The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

NDDC Nottingham Digestive Diseases Centre

Nottingham University Hospitals NHS Trust

NHS National Institute for Health Research

Obesity and Liver

Nottingham Digestive Diseases Biomedical Research Unit

Guruprasad P. Aithal

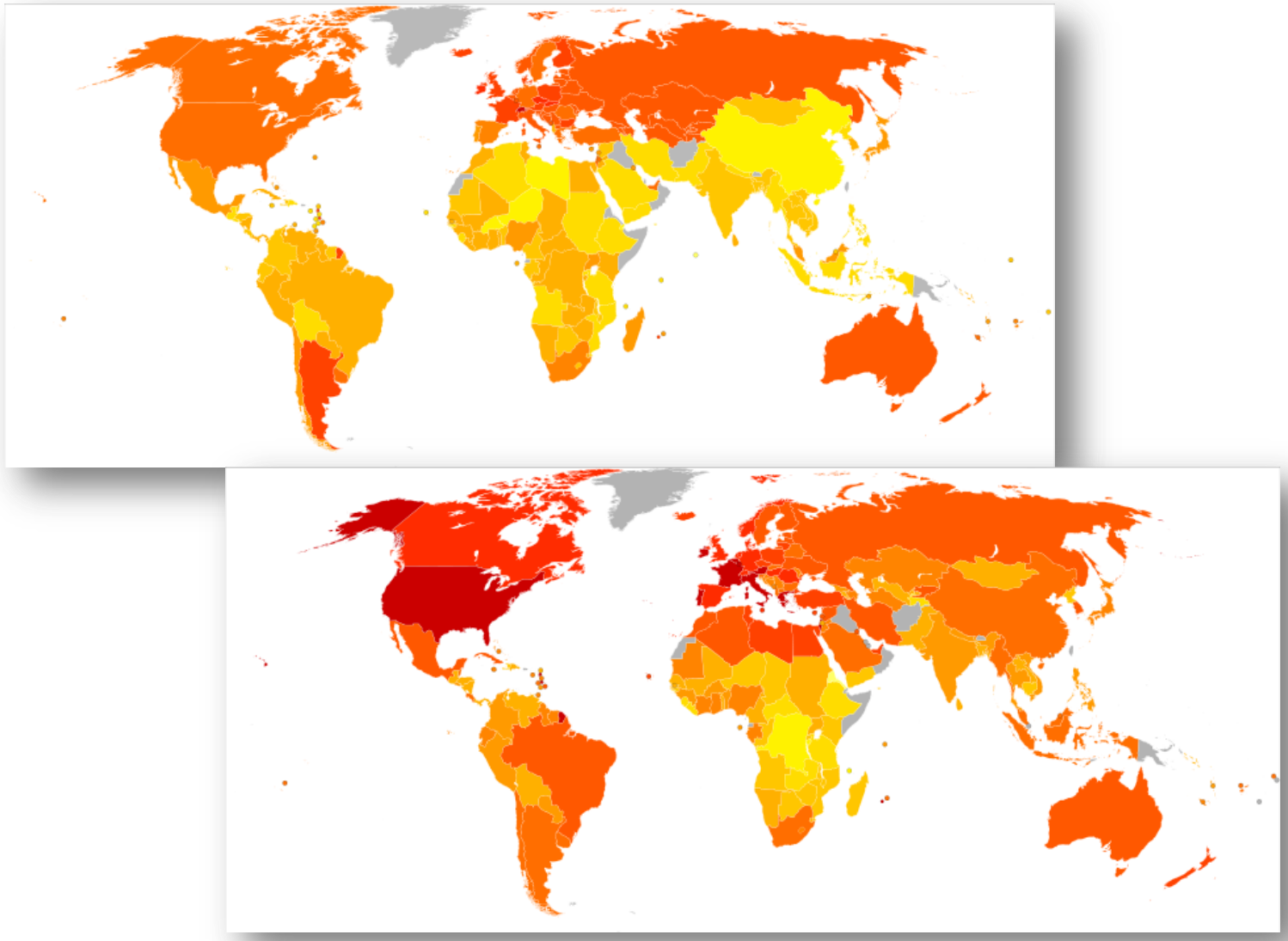
‘La poire’of Willendorf Venus of Hohl Fels

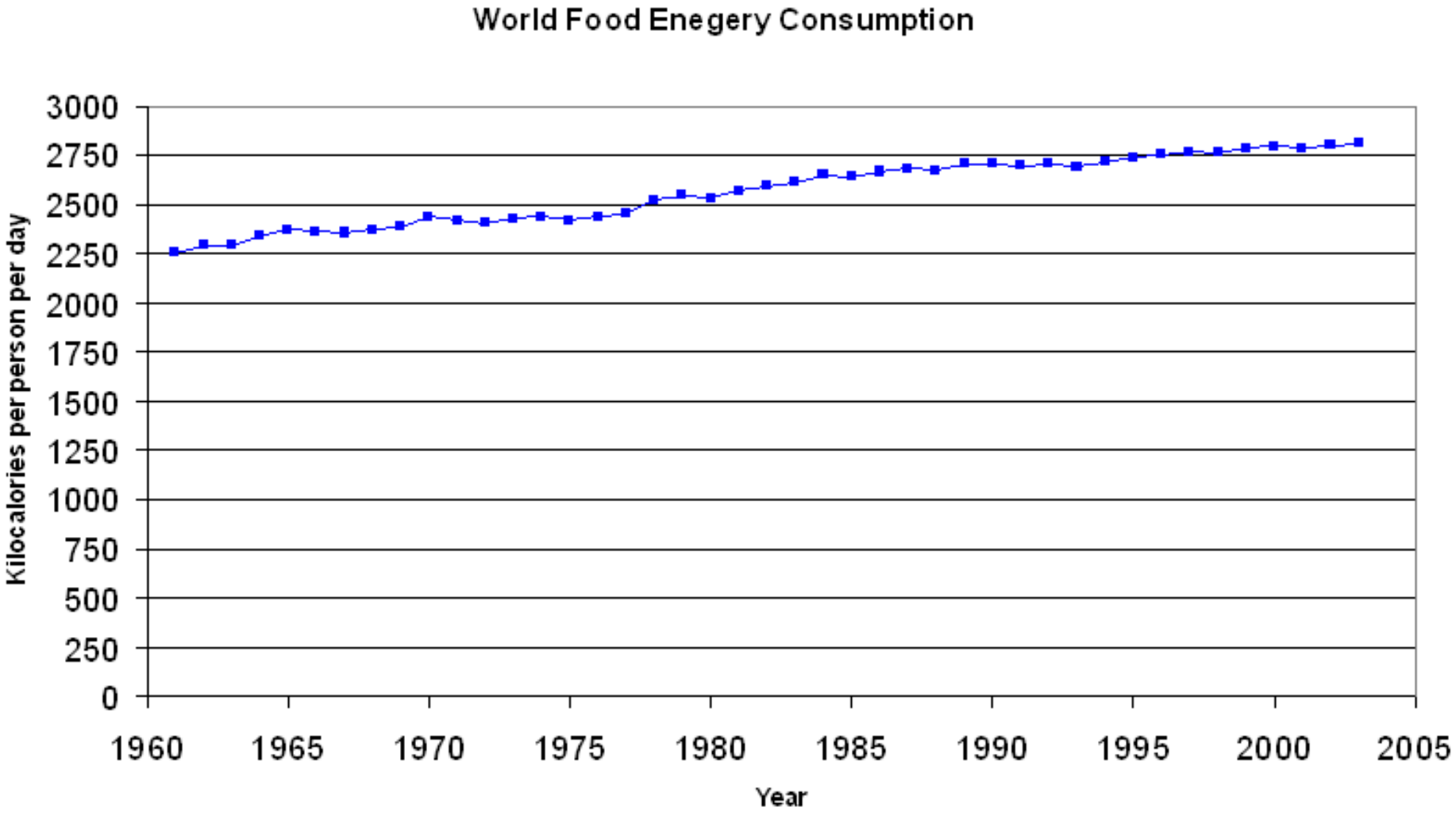
Conrad NJ. Nature 2009;489: 248-52.

