Fast-food, Fatty liver, & Insulin Resistance

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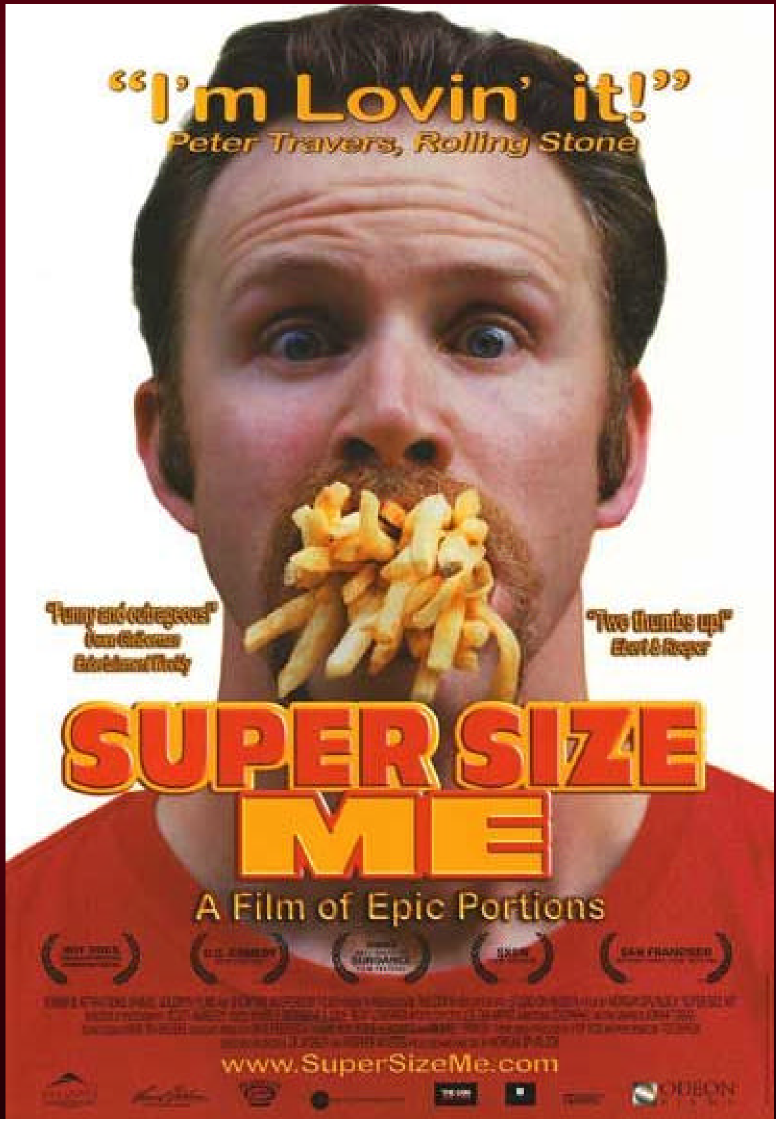
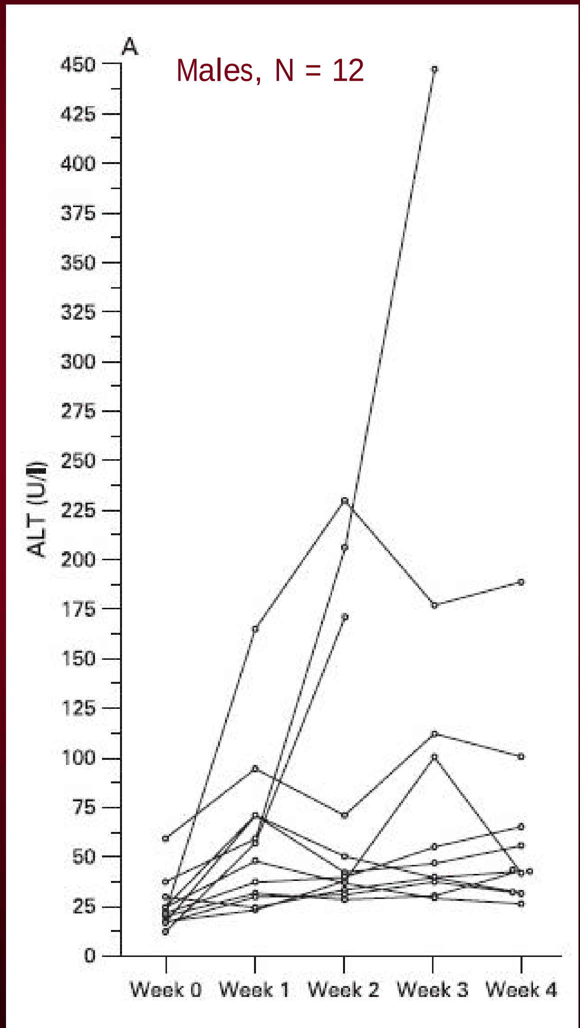
Supersize Me
Unhealthy Effects of Fast Food



- After consuming three meals a day in a fast-food restaurant for 1 month, Morgan Spurlock increased by nearly 10 kg
- His liver enzymes peaked at 290 U/l [alanine aminotransferase (ALT)] from baseline values of 20 U/l, accompanied by increased total cholesterol, uric acid and the onset of clinical features of the metabolic syndrome
- No doubt that elevated ALT are a marker of hepatic dysfunction, but are they related to any specific dietary component of fast food-based diet, or simply to weight gain and obesity-associated non-alcoholic fatty liver disease (NAFLD)?

Supersize Me
Effect of Fast Food on liver fat



18 subjects doubled caloric intake by a fast food-based diet for 4 weeks
Limited physical activity <5000 steps/day

+6.4 kg, 10% weight gain in 4 weeks
Serum ALT, on average from 22 U/L to 68 (+220%, much more in males)
Liver fat (MRS), 1.1% to 2.8 (+155%)

Kechagias, Gut 2008

Potential mechanisms of fast-food toxicity

- High-fructose corn syrup
  - Foods more palatable
  - Decreased central satiety (effect on ghrelin)
- High glycemic index of the diet
- Caramel coloring rich in advanced glycated end-products
- Increased consumption of red meat

- Increased calorie intake

Red meat & Mortality

Meat Intake and Mortality

A Prospective Study of Over Half a Million People

Rashmi Sinha, PhD; Amanda J. Cross, PhD; Barry I. Graubard, PhD; Michael F. Leitzmann, MD, DrPH; Arthur Schatzkin, MD, DrPH

Conclusion: Red and processed meat intakes were associated with modest increases in total mortality, cancer mortality, and cardiovascular disease mortality.

Arch Intern Med. 2009;169(6):562-571

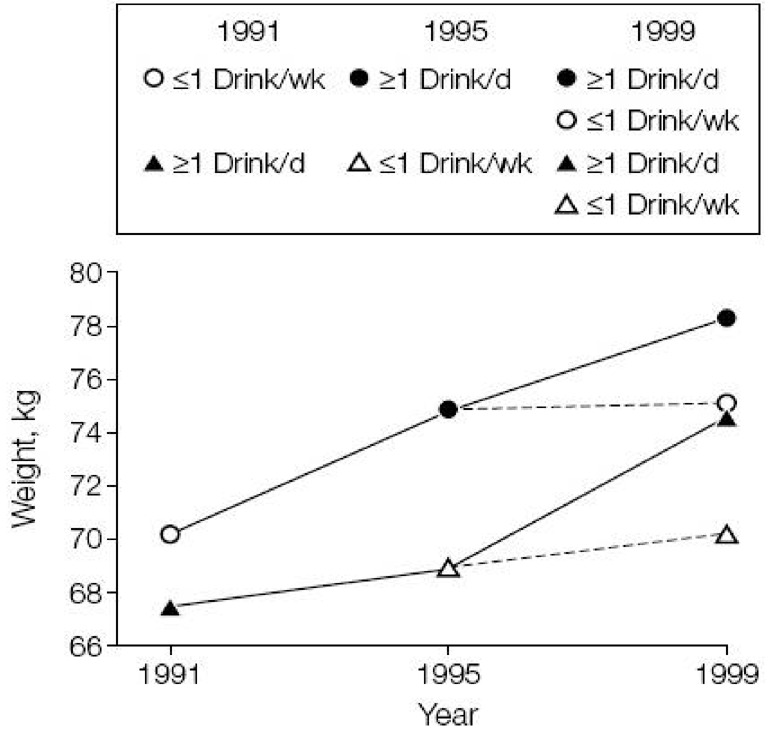
Red meat & Mortality - A global perspective

- Red meat & processed meat consumption in a global perspective
  - Red meat increases the risk of obesity
- The increase in food price and the role of red meat and other animal sources
  - Part of cereal production is moved to support animal feeding
- Global water, climate and energy crises
  - The tsunami of water and food crisis
  - Meat is on top of the food chain; water use is 2-5 times higher for animal source food than for basic crops
  - 15-23% of total world water goes to livestock use
  - Livestock production accounts for 1/3 of total nitrogen pollution and 50% of antibiotic use
- Future policy challenges
  - To correct the distortion created by subsidies on creating cheap pork, beef and other animal source food

Popkin, Arch Intern Med 2009

Soft drinks & Energy intake

Figure 2. Mean Weight in 1991, 1995, and 1999 According to Trends in Sugar-Sweetened Soft Drink Consumption in 1969 Women Who Changed Consumption From 1991 to 1995 and Either Changed or Maintained Level of Consumption Until 1999

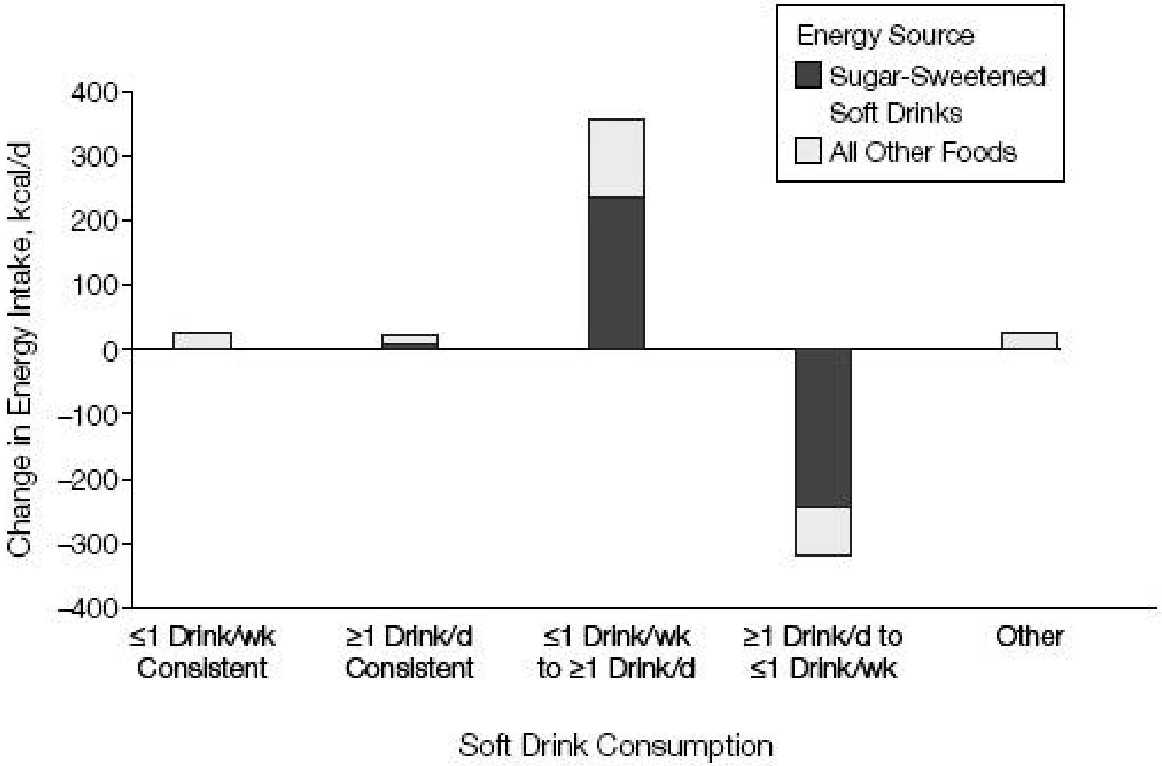


- Nurses Health Study II (over 90,000 Nurses in the diabetes study, over 50,000 in the weight change study
- Time trends between 1991-95 and 1995-99
- Data adjusted for a lot of confounders, including physical activity
- Women consuming =1 sugar-sweetened soft drinks/day had a relative risk of T2DM of 1.83 (95% CI, 1.42-2.36; *P* .001 for trend) compared with those who consumed less than 1 beverage/month

Schulze, JAMA 2004

Soft drinks & Energy intake

Figure 1. Mean Change in Energy Consumption According to Time Trends in Sugar-Sweetened Soft Drink Consumption Between 1991 and 1995 in 51603 Women



Schulze, JAMA 2004

Soft drinks & Energy intake

Weight Gain and Diabetes

Diabetes is a common disorder in which the body has difficulty controlling levels of sugar in the bloodstream. Normally, the hormone **insulin** made by the **pancreas** (an organ in the abdomen) regulates blood sugar levels. The bodies of individuals with **type 1 diabetes**, which usually starts by the early teen years, do not make enough insulin to control blood sugar, so they must receive insulin injections. The bodies of persons with type 2 diabetes are resistant to the effects of insulin. **Type 2 diabetes**, also known as "adult-onset" diabetes, usually develops in adulthood but can also occur in overweight children. Family history of diabetes and excess weight, especially weight carried around the middle, are strong risk factors for developing type 2 diabetes. Losing weight greatly reduces your chances for type 2 diabetes and can help bring your blood sugar under control if you already have type 2 diabetes. Type 2 diabetes can be treated with diet, exercise, and oral prescription medications but may require insulin shots.

The August 25, 2004, issue of *JAMA* includes an article reporting that women who increased drinking sugar-sweetened beverages to 1 or more drinks per day were more likely to gain weight and that a high consumption of these beverages was also related to a higher risk of type 2 diabetes.

