Fat vs. Sugar 2.0

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Member, Institute for Health Policy Studies
Adjunct Professor, Touro University-California
Adjunct Professor UC Hastings College of the Law
Chief Science Officer, Eat REAL

AOK, Berlin, October 17, 2018
Disclosures
Decrease in U.S. Deaths from Heart Disease 1980–2000
offset by Type 2 Diabetes — and they’re not dying!


<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>1980</th>
<th>2000</th>
<th>Change in Risk Factor</th>
<th>Beta Regression Coefficient for Change in Mortality Rate</th>
<th>Deaths Prevented or Postponed</th>
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<tbody>
<tr>
<td>Smoking prevalence (%)</td>
<td></td>
<td></td>
<td>Absolute Change (%)</td>
<td>Reynolds-adjusted mortality rate coefficient</td>
<td>Best Estimate</td>
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<tr>
<td>Men</td>
<td>36.3</td>
<td>24.6</td>
<td>-11.7</td>
<td>-32.2</td>
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<td></td>
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<td>Systolic blood pressure (mm Hg)</td>
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<td>123.9</td>
<td>-5.1</td>
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<td>Men</td>
<td></td>
<td></td>
<td></td>
<td>-0.9458</td>
<td>17,445</td>
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<tr>
<td>Women</td>
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<td></td>
<td></td>
<td>-0.9121</td>
<td>1.27</td>
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<tr>
<td>Total cholesterol (mmol/liter)</td>
<td>5.67</td>
<td>5.33</td>
<td>-0.34</td>
<td>-0.0413</td>
<td>25,905</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td>-0.297</td>
<td>1.93</td>
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<td>Women</td>
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<td>-0.297</td>
<td>2.59</td>
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<td>Physical inactivity (%)</td>
<td>29.6</td>
<td>27.3</td>
<td>-2.3</td>
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<td>Men</td>
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</table>
T2DM increasing around the world

People with DM (in millions) for 2000, projection for 2010, and % increase

Projected annualized inflation rate 3.88%

People with DM (in millions) for 2000, projection for 2010, and % increase

285 MILLION IN 2010

T2DM increasing around the world

Actual  annualized inflation rate  6.55%

T2DM increasing around the world

People with DM (in millions) for 2000, projection for 2010, and % increase

Actual       annualized inflation rate  10.30%

People with DM (in millions) for 2000, projection for 2010, and % increase


T2DM increasing around the world

422 MILLION IN 2014

Was Zum Teufel??
Diabetes in Germany

Tamayo et al. Dtsch Arztebl Int 113:177, 2016
The money is not going to hospitals, physicians, or Big Pharma
The money is not going to hospitals, physicians, or Big Pharma. It’s going to chronic metabolic disease.
Two inconvenient truths
Two inconvenient truths

• There is no medicalized prevention for chronic metabolic disease

• There’s just long-term treatment
Meta-analysis of T2DM Prevention Strategies: Lifestyle and/or Medication

Lifestyle RR: 0.61
Med RR: 0.64
For Both: Number needed to treat (NNT): 25

Haw et al. JAMA Int Med 177:1808, 2017
Two inconvenient truths

• There is no medicalized prevention for chronic metabolic disease
• There’s just long-term treatment

• You can’t fix healthcare until you fix health
• You can’t fix health until you fix the diet
• And you can’t fix the diet until you know what is wrong
Fat for Life?

Six Million Kids Are Seriously Overweight. What Families Can Do.

By Geoffrey Cowley & Sharon Begley
The Fiction

“Beating obesity will take action by all of us, based on one simple common sense fact: All calories count, no matter where they come from, including Coca-Cola and everything else with calories…”

-The Coca Cola Company, “Coming Together”, 2013
History
1955

IKE HAS HEART ATTACK
Hospitalized. Condition Is ‘Good’
The macronutrient wars 1970-1980

SEVEN COUNTRIES
Ancel Keys

A Multivariate Analysis of Death and Coronary Heart Disease

John Yudkin

Pure, White and Deadly

Viking
1972, 1986
The Original Case Against Fat

Ancel Keys “7-Country Study” in fact listed 6, studied 22
Started in 1958, continued for 15 yr

Figure 1A. Correlation between the total fat consumption as a percent of total calorie consumption, and mortality from coronary heart disease in six countries. Data from Keys.7
The Original Case Against Fat

Ancel Keys “7-Country Study” in fact listed 6, studied 22
Started in 1958, continued for 15 yr

Figure 1A. Correlation between the total fat consumption as a percent of total calorie consumption, and mortality from coronary heart disease in six countries. Data from Keys.