NHS
National Institute for Health Research

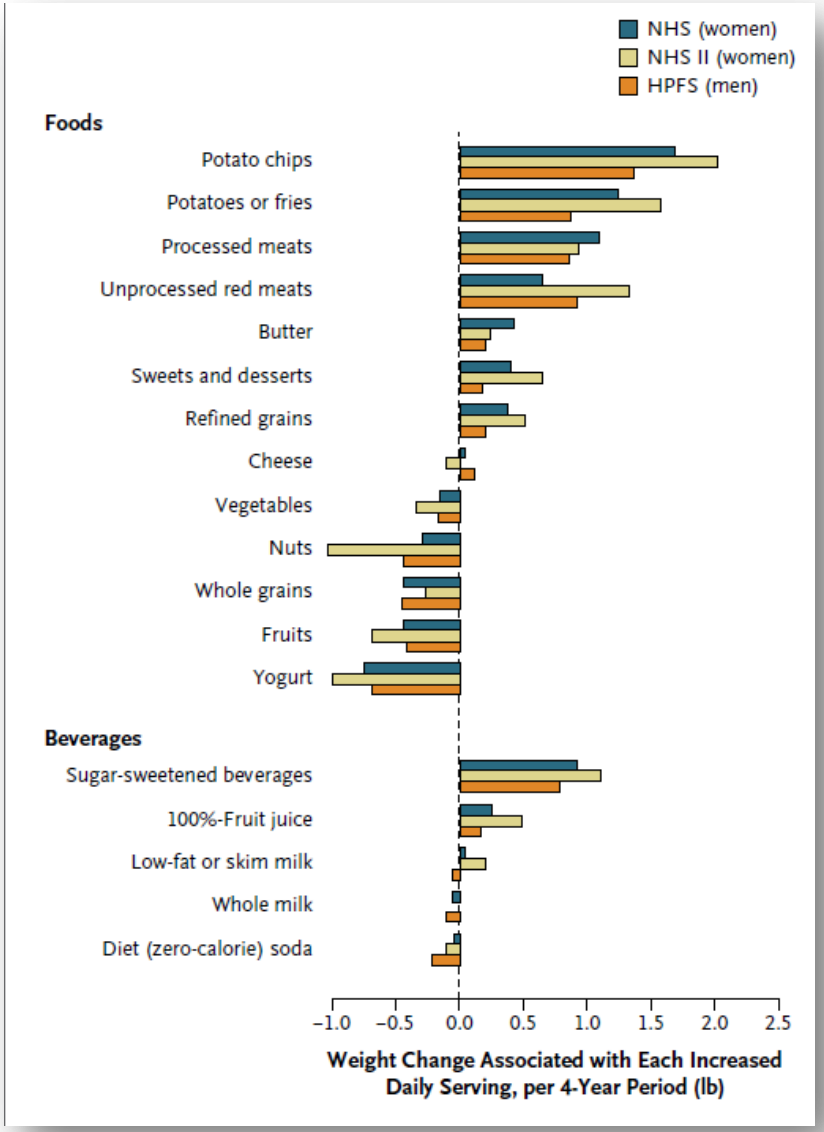
Fat depots
Insulin resistance
Interventions
Outcomes

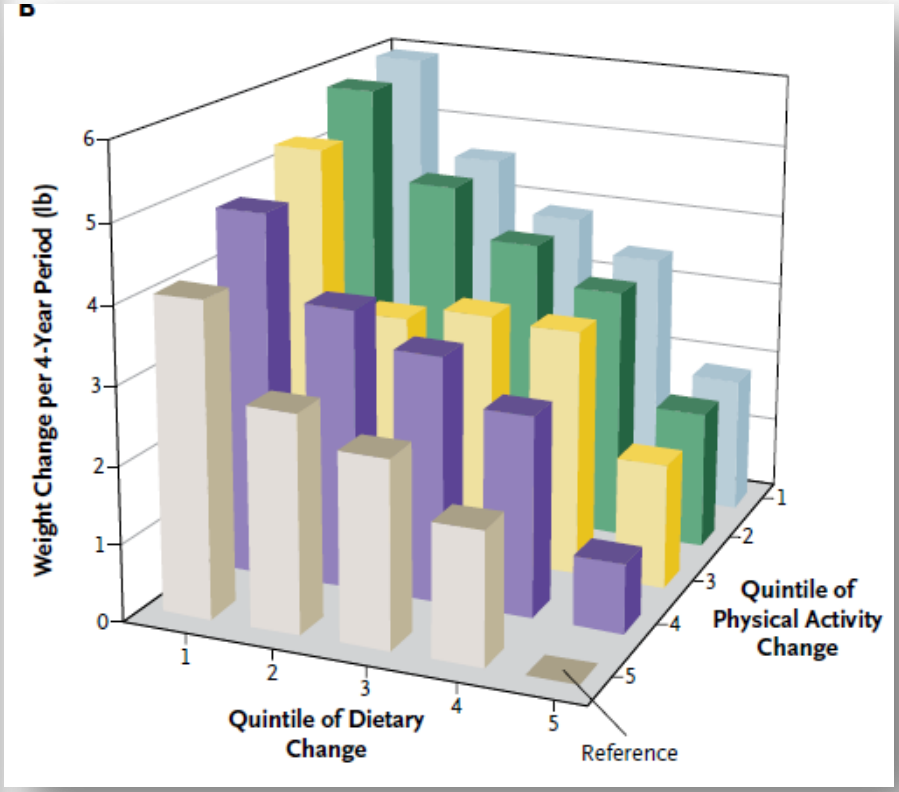
Dietary Energy Availability




World Food Enegery Consumption
Kilocalories per person per day
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
250
0
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
Year