Fast-food frequency, Weight gain & Insulin resistance - the CARDIA study

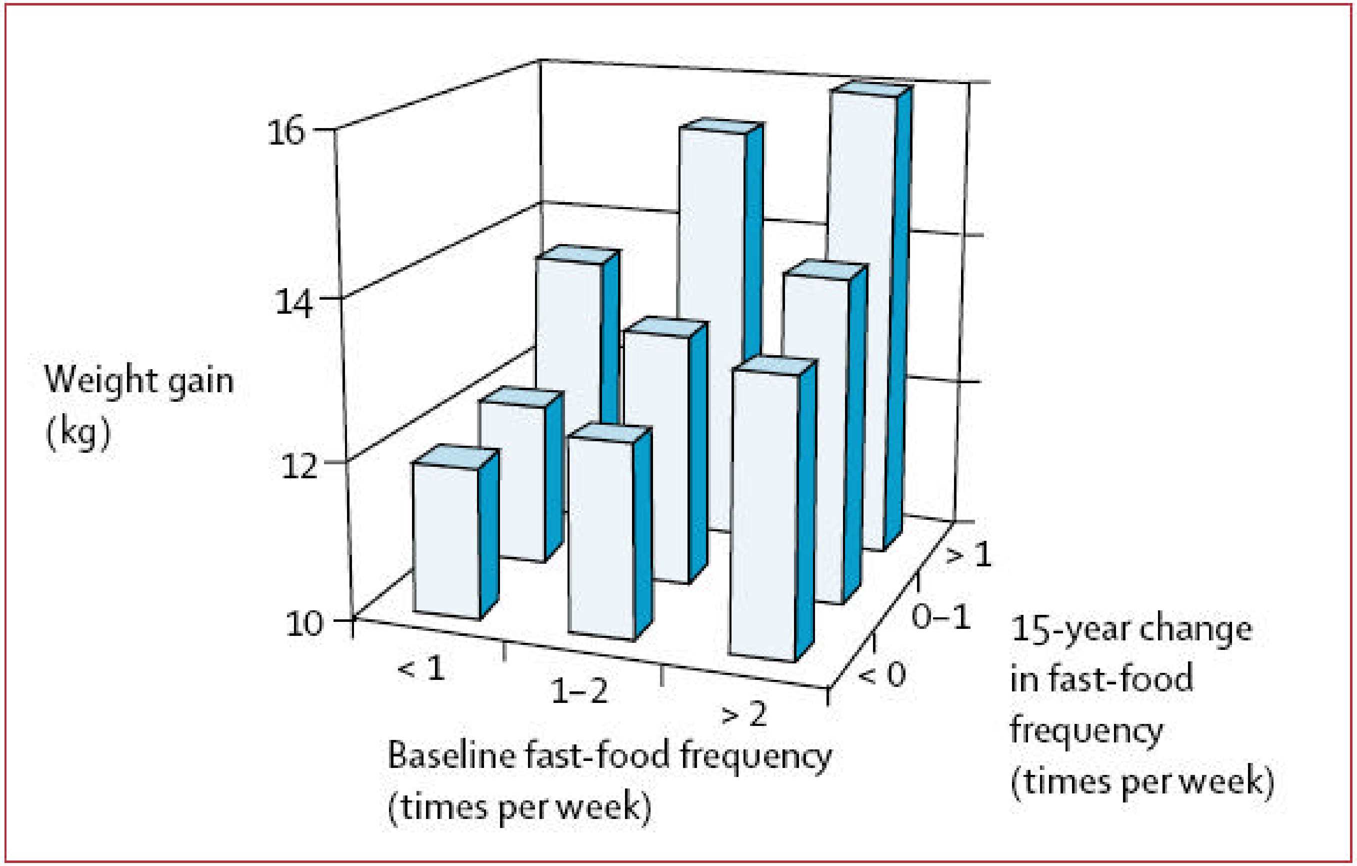


Figure **1: Joint association of year 0 fast-food frequency and 15-year changes in fast-food frequency with 15-year changes in bodyweight**

Pereira, Lancet 2005

Fast-food frequency, Weight gain & Insulin resistance - the CARDIA study

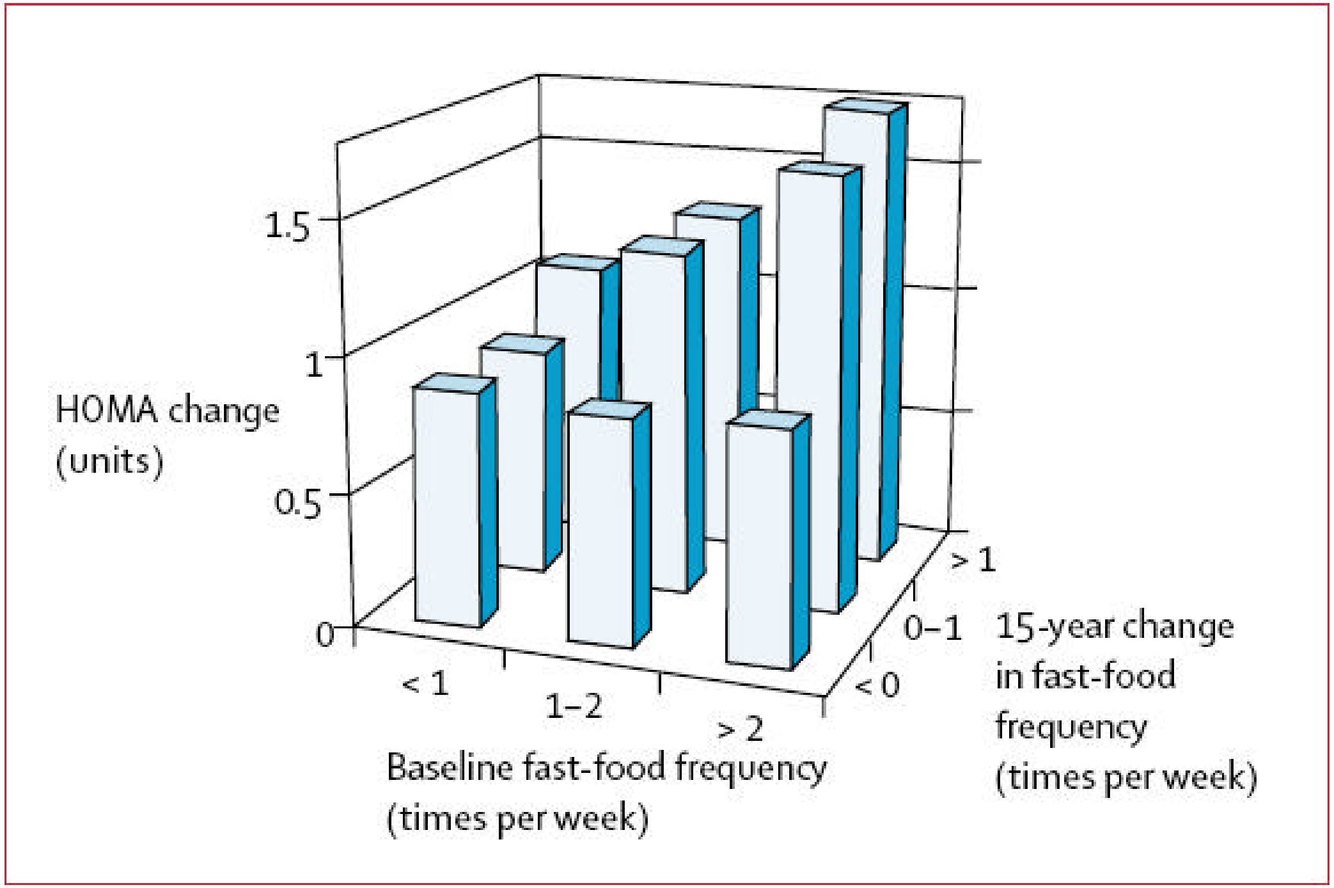


Figure 2: Joint association of year 0 fast-food frequency and 15-year changes in fast-food frequency with 15-year changes in HOMA insulin resistance

Pereira, Lancet 2005

Fast-food frequency, Weight gain & Insulin resistance - the CARDIA study

	Black people			p*	White people			p*
	<1 (n=450)	1–2 (n=508)	>2 (n=486)		<1 (n=625)	1–2 (n=517)	>2 (n=445)	
Year 0 fast-food frequency (times per week)	0·4	1·4	4·6	<0·0001	0·4	1·4	4·8	<0·0001
15-year change in fast food (times per week)	1·4	0·7	−1·8	<0·0001	0·7	0·1	−2·5	<0·0001
Foods typical of fast food (times per week)†	1·5	2·4	4·3	<0·0001	0·8	1·7	3·6	<0·0001
Age (years)	25·0	24·4	24·0	<0·0001	26·1	25·5	25·1	<0·0001
Women (%)	61·7	56·6	47·7	<0·0001	59·5	46·8	37·9	<0·0001
Bodyweight (kg)‡	72·4	73·5	72·9	0·6506	69·8	71·5	70·8	0·1598
HOMA insulin resistance score	2·4	2·4	2·6	0·1387	1·8	2·0	1·9	0·3277
Healthy lifestyle score	3·6	3·7	3·5	0·2257	4·9	4·6	4·1	<0·0001
Education (years)	13·8	13·9	14·0	0·1723	16·0	15·5	15·5	0·0011
Physical activity (exercise units)	360	389	394	0·0713	480	454	440	0·0298
Television (h/day)§	3·2	3·1	3·1	0·5334	1·6	1·7	1·9	0·0003
Current smokers (%)	36·2	27·7	29·5	0·0256	20·1	23·6	30·7	0·0002
Alcohol intake (mL/day)	12·3	9·9	11·7	0·7304	12·1	11·9	17·6	<0·0001
Total energy intake (kcal/day)	2829	3169	3485	<0·0001	2451	2694	2978	<0·0001
Total fat (g/day)	110·1	123·2	138·7	<0·0001	91·5	103·9	117·7	<0·0001
Total fat (% energy)	34·3	34·7	35·6	0·0006	33·2	34·5	35·4	<0·0001
Saturated fat (% energy)	13·8	14·1	14·4	0·0011	13·6	14·1	14·5	<0·0001
Trans fat (g/day)	4·2	4·3	4·8	0·0192	3·3	3·5	3·5	0·1316
Soft drink intake (times per week)	6·2	6·9	8·6	<0·0001	2·5	4·3	6·4	<0·0001
Meat intake (times per week)	10·6	12·3	13·8	<0·0001	6·8	8·9	10·8	<0·0001
Refined grain intake (times per week)	23·4	26·9	26·5	0·0114	18·9	20·0	22·1	<0·0001
Wholegrain intake (times per week)	7·7	8·3	8·7	0·1242	11·9	10·5	8·6	<0·0001
Fruit and non-starchy vegetable intake (times per week)	14·2	15·1	15·2	0·9386	22·5	19·1	16·3	<0·0001
Fibre intake (g/1000 kcal per day)¶	7·6	7·5	6·8	<0·0001	10·2	8·7	8·2	<0·0001
Reduced-fat dairy intake (times per week)	3·6	3·9	3·5	0·8452	11·2	10·5	9·6	0·0286

Data are mean values, and are adjusted for age, sex, and study centre. Data are from year 0 except for those noted. *Highest compared with lowest fast food category. †Sum of french fries, hamburgers, breakfast items, and chicken items reported during the CARDIA diet history interview, which may have been obtained at fast-food restaurants. ‡Bodyweight was also adjusted for height. §Measured at year 5. ¶Measured at year 7.

Table 2: Adjusted demographic and dietary factors by frequency of fast-food restaurant visits at year 0 (1985–86)

