Fructose and the liver: More than just extra calories?

Robert H. Lustig, M.D., M.S.L.
Division of Endocrinology, Department of Pediatrics
Institute for Health Policy Studies
University of California, San Francisco

Adjunct Faculty, UC Hastings College of the Law

President, Institute for Responsible Nutrition

STOPNASH Symposium, Washington, DC, Oct. 7, 2015

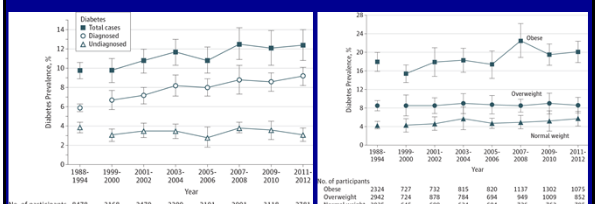
- No disclosures

Then

Now

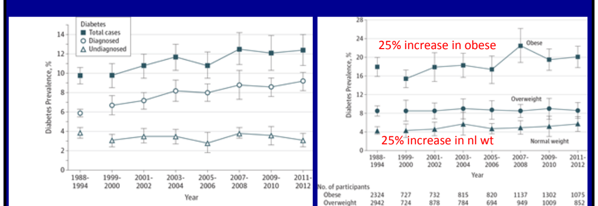
This video is from the WebMD Video Archive

Secular trend in diabetes among U.S. adults, 1988-2012



JAMA 314:1021, 2015, doi:10.1001/jama.2015.10029

Secular trend in diabetes among U.S. adults, 1988-2012



JAMA 314:1021, 2015, doi:10.1001/jama.2015.10029

Criticism from the nutritional community

Nutrition Research Reviews (2014), 27, 119–130 doi:10.1017/S0954422414000067

Misconceptions about fructose-containing sugars and their role in the obesity epidemic

Vincent J. van Buul[1], Luc Tappy[2] and Fred J. P. H. Brouns[1]*
[1]Maastricht University, Faculty of Health, Medicine and Life Sciences, Department of Human Biology, PO Box 616, 6200 MD, Maastricht, The Netherlands
[2]University of Lausanne, Department of Physiology, 7 Rue du Bugnon, CH-1005, Lausanne, Switzerland

"To say that fructose is toxic is a total misconception of the nature of the molecule….If you have too much oxygen, it is toxic. If you get too much water, you have water intoxication. That doesn't mean we say oxygen is toxic".

– Fred Brouns, Atlantic Monthly, USA, June 5, 2014

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[2]*University of Lausanne, Department of Physiology, 7 Rue du Bugnon, CH-1005, Lausanne, Switzerland*

Vincent Van Buul	Product Development Coordinator, Gruma/Mission Foods
Luc Tappy	Recipient of Numerous Fructose Grants, Nestle
Fred Brouns	Cargill Manager of Nutritional Sciences until 2008, now runs nutrition and health consulting firm

Toxicity:

The degree to which a substance can damage an organism

- Does not distinguish acute vs. chronic toxicity

Requisites:

- Must be an “independent risk factor”
- Exclusive of calories
- Exclusive of obesity
- Must establish causation

Criticisms of Fructose Toxicity

- **Animal models, not human studies**
- **Administration of excessive doses of fructose**

Criticisms of Fructose Toxicity

- Animal models, not human studies
- Administration of excessive doses of fructose

WILL LIMIT DISCUSSION TO:
HUMAN DATA,
HUMAN CONSUMPTION,
AND IN DOSES ROUTINELY INGESTED

Sugar and Diabetes

(Prospective Correlation)

SSB's and BMI-adjusted risk of diabetes in EPIC-Interact (Europe)

Table 2 HRs (and 95% CIs) for type 2 diabetes according to type and amount of sweet beverage consumption in the EPIC-InterAct study