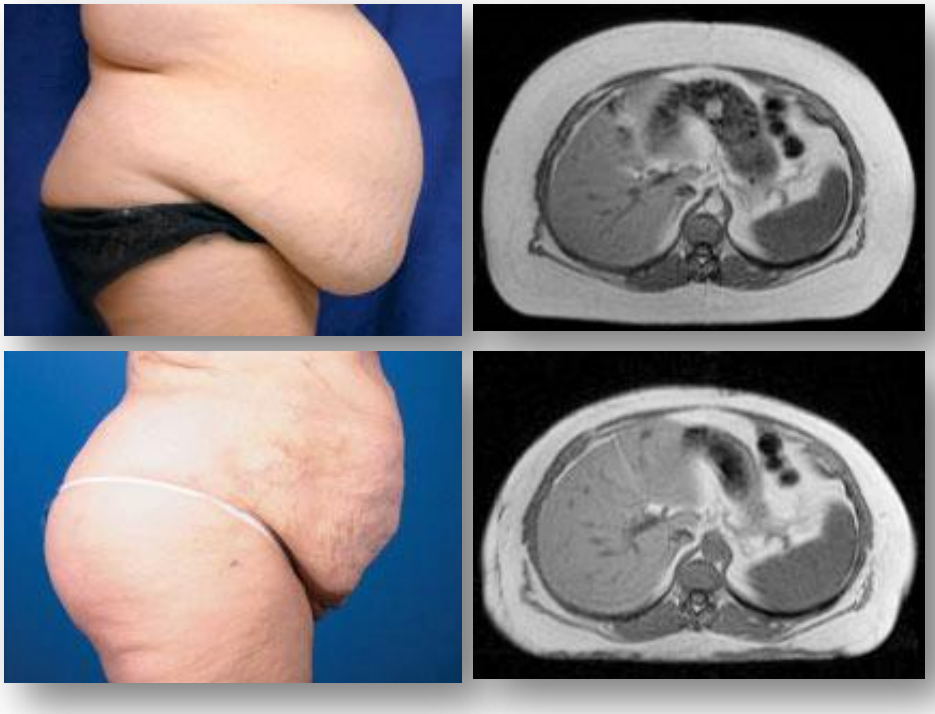
Life Style Factors and Weight





Mozaffarian *et al.*, *NEJM* 2011

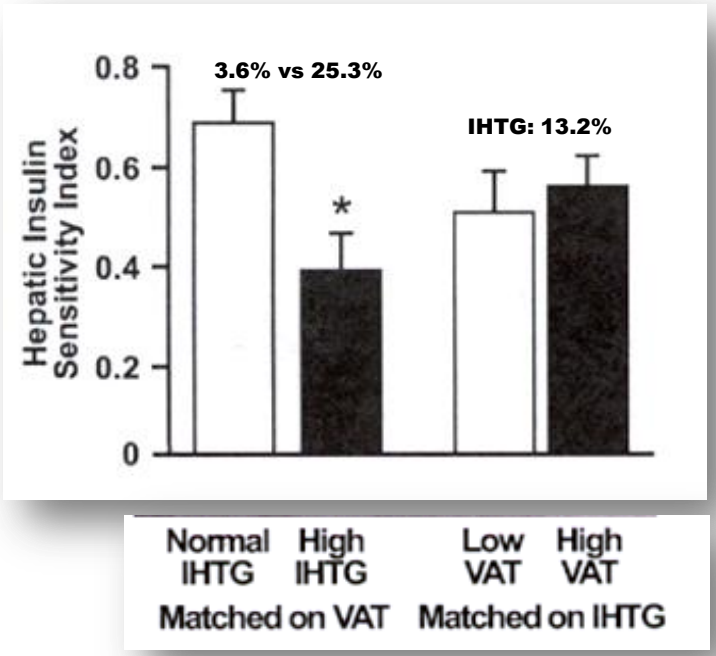
Spot the Difference

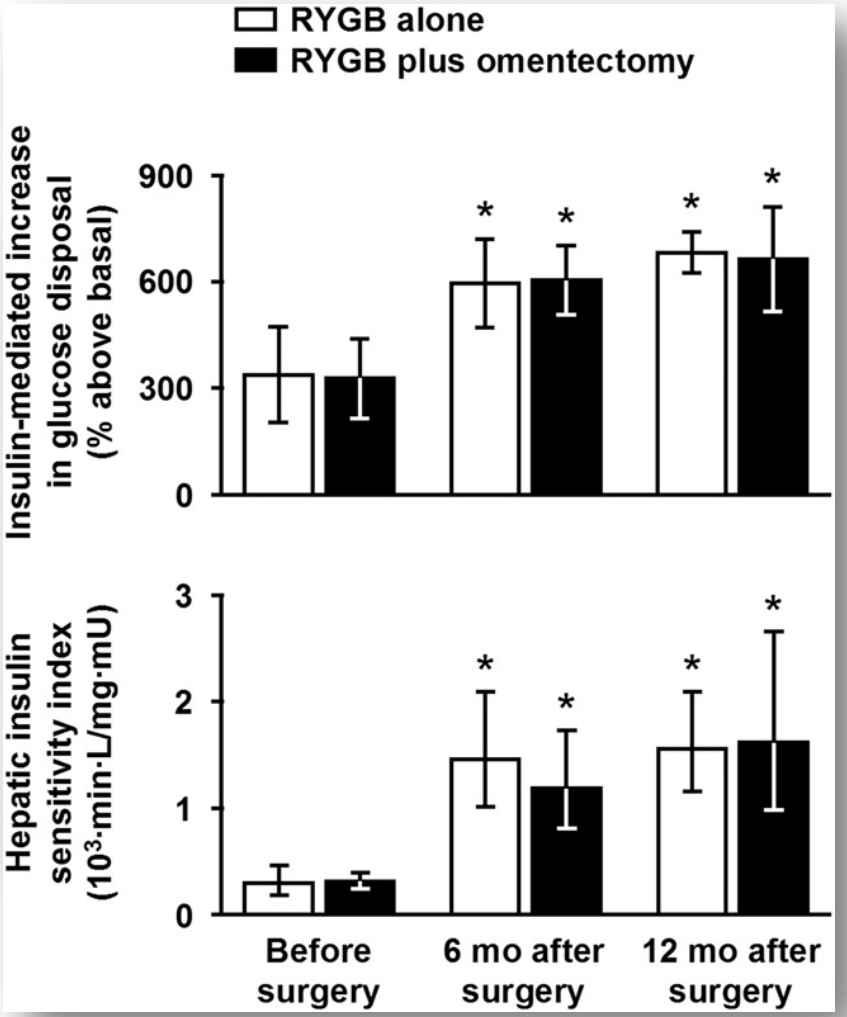


- Liposuction
  - 28%-44% of abd fat
- 18% of total fat
- No change in insulin sensitivity
  - muscle
  - liver
  - adipose tissue
- No change
  - adiponectin, TNF alpha, IL 6
  - risk factors for CV disease

Klein *et al.*, *NEJM* 2004

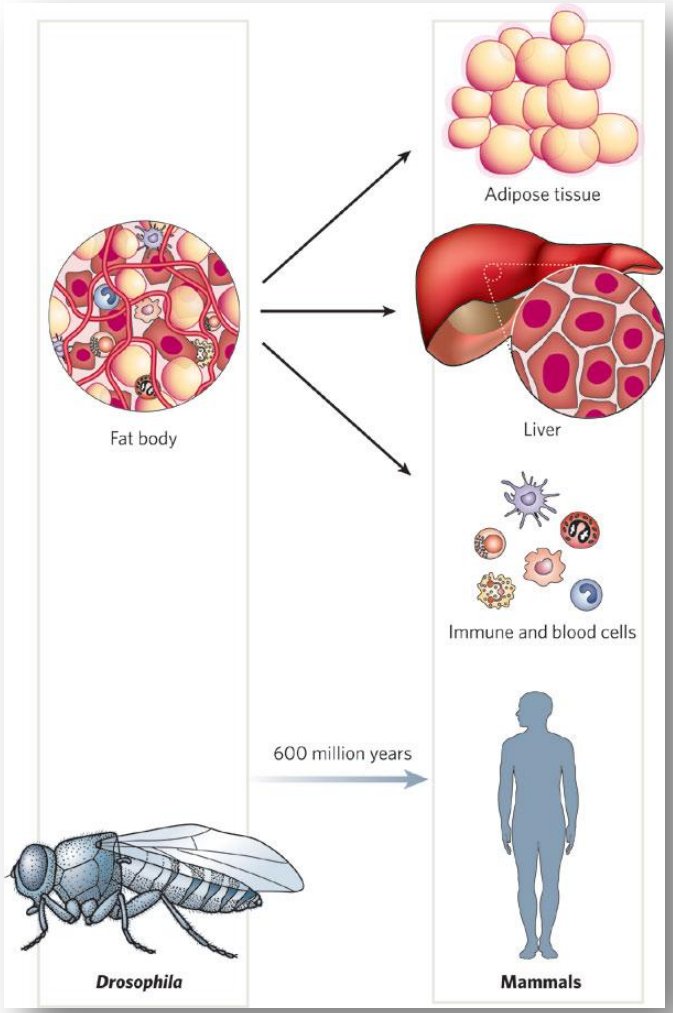
Fat Matters

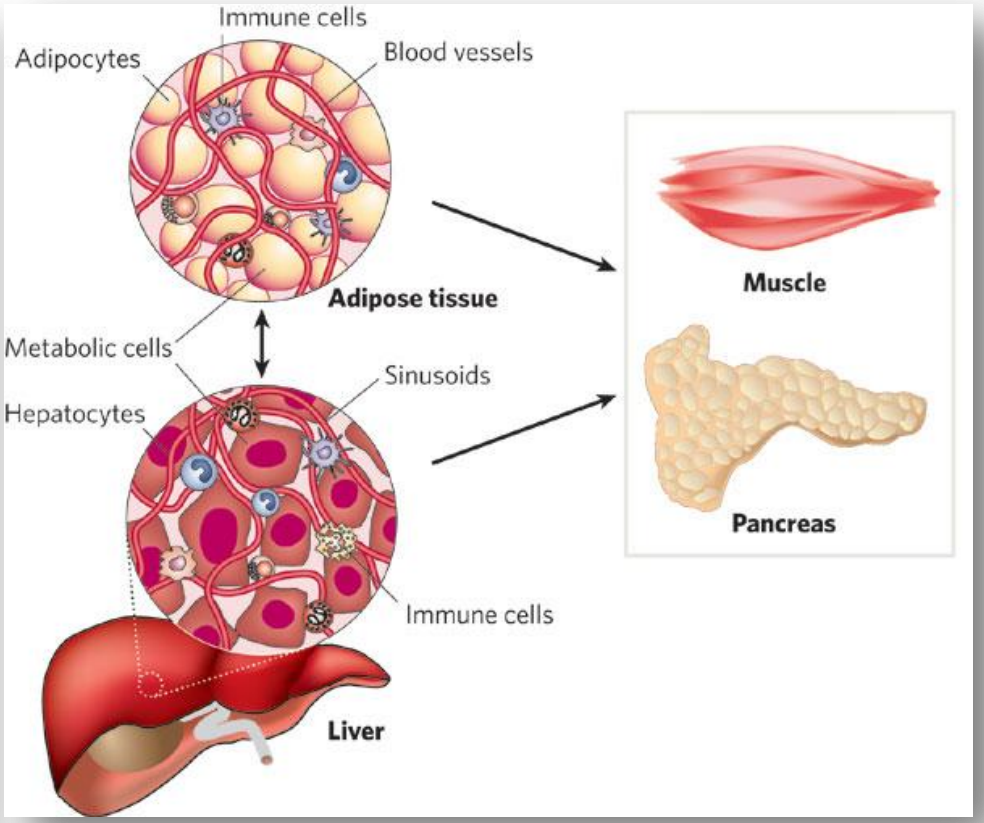




Fabbrini *et al Proc Natl Acad Sci 2009; Gastroenterology 2011*

‘Fat body’ and Liver





Hotamisligil *Nature* 2006

Which came first?

- 38 yr male, BMI 36
- Scrotal swelling- cellulitis
- Venous blood glucose 33.3
  - Wt loss 6 mo; polydipsia 3 mo
  - Alcohol 20 unit
  - Maternal aunt with T2DM
- PH 7.383; bicarb 20
  - urine 3+ ketones;
  - HbA1C 13.8%
  - Chol 7.6; Triglyceride 20.3
  - GGT 69
- Started on Insulin and statin

