Sugar, women, children, babies, and fetuses

Robert H. Lustig, M.D., M.S.L.
Emeritus Professor, Division of Endocrinology
Department of Pediatrics
Institute for Health Policy Studies
University of California, San Francisco
Adjunct Faculty, Touro University-California
Disclosure

• Neither I nor any member of my immediate family has a financial relationship or interest (currently or within the past 12 months) with any proprietary entity producing health care goods or services consumed by, or used on, patients related to the content of this CME activity.

• I do not intend to discuss an unapproved/investigative use of a commercial product/device.
Disclosures
People with DM (in millions) for 2000, projection for 2010, and % increase


Projected annualized inflation rate 3.88%
T2DM increasing around the world

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


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%
T2DM increasing around the world

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


WTF??

422 MILLION IN 2014
OGTT in ‘healthy’ volunteers from ~1970 till 2014
So in 40-50 years our need for insulin increased 2-4 fold: e.g. did we became 2-4 fold more insulin resistant?
The standard model of insulin resistance
The standard model of insulin resistance

Cytokines

Islet Cells

Fat

Decreased Insulin Sensitivity

Increased Portal FFA

Cytokines

Liver

Increased Hepatic Gluconeogenesis

Further Hyperinsulinemia

Source: Clin Endocrinol © 2005 Blackwell Publishing
The standard model of insulin resistance
Obese
Low Liver Fat = 2.6%
MRI Fat Fraction Maps

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%

Normal Weight
High Liver Fat = 23%
MRI Fat Fraction Maps

Obese
- Low Liver Fat = 2.6%

Obese
- High Liver Fat = 24%

Normal Weight
- High Liver Fat = 23%
MRI Fat Fraction Maps

Obese
Low Liver Fat = 2.6%
Fat Healthy

Obese
High Liver Fat = 24%
Fat Sick

Normal Weight
High Liver Fat = 23%
Thin Sick
Sugar
The change in our global food supply

Addition of fructose
- palatability (esp. with decreased fat)
- browning agent

Removal of fiber
- shelf life
- freezing

Substitution of trans-fats
- hardening agent, shelf life
- now removed due to heart disease risk
High Fructose Corn Syrup is 42-55% Fructose; Sucrose is 50% Fructose

Glucose

Fructose

Sucrose
Detrimental Effects of Fructose

Fructose
Fructose-1-P
Inflammation

Dihydroxyacetone-P
Glyceraldehyde

Fructose-6-P
Fructose-1,6-bis-P

PGC-1β
MKK7
JNK1

ChREBP
SREBP1c

Lipid droplet

Hyperglycemia

Fructose

Glut5

Fructokinase

ATP
ADP
AMP
IMP
Uric Acid

AMP deaminase 1

BP
NO

Leptin Resistance

Insulin

FFA
Dyslipidemia

Muscle IR

TG Obesity

Leptin

IR

VLDL

LPL

O2
ATP
CO2

TCA cycle

Pyruvate
Acetyl-CoA
Malonyl-CoA
Acyl-CoA

ACL ACC FAS
CPT-1
Sugar and disease

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

• **Correlation**
  – Cancer
  – Dementia
A different model of insulin resistance

- Cytokines
- Fructose
- Fatty liver
- Sensitivity
- Hepatic insulin resistance
A different model of insulin resistance

- Fructose
- Fatty liver
- Islet cells
- Increased portal FFA
- Decreased insulin sensitivity
- Fat
- Further hyperinsulinemia
- Hepatic insulin resistance
A different model of insulin resistance
Women
NAFLD is more common in men...

Ballestri et al. Adv Ther 34:1291, 2017
NAFLD is associated with diabetes, even in normal weight people
...until menopause, when the ratio shifts

Ballestri et al. Adv Ther 34:1291, 2017
Heart disease is more common in men

Table 1. Incidence of Cardiovascular Disease by Age and Sex. Framingham Study: 20-Year Follow-up

<table>
<thead>
<tr>
<th>Age at Examination</th>
<th>Rate per 1000 per Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
</tr>
<tr>
<td>yrs</td>
<td></td>
</tr>
<tr>
<td>29 to 34</td>
<td>3.4</td>
</tr>
<tr>
<td>35 to 39</td>
<td>2.9</td>
</tr>
<tr>
<td>40 to 44</td>
<td>5.7</td>
</tr>
<tr>
<td>45 to 49</td>
<td>9.1</td>
</tr>
<tr>
<td>50 to 54</td>
<td>16.5</td>
</tr>
<tr>
<td>55 to 59</td>
<td>25.1</td>
</tr>
<tr>
<td>60 to 64</td>
<td>27.6</td>
</tr>
<tr>
<td>65 to 69</td>
<td>26.7</td>
</tr>
<tr>
<td>70 to 74</td>
<td>37.8</td>
</tr>
<tr>
<td>75 to 79</td>
<td>53.0</td>
</tr>
</tbody>
</table>