Figure 1B - as Figure 1A, but with all countries where data were available when Keys published. 1 Australia 2 Italy 3 Canada 4 Ceylon 5 Chile 6 Denmark 7 Finland 8 France 9 W Germany 10 Ireland 11 Israel 12 Italy 13 Japan 14 Mexico 15 Holland 16 New Zealand 17 Norway 18 Portugal 19 Sweden 20 Switzerland 21 Great Britain 22 USA. Data from Yerushalayim and Hilleboe.
Add in the Maasai, Inuit, Rendille, and Tokelau indigenous tribes
Seven Countries
Correlation of CHD with dietary fat

[Graph showing the correlation between percent calories from fat and CHD deaths per 1000 population.]
The fact that the incidence rate of coronary heart disease was significantly correlated with the average percentage of calories from sucrose in the diets is explained by the intercorrelation of sucrose with saturated fat. Partial correlation analysis shows that with saturated fat constant there was no significant correlation between dietary sucrose and the incidence of coronary heart disease.

Comparisons of coronary death rates with estimates of national diets in international statistics indicate no direct relationship with saturated fats.
The USDA, AMA, and AHA call for dietary fat reduction

- Early 1970’s: discovery of LDL
- Mid 1970’s: Dietary fat raises LDL (A $\rightarrow$ B)
- Late 1970’s: LDL correlated with CVD (B $\approx$ C)

If A $\rightarrow$ B, and B $\approx$ C, then A $\rightarrow$ C, therefore no A, no C
1. Increase carbohydrate consumption to account for 55 to 60 percent of the energy (caloric) intake.

2. Reduce overall fat consumption from approximately 40 to 30 percent energy intake.

3. Reduce saturated fat consumption to account for about 10 percent of total energy intake; and balance that with poly-unsaturated and mono-unsaturated fats, which should account for about 10 percent of energy intake each.

4. Reduce cholesterol consumption to about 300 mg. a day.

5. Reduce sugar consumption by about 40 percent to account for about 15 percent of total energy intake.

6. Reduce salt consumption by about 50 to 85 percent to approximately 3 grams a day.
U.S. DIETARY GOALS 1977

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Nothing about fruit, vegetable, or fiber consumption
The content of low-fat home-cooked food can be controlled.

But low-fat processed food means substitution with carbohydrate.

Which carbohydrate?

Either
- High fructose corn syrup (55% fructose)
- Sucrose (50% fructose)

E.g. Nabisco Snackwells® Oreos
—2g fat, +13g CHO (+4g sugars)
The SFUSD School Milk Program

Courtesy of M. Lustig
Carbohydrate
Fat
Protein

Trends in macronutrient intake and obesity

Trends in macronutrient intake and diabetes

Figure 1: Association between estimated percentage energy from nutrients and total mortality and major cardiovascular disease (n=135,335)
Adjusted for age, sex, education, waist-to-hip ratio, smoking, physical activity, diabetes, urban or rural location, centre, geographical regions, and energy intake.
Major cardiovascular disease=fatal cardiovascular disease+myocardial infarction+stroke+heart failure.
Prospective Urban and Rural Epidemiology (PURE)

Figure 3: Risk of clinical outcomes associated with isocaloric (5% of energy) replacement of carbohydrate with other nutrients (n=135 335)
The animal-based food effect on T2DM goes away after you control for iron/heme intake.
Branched chain amino-acids or choline in red meat may contribute to insulin resistance and inflammation

Trimethylamine Oxide (TMAO), a bacterial metabolite of dietary choline, appears to be pro-inflammatory

Blood levels of dairy saturated fatty acids correlate with protection from T2DM

Dairy saturated fats 15:0, 17:0, and t16:1n-7 are protective against Type 2 diabetes