…..2009

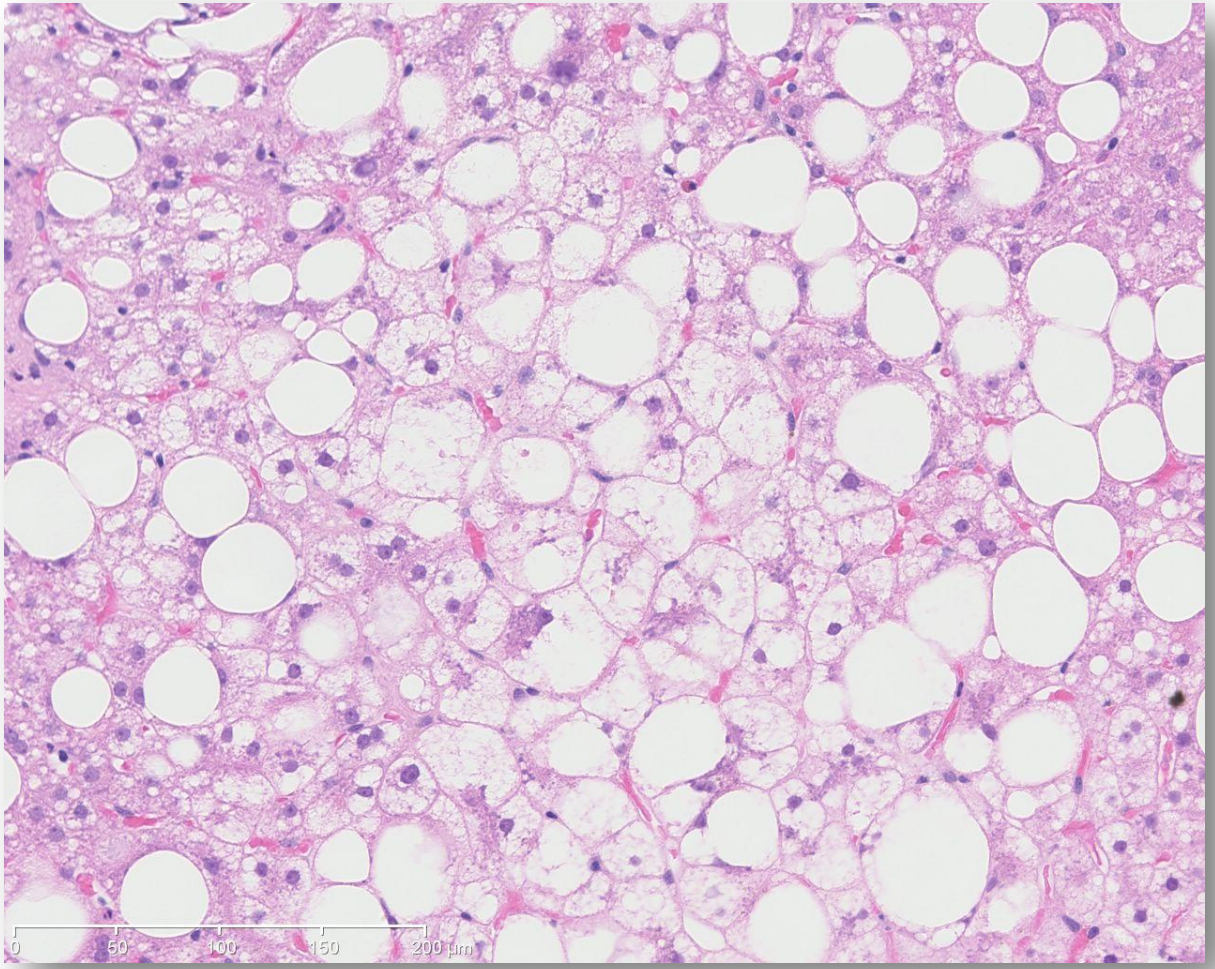
Progress 2010-12

ALT: 91

GGT: 130

Ferritin: 452

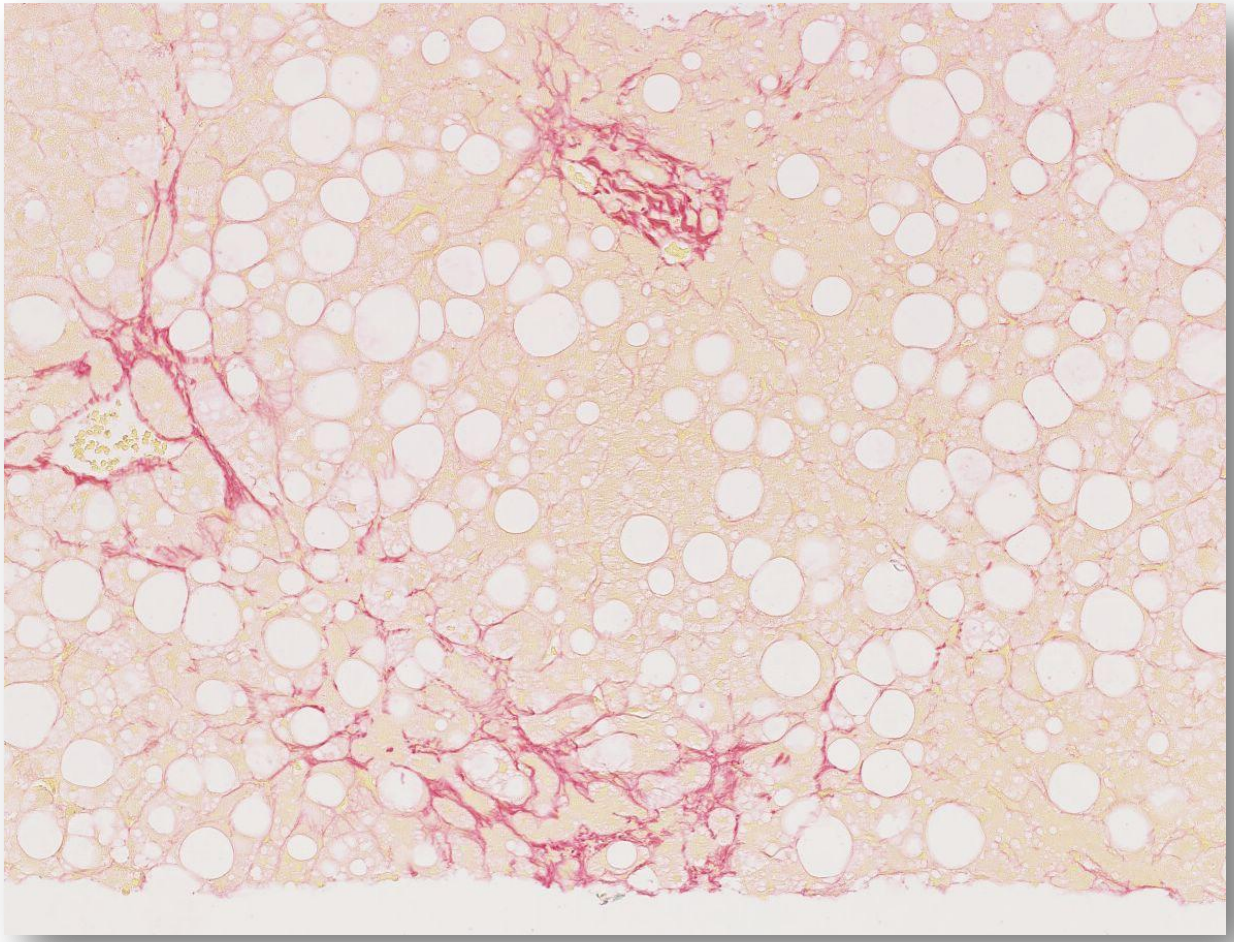
HbA1C: 6.6-10-12%



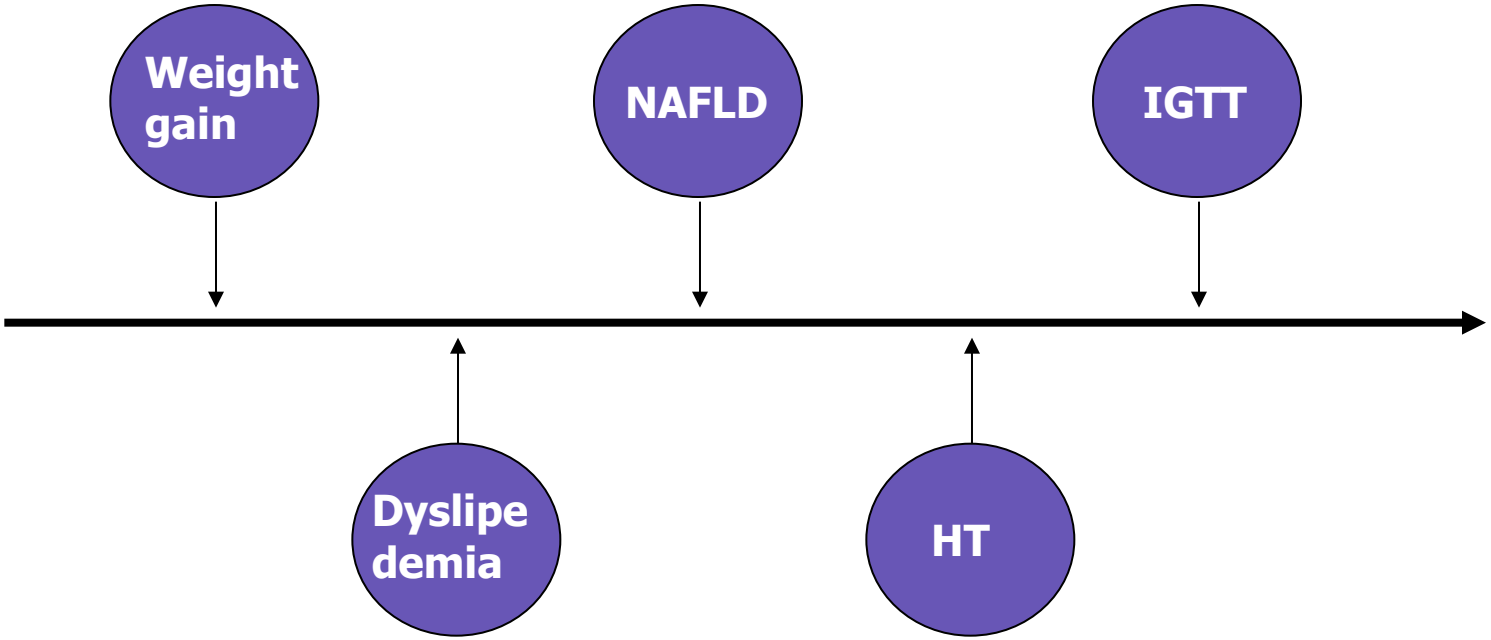
Update

C peptide: 2473 pmol/L

Anti Glutamic acid decarboxylase antibody: negative



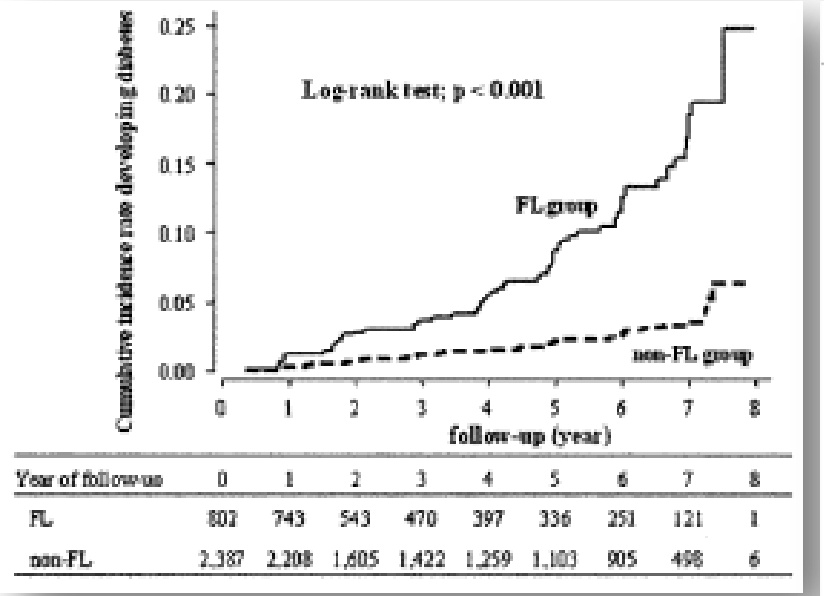
Chronology of Metabolic syndrome



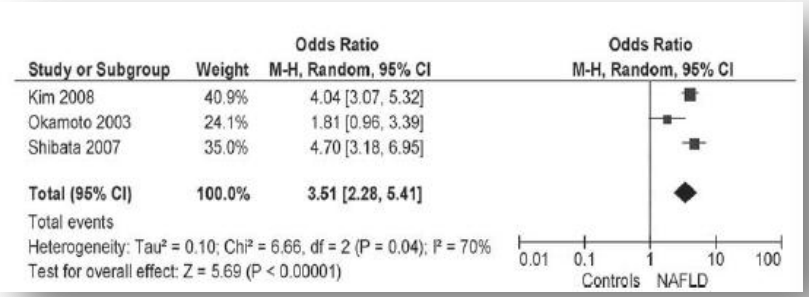
- Adult treatment panel III criteria