Variable and model	<1 glass[a]/ month HR	1–4 glasses[a]/ month HR[b] (95% CI)	>1–6 glasses[a]/ week HR[b] (95% CI)	≥1 glass[a]/ day HR[b] (95% CI)	p for trend
Juices and nectars (median intake, g/day)	(0.0)	(17.1)	(100.0)	(338.3)	
No. cases	5,837	1,702	3,425	720	
Crude model	1.00 (ref)	0.88 (0.80, 0.98)	0.89 (0.83, 0.94)	0.97 (0.85, 1.11)	0.64
Adjusted model	1.00 (ref)	0.91 (0.80, 1.02)	0.96 (0.88, 1.04)	1.00 (0.87, 1.15)	0.63
Adjusted model+EI	1.00 (ref)	0.91 (0.81, 1.02)	0.96 (0.88, 1.04)	0.99 (0.86, 1.14)	0.84
Adjusted model+EI+BMI	1.00 (ref)	0.97 (0.86, 1.10)	1.04 (0.96, 1.13)	1.06 (0.90, 1.25)	0.21
Total soft drinks[c] (median intake, g/day)	(0.0)	(20.0)	(95.1)	(413.1)	
No. cases	5,794	1,604	2,987	1,299	
Crude model	1.00 (ref)	1.21 (1.07, 1.36)	1.30 (1.18, 1.43)	1.78 (1.55, 2.04)	<0.0001
Adjusted model	1.00 (ref)	1.21 (1.07, 1.37)	1.26 (1.13, 1.42)	1.58 (1.35, 1.84)	<0.0001
Adjusted model+EI	1.00 (ref)	1.21 (1.07, 1.37)	1.27 (1.12, 1.43)	1.59 (1.35, 1.88)	<0.0001
Adjusted model+EI+BMI	1.00 (ref)	1.17 (0.97, 1.42)	1.11 (0.98, 1.26)	1.21 (1.05, 1.41)	0.0005
Sugar-sweetened soft drinks[d] (median intake, g/day)	(0.0)	(19.3)	(94.3)	(425.7)	
No. cases	3,948	964	1,599	605	
Crude model	1.00 (ref)	1.14 (0.97, 1.35)	1.16 (1.05, 1.28)	1.68 (1.40, 2.02)	<0.0001
Adjusted model	1.00 (ref)	1.13 (0.97, 1.31)	1.04 (0.94, 1.15)	1.39 (1.16, 1.67)	<0.0001
Adjusted model+EI	1.00 (ref)	1.12 (0.96, 1.31)	1.04 (0.94, 1.15)	1.39 (1.15, 1.69)	0.001
Adjusted model+EI+BMI	1.00 (ref)	1.19 (0.91, 1.56)	1.07 (0.94, 1.21)	1.29 (1.02, 1.63)	0.013
Artificially sweetened soft drinks[e] (median intake, g/day)	(0.0)	(18.3)	(89.0)	(500.0)	
No. cases	5,242	689	894	291	
Crude model	1.00 (ref)	1.09 (0.97, 1.23)	1.52 (1.36, 1.69)	1.84 (1.52, 2.23)	<0.0001
Adjusted model	1.00 (ref)	1.10 (0.93, 1.29)	1.46 (1.29, 1.65)	1.93 (1.47, 2.54)	<0.0001
Adjusted model+EI	1.00 (ref)	1.08 (0.93, 1.26)	1.46 (1.29, 1.65)	1.88 (1.44, 2.45)	<0.0001
Adjusted model+EI+BMI	1.00 (ref)	1.05 (0.81, 1.35)	1.18 (1.03, 1.35)	1.13 (0.85, 1.52)	0.24

Romaguera-Bosch et al. Diabetologia 56:1520, 2013

Associations between consumption of sugar sweetened beverages and fruit juice and incident type 2 diabetes: meta-analysis of prospective cohort studies

Sugar Sweetened Beverages (n=17)	Not Adjusted for Adiposity: Relative Risk	I^2	Adjusted for Adiposity: Relative Risk	I^2
Meta-analysis, crude:	1.25 (1.14 to 1.37)	89	—	—
+multivariable adjusted	1.18 (1.09 to 1.28)	89	1.13 (1.06 to 1.21)	79
+calibration for information bias	1.43 (1.20 to 1.70)	86	1.28 (1.12 to 1.46)	73
+calibration for publication bias	1.42 (1.19 to 1.69)	85	1.27 (1.10 to 1.46)	73

Fruit Juices (n=13)	Not Adjusted for Adiposity: Relative Risk	I^2	Adjusted for Adiposity: Relative Risk	I^2
Meta-analysis, crude:	0.97 (0.90 to 1.06)	79	—	
+multivariable adjusted	1.05 (0.99 to 1.11)	58	1.07 (1.01 to 1.14)	51
+calibration for information bias	1.06 (0.98 to 1.14)	49	1.10 (1.01 to 1.20)	29
+calibration for publication bias	Not detected	—	Not detected	—