<table>
<thead>
<tr>
<th>Fatty acid</th>
<th>Cohort</th>
<th>Country</th>
<th>N</th>
<th>Cases</th>
<th>Relative Risk (95% CI) weight</th>
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<td>15:0</td>
<td>MICS</td>
<td>Australia</td>
<td>484</td>
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<tr>
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<td>US</td>
<td>586</td>
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<td>Europe</td>
<td>12132</td>
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<td>0.52 (0.44, 0.60) 29.7</td>
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<td>0.55 (0.38, 0.80) 2.7</td>
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<tr>
<td></td>
<td>Three C</td>
<td>France</td>
<td>39</td>
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<td>0.56 (0.25, 1.11) 0.7</td>
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<tr>
<td></td>
<td>METSIM</td>
<td>Finland</td>
<td>71</td>
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<td>0.62 (0.26, 1.43) 0.9</td>
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<tr>
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<td>0.81 (0.69, 0.94) p=0.02</td>
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<td>Total</td>
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<td>0.24 (0.08, 0.73) 0.8</td>
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<td>0.62 (0.36, 0.99) p=0.02</td>
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Association of full-fat dairy with cardiovascular protection

### FULL FAT DAIRY

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<th>Outcome</th>
<th>p-value</th>
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<td>Composite outcome</td>
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</tr>
<tr>
<td>Major cardiovascular disease</td>
<td>0.0001</td>
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</table>

<table>
<thead>
<tr>
<th>Median intake per day (QR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.5 servings</td>
</tr>
<tr>
<td>0.5-1 servings</td>
</tr>
<tr>
<td>1-2 servings</td>
</tr>
<tr>
<td>&gt;2 servings</td>
</tr>
</tbody>
</table>

### TOTAL (FULL/LOW FAT) DAIRY

<table>
<thead>
<tr>
<th>Outcome</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite outcome</td>
<td>0.24</td>
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<td>Major cardiovascular disease</td>
<td>0.30</td>
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</tr>
<tr>
<td>1-2 servings</td>
</tr>
<tr>
<td>&gt;2 servings</td>
</tr>
</tbody>
</table>

Surrogate markers
LDL correlates with CVD, but not all that well
BMJ Open Lack of an association or an inverse association between low-density-lipoprotein cholesterol and mortality in the elderly: a systematic review

Uffe Ravnskov, David M Diamond, Rokura Hama, Tomohito Hamazaki, Björn Hammarskjöld, Niamh Hynes, Malcolm Kendrick, Peter H Langsjoen, Aseem Malhotra, Luca Mascitelli, Kilmer S McCully, Yoichi Ogushi, Harumi Okuyama, Paul J Rosch, Tore Schersten, Sherif Sultan, Ralf Sundberg

Hypert triglyceridemia is a better CVD risk factor

In Meta-Analysis
(univariate risk)
46,413 Men (16 studies)
  2445 Events
  8.4 yr f/u

10,864 women (5 studies)
  439 events
  11.4 yr f/u

holds up in multivariate analysis

Austin et al, Am J Cardiol 81:7B, 1998
Classification of Lipoproteins

"Bad" (Non-HDL)

Chylomicron and Chylomicron remnant
1000 nm

VLDL (Very Low Density Lipoprotein)
70 nm

IDL (Intermediate Density Lipoprotein)
40 nm

LDL (Low Density Lipoprotein)
20 nm

"Good"

HDL (High Density Lipoprotein)
10 nm
Atherogenic dyslipidemia—It’s not about LDL cholesterol, it’s about LDL particle number

The lipoprotein continuum

“Total LDL” won’t tell you particle number - There’s more LDL\(_B\) than LDL\(_A\) at the same total concentration
TG and HDL change with LDL sizing

Rizzo and Berneis, Quart J Med 99:1, 2006
Randomized Clinical Trials
Conclusions: A dietary intervention that reduced total fat intake and increased intakes of vegetables, fruits, and grains did not significantly reduce the risk of CHD or stroke.