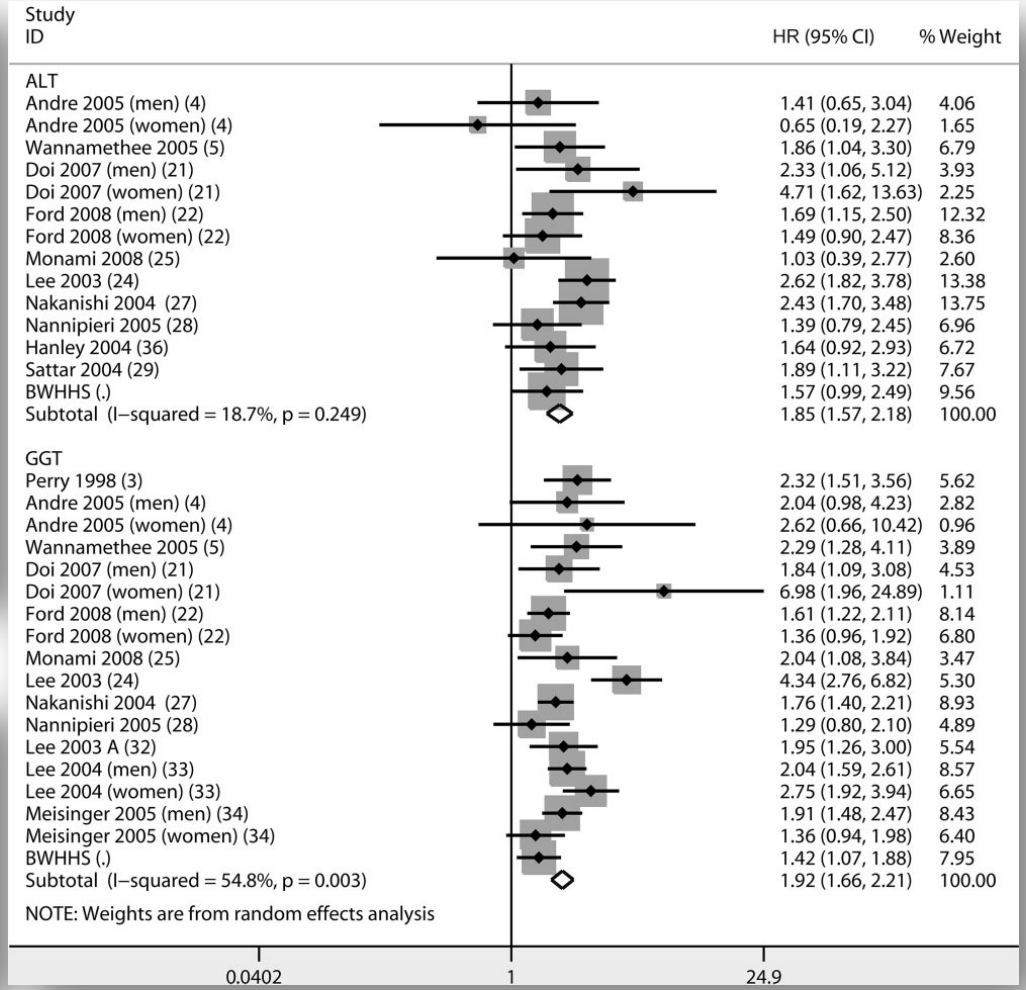
Suzuki *et al.*, *Hepatology* 2005; Sattar *et al.*, *Diabetes* 2005, 2007; Shibata *et al.*, *Diabetes care* 2007, Lawlor *et al.*, *Am J Epidemiol* 2005; Ghouri *et al.*, *Hepatology* 2010

NAFLD is pre-Diabetes



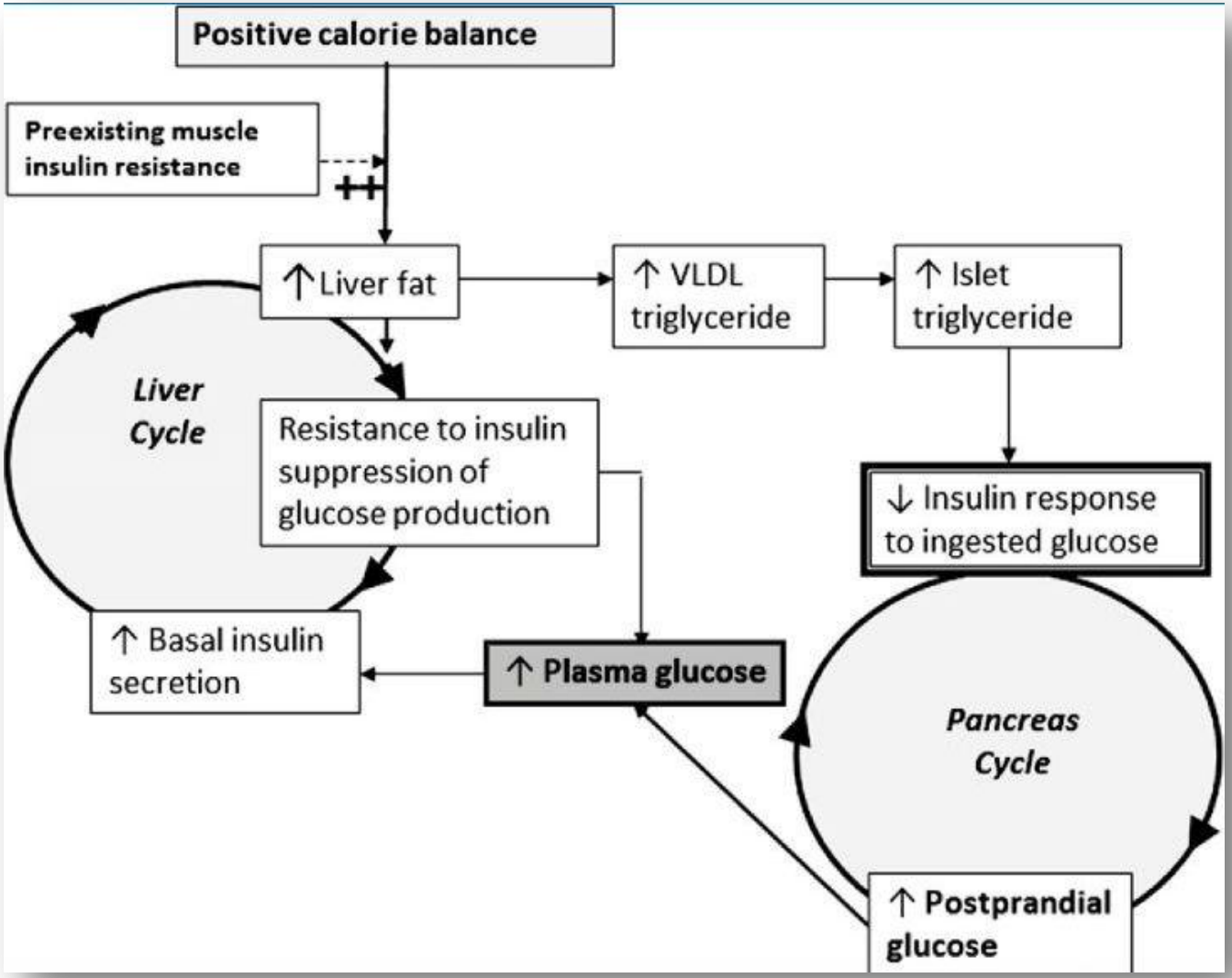
Year of follow-up	0	1	2	3	4	5	6	7	8
FL	802	743	543	470	397	336	251	121	1
non-FL	2,387	2,208	1,605	1,422	1,259	1,103	905	498	6