Imamura et al. BMJ dx.doi.org/10.1136/bmj.h3576 (epub 21 July 2015)

Sugar and Diabetes

(Econometric Analysis)

An international econometric analysis of diet and diabetes

Food and Agriculture Organization (FAO); FAOSTAT

Food Supply data in kcal/capita/day calculation:
Food Supply= ∑Supply Elements - ∑Utilization Elements =
(Production + Import Quantity + Stock Variation – Export Quantity)
- (Feed + Seed + Processing + Waste).
Only industrial waste factored in.

Extracted Food Supply data for 2000 and 2007:

Total Calories	Roots & Tubers, Pulses, Nuts, Vegetables
Fruits-Excluding Wine	Meat
Oils	Cereals
Sugar, Sugarcrops & Sweeteners	

International Diabetes Federation (IDF)

2000 (1st ed) and 2010 (3rd ed)

The World Bank World Development Indicators Database

GDP expressed in purchasing power parity in 2005 US dollars for comparability among countries

Basu et al. PLoS One, e57873, 2013

An international econometric analysis of diet and diabetes

Total 175 countries; complete data for 154 countries (21 not different)

Basu et al. PLoS One. e57873. 2013

An international econometric analysis of diet and diabetes

Total 175 countries; complete data for 154 countries (21 not different)

Data monitoring and quality

- Generalized estimating equations
- Conservative fixed effects approach (Hausman test)
- Hazard model to control for selection bias (Heckman selection model)
- Longitudinal data to determine what preceded diabetes (Granger causality)
- Period effects controlled for secular trends that may have occurred as a result of changes diabetes detection capacity or importation policies.

Basu et al. PLoS One. e57873. 2013

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- Period effects controlled for secular trends that may have occurred as a result of changes diabetes detection capacity or importation policies.

Controlled for:

- GDP per capita
- Obesity
- % population living in urban areas
- % of population over age 65
- physical inactivity

Basu et al. PLoS One. e57873. 2013

An international econometric analysis of diet and diabetes

Diabetes prevalence rose from 5.5% to 7.0% for 175 countries 2000-2010

Basu et al. PLoS One. e57873. 2013

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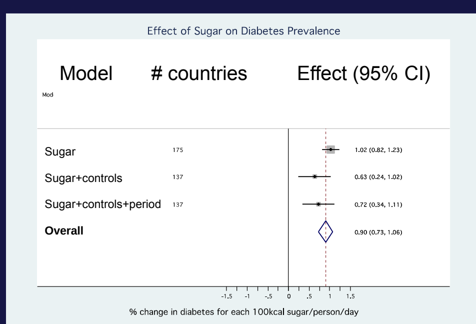
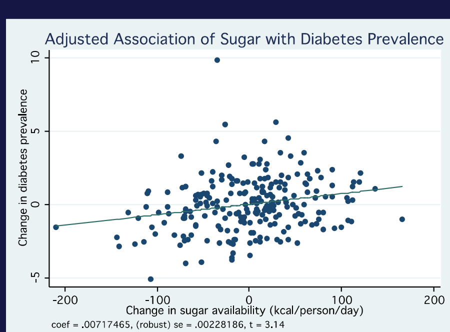


Basu et al. PLoS One. e57873. 2013

An international econometric analysis of diet and diabetes



Basu et al. PLoS One. e57873. 2013

An international econometric analysis of diet and diabetes

Only changes in sugar availability predicted changes in diabetes prevalence

Every extra 150 calories increased diabetes prevalence by 0.1%

But if those 150 calories were a can of soda, diabetes prevalence increased 11-fold, by 1.1% (95% CI 0.03 — 1.71%, p <0.001)

This study meets the Bradford Hill criteria for Causal Medical Inference:

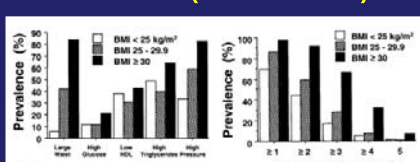
—dose —duration —directionality —precedence

