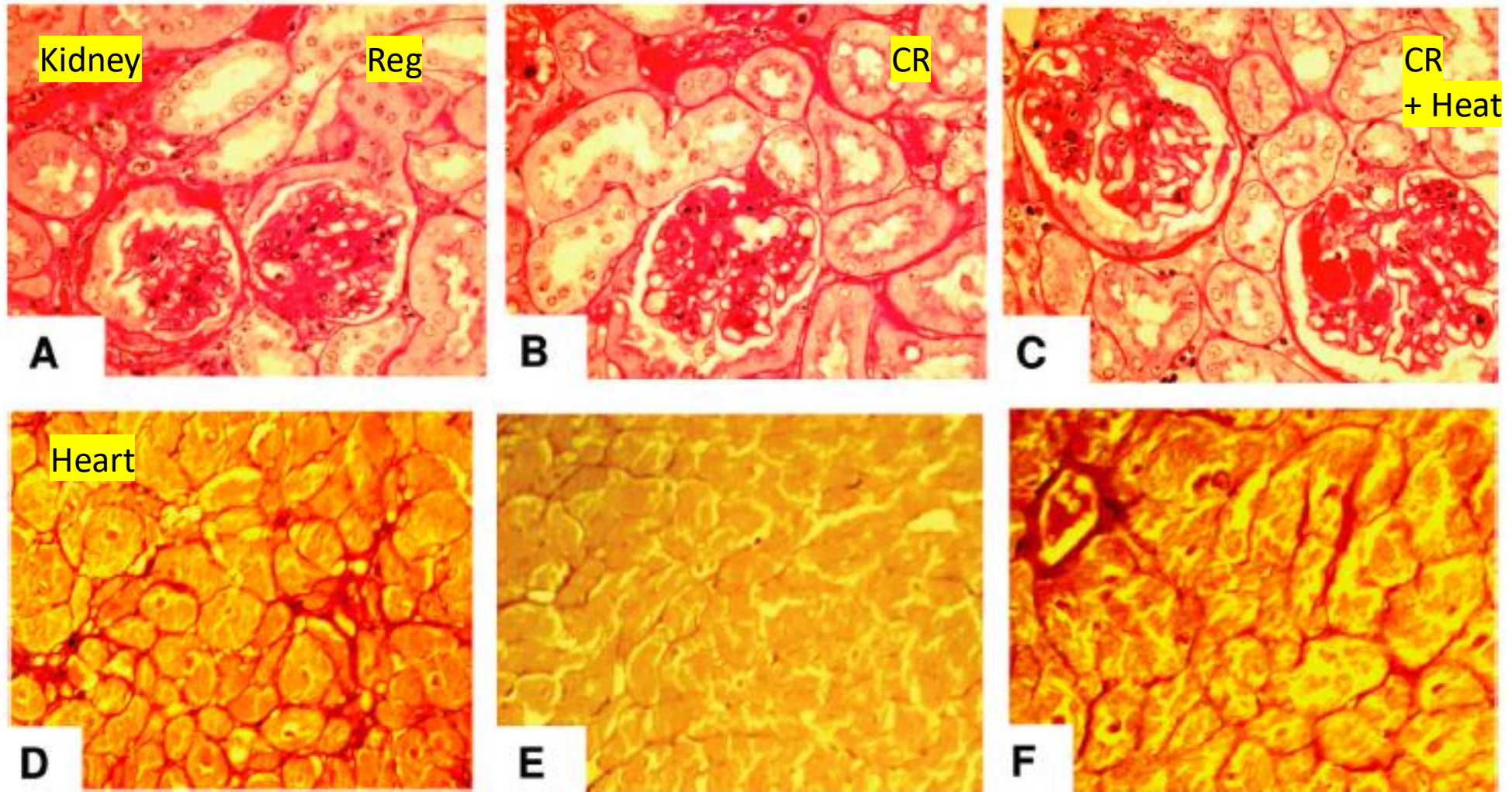


Figure 9. Kidney and heart histology, chronic study. **A–C:** Periodic acid-Schiff-stained kidney cortical sections at 26 months of age ($n = 5$ per group). **A:** Reg: moderate glomerular and tubulointerstitial sclerosing changes. **B:** CR: scattered areas of interstitial fibrosis and tubular atrophy. The glomeruli were of normal size, but had recognizable sclerotic changes. **C:** CR-high: enlarged glomeruli and diffuse glomerular sclerosis, with tubular and interstitial changes more marked than CR mice. **D–F:** Sirius Red-stained coronal mid-ventricular sections ($n = 5$ mice/group), at 26 months. **D:** Reg: bands of connective tissue, concentrated near blood vessels; **E:** CR: no increase in connective tissue; **F:** CR-high: diffuse increase in connective tissue bands in the perivascular regions and fine bundles that surround irregularly enlarged bundles of myocytes. Original magnifications, $\times 250$.