But after menopause, women catch up

Table 2. Incidence of Cardiovascular Disease by Age and Menopausal Status. Framingham Study: 20-Year Follow-up

<table>
<thead>
<tr>
<th>Age at Examination, Menopausal Status at Risk</th>
<th>Person-Years at Risk</th>
<th>New CVD N</th>
<th>Rate per 1000 per Year</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 40 yrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopausal</td>
<td>4718</td>
<td>3</td>
<td>0.6</td>
<td>0.308</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>454</td>
<td>1</td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td>40 to 44 yrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopausal</td>
<td>4922</td>
<td>3</td>
<td>0.6</td>
<td>0.016</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>1386</td>
<td>5</td>
<td>3.6</td>
<td></td>
</tr>
<tr>
<td>45 to 49 yrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopausal</td>
<td>4492</td>
<td>9</td>
<td>2.0</td>
<td>0.105</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>3792</td>
<td>15</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>50 to 54 yrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopausal</td>
<td>1382</td>
<td>5</td>
<td>3.6</td>
<td>0.203</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>7524</td>
<td>49</td>
<td>6.5</td>
<td></td>
</tr>
<tr>
<td>Total less than 55 yrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopausal</td>
<td>15514</td>
<td>20</td>
<td>2.7‡</td>
<td></td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>13156</td>
<td>70</td>
<td>5.3</td>
<td></td>
</tr>
</tbody>
</table>
Oral hormone replacement therapy doesn’t lower triglycerides, but transdermal estrogen does.

Effects of oral estrogen + progestin from 0 to 12 months

Effects of transdermal estrogen from 12 to 24 months

Sanada et al. Menopause 11:331, 2004
LDL and triglycerides are most affected by menopause

Figure 1. Adjusted within-woman change in lipids attributable to changes in menopausal status, age, estradiol, and follicle-stimulating hormone during the transition from pre- to late perimenopause, Study of Women’s Health Across the Nation, 1995–2004. LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; Lp(a), lipoprotein(a); E2, estradiol; FSH, follicle-stimulating hormone. The statistical significance of within-woman changes is shown. Bonferroni correction for multiple comparisons was applied.
Fructose (not glucose) causes rise in triglycerides in post-menopausal women

Children in the crosshairs
De novo Lipogenesis

DNL

Ac CoA* → Malonyl CoA → Fatty Acid* → TG* → VLDL*
Glycerol-P

Schwarz et al. Gastroenterology 133:742, 2017
De novo Lipogenesis
DNL

Ac CoA* → Malonyl-CoA → Fatty Acid* → TG* → VLDL*

Glycerol-P

9 days fructose restriction

LIVER FAT

DNL

Visceral fat

Schwarz et al. Gastroenterology 133:742, 2017
De novo Lipogenesis
DNL

Glycerol-P
Ac CoA
Malonyl CoA
Fatty Acid
TG*

9 days fructose restriction

Improved Insulin kinetics

LIVER
DNL

FAT

Visceral fat

Schwarz et al. Gastroenterology 133:742, 2017
Independent Confirmation

Preliminary Communication
January 22, 2019

Effect of a Low Free Sugar Diet vs Usual Diet on Nonalcoholic Fatty Liver Disease in Adolescent Boys
A Randomized Clinical Trial

Jeffrey B. Schwimmer, MD1,2; Patricia Ugalde-Nicalo, MD1; Jean A. Welsh, PhD, MPH, RN3,4,5; et al

Author Affiliations
Isocaloric Fructose Restriction Reduces Serum D-Lactate Concentration in Children With Obesity and Metabolic Syndrome

Ayca Erkin-Cakmak,1 Yasmin Bains,2 Russell Caccavello,2 Susan M. Noworolski,3 Jean-Marc Schwarz,4 Kathleen Mulligan,4 Robert H. Lustig,1 and Alejandro Gugliucci2

1Department of Pediatrics, Division of Pediatric Endocrinology, University of California San Francisco, San Francisco, California; 2Glycation, Oxidation and Disease Laboratory, Department of Research, Touro University California College of Osteopathic Medicine, Vallejo, California; 3Department of Radiology and Biomedical Imaging, University of California San Francisco, San Francisco, California; and 4Department of Medicine, Division of Endocrinology, University of California San Francisco, San Francisco, California

ORCiD numbers: 0000-0003-1580-9163 (A. Erkin-Cakmak).
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

![Pie chart showing sources of added sugars](chart.png)