We estimate that 25% of diabetes worldwide is explained by sugar

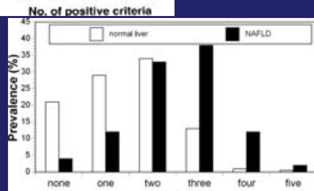
Basu et al. PLoS One. e57873, 2013

Sugar and Fatty Liver Disease

NAFLD and Metabolic Syndrome are congruent (if not the same)



Adults:
Marchesini et al. Hepatology 37:917, 2003



Children:
Schwimmer et al. Circulation 118:277, 2008

NAFLD is a primary predictor of T2DM in Korean adults

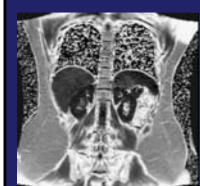
TABLE 2. OR for T2DM at 5-yr follow-up

	T2DM -no./total no. (%)-		OR (95% confidence interval)		
	No fatty liver	Fatty liver	Unadjusted	Adjusted[a]	Adjusted[a] · baseline glucose
All	54/8120 (0.7%)	120/2971 (4%)	6.29 (4.55-8.69)	3.24 (2.19-4.78)	2.05 (1.35-3.12)
Insulin					
Quartile 1	13/2468 (0.5%)	8/307 (2.6%)	5.05 (2.08-12.29)	3.47 (1.23-9.79)	1.96 (0.63-6.13)
Quartile 2	16/2262 (0.7%)	6/511 (1.2%)	1.67 (0.65-4.28)	1.34 (0.46-3.87)	0.71 (0.22-2.26)
Quartile 3	11/2002 (0.6%)	22/768 (2.9%)	5.34 (2.58-11.06)	3.74 (1.59-8.84)	2.92 (1.12-7.62)
Quartile 4	14/1388 (1.0%)	84/1385 (6.1%)	6.34 (3.58-11.21)	3.31 (1.76-6.20)	2.42 (1.23-4.75)

[a] Adjusted for age, gender, BMI, alcohol (grams per day), education (· 16 yr, · 16 yr), smoking (never or past, current), and exercise (· 1 time/wk, · 1 time/wk).

Sung and Kim, J Clin Endocrinol Metab 96:1093, 2011

MRI Fat Fraction Maps



Obese
Low Liver Fat = 2.6%

MRI Fat Fraction Maps

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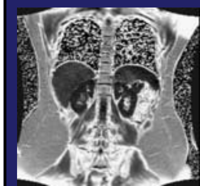
MRI Fat Fraction Maps



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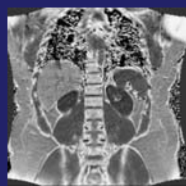
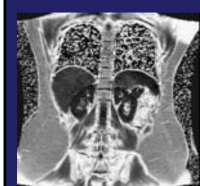


Obese
High Liver Fat = 24%

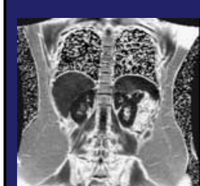
MRI Fat Fraction Maps



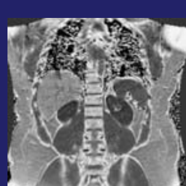
Obese
Low Liver Fat = 2.6%

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%

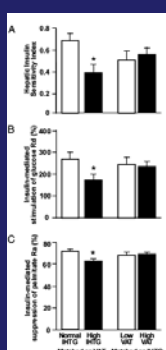
Thin
High Liver Fat = 23%

Intrahepatic fat explains metabolic perturbation better than visceral fat

Hepatic Insulin Sensitivity Index

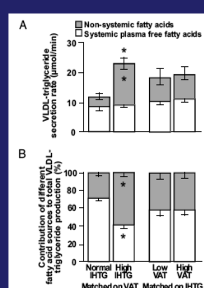
Insulin Stimulated Glucose Disposal Rate