Shibata M *et al. Diabetes Care* 2007. Fraser *et al. Diabetes Care* 2009 . Musso G *et al.* Ann Med. 2011

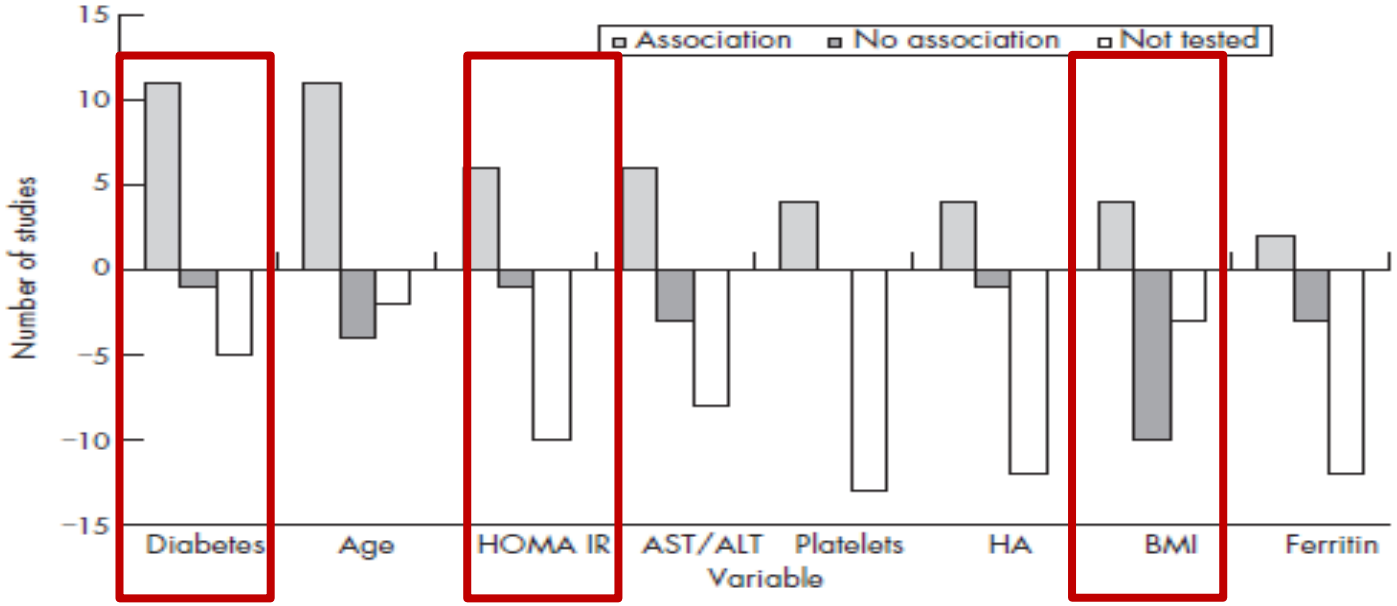
Twin cycle hypothesis



Taylor R. Diabetologia 2008;51:1781–1789.

Roots above, branches below

Risk = Disease

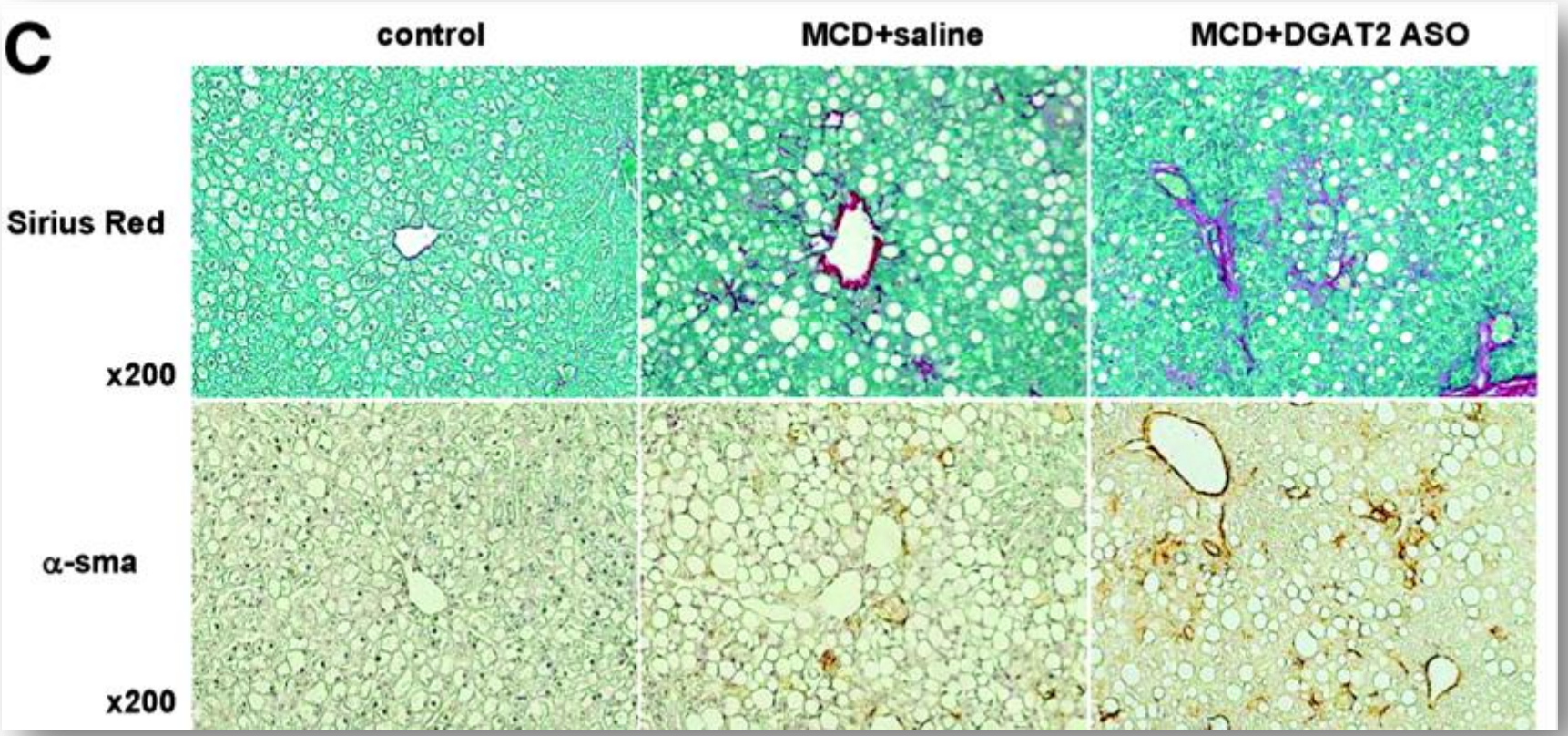


- BARD score
  - BMI ≥28 =1
  - AST/ALT ratio ≥0.8=2
  - DM=1
- BARD score 2-4 = advanced fibrosis (OR: 17 [9-32])