Pereira, Lancet 2005

Sugar & the obesity epidemics

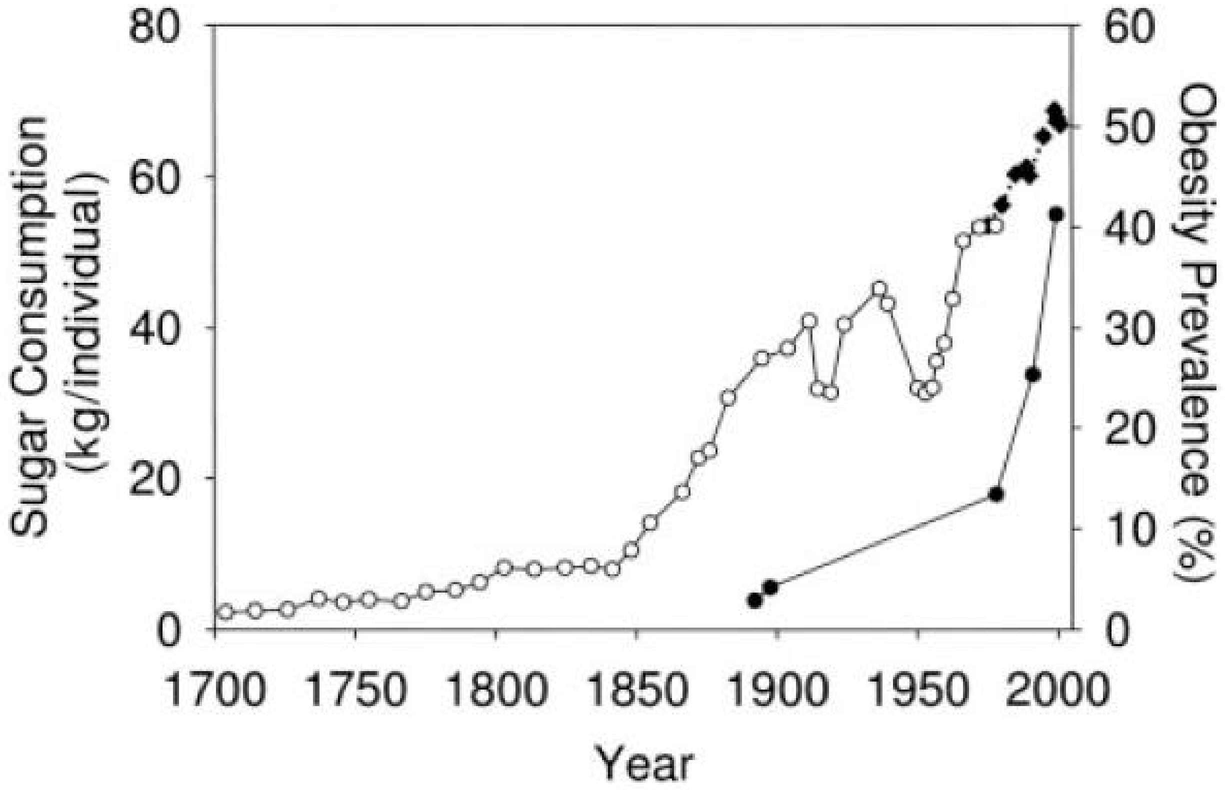
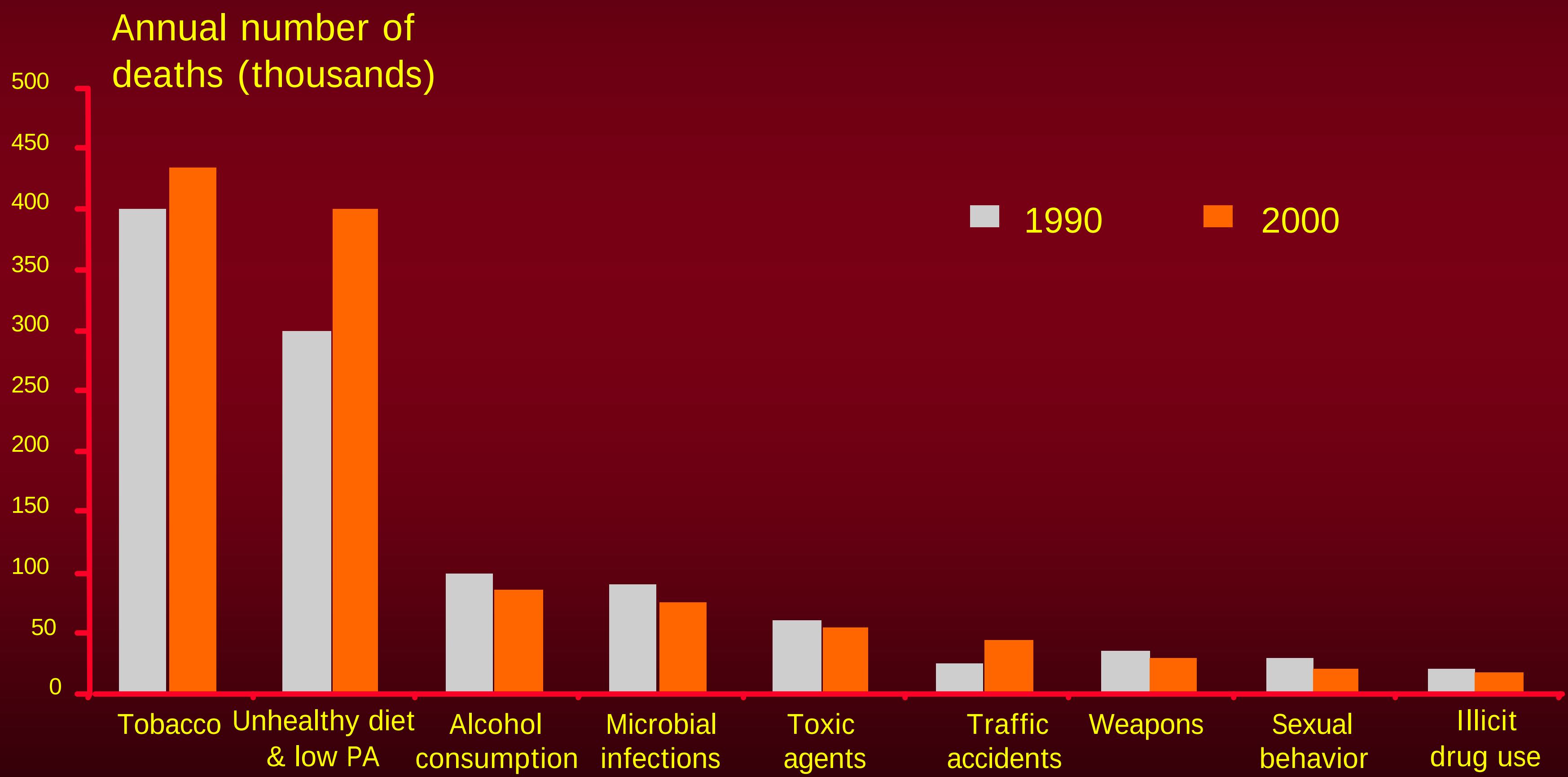


FIGURE 1. Sugar intake per capita in the United Kingdom from 1700 to 1978 (30, 31; ○) and in the United States from 1975 to 2000 (32; ◆) is compared with obesity rates in the United States in non-Hispanic white men aged 60–69 y (17; ●). Values for 1880-1910 are based on studies conducted in male Civil War veterans aged 50–59 y (18).

Johnson, Am J Clin Nutr 2007

Causes of death in U.S.A.



Adapted from Mokdad et al. *JAMA* 2004

Mediterranean diet & Diabetes risk

Table 2 | Incidence and relative risk of type 2 diabetes (confirmed cases) during follow-up according to adherence (Trichopoulou's score[22]) to Mediterranean food pattern at baseline

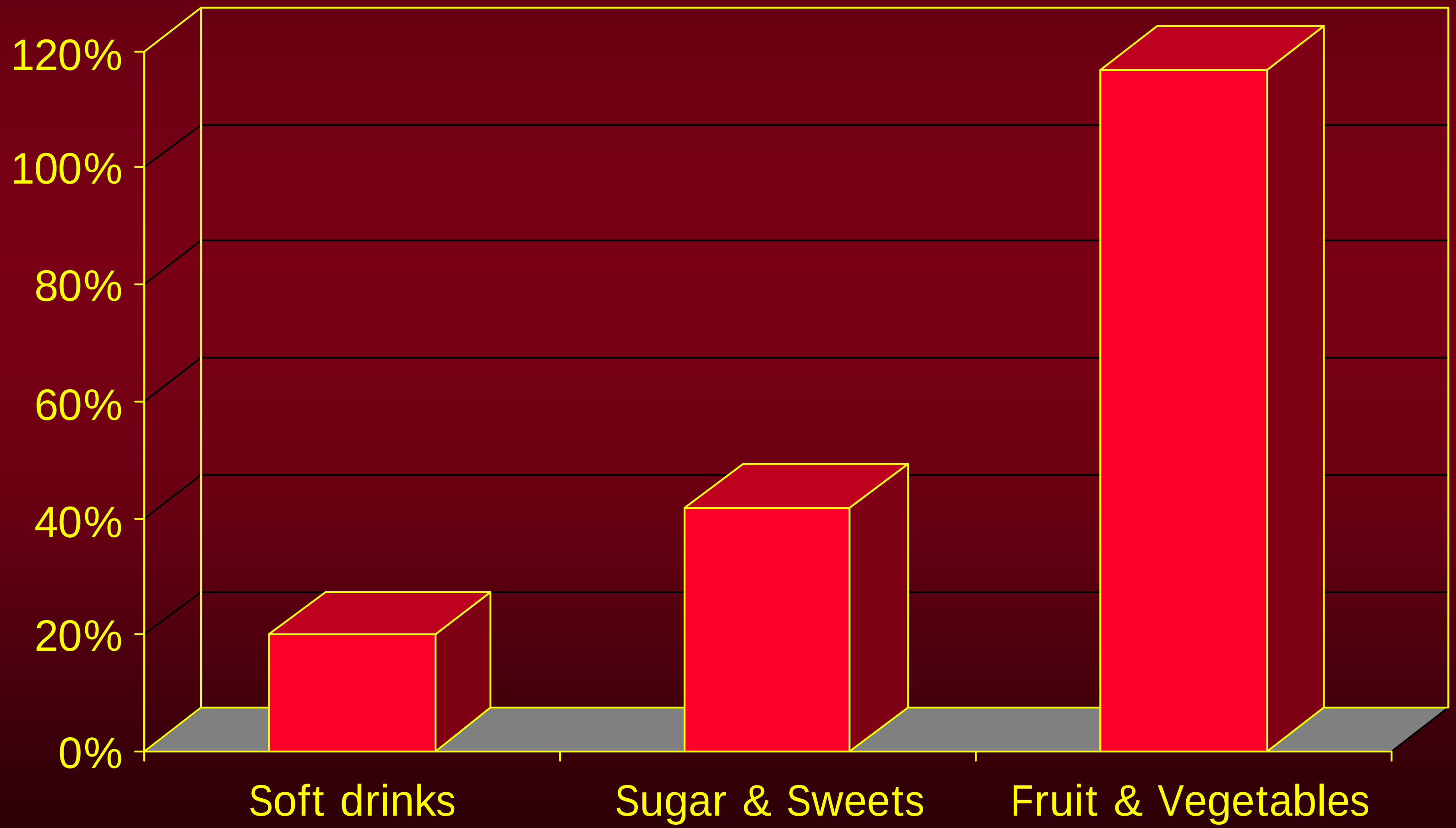
	No in group	Unadjusted cumulative incidence of type 2 diabetes (%)	Incidence rate ratio* adjusted for age and sex (95% CI)	Multivariate adjusted incidence rate ratio (95% CI)†
Low (score 0-2)	2253	0.40	1 (reference)	1 (reference)
Moderate (score 3-6)	9604	0.23	0.41 (0.19 to 0.87)	0.40 (0.18 to 0.90)
High (score 7-9)	1523	0.13	0.17 (0.04 to 0.75)	0.17 (0.04 to 0.72)

*Poisson regression model with robust standard errors.
†Adjusted for sex, age, years of university education (three categories), body mass index (continuous), family history of diabetes (two categories), hypertension at baseline (two categories), physical activity (three categories), hours/week sitting down (five categories), smoking (three categories), total energy intake (continuous). P=0.04 for trend from likelihood ratio test when Trichopoulou's score was introduced as continuous variable in fully multivariate adjusted model.

13380 Spanish university graduates followed for 4.4 years

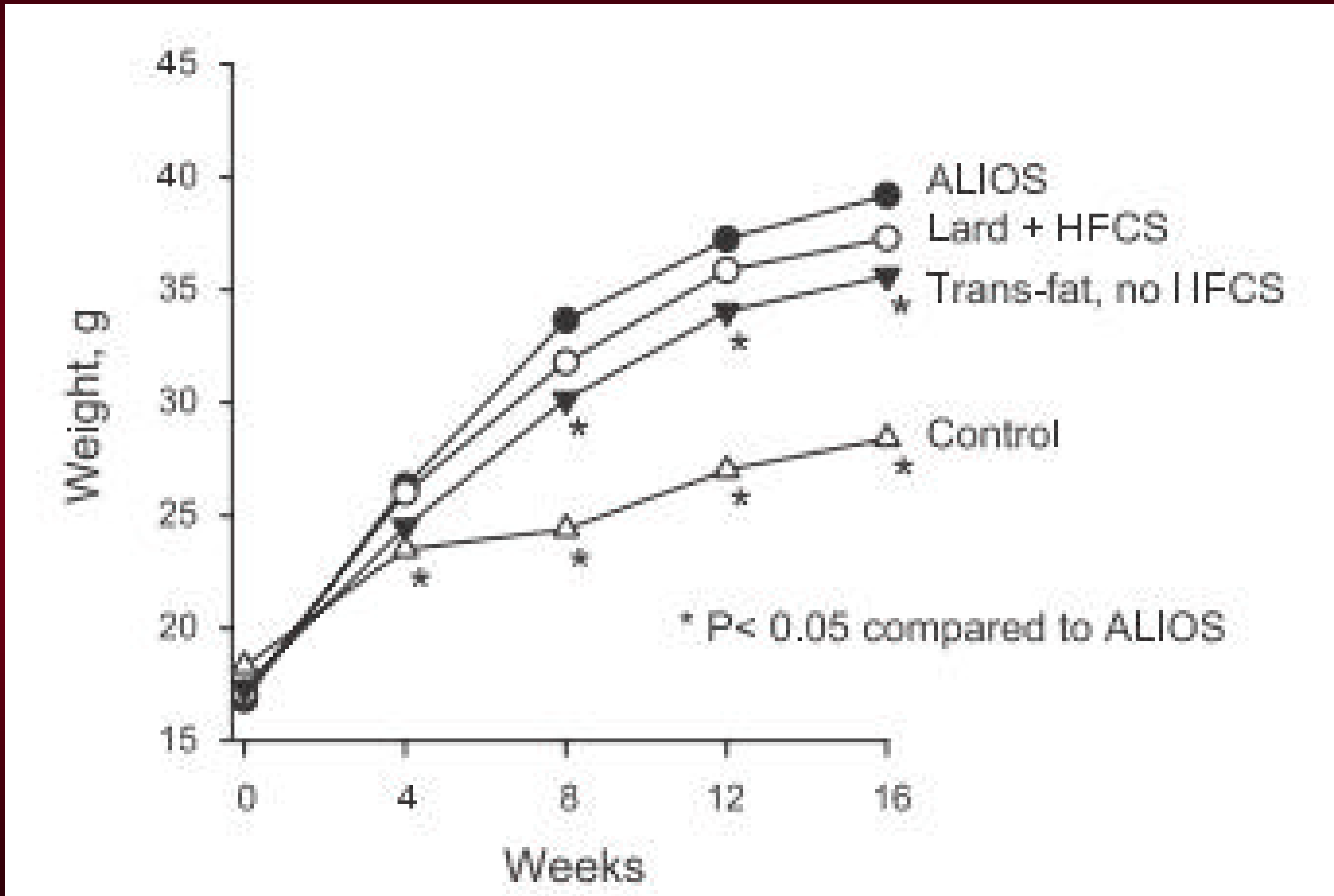
Martinez-Gonzales, BMJ 2008

Percent cost increase of food (U.S., 1985-2000)