Howard et al. JAMA 295:655, 2006
Randomized controlled trials (RCTs) of drug (41) or dietary (3) interventions

- No overall benefit on mortality
- Most of these trials did not reduce CVD events
- Some of the drug studies reported harm
A high intake of omega-6 fats (vegetable oils) has not been proven as beneficial for our health and trans-fats have been shown to have negative health effects. The higher intake of vegetable oils and the increase in carbohydrate consumption in the last 30-40 years are the two leading factors behind the high rates of obesity and metabolic syndrome in the U.S. Saturated and monounsaturated fats are not.
Saturated fat does not clog the arteries: coronary heart disease is a chronic inflammatory condition, the risk of which can be effectively reduced from healthy lifestyle interventions

Aseem Malhotra, Rita F Redberg, Pascal Meier

AM National Health Trust, UK
RR Editor-in-Chief, JAMA Int Med
PM Editor-in-Chief, BMJ Open Heart

Figure 1  Lifestyle interventions for the prevention and treatment of coronary disease.
Histology of (N)AFLD

Normal (N)AFLD
NAFLD is a worldwide problem, even in normal weight people

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>n</th>
<th>Mode of diagnosis</th>
<th>NAFLD prevalence BMI &lt;25</th>
<th>NAFLD prevalence BMI &gt;25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Younossi et al.2012</td>
<td>United States</td>
<td>11,613</td>
<td>Ultrasound</td>
<td>9.6%</td>
<td>28.8%</td>
</tr>
<tr>
<td>Xu et al.2013</td>
<td>China</td>
<td>6,905</td>
<td>Ultrasound</td>
<td>7.2%</td>
<td>Not studied</td>
</tr>
<tr>
<td>Das et al.2010</td>
<td>India</td>
<td>1,911</td>
<td>Ultrasound/CT</td>
<td>5.1%</td>
<td>31.7%</td>
</tr>
<tr>
<td>Kwon et al.2012</td>
<td>Korea</td>
<td>29,994</td>
<td>Ultrasound</td>
<td>12.6%</td>
<td>50.1%</td>
</tr>
<tr>
<td>Bellentani et al.2000</td>
<td>Italy</td>
<td>257</td>
<td>Ultrasound</td>
<td>16.4%</td>
<td>75.8%</td>
</tr>
<tr>
<td>Sinn et al.2012</td>
<td>Korea</td>
<td>5,878</td>
<td>Ultrasound</td>
<td>27% (BMI 20-25) 16% (BMI &lt;20)</td>
<td>Not studied</td>
</tr>
<tr>
<td>Wei et al.2015</td>
<td>Hong Kong</td>
<td>911</td>
<td>Magnetic Resonance</td>
<td>19.3%</td>
<td>60.5%</td>
</tr>
</tbody>
</table>

*Kumar and Mohan, J Clin Trans Hepat 5:216, 2017*
NAFLD is associated with diabetes, even in normal weight people

MRI Fat Fraction Maps

Obese
Low Liver Fat = 2.6%
Obese
Low Liver Fat = 2.6%
MRI Fat Fraction Maps

Obese
Low Liver Fat = 2.6%

Obese
High Liver Fat = 24%
MRI Fat Fraction Maps

Obese
Low Liver Fat = 2.6%

Obese
High Liver Fat = 24%
MRI Fat Fraction Maps

Obese
Low Liver Fat = 2.6%
Obese
High Liver Fat = 24%
Thin
High Liver Fat = 23%
MRI Fat Fraction Maps

Obese
Low Liver Fat = 2.6%

Obese
High Liver Fat = 24%

Thin
High Liver Fat = 23%
Can you name an energy source that is:
Can you name an energy source that is:

Not necessary for life
Can you name an energy source that is:

- Not necessary for life
- There is no biochemical reaction in the body that requires it
Can you name an energy source that is:

Not necessary for life

There is no biochemical reaction in the body that requires it

Is not nutrition
Can you name an energy source that is:

- Not necessary for life
- There is no biochemical reaction in the body that requires it
- Is not nutrition
- When consumed in excess it is toxic
Can you name an energy source that is:

- Not necessary for life
- There is no biochemical reaction in the body that requires it
- Is not nutrition
- When consumed in excess it is toxic
- We love anyway, and it’s addictive
Can you name an energy source that is:

Not necessary for life

There is no biochemical reaction in the body that requires it

Is not nutrition

When consumed in excess it is toxic

We love anyway, and it’s addictive

**Answer: Ethanol**
Metabolism of Ethanol

Ethanol

Alcohol Dehydrogenase 1B

Acetaldehyde

ROS

Aldehyde Dehydrogenase 2

Citrate → Acetyl-CoA → Malonyl-CoA → Acyl-CoA → VLDL

ACL, ACC, FAS

CPT 1

PKC

SREBP1

Lipid droplet

FTTAD

FFA

Insulin

Dyslipidemia

Muscle IR

TG

TCA cycle

Acetyl-CoA, ACCS2

Gluconeogenesis

O2, ATP, CO2
Sugar and Diabetes

(Causation)
Sugar is toxic unrelated to calories

Isocaloric Fructose Restriction and Metabolic Improvement in Children with Obesity and Metabolic Syndrome


Short-term isocaloric fructose restriction lowers apoC-III levels and yields less atherogenic lipoprotein profiles in children with obesity and metabolic syndrome


Effects of Dietary Fructose Restriction on Liver Fat, De Novo Lipogenesis, and Insulin Kinetics in Children With Obesity

Schwarz et al. Gastroenterology 153:743, 2017
Strategy

• Isocaloric fructose restriction x 9 days in children who are habitual sugar consumers
• No change in weight
• Substitute complex carbs for sugar
• Maintain baseline macronutrient composition of the diet
• Study in PCRC at Day 0 and Day 10
• Assess changes in organ fat, de novo lipogenesis, and metabolic health
## Fasting Labs

<table>
<thead>
<tr>
<th></th>
<th>Day 0</th>
<th>Day 10</th>
<th>β−coefficient (Adjusted Change) [95% CI]</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (bpm)</td>
<td>83.1 ± 10.7</td>
<td>80.1 ± 11.3</td>
<td>-2.8 [-6.5, +0.9]</td>
<td>0.13</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>122.6 ± 10.5</td>
<td>121.1 ± 9.9</td>
<td>-1.39 [-4.9, +2.1]</td>
<td>0.43</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>68.8 ± 8.9</td>
<td>63.7 ± 7.5</td>
<td>-4.9 [-8.1, -1.8]</td>
<td>0.003</td>
</tr>
<tr>
<td>Fasting lactate (mmol/L)</td>
<td>1.2 ± 0.4</td>
<td>0.9 ± 0.3</td>
<td>-0.3 [-0.5, -0.2]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lactate AUC (mM/120 min)</td>
<td>160.0 ± 34.5</td>
<td>129.0 ± 34.5</td>
<td>-31.2 [-41.9, -20.5]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>7.9 ± 4.8</td>
<td>5.2 ± 2.6</td>
<td>-2.7 [-3.8, -1.5]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AST (U/L) *</td>
<td>27.4 ± 14.1</td>
<td>23.8 ± 8.9</td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>ALT (U/L) ¥</td>
<td>28.9 ± 22.8</td>
<td>26.7 ± 19.6</td>
<td>-2.2 [-4.7, +0.3]</td>
<td>0.09</td>
</tr>
<tr>
<td>Fasting TG (mM)</td>
<td>1.4 ± 0.9</td>
<td>1.0 ± 0.5</td>
<td>-0.4 [-0.6, -0.2]</td>
<td>0.002</td>
</tr>
<tr>
<td>Fasting LDL-C (mM)</td>
<td>2.4 ± 0.6</td>
<td>2.1 ± 0.6</td>
<td>-0.3 [-0.4, -0.1]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting HDL-C (mM)</td>
<td>1.2 ± 0.2</td>
<td>1.0 ± 0.2</td>
<td>-0.1 [-0.2, -0.1]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting FFA (mM)</td>
<td>0.6 ± 0.2</td>
<td>0.7 ± 0.2</td>
<td>+0.1 [+0.1, +0.2]</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
DNL is the Conversion of Dietary Carbohydrates into Lipids

Sugar \[\rightarrow\] Fat (lipids)

Fructose \[\rightarrow\] Acetate \[\rightarrow\] Palmitate

New Tracer Method using MIDA: Hellerstein and Neese, AJP 1999
DNL AUC Pre and Post Fructose Restriction

Day 0
Day 10
Oral glucose tolerance test before and after isocaloric fructose restriction
Changes in liver, visceral, and subcutaneous fat
(n = 37)
### LDL subclasses