Harrison *et al.*, *Gut 2008*

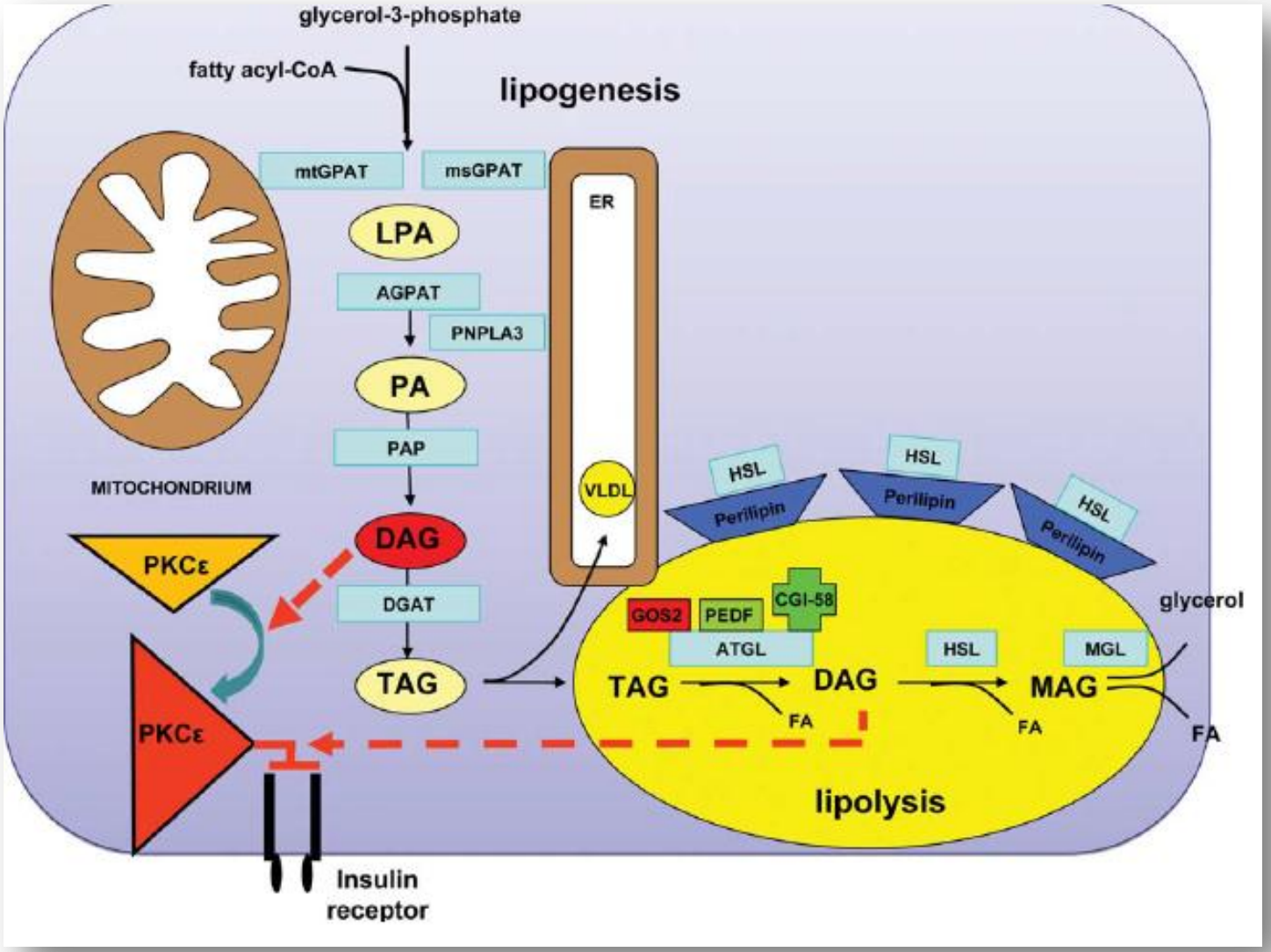
Good Fat, Bad Fat

- Db/Db mice fed MCD diet
- Diacyl glyceral acyl transferase 2 antisense oligonucleotide treatment



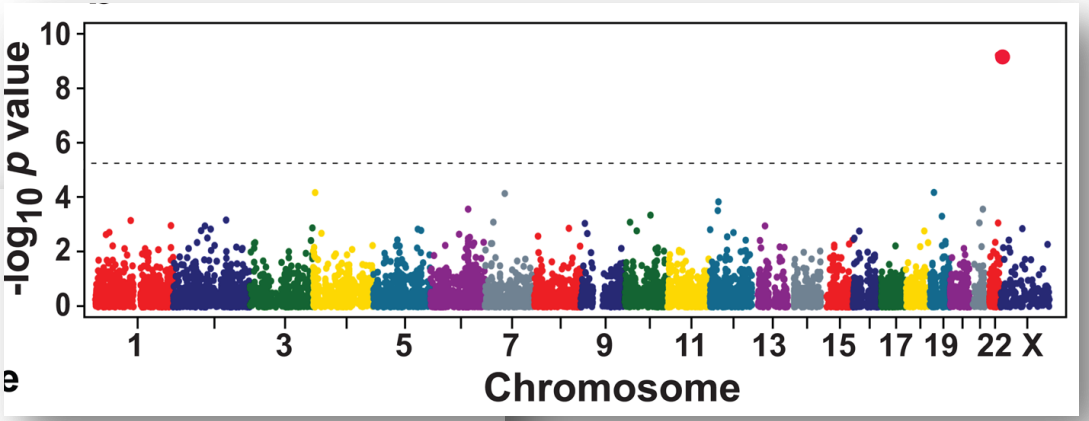
Yamaguchi *et al. Hepatology* 2007

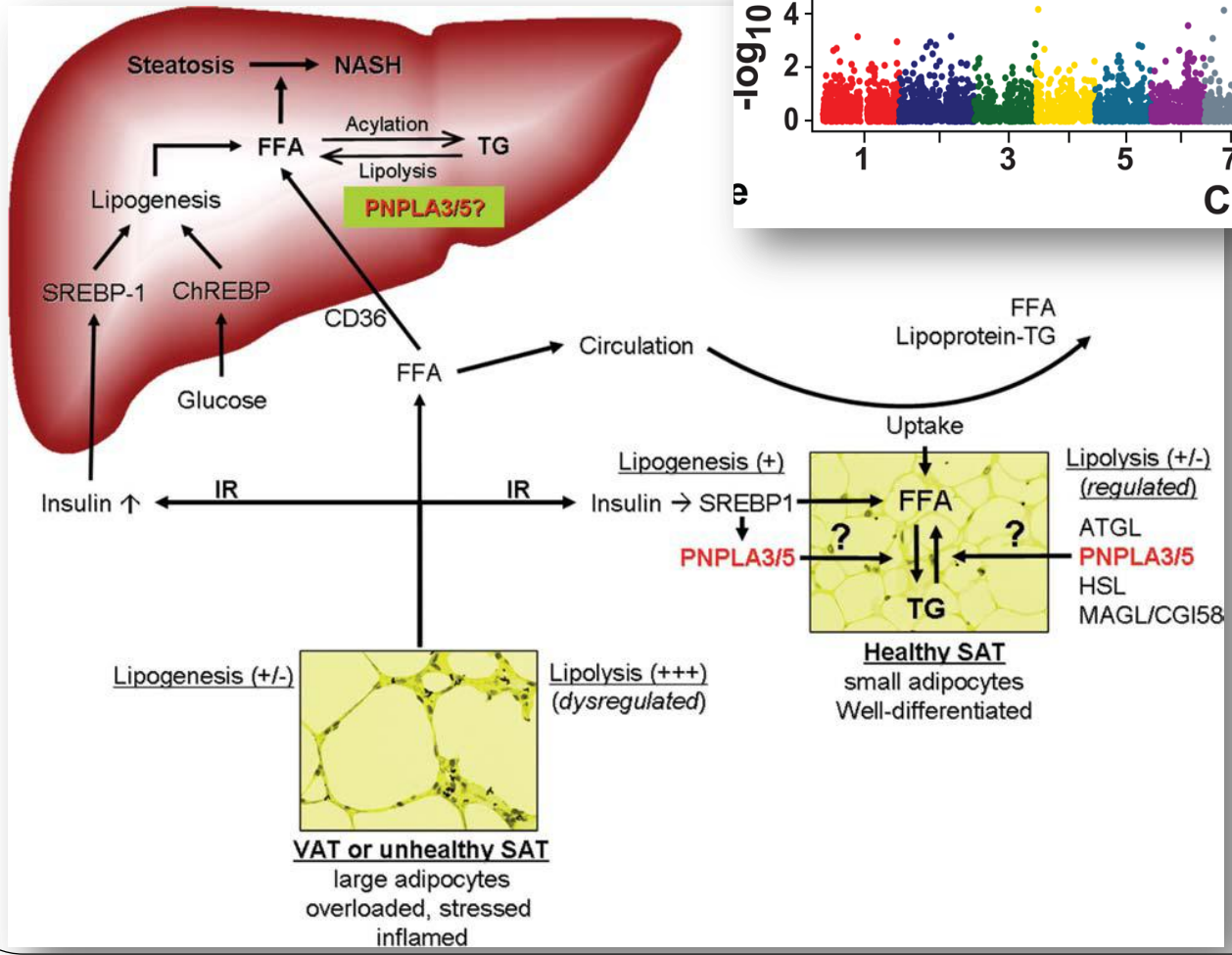
Fat and insulin signalling



Samuel VT *et al. Cell* 2012, Birkenfield AL *et al. Hepatology* 2014

Lipogenesis or lipolysis





Romeo *et al. Nat Genet* 2008
Farrell. *Hepatology* 2010

Coffee: magic

Table 4. Studies assessing impact on coffee on liver related health outcomes – *Non-alcoholic fatty liver disease*