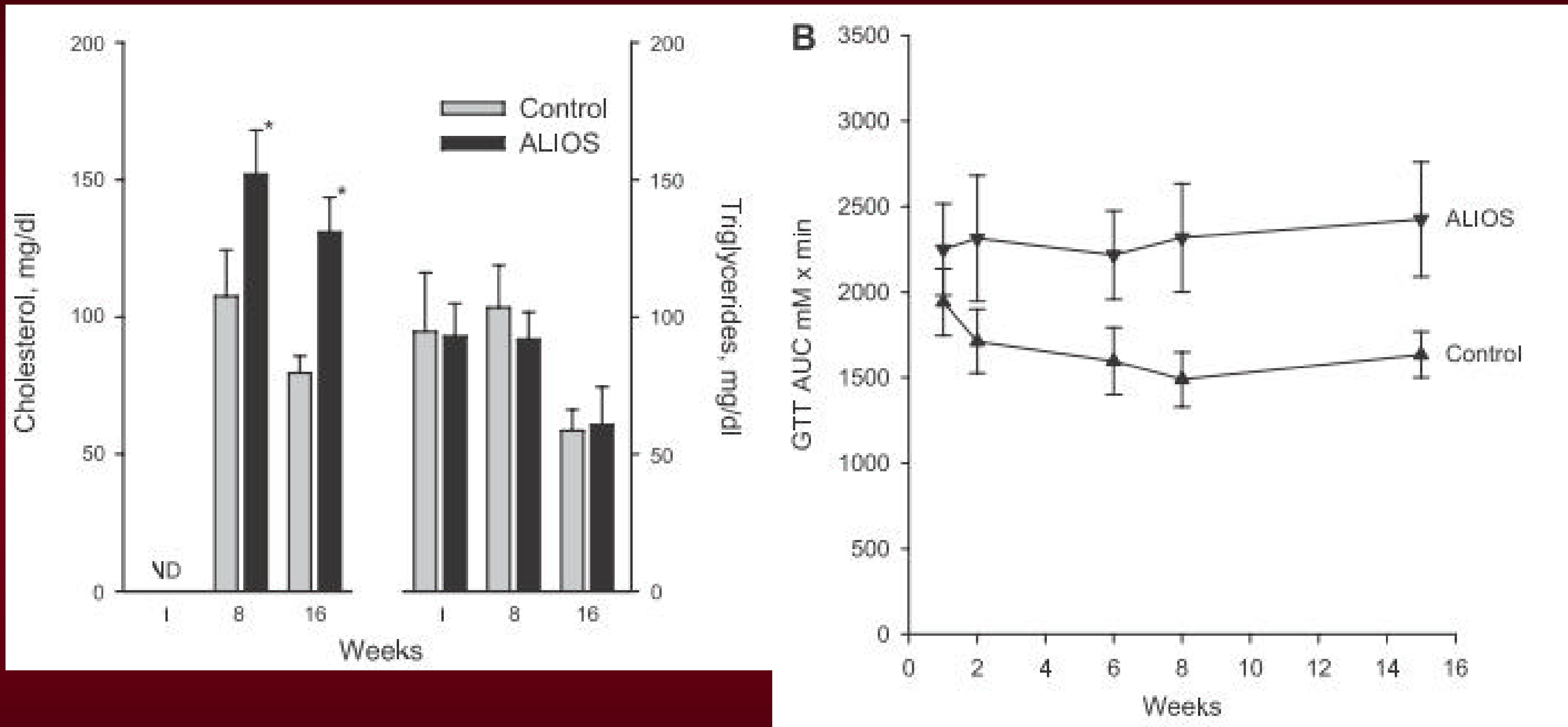
Putnam et al. Food Rev, 2002

Metabolic effects of HFCS



Tetri et al, AJP Gastrointest Liver Physiol 2008

Metabolic effects of HFCS

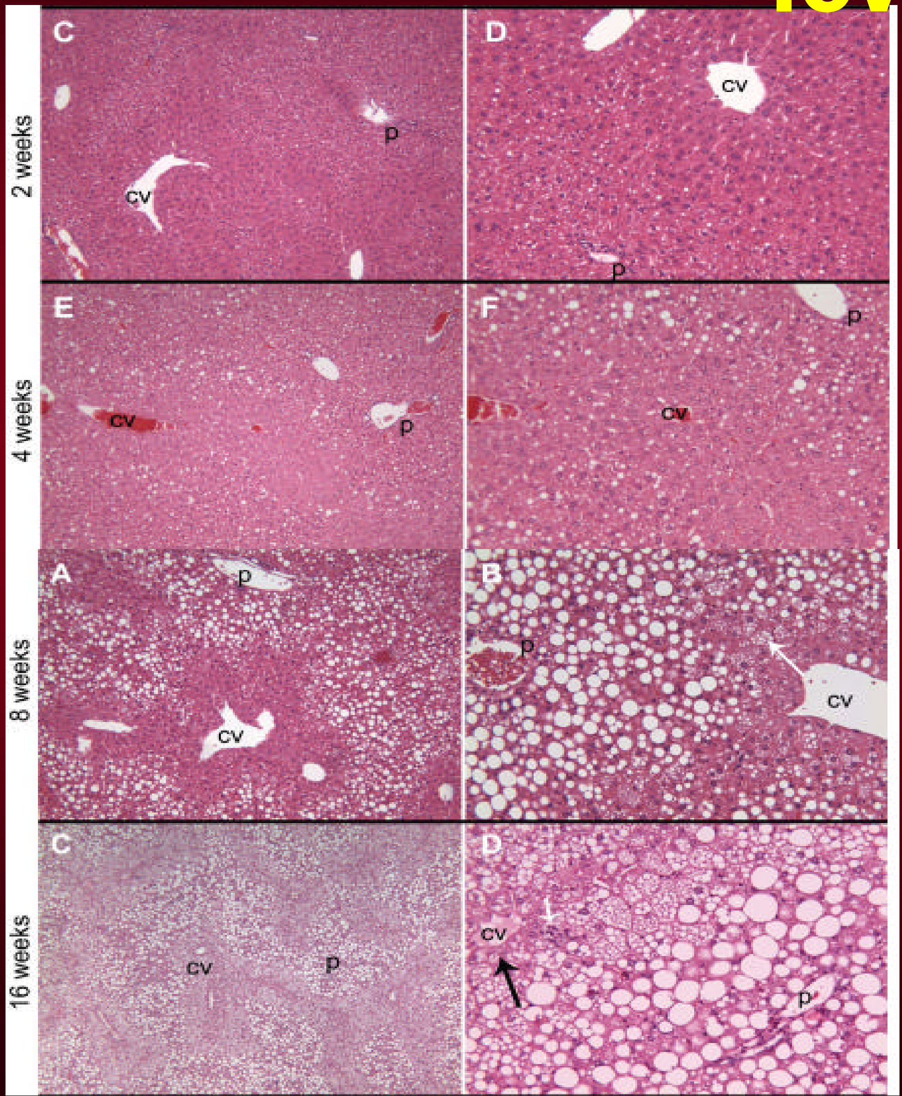


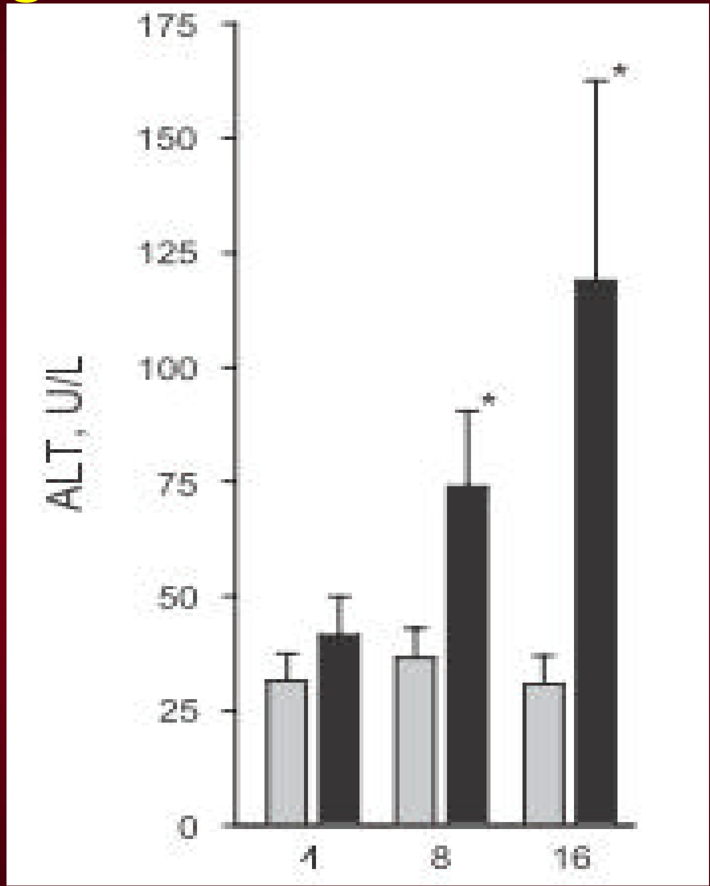
Glucose tolerance

- Hyperinsulinemia
- Impaired insulin responsiveness
- Increased leptin and resistin levels

Tetri et al, AJP Gastrointest Liver Physiol 2008

Liver histology and ALT levels





Increased hepatic TNF-alfa and procollagen a1 mRNA expression

Tetri et al, AJP Gastrointest Liver Physiol 2008

Conclusions

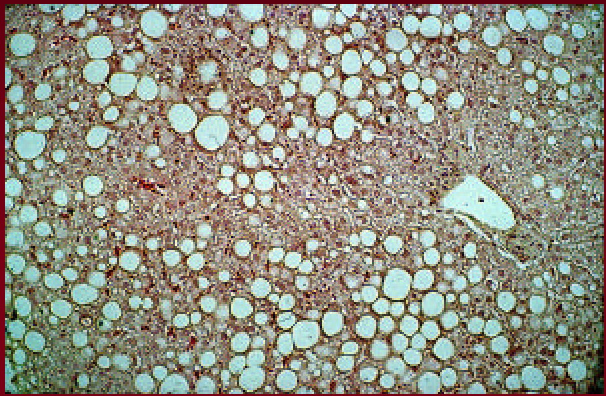
- Mice treated with a combination of “fast food” diet and sedentary behavior develop a severe phenotype of NAFLD in a setting of obesity, impaired glucose tolerance and reduced insulin responsiveness.
- HFCS promotes food intake and contributes to impaired insulin sensitivity.
- Trans fats promote fat retention and hepatocellular injury

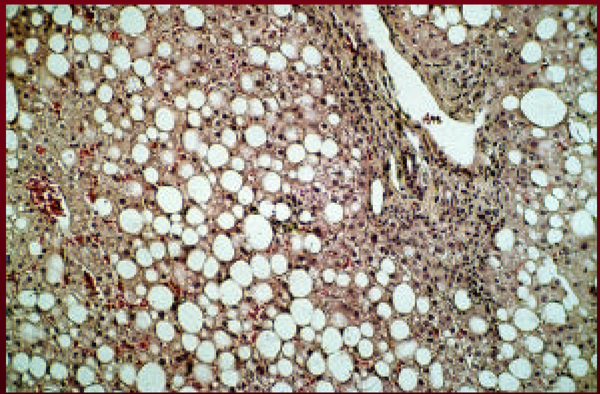
Tetri et al, AJP Gastrointest Liver Physiol 2008

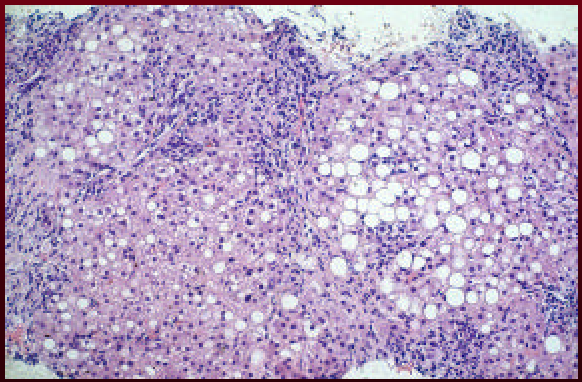
NAFLD as the Hepatic Expression of the Metabolic Syndrome

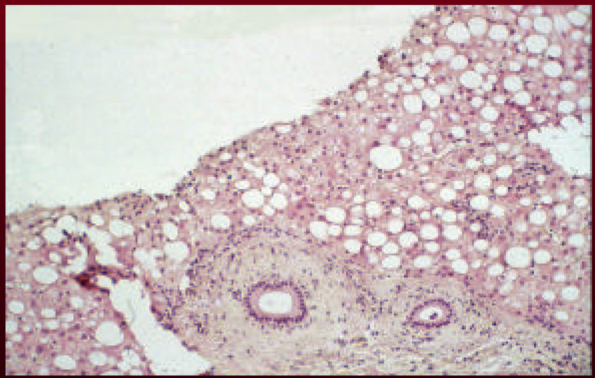
Table 2. Clinical syndromes associated with insulin resistance.