Caloric restriction increases lifespan, Caloric restriction plus heating doesn't

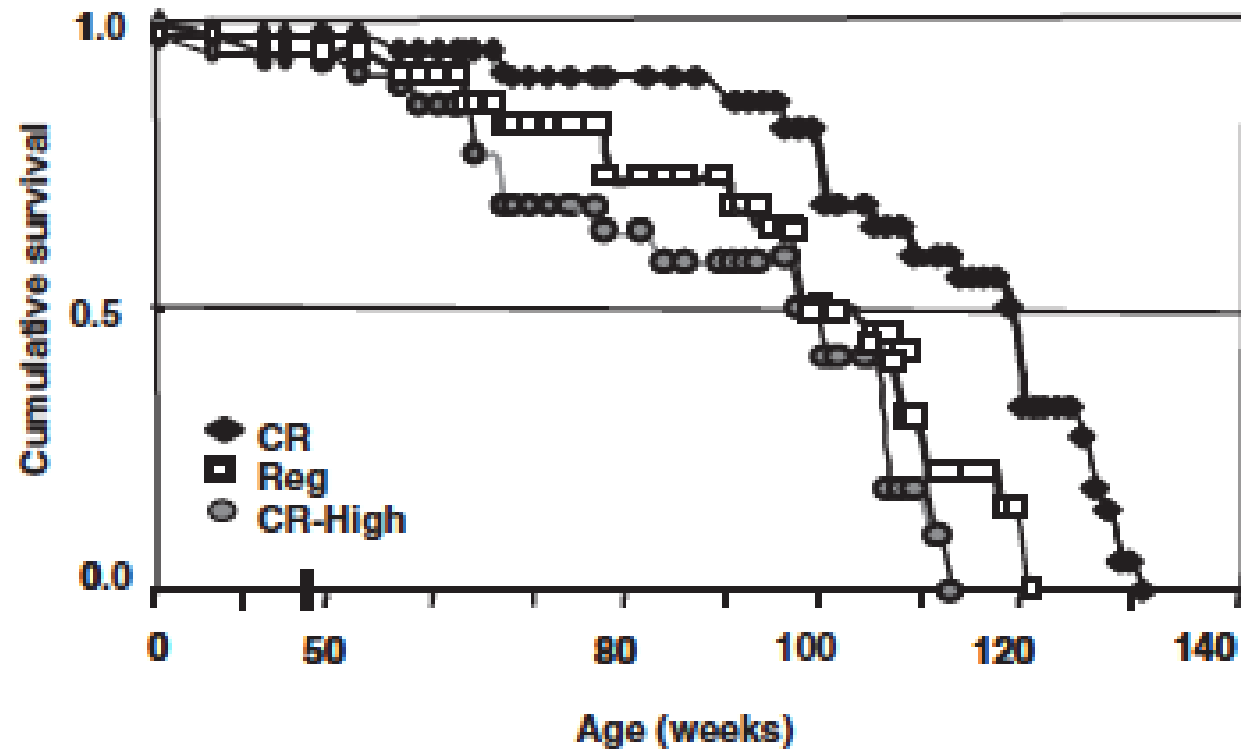


Figure 10. Survival, chronic study. Kaplan-Meier survival curves in Reg mice (open squares), CR mice (filled triangles), and CR-high mice (filled circles) ($n = 22$ per group). Lifespan of Low and CR groups was significantly longer than in Reg ($P < 0.004$) and CR-high groups ($P < 0.0001$). Lifespan in CR-high mice was significantly shorter than in Reg ($P < 0.02$), CR ($P < 0.001$). Differences between the curves were estimated by the log rank test (see Table 3 for detailed analyses).

TABLE 10.2

Possible Mechanisms between AGEs and Cognitive Decline

Direct effects of AGEs

- Receptor for AGEs transfers A β through the BBB.
- Aggregation of A β is increasing due to glycation.
- Glycated A β are more toxic.
- APP is higher due to AGEs.
- AGEs promote phosphorylation of tau proteins.
- Promoting apoptosis in neuron cells.

Mediating effects of AGEs on dementia

- AGEs increase oxidative stress.
 - AGEs promote inflammation.
 - AGEs promote diabetes and its complications.
 - AGEs promote cardiovascular and cerebrovascular diseases.
-

Also true for Parkinson's Disease
and possibly Huntington's Disease

A ROS-reducing diet and Alzheimer's Disease

scientific reports

OPEN

The long-term neuroprotective effect of MIND and Mediterranean diet on patients with Alzheimer's disease

Xiaofang Liu[✉], Bo Yang, Qiong Liu, Mengge Gao & Miaoqing Luo

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antioxidants



Review

Anti-Oxidant and Anti-Inflammatory Activity of Ketogenic Diet: New Perspectives for Neuroprotection in Alzheimer's Disease

Alessandro Pinto^{1,*}^{ORCID}, Alessio Bonucci², Elisa Maggi², Mariangela Corsi² and Rita Businaro²^{ORCID}



nutrients

Review

Mediterranean Diet, Polyphenols, and Neuroprotection: Mechanistic Insights into Resveratrol and Oleuropein

Mónika Fekete^{1,2,3,*}^{ORCID}, Tamás Jarecsny^{3,4,†}^{ORCID}, Andrea Lehoczki^{1,2,3}^{ORCID}, Dávid Major^{1,2,3}^{ORCID}, Vince Fazekas-Pongor^{1,2,3}^{ORCID}, Tamás Csípő^{1,2}, Ágnes Lipécz^{1,2}^{ORCID}, Ágnes Szappanos^{5,6}, Eszter Melinda Pázmándi^{3,7}^{ORCID}, Péter Varga^{1,2,3} and János Tamás Varga^{8,*}^{ORCID}

Original Article

Ketogenic diet decreases oxidative stress and improves mitochondrial respiratory complex activity




Tiffany Greco^{1,2}, Thomas C Glenn^{1,2}, David A Hovda^{1,2,3,4} and Mayumi L Prins^{1,2,3}

JCBFM

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SAGE

Summary

1. Alzheimer's Disease is not treatable, but it is preventable.
2. **From Within:** ROS's are normal products of mitochondrial metabolism, but also feedback to divert energy and reduce ATP generation, unless quenched by anti-oxidants.
3. **From Without:** Dietary AGE's found in ultraprocessed foods increase ROS's and damage tissues.
- 4.a. **Hypothesis:** Exposures  brain ROS's  reduced mitochondrial ATP generation.
- 4.b. ROS's promote inflammation  neuron loss and dementia.
5. You can't get rid of ROS's, but you can reduce them (exposures, diet, anti-oxidants), and doing so prevents dementia.

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