Insulin Stimulated Palmitate Suppression Rate

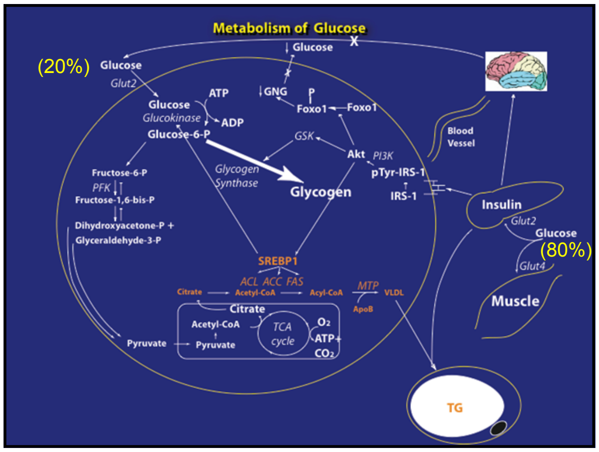


VLDL Secretion Rate

Contribution Of Free Fatty Acids To VLDL



Fabbrini et al. Proc Natl Acad Sci 106:15430, 2009



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:

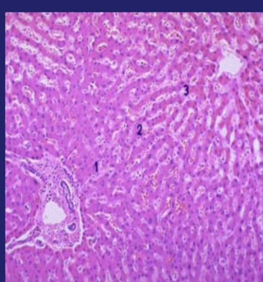
- Not necessary for life
- There is no biochemical reaction in the body that requires it
- Is not nutrition
- When consumed in excess it is toxic
- We love anyway

Can you name an energy source that is:

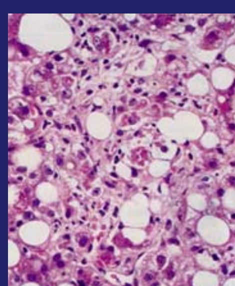
- Not necessary for life
- There is no biochemical reaction in the body that requires it
- Is not nutrition
- When consumed in excess it is toxic
- We love anyway

Answer: Ethanol

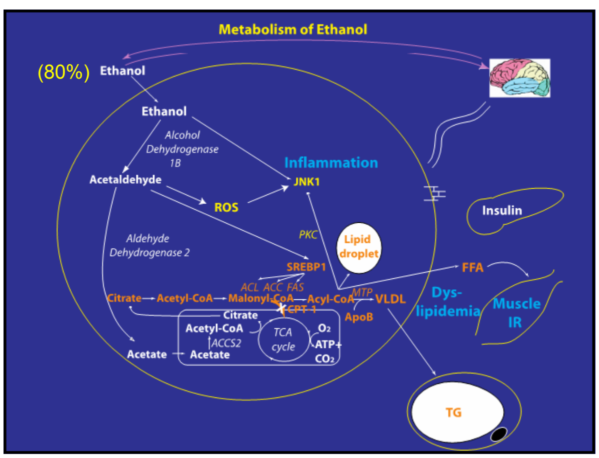
Histology of (N)AFLD

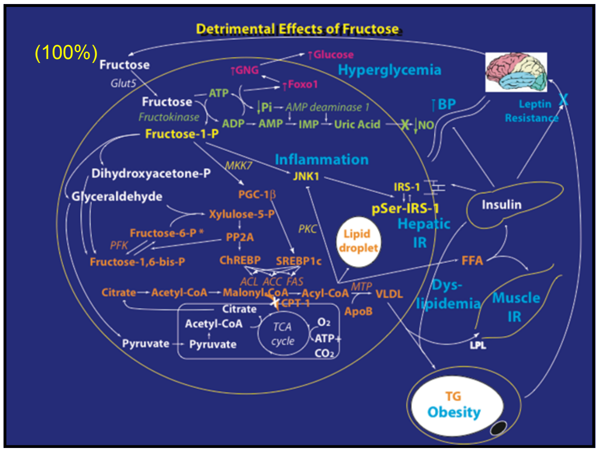


Normal



Alcohol?
Sugar?





Sugar and Diabetes

(Causation)

Current Press Releases

Current Press Releases
Press Release Archives
ENDO Annual Meeting
Media Webinars
Journalism Award
Science Writers Conference
Endocrinology Glossary

Restricting Fructose in Obese Latino and African American Children May Reduce Fat Accumulation in Their Liver

March 05, 2015

Contact: Aaron Lohr
Director, Media Relations
Phone: 202.971.3654
alohr@endocrine.org

Contact: Jenni Glenn Gingery
Associate Director, Media Relations
Phone: 202.971.3655
jgingery@endocrine.org