- Type 2 diabetes
- CVD
- Essential hypertension
- Polycystic ovary syndrome
- Nonalcoholic fatty liver disease
- Certain forms of cancer
- Sleep apnea



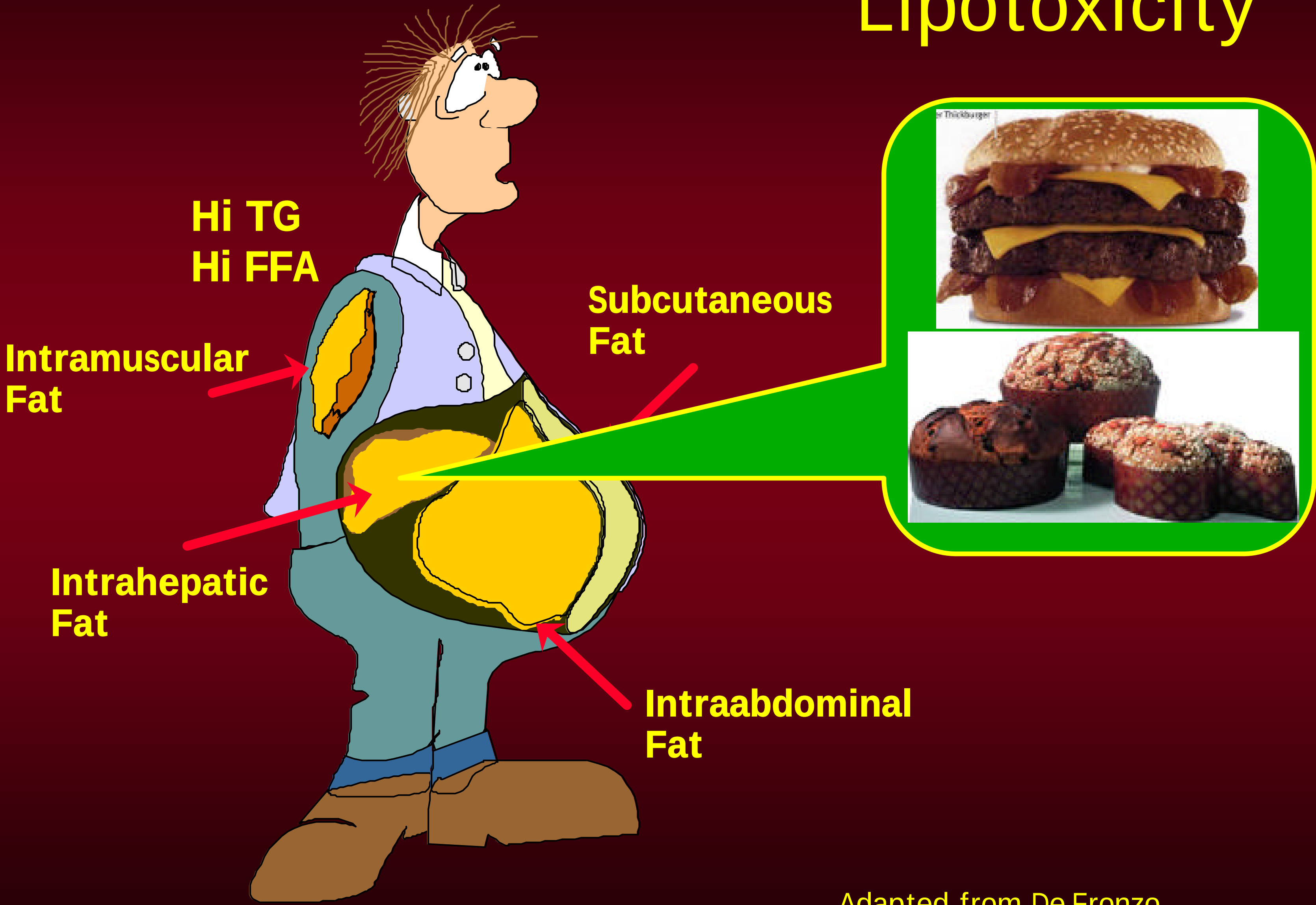






Reaven, Clin Chem 2005

Lipid Depots & Lipotoxicity



Adapted from De Fronzo

Weight Gain & Lipotoxicity

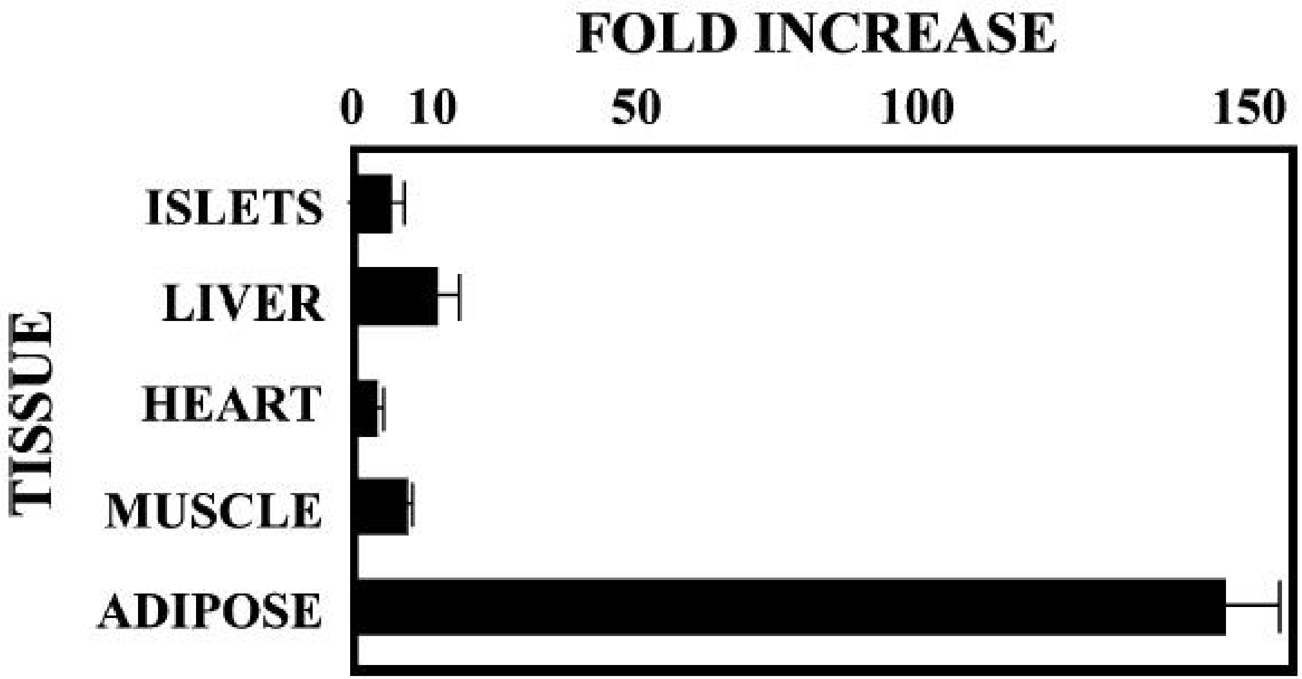


Figure 2 Antisteatotic protection in normal animals. After the feeding of a 60% fat diet for 8 weeks, a 150-fold increase in body fat, estimated by magnetic resonance spectroscopy (MRS), has occurred, but nonadipose tissues exhibit only a minimal rise in their triacylglycerol content.

Unger, Ann Rev Med 2002

Hepatic Triglyceride Content and Body Adiposity

Intra-hepatocellular lipids increase by:

- **22% for 1% increase in total adipose tissue (AT);**
- **21% for 1% increase in subcutaneous AT;**
- **104% for 1% increase in intra-abdominal AT**

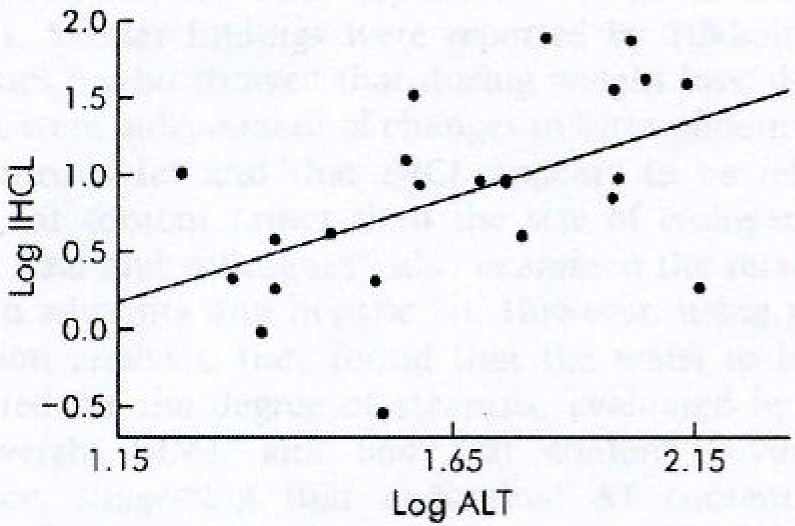
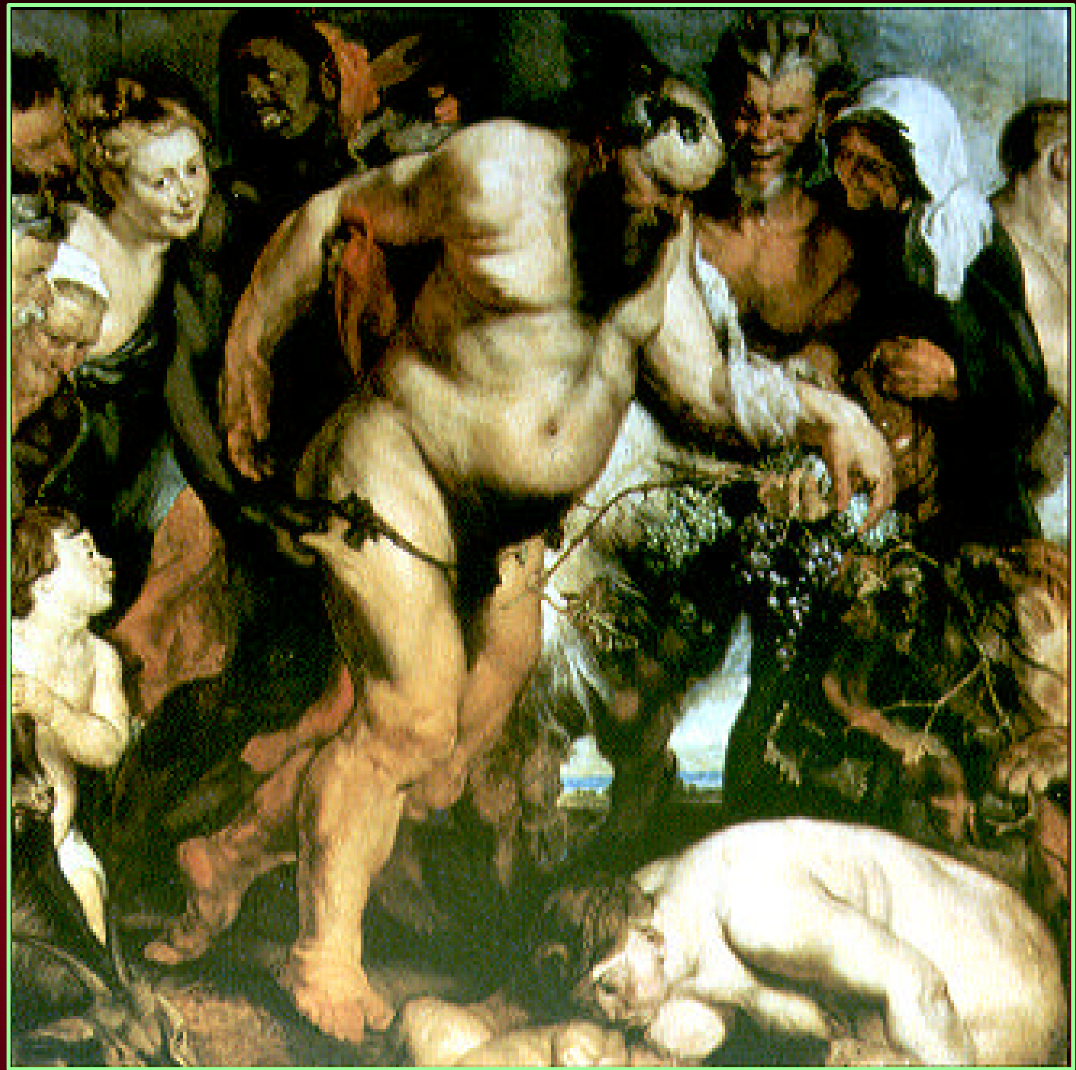


Figure 4 Relationship between intrahepatocellular lipid (IHCL) content and serum alanine aminotransferase (ALT): $\log_e \mathrm{IHCL} = -3.271 + 1.3377 \log_e \mathrm{ALT}$ ($r = 0.57$, $p = 0.006$).