<table>
<thead>
<tr>
<th></th>
<th>Day 0</th>
<th>Day 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>VLDL</td>
<td>21.0</td>
<td>24.8</td>
</tr>
<tr>
<td>MID</td>
<td>7.6</td>
<td>4.9</td>
</tr>
<tr>
<td>LDL1</td>
<td>14.6</td>
<td>12.7</td>
</tr>
<tr>
<td>LDL2</td>
<td>14.3</td>
<td>9.9</td>
</tr>
<tr>
<td>LDL3</td>
<td>8.9</td>
<td>12.8</td>
</tr>
<tr>
<td>(sd-LDL)</td>
<td>21.0</td>
<td>6.1</td>
</tr>
</tbody>
</table>

### HDL subclasses

<table>
<thead>
<tr>
<th></th>
<th>Day 0</th>
<th>Day 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large</td>
<td>17.9</td>
<td>24.9</td>
</tr>
<tr>
<td>Intermediate</td>
<td>9.6</td>
<td>9.5</td>
</tr>
<tr>
<td>Small</td>
<td>23.1</td>
<td>14.8</td>
</tr>
</tbody>
</table>

## Changes in Lipoprotein Subfractions

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Day 0*</th>
<th>Day 10*</th>
<th>Change (adj. for weight)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-1** (%)</td>
<td>37</td>
<td>30.1 ± 10.7</td>
<td>26.5 ± 9.3</td>
<td>- 26%</td>
<td>0.009</td>
</tr>
<tr>
<td>LDL-2† (%)</td>
<td>37</td>
<td>16.5 ± 13.5</td>
<td>11.8 ± 8.3</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>sdLDL (3) (%)</td>
<td>10</td>
<td>1.9 ± 1.7</td>
<td>0.6 ± 0.7</td>
<td>-1.3</td>
<td>0.04</td>
</tr>
<tr>
<td>LDL Size (nm)</td>
<td>37</td>
<td>271.3 ± 3.1</td>
<td>272.2 ± 2.5</td>
<td>+ 0.87</td>
<td>0.008</td>
</tr>
<tr>
<td>Small HDL (%)</td>
<td>37</td>
<td>14.6 ± 6.1</td>
<td>11.8 ± 5.5</td>
<td>- 2.73</td>
<td>0.001</td>
</tr>
<tr>
<td>Large HDL (%)</td>
<td>37</td>
<td>26.8 ± 7.9</td>
<td>29.3 ± 7.7</td>
<td>+ 2.42</td>
<td>0.04</td>
</tr>
<tr>
<td>Apo-B** (mg/dl)</td>
<td>37</td>
<td>78 ± 24</td>
<td>66 ± 24</td>
<td>- 32%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ApoC-II** (mg/dl)</td>
<td>37</td>
<td>8.7 ± 3.7</td>
<td>8.3 ± 4.2</td>
<td>- 15%</td>
<td>0.19</td>
</tr>
<tr>
<td>ApoC-III** (mg/dl)</td>
<td>37</td>
<td>8.7 ± 3.5</td>
<td>6.5 ± 2.6</td>
<td>- 49%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TG / HDL ratio**</td>
<td>43</td>
<td>3.1 ± 2.5</td>
<td>2.4 ± 1.4</td>
<td>- 38%</td>
<td>0.02</td>
</tr>
</tbody>
</table>

** not normally distributed, log transformed, percent change, † non-parametric, Kruskal-Wallis

De novo
Lipogenesis
DNL

Glycerol-R

TG*

Ac CoA*

Malonyl CoA

Fatty Acid*

VLDDL*
De novo Lipogenesis (DNL)

Glycerol-3-P

Acyl-CoA

Malonyl-CoA

Fatty Acid

TG*

VLDL*

9 days fructose restriction
De novo Lipogenesis

DNL

Glycerol-R

TG* → VLDL*

Ac CoA* → Malonyl CoA → Fatty Acid*

9 days fructose restriction

LIVER

FAT

DNL

Visceral fat

VLDL*
De novo Lipogenesis (DNL)