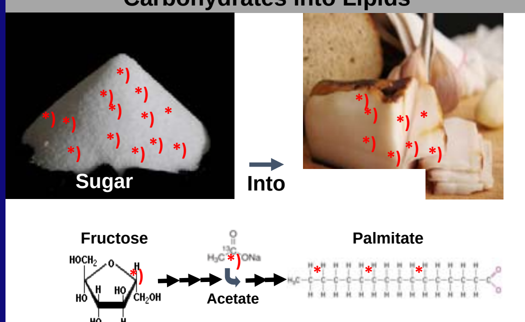
San Diego, CA – In obese Latino and African American children, restricting dietary fructose, but not

Schwarz et al. Endocrine Society, March 5, 2015

Strategy

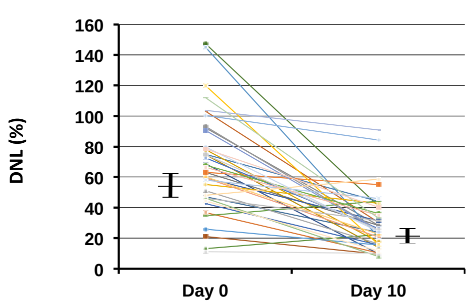
- Isocaloric fructose restriction x 9 days in children who are habitual sugar consumers
- No change in weight
- Substitute complex carbs for sugar
- Maintain baseline macronutrient composition of the the diet
- Study in PCRC at Day 0 and Day 10
- Assess changes in organ fat, *de novo* lipogenesis, and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

DNL is the Conversion of Dietary Carbohydrates into Lipids



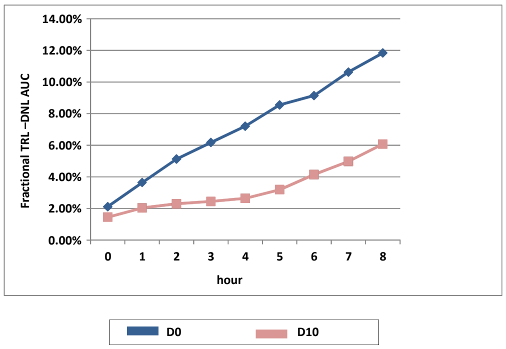
New Tracer Method using MIDA: Hellerstein and Neese, AJP 1999

DNL AUC Pre and Post Fructose Restriction



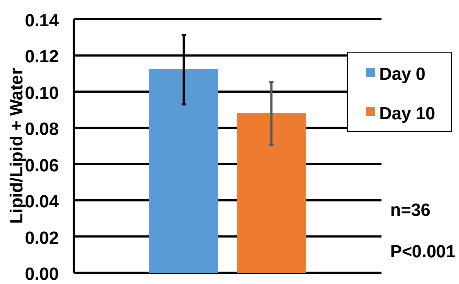
Endocrine Society, March 5, 2015

Triglyceride-rich Lipoprotein DNL AUC (n=17)



Endocrine Society, March 5, 2015

Fructose Restriction Reduced Liver Fat



Endocrine Society, March 5, 2015

Changes in fat depots by Magnetic Resonance Spectroscopy

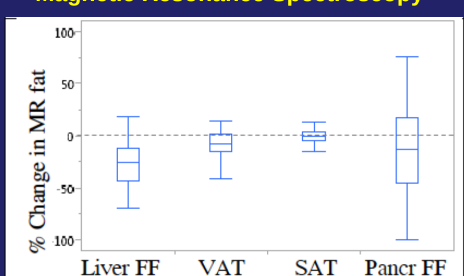
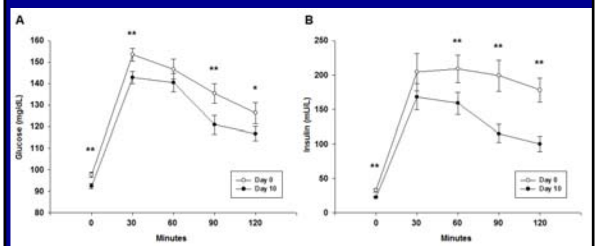


Figure 1 – Box plots of %change of MR fat measures from Day 0 to Day 10.