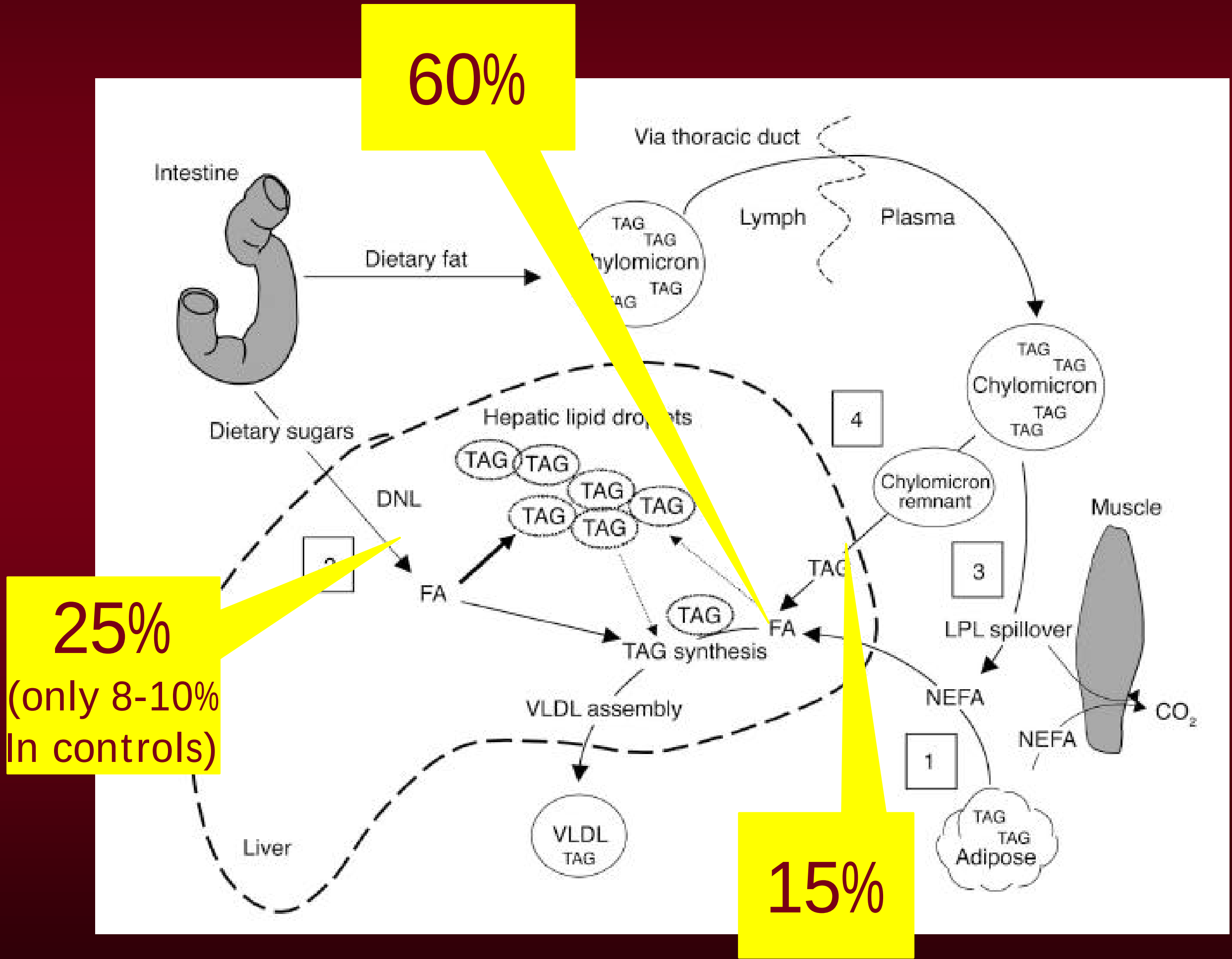
Thomas, Gut 2005

Peripheral Obesity



Central Obesity

Source of Liver TAG in NAFLD



TAG, Triacylglycerol
DNL, De novo lipogenesis
FA, Fatty acids

Donnelly, J Clin Invest 2005

Liver Fat & Insulin Resistance

Liver Fat and Insulin Resistance, Tiikkainen et al.

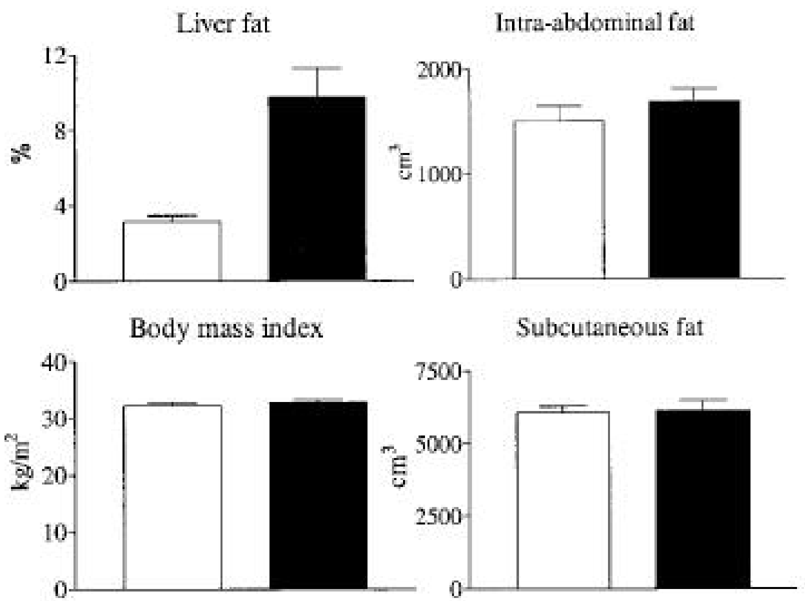


Figure 2: Liver fat content, body mass index, intra-abdominal and subcutaneous fat content in women with low (□) $n = 13$ and high (■) $n = 14$ LFAT.

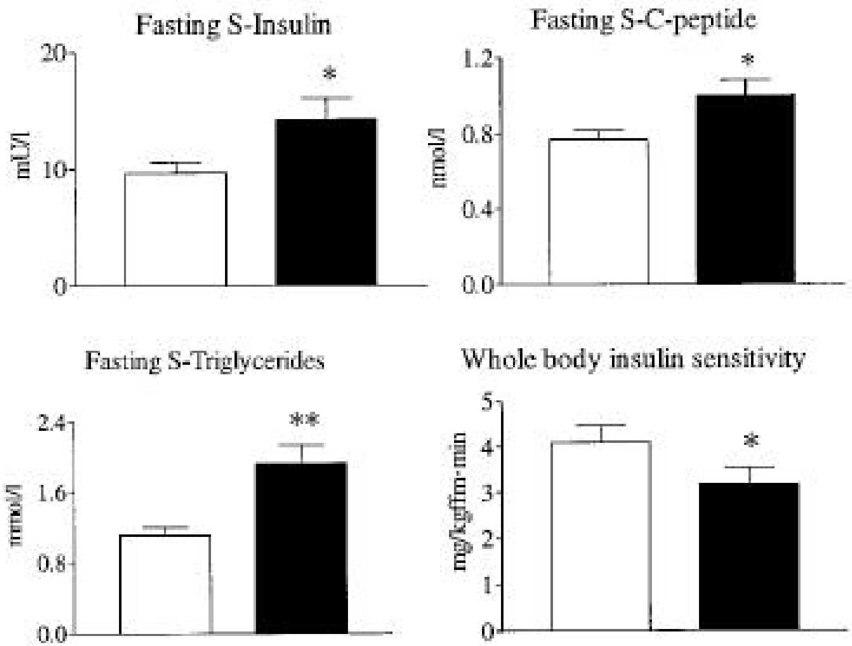


Figure 3: Fasting serum insulin and C-peptide concentrations, triglycerides, and whole-body insulin sensitivity in women with low (□) and high (■) LFAT. $^{*}p < 0.05$ and $^{**}p < 0.01$ for high vs. low-LFAT.

Fasting insulin, triglycerides and arterial pressure were associated with LFAT. The relationship remained significant after adjustment for intra-abdominal or subcutaneous fat or BMI.

Tiikkainen, Obes Res 2002

Liver Fat & Insulin Resistance

Effect of Weight Loss

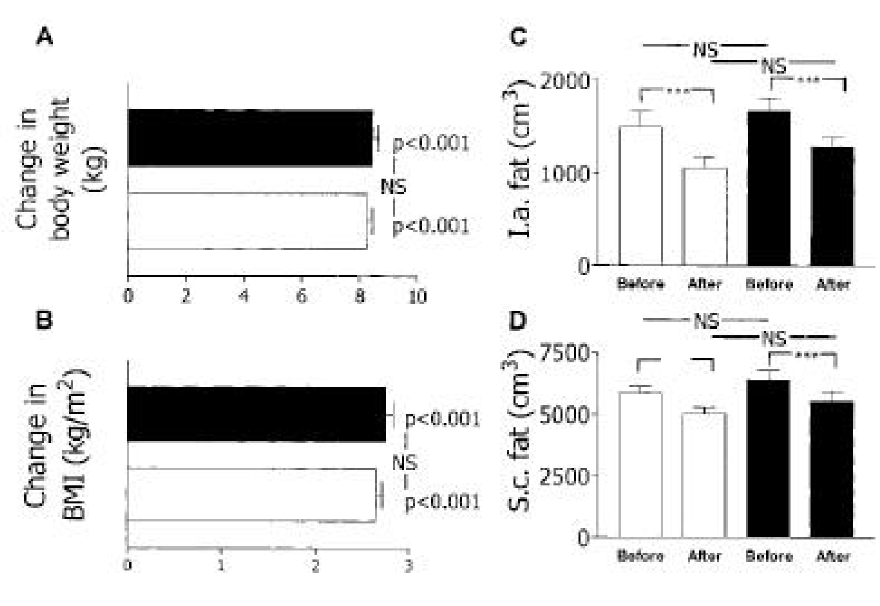


FIG. 3. Effects of weight loss on measures of body composition in women with low (□, $n = 12$) and high (■, $n = 11$) LFAT. Change in body weight (*A*) and BMI (*B*) by weight loss. Intra-abdominal (I.a.) (*C*) and subcutaneous (S.c.) (*D*) fat volumes before and after weight loss. $***P < 0.001$ before vs. after weight loss.

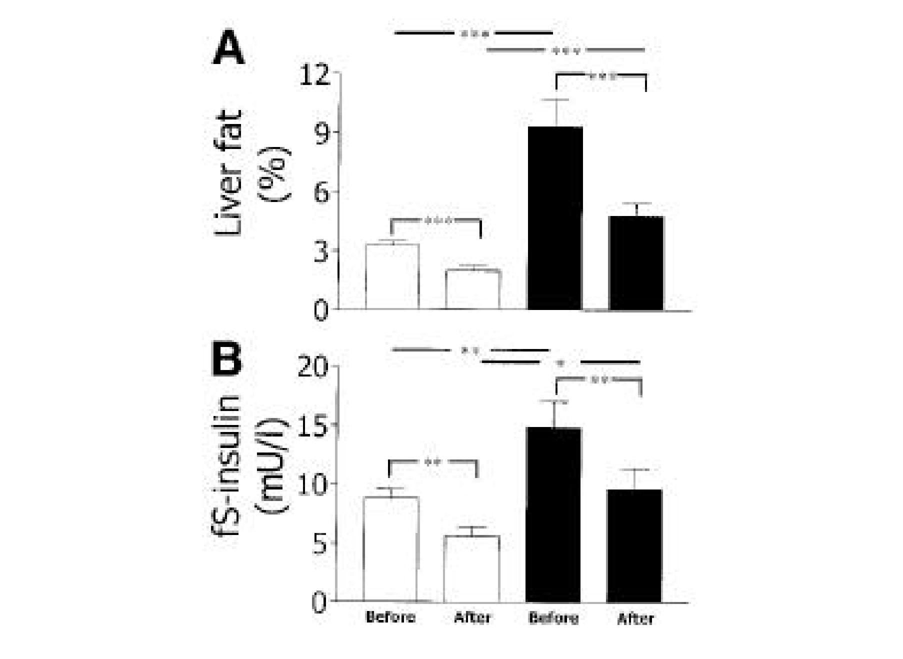


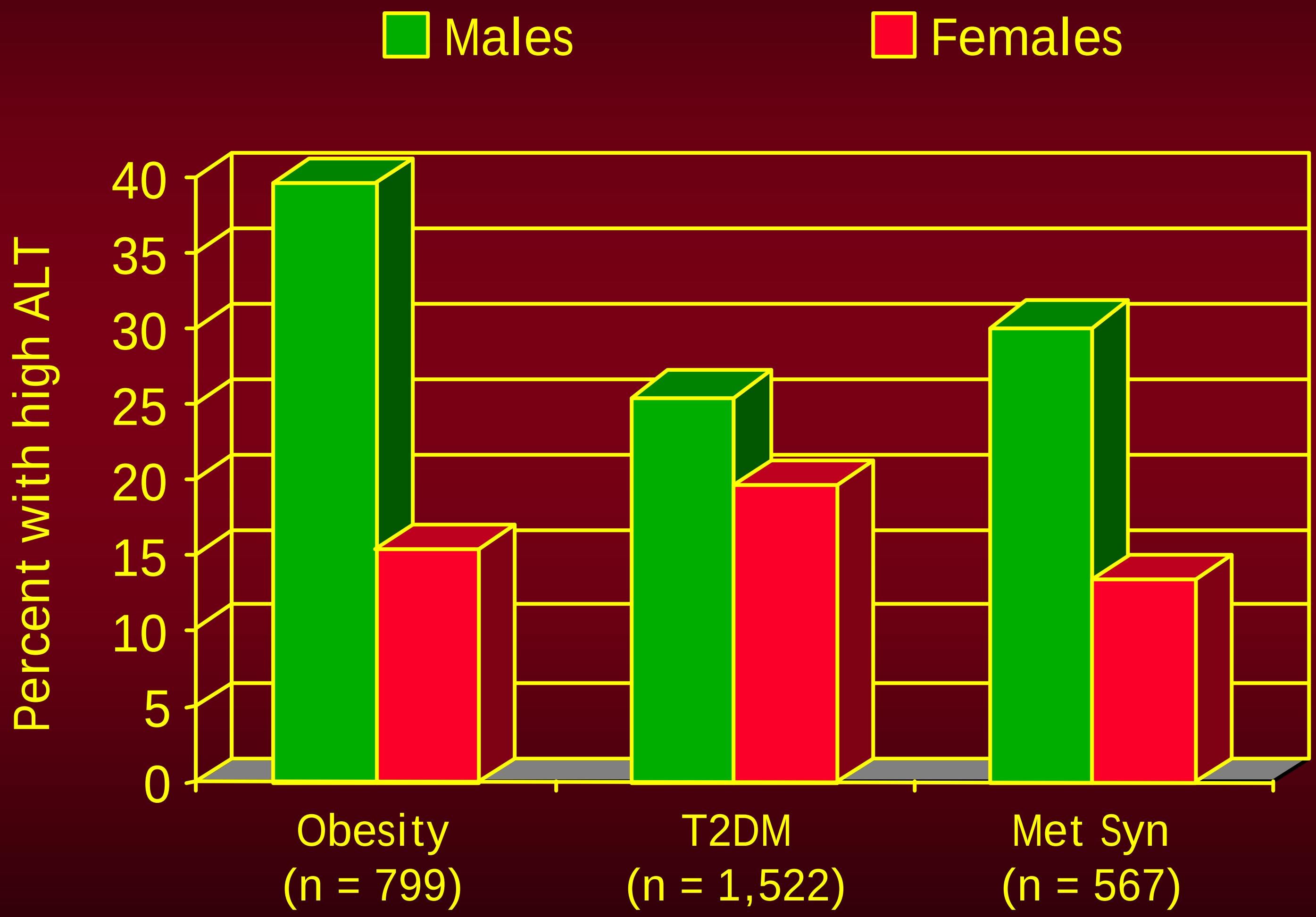
FIG. 4. Effects of weight loss on LFAT (*A*) and fasting serum insulin concentrations (*B*) in women with low (□) and high (■) LFAT. $*P < 0.05$, $**P < 0.01$, $***P < 0.001$.