- Glycerol-R
- TG*
- Ac CoA*
- Malonyl-CoA
- Fatty Acid*

VLDL*

Improved Insulin kinetics

9 days fructose restriction

LIVER FAT

DNL

Visceral fat

SUGAR
Sugar and disease

• Causation
  – Diabetes
  – Heart Disease
  – Fatty Liver Disease
  – Tooth Decay

• Correlation
  – Cancer
  – Dementia
Early warning signals of the coronary heart disease (CHD) risk of sugar (sucrose) emerged in the 1950s. We examined Sugar Research Foundation (SRF) internal documents, historical reports, and statements relevant to early debates about the dietary causes of CHD and assembled findings chronologically into a narrative case study. The SRF sponsored its first CHD research project in 1965, a literature review published in the New England Journal of Medicine, which singled out fat and cholesterol as the dietary causes of CHD and downplayed evidence that sucrose consumption was also a risk factor. The SRF set the review’s objective, contributed articles for inclusion, and received drafts. The SRF’s funding and role was not disclosed. Together with other recent analyses of sugar industry documents, our findings suggest the industry sponsored a research program in the 1960s and 1970s that successfully cast doubt about the hazards of sucrose while promoting fat as the dietary culprit in CHD. Policymaking committees should consider giving less weight to food industry-funded studies and include mechanistic and animal studies as well as studies appraising the effect of added sugars on multiple CHD biomarkers and disease development.
The cholesterol and calorie hypotheses are both dead — it is time to focus on the real culprit: insulin resistance.

Emerging evidence shows that insulin resistance is the most important predictor of cardiovascular disease and type 2 diabetes.
The science against sugar, alone, is insufficient in tackling the obesity and type 2 diabetes crises – We must also overcome opposition from vested interests

Authors:
Aseem Malhotra
Grant Schofield
Robert H. Lustig
Where’s the sugar?

1/3 in beverages
1/6 in desserts
½ hidden in foods that didn’t used to have sugar
e.g. salad dressings
yogurt
tomato sauce, ketchup, condiments
 crackers, other carbohydrate products
Processed food is the culprit

Table 2: Prevalence of obesity among adults in nineteen European countries (1991–2008)

<table>
<thead>
<tr>
<th>Country</th>
<th>Survey year</th>
<th>Prevalence of obesity (%)</th>
<th>Measurement method</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>1999</td>
<td>12.9</td>
<td>Self-reported</td>
<td>(42)</td>
</tr>
<tr>
<td>Belgium</td>
<td>2001</td>
<td>12.7</td>
<td>Direct measure</td>
<td>(43)</td>
</tr>
<tr>
<td>Croatia</td>
<td>2003</td>
<td>20.3</td>
<td>Direct measure</td>
<td>(44)</td>
</tr>
<tr>
<td>Cyprus</td>
<td>2003</td>
<td>12.3</td>
<td>Direct measure</td>
<td>(45)</td>
</tr>
<tr>
<td>Finland</td>
<td>1998</td>
<td>22.4</td>
<td>Self-reported</td>
<td>(46)</td>
</tr>
<tr>
<td>France</td>
<td>1991</td>
<td>7.1</td>
<td>Self-reported</td>
<td>(47)</td>
</tr>
<tr>
<td>Germany</td>
<td>1998</td>
<td>20.8</td>
<td>Direct measure</td>
<td>(48)</td>
</tr>
<tr>
<td>Greece</td>
<td>2004</td>
<td>13.4</td>
<td>Direct measure</td>
<td>(49)</td>
</tr>
<tr>
<td>Hungary</td>
<td>1994</td>
<td>21.1</td>
<td>Direct measure</td>
<td>(50)</td>
</tr>
<tr>
<td>Ireland</td>
<td>1999</td>
<td>18.0</td>
<td>Self-reported</td>
<td>(47)</td>
</tr>
<tr>
<td>Italy</td>
<td>1994</td>
<td>8.2</td>
<td>Self-reported</td>
<td>(51)</td>
</tr>
<tr>
<td>Latvia</td>
<td>2006</td>
<td>16.3</td>
<td>Self-reported</td>
<td>(52)</td>
</tr>
<tr>
<td>Lithuania</td>
<td>2002</td>
<td>16.0</td>
<td>Self-reported</td>
<td>(53)</td>
</tr>
<tr>
<td>Malta</td>
<td>2003</td>
<td>19.8</td>
<td>Self-reported</td>
<td>(54)</td>
</tr>
<tr>
<td>Norway</td>
<td>1997</td>
<td>16.4</td>
<td>Direct measure</td>
<td>(55)</td>
</tr>
<tr>
<td>Portugal</td>
<td>2005</td>
<td>15.2</td>
<td>Direct measure</td>
<td>(56)</td>
</tr>
<tr>
<td>Slovakia</td>
<td>2002</td>
<td>14.3</td>
<td>Self-reported</td>
<td>(57)</td>
</tr>
<tr>
<td>Spain</td>
<td>2000</td>
<td>13.7</td>
<td>Direct measure</td>
<td>(58)</td>
</tr>
<tr>
<td>UK</td>
<td>2008</td>
<td>24.5</td>
<td>Direct measure</td>
<td>(59)</td>
</tr>
</tbody>
</table>