SM Noworolski et al. Int Soc Mag Res Med, Toronto, May 30, 2015

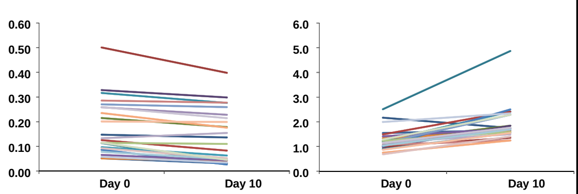
Oral glucose tolerance test before and after isocaloric fructose restriction



Lustig et al. Obesity (in press)

For pediatric subjects with hepatic steatosis (n = 25)

Change in Liver Fat and Insulin Sensitivity



Liver Fat

-30% (-50, -20); p <0.001

Composite Insulin Sensitivity Index

+0.65 (0.41, 0.88); p <0.001

Adjusted for change in weight

Lustig et al. Obesity Society, Nov. 4, 2015

Correlation between Insulin Sensitivity & Liver Fat vs Visceral Fat

Spearman R	Day 0		Day 10		Change in fat (Absolute)	
	Liver Fat Fraction	Visceral Fat	Liver Fat Fraction	Visceral Fat	Liver Fat Fraction	Visceral Fat
Insulin Sensitivity (CISI) DAY 0	- 0.36 §	- 0.57*				
Insulin Sensitivity (CISI) DAY 10			- 0.28	- 0.34 §		
Change in Insulin sensitivity (ΔCISI)					- 0.56*	0.09

* p <0.05
§ 0.05 < p < 0.1

Lustig et al. Obesity Society, Nov. 4, 2015

Association between Insulin Sensitivity (CISI) and Liver Fat vs. Visceral Fat

Liver Fat

- Every unit decrease in liver fat increases CISI by 10.49 (p = 0.008).
- Every unit decrease in %liver fat increases %CISI by 0.8 (p= 0.03).

Visceral Fat

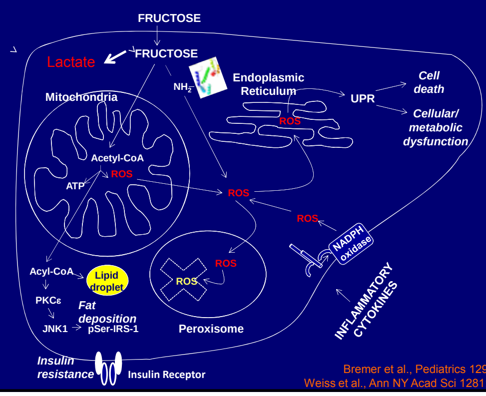
- Every unit decrease in visceral fat is non-significantly increases CISI by 0.002 (p = 0.77).
- Every unit decrease in %visceral fat non-significantly increases %CISI by 0.69 (p = 0.28).

Lustig et al. Obesity Society, Nov. 4, 2015

Summary

- Prospective correlational data demonstrate **associations** between added sugar and heart disease, **exclusive of calories or obesity**
- Econometric data show **causal medical inference** for added sugar and diabetes, **exclusive of calories or obesity**
- Interventional **isocaloric glucose for fructose** study shows improvements in fatty liver disease, insulin resistance and metabolic health in children in 10 days, and insulin resistance is driven by liver fat

Toward a unifying hypothesis of metabolic syndrome



Bremer et al., Pediatrics 129:557, 2012
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Collaborators

UCSF Dept. of Pediatrics
Patrika Tsai, M.D., M.P.H.
Emily Perito, M.D., M.P.H.
Rachel Lipman, C.P.N.P.
Kelly Jordan
Sally Elliott
Katrina Koslov, Ph.D.
Ayca Erkin-Cakmak, M.D., M.P.H.

UCSF PCRC
Jeannie Addis, R.N.
Sarah Furstenburg, R.N.
Erin Matsuda, R.N., C.P.N.P.
Abby Lincoln, R.N.

Touro University Dept. of Biochemistry
Jean-Marc Schwarz, Ph.D.
Alejandro Gugliucci, M.D., Ph.D.
Grace Jones, Ph.D.
Moises Alin

UCSF Dept. of Radiology
Susan Noworolski, Ph.D.
Natalie Korn
Kyle Tillinghast

UCSF Dept. of Medicine
Kathleen Mulligan, Ph.D.
Mike Wen

UCSF Institute for Health Policy Studies
Laura Schmidt, Ph.D., M.S.W., Dr.P.H.
Claire Brindis, Dr.P.H.
Cristin Kearns, D.D.S.
Stanton Glantz, M.D.

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