Identical weight loss produces different effects on hepatic steatosis in subjects with low or high Liver FAT. The effects on subcutaneous and intra-abdominal fat depots were identical.

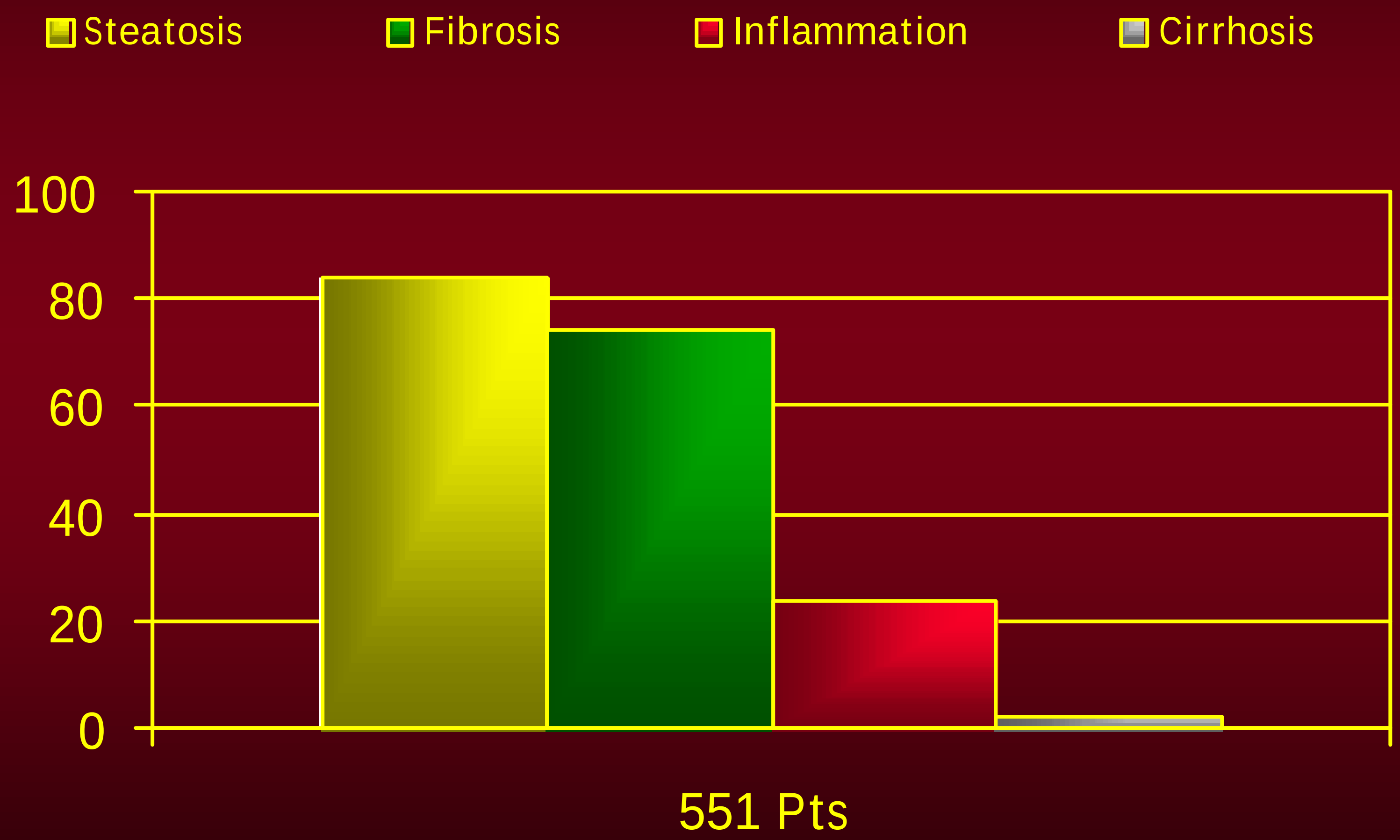
Conclusion: Liver Fat does not simply reflect fat stores; Regulation by dietary fat.

Tiikkainen, Diabetes 2003

Raised ALT in Metabolic Diseases

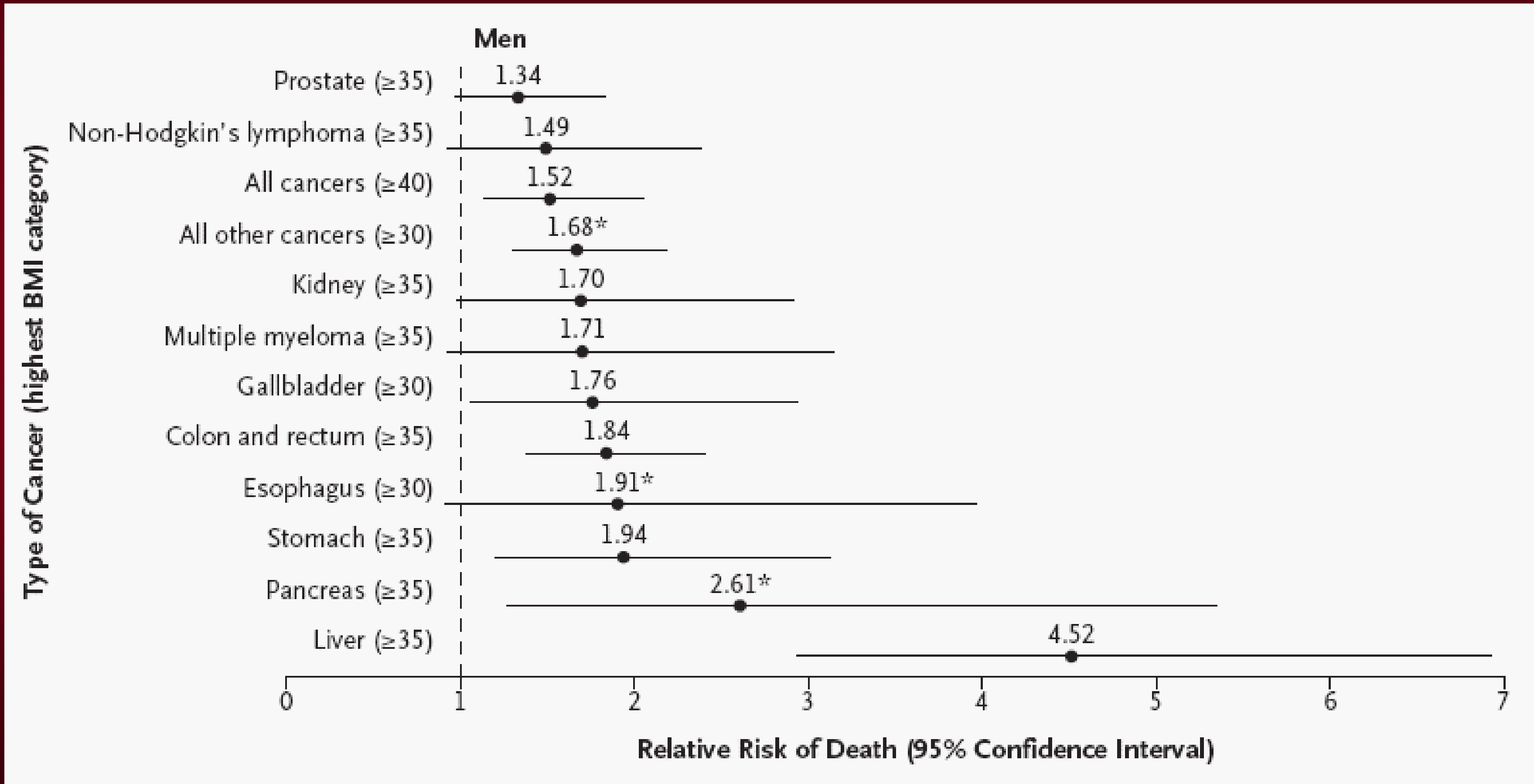


Liver Pathology in Morbidly Obese



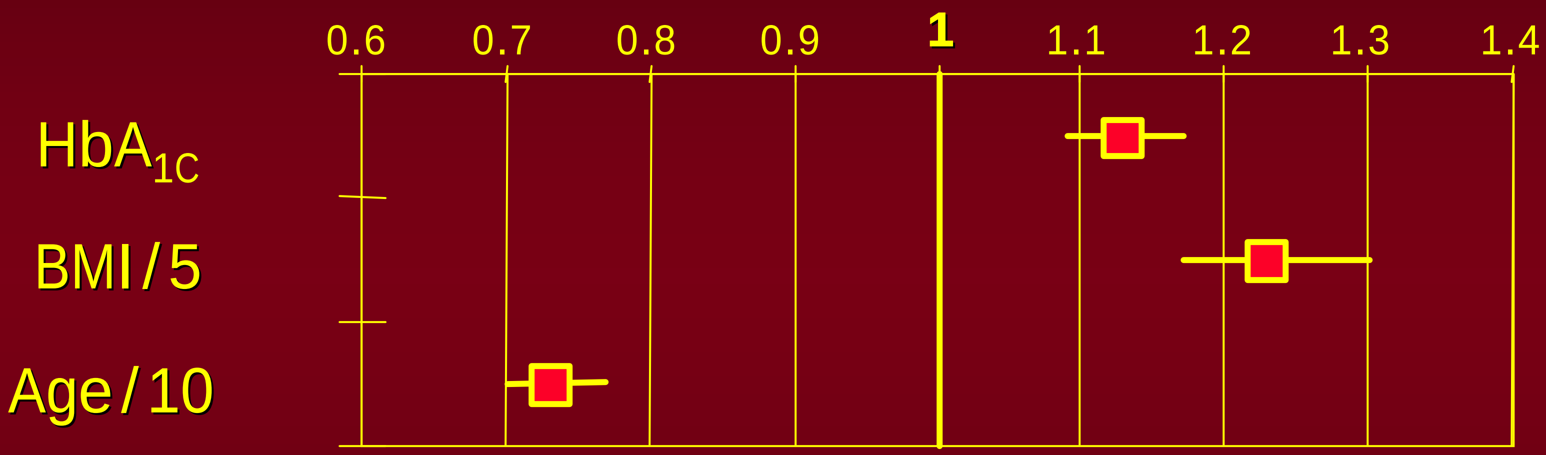
Marceau et al, JCEM 1999

Obesity as a risk factor for liver cancer



Calle, N Engl J Med 2003

Factors Associated with High ALT Levels in T2DM



- The prevalence of high ALT is associated with poor metabolic control and obesity grade
- Age has a negative effect

Forlani, J Endocrinol Invest 2008

Dietary Intake in NASH

Daily Intake	NASH (25)	Cont (25)	P value
Total energy (kcal)	2,638 ± 444	2,570 ± 739	NS
Energy per b.w. (kcal/kg)	33 ± 5	32 ± 6	NS
Protein (g)	121.2 ± 25.2	107.2 ± 32.7	0.096
Carbohydrates (g)	295.1 ± 53.7	315.2 ± 101.9	NS
Total Fat (g)	102.8 ± 31.6	92.1 ± 35.2	NS
Saturated FA (g)	40.2 ± 12.7	28.7 ± 11.1	0.001
Monounsaturated FA (g)	52.1 ± 17.4	47.8 ± 16.7	NS
Polyunsaturated FA (g)	10.3 ± 4.9	13.4 ± 4.1	0.019
Poly/Sat ratio	0.24 ± 0.10	0.46 ± 0.12	< 0.001
Cholesterol (mg)	506 ± 108	405 ± 111	0.002
Fiber (g)	12.9 ± 4.1	23.2 ± 7.8	< 0.001
Vitamin A (µg)	583 ± 384	647 ± 507	NS
Vitamin C (mg)	84.3 ± 43.1	144.2 ± 63.1	< 0.001
Vitamin E (mg)	5.4 ± 1.9	8.7 ± 2.9	< 0.001

Musso et al, Hepatology 2003

Dietary Intake in NASH

	Recommendations	Mean (min.-max.)	Low to recommendation	Over recommendation
Proteins (% kcal)	10-35%[a]	19.6 (11.7-29.1)	0%	0%
Carbohydrates (% kcal)	45-65%[a]	46.6 (34.2-62.3)	46.7%	0%
Total fat (% kcal)	20 a 35%[a]	34.9 (22.3-44.8)	0%	44.4%
Saturated fat (% kcal)	<7%[b]	9.9 (6.2-13.9)		93.3%
Mono fat (% kcal)	Up to 20%[b]	16.5 (8.0-23.8)	82.2%	
Poly fat (% kcal)	Up to 10%[b]	5.4 (3.8-8.6)	100%	
n-3 fatty acids (% kcal)	0.6-1.2%[a]	0.6 (1-3.2)	51.1%	0%
n-6 fatty acids (% kcal)	5-10%[a]	4.1 (2.5-7.8)	82.2%	0%
Cholesterol (mg)	<200 mg /d[b]	329.3 (75-819)		80%
Total fibre (g)	20-30 g/d[b]	25.5 (9.1 - 55.4)	33.3%	31.1%