- Sodas: 22.8%
- Cakes and cookies: 9.4%
- Other foods: 6.48%
- Dairy desserts: 3.8%
- Ready-to-eat cereals: 3%
- Breads and muffins: 2.1%
- Yogurt: 1.1%
- Other foods: 6.48%
- Fructose & sports drinks: 7.4%
- Energy drinks: 1.5%
- Sweetened milk: 1.9%
- Alcohol beverages: 36%
- Coffee and tea: 3.5%
**SUGAR IN CHILDREN’S CEREALS:**
POPULAR BRANDS PACK MORE SUGAR THAN SNACK CAKES AND COOKIES

---

**10 Worst Children’s Cereals**
Based on percent sugar by weight

1. Kellogg’s Honey Smacks 
2. Post Golden Crisp 
3. Kellogg’s Froot Loops Marshmallow 
4. Quaker Oats Cap’n Crunch’s OOPS! All Berries 
5. Quaker Oats Cap’n Crunch Original 
6. Quaker Oats Oh!s 
7. Kellogg’s Smorzs 
8. Kellogg’s Apple Jacks 
9. Quaker Oats Cap’n Crunch’s Crunch Berries 
10. Kellogg’s Froot Loops Original

Percent sugar by weight:

- 55.6%
- 51.9%
- 48.3%
- 46.9%
- 44.4%
- 44.4%
- 43.3%
- 42.9%
- 42.3%
- 41.4%

Source: EWG analysis of nutrition labels for 84 children’s cereals.
Sugar is the ‘alcohol of the child’, yet we let it dominate the breakfast table

Robert Lustig

With kids consuming half their sugar quota first thing, it’s no wonder they’re getting diabetes and liver disease. We have to fight corporate interests.

‘On average, cereal contains a whopping 12g of sugar, all added, in a typical serving.’ Photograph: Stockbyte/Rex Features

Wednesday 4 January 2017 08:31 EST
The SFUSD School Milk Program

Courtesy of M. Lustig
The SFUSD School Milk Program

Courtesy of
M. Lustig
Babies
## Commercial infant foods and health claims

| Table 6. High sodium or high sugar content among products with different claims.
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>High sodium (&gt;130mg)</td>
<td>p value</td>
<td>n</td>
<td>High sugar (&gt;10%)</td>
</tr>
<tr>
<td>Total</td>
<td>363</td>
<td>85 (23.4)</td>
<td>237</td>
<td>129 (54.4)</td>
<td></td>
</tr>
<tr>
<td>Food claim</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composition claim</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>320</td>
<td>66 (20.6)</td>
<td>0.001</td>
<td>224</td>
<td>122 (54.5)</td>
</tr>
<tr>
<td>No</td>
<td>43</td>
<td>19 (44.2)</td>
<td>13</td>
<td>7 (53.8)</td>
<td></td>
</tr>
<tr>
<td>Nutrition claim</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>151</td>
<td>34 (22.5)</td>
<td>0.733</td>
<td>131</td>
<td>68 (51.9)</td>
</tr>
<tr>
<td>No</td>
<td>212</td>
<td>51 (24.1)</td>
<td>106</td>
<td>61 (57.5)</td>
<td></td>
</tr>
<tr>
<td>Health claim</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>182</td>
<td>61 (33.5)</td>
<td>&lt;0.001***</td>
<td>146</td>
<td>68 (46.6)</td>
</tr>
<tr>
<td>No</td>
<td>181</td>
<td>24 (13.3)</td>
<td>91</td>
<td>61 (67.0)</td>
<td></td>
</tr>
<tr>
<td>Salt related claim</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No added salt</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>19</td>
<td>0 (0.0)</td>
<td>0.013*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>344</td>
<td>85 (24.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No added seasoning</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>78</td>
<td>4 (5.1)</td>
<td>&lt;0.001***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>285</td>
<td>81 (28.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sugar claim</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No added sugar</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>48</td>
<td>35 (72.9)</td>
<td>0.004**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>189</td>
<td>94 (49.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 Data are presented as the number (percentage).

* p < 0.05;

** p < 0.01;

*** p < 0.001 by chi-square test.
What about WIC?

Has the WIC Incentive to Formula-Feed Led to an Increase in Overweight Children?\textsuperscript{1,2}

Donald Rose,\textsuperscript{*3} J. Nicholas Bodor\textsuperscript{*} and Mariana Chilton\textsuperscript{†}

\textsuperscript{*}Department of Community Health Sciences, Tulane University School of Public Health and Tropical Medicine, New Orleans, LA 70112 and \textsuperscript{†}Center for Community Health and Prevention, Drexel University School of Public Health, Philadelphia, PA 19102
Could this be the reason for obesity in 6-month olds?