Table 3: Results from linear regression models of obesity prevalence among adults (%) v. household availability of ultra-processed foods (% of total energy) in nineteen European countries (1991–2008)

<table>
<thead>
<tr>
<th>Model</th>
<th>Mean</th>
<th>95% CI</th>
<th>P value</th>
<th>Model $R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude</td>
<td>0.20</td>
<td>0.04, 0.35</td>
<td>0.02</td>
<td>0.30</td>
</tr>
<tr>
<td>Adjusted 1*</td>
<td>0.25</td>
<td>0.07, 0.43</td>
<td>0.01</td>
<td>0.62</td>
</tr>
<tr>
<td>Adjusted 2†</td>
<td>0.23</td>
<td>0.05, 0.45</td>
<td>0.02</td>
<td>0.63</td>
</tr>
</tbody>
</table>

*Adjusted for the countries per capita GDP, squared per capita GDP, time lag in years between the estimates on obesity and availability of ultra-processed foods, and measurement method of obesity (self-reported or directly measured). Adjusted as in model 1 plus for prevalence of physical inactivity and of smoking.

Monteiro et al. Pub Health Nutr 21:18, 2017
Ten conglomerates
Processed Food—An Experiment That Failed

Those of us who have participated in science know that 9 of every 10 experiments are failures. Now imagine that the last 50 years has been a grand clinical research experiment, with the American population as unwitting participants, conducted by 10 principal investigators—Coca-Cola, PepsiCo, Kraft, Unilever, General Mills, Nestlé, Mars, Kellogg, Proctor & Gamble, and Johnson & Johnson. In 1965, these corporations posed the hypothesis that processed food is better than real food. To determine if the experiment was a success or a failure, we have nitrate. Nitrates (cured meat) can be metabolized into nitrosoureas, which can predispose individuals to colon cancer. (9) Too much salt. Approximately 15% of the population is salt sensitive and can manifest with hypertension and cardiac disease. (10) Too much ethanol. Ethanol is converted into liver fat and drives oxidative stress. While clearly a concern in adults, it is less likely that ethanol poses a metabolic risk in most children, as their access is limited. (11) Too much fructose. Children consume fructose instead. In fact, fructose is metabolized...
Conclusions  A high intake of dietary fiber, particularly of the soluble type, above the level recommended by the ADA, improves glycemic control, decreases hyperinsulinemia, and lowers perturbations in patients with type 2 diabetes. (Chandalia et al. N Engl J Med 2000;342:1392-8.)
**Conclusions**: Real food led to weight loss, in either a high-fat or high-carb diet. Processed food did not.

Gardner et al. JAMA 319:667, 2018
PROCESSED food is high-sugar, low fiber
PROCESSED food is high-sugar, low fiber

REAL food is low-sugar, high-fiber
PROCESSED food is high-sugar, low fiber
REAL food is low-sugar, high-fiber
All diets that work are REAL food
PROCESSED food is high-sugar, low fiber

REAL food is low-sugar, high-fiber

All diets that work are REAL food

PROCESSED FOOD IS TOXIC
An educational moment

Let’s rebrand “Type 2 diabetes”: 
An educational moment

Let’s rebrand “Type 2 diabetes”:

PROCESSED FOOD DISEASE
Let food be thy medicine
–Hippocrates
Good food is medicine
Bad food needs medicine
REAL Certified

eatreal.org