Cortez Pinto et al, Clin Nutr 2006

Low CHO Diet & Intrahepatic TG Content

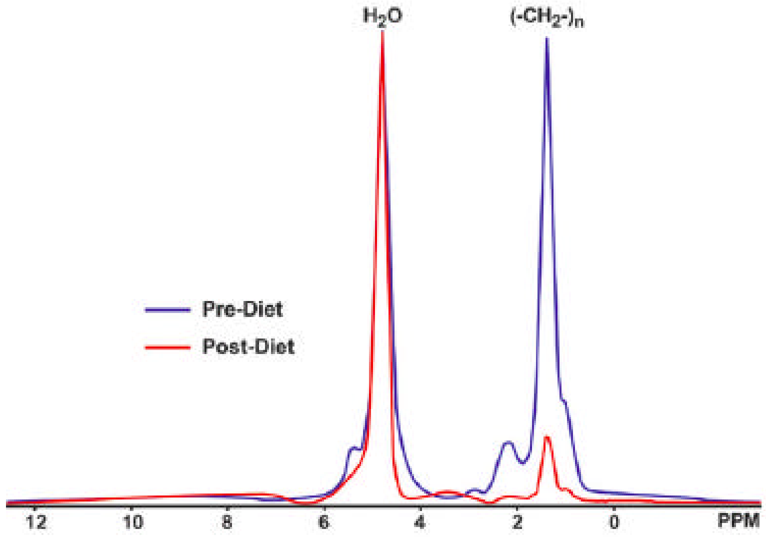


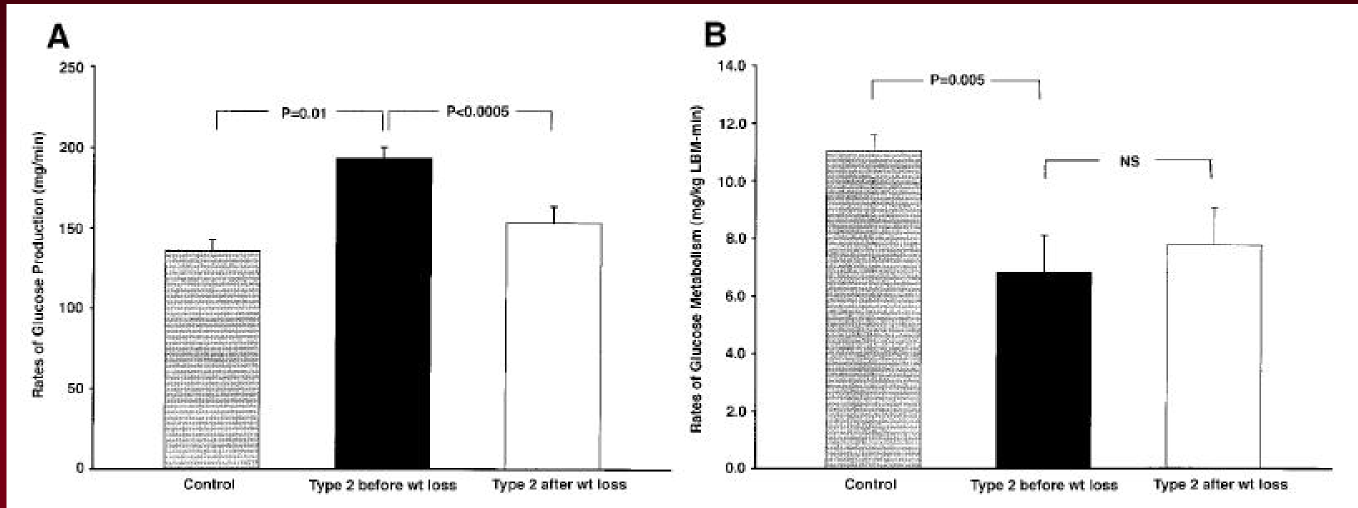
Fig. 1. Serial proton magnetic resonance spectra. Spectra were obtained from a 27-cm^3 voxel positioned within the liver to avoid major blood vessels, bile ducts, and the liver edge. Liver triglyceride content is calculated as the ratio of the area under the triglyceride signal (methylene groups: $(-CH_2-)_n$) to the area under both the water signal (H_2O) and the triglyceride signal. The spectrum depicted in blue was obtained before initiation of therapy and corresponds to a liver triglyceride content of 44.6%. The spectrum depicted in red was obtained 5 weeks after initiation of a low-carbohydrate diet and a moderate exercise program and corresponds to a nearly fourfold reduction in liver triglyceride (11.9%).

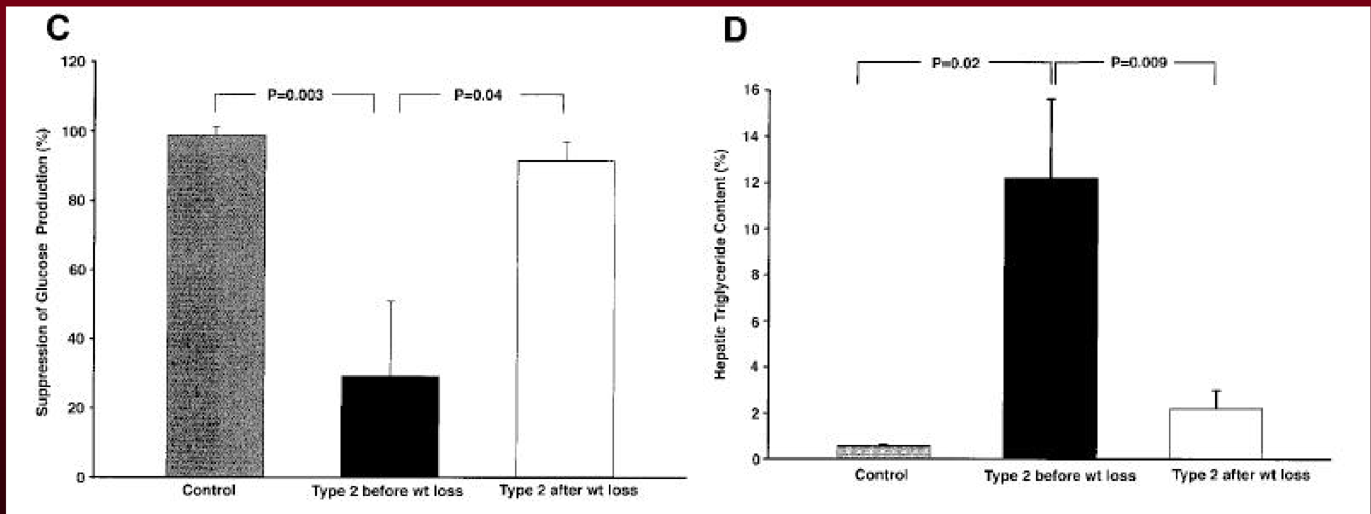
- Treatment with Atkins diet for 2 weeks
  - Total calories, 1000
  - CHO, 5%; Protein, 54%; Lipid, 41%
    - » PUFA, 8%; MUFA, 35%; SFA, 57%.
  - Glycogenolysis, 25% HGO; Gluconeogenesis from glycerol, 6% (Normal, 53% and 3%, respectively)

Browning, Hepatology 2006

NAFLD & Weight Loss in DM

WL (10%) by a very low fat, liquid formula diet (3%)

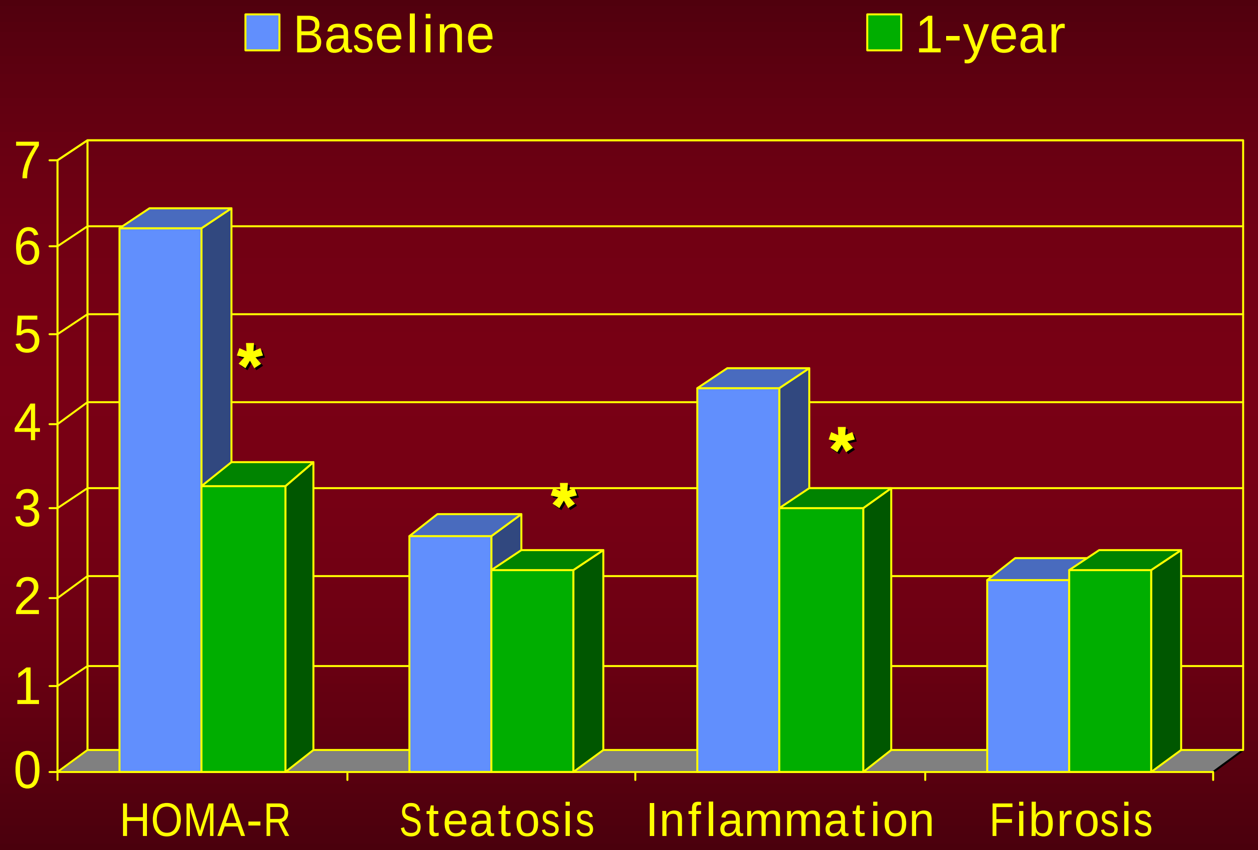




A WL, low fat diet reduces IHL and restores hepatic insulin sensitivity, without changes in IML

Petersen et al, Diabetes 2005

Effect of Counseling



Results remarkably better in 9 patients compliant to treatment

Huang et al, Am J Gastroenterol 2005

Lifestyle Intervention & ALT Normalization

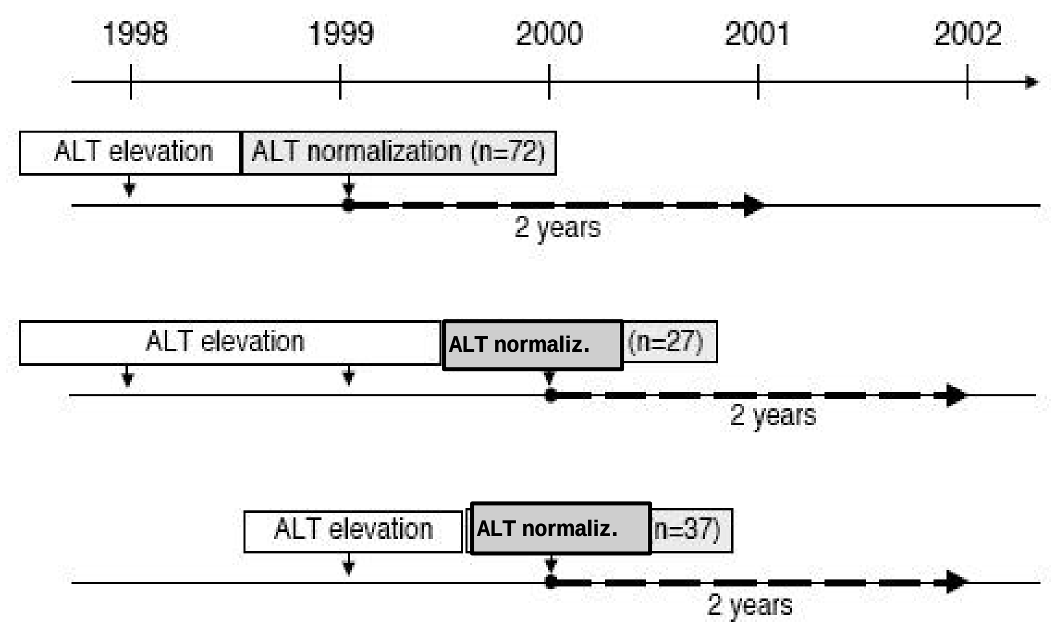


Fig. 2. Study design for the association between maintaining lifestyle modification and persistently normal ALT levels

- 1546 employees (469 with elevated ALT, 348 by excluding those with other causes of liver disease)
- Followed for one year to assess the association of change in lifestyle with change in serum ALT
- 136 subjects had ALT normalization
- Followed for two years to assess the association between lifestyle change and persistently normal ALT

Suzuki, J Hepatol 2005

Lifestyle Intervention & ALT Normalization

Serum ALT change/ALT normalization and changes in body weight, regular exercise, smoking, alcohol consumption

Variables	N=356,	ALT normalization			
		Adjusted for baseline ALT[a]		Adjusted for all variables[b]	
		OR[95%CI]	P-value	OR[95%CI]	P-value
Weight reduction (every 5% reduction)		3.6[2.3, 5.7]	<0.0001	3.6[2.1, 6.2]	<0.0001
Exercise (>once/week)					
No exercise	184(55)	–	–	–	–
Quit exercise	32(10)	1.4[0.7, 3.1]	0.367	1.7[0.7, 4.3]	0.239
Keep exercise	78(23)	1.9[1.1, 3.3]	0.030	2.5[1.3, 4.8]	0.007
Start exercise	39(12)	1.6[0.8, 3.4]	0.194	1.5[0.6, 3.6]	0.394

Subjects who practice physical activity are much more prone to maintain ALT normalization

In adjusted analysis, weight loss and regular exercise were significantly associated with improvement in serum ALT and increased the odds of ALT normalization

Subjects achieving >5% weight reduction showed improvement in serum ALT

Suzuki, J Hepatol 2005

What we learned from intervention studies