INGREDIENTS (Powder)
((U) Pareve*)

43.2% Corn syrup solids,
14.6% soy protein isolate,
11.5% high oleic safflower oil,
10.3% sugar (sucrose),
8.4% soy oil,
8.1% coconut oil

Courtesy of M. Walker
Fructose in breast milk predicts weight and fat mass at 6 mos of age

Goran et al. Nutrients 9:146, 2017
Fetuses
Obesity Before Birth
Maternal and Prenatal Influences on the Offspring

Obesity obeys the First Law of Thermodynamics. The routine assumption is that obesity is the result of a mismatch between calories in and calories out; in other words, the result of two divergent behaviors. However, there is mounting evidence that biochemical forces can drive oblate weight gain, and that the observed behaviors of increased energy intake and decreased energy expenditure are secondary to these processes. Furthermore, many of these biochemical forces are determined in utero; resulting in a developmental drive toward obesity and disease in later life. Four distinct prenatal forces have thus far been identified: 1) genetics; 2) epigenetics; 3) developmental programming; and 4) environmental obesogens. This volume explores the evidence for each of these in detail in human and animal models, and attempts to provide a cohesive analysis of the biochemical bases of obesity.

This volume will appeal to geneticists, developmental biologists, endocrinologists, epidemiologists, toxicologists, obstetrician/gynecologists, nutritionists, veterinary scientists, animal husbandry researchers, domestic species researchers, and obesity researchers and practitioners.

This very timely volume provides an in-depth scholarly overview of a critical challenge facing our society—the obesity epidemic. Dr. Robert H. Lustig has assembled expert authors to address the fundamental contribution of preprogrammed genetic disorders leading to obesity, as well as the role of very early environmental influences. The chapters range from classic genetic mechanistic understanding through intra-uterine epigenetic influences, factors determining developmental programming, and the new clinical science of perinatal obesogens.

Obesity Before Birth. Maternal and prenatal influences on the offspring, brings easily accessible, cutting edge information to geneticists, pediatricians, endocrinologists, as well as those clinicians and scientists pursuing the complex yet elusive causes of childhood obesity and related disorders.

Shlomo Melmed, M.D. Series Editor
Maternal body fat correlates with umbilical cord gene expression for inflammation and insulin sensitivity

Thakali et al. Ped Research 76:202, 2014
Postulated effect of maternal fructose consumption on the offspring

Maternal diet
High fructose intake during pregnancy and/or breast feeding

- Increased adipogenesis
  - High lipogenic potential of fructose increases adipocyte number and fat mass

- Disruption of hypothalamic development
  - Alteration of pathways involved in regulation of energy balance

- Increased appetite
  - Alteration of hunger-signalling hormones and taste preferences

Obesity and metabolic disruption in offspring during early development and throughout life

Figure 1 | Links between obesity and fructose exposure during critical developmental periods. High levels of exposure to fructose during gestation and infancy influence the development of adipose tissue, hypothalamic signalling and appetite regulation. In turn, these changes promote long-term obesity, metabolic dysfunction and disease.

Experimental maternal fructose ingestion: effects on the placenta

Experimental maternal fructose ingestion: effects on the offspring
Summary

- Fructose, the sweet molecule of sugar, is preferentially turned into liver fat
- That liver fat can either be exported out (as triglyceride), leading to heart disease;
- or the fat will precipitate in the liver, leading to NAFLD and NCD’s
- Premenopausal women (high estrogen levels) metabolize TG’s faster, and so have lower incidence of heart disease and NAFLD than do men
- But after menopause, protection is lost; sugar drives TG levels higher, leading to increased risk for heart disease and NAFLD
- Kid’s and baby food are oversweetened on purpose, and then misbranded
- Maternal fructose ingestion can cross into breast milk, and possibly increase infant weight gain and body fat
- Fructose can also cross the placenta, leading to placental insufficiency, and induction of fat-making enzymes in the fetus
Collaborators

UCSF
Andrea Garber, Ph.D., R.D.
Patrika Tsai, M.D., M.P.H.
Emily Perito, M.D., M.P.H.

Touro University Dept. of Biochemistry
Jean-Marc Schwarz, Ph.D.
Alejandro Gugliucci, Ph.D.

SFGH Depts. of Medicine & Radiology
Susan Noworolski, Ph.D.
Kathleen Mulligan, Ph.D.

Stanford Prevention Institute
Sanjay Basu, M.D., Ph.D.

Union of Concerned Scientists
Eat REAL

Environmental Working Group
Dietitians for Professional Integrity

UCSF Clinical/Translational Science Institute
Laura Schmidt, Ph.D.
Claire Brindis, Dr.P.H.
Cristin Kearns, D.D.S.
Stanton Glantz, M.D.

UC Hastings College of the Law
David Faigman, J.D.
Marsha Cohen, J.D.

UC Berkeley Dept. of Nutr. Sciences
Pat Crawford, R.D., Ph.D.
Kristine Madsen, M.D., M.P.H.
Lorrenee Ritchie, Ph.D.
Paula Yoffe, B.A.

Health Evolution Partners
David Brailer, Ph.D.