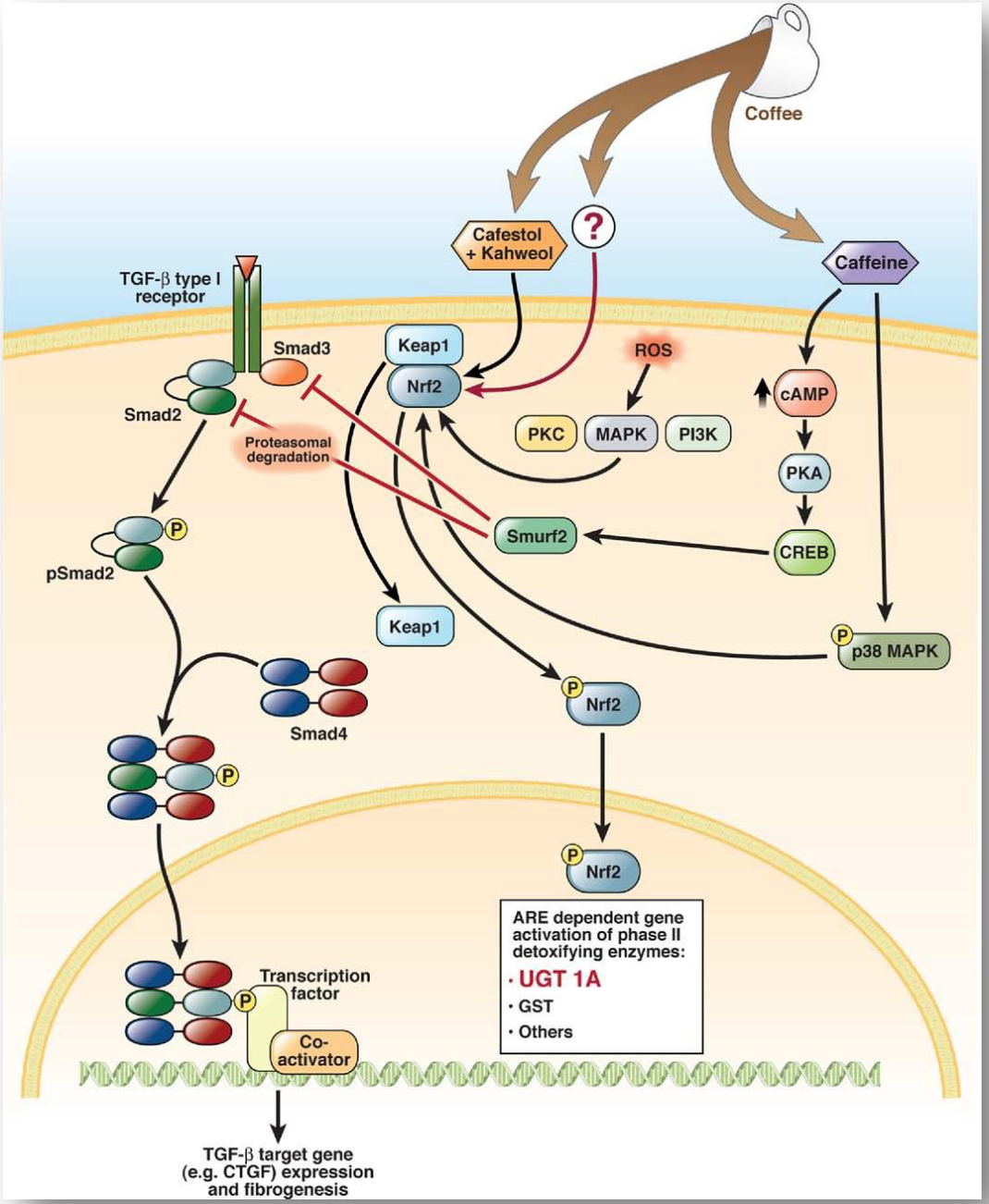
Reference	Year	Design	Cohort*		Country	Findings
Anty *et al.*(50)	2012	Cross-Sectional		195	France	Regular but not espresso coffee protective against liver fibrosis in patients with NAFLD
Birerdinc *et al.*(46)	2011	Cross-Sectional		1782	USA	Caffeine associated with a lower risk of NAFLD
Catalano *et al.*(47)	2010	Case- Control	Cases	157	Italy	Coffee inversely related to severity of NAFLD
			Controls	153		
Gutièrrez-Grobe *et al.*(48)	2012	Case-Control	Cases	57	Mexico	Coffee protectiveagainstNAFLD
			Controls	73		
Molloy *et al.*(49)	2012	Cross-Sectional		306	USA	Coffee caffeine associated with a significant reduction in risk of fibrosis among NASH patients

Table 4—*Adjusted* associations of coffee with incident type 2 diabetes by baseline glucose level, Rancho Bernardo Study, 1984–1987*

Coffee exposure	Total nondiabetic	Normal glucose†	Impaired glucose†
n	910	593	317
Coffee status			
Past drinker/never drank	13/18, 0.38 (0.17–0.87)	4/3, 0.63 (0.12–3.21)	9/15, 0.31 (0.11–0.87)
Current drinker/never drank	53/18, 0.36 (0.19–0.68)	14/3, 0.40 (0.10–1.65)	39/15, 0.36 (0.16–0.83)
Daily coffee consumption after age 45 years (cups)			
1–2/0	31/31, 0.66 (0.38–1.14)	8/7, 0.64 (0.22–1.89)	23/24, 0.71 (0.35–1.41)
3–4/0	13/31, 0.53 (0.26–1.08)	4/7, 0.54 (0.15–2.00)	9/24, 0.55 (0.22–1.36)
≥5/0	9/31, 0.60 (0.26–1.40)	2/7, 0.33 (0.06–1.80)	7/24, 1.01 (0.33–3.13)
Cup-years (per 20)‡	0.99 (0.93–1.05)	1.01 (0.92–1.12)	0.98 (0.90–1.06)

Saab et *al.*, *Liv International* 2013
Smith *et al.*, *Diabetes Care* 2006

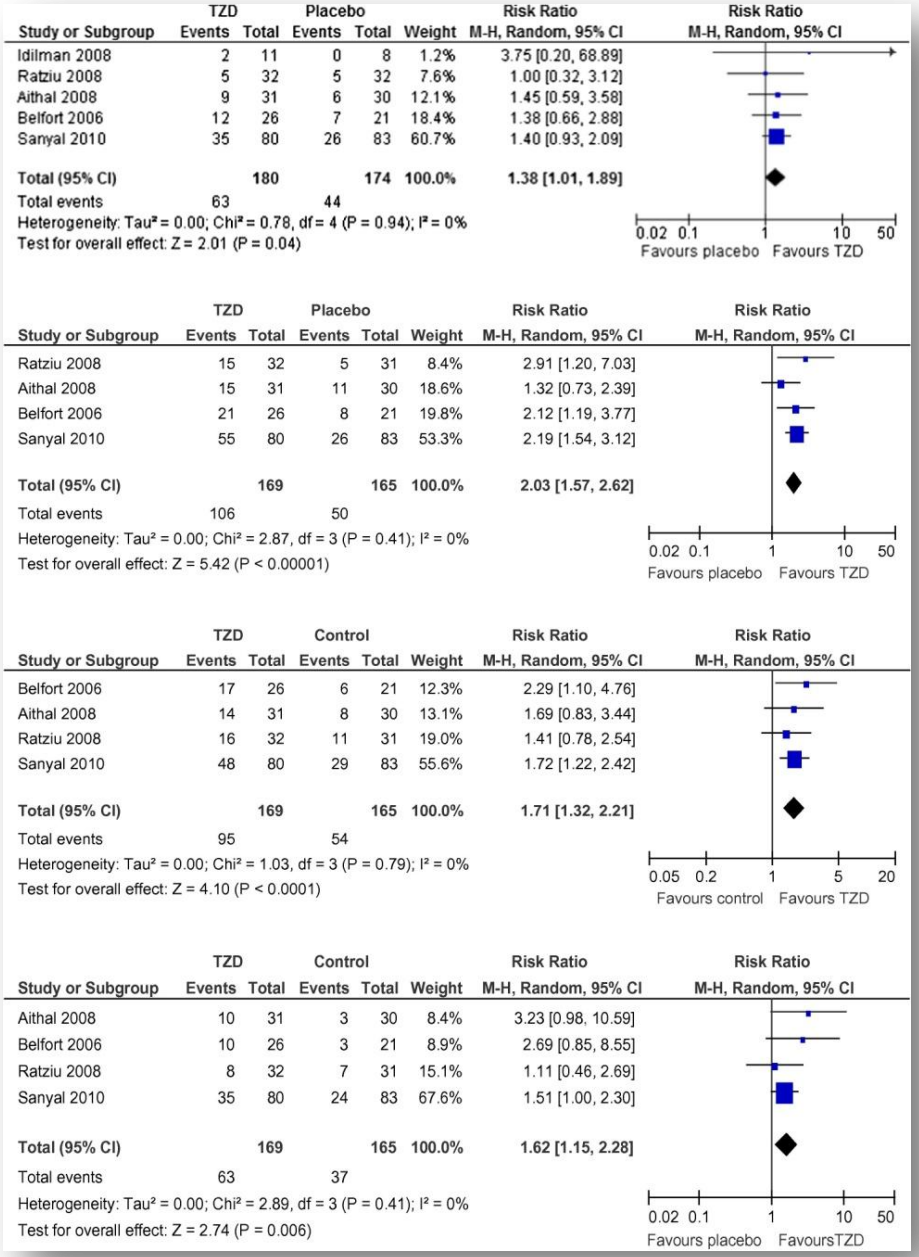
Coffee effect



Greesner. *Gastroenterology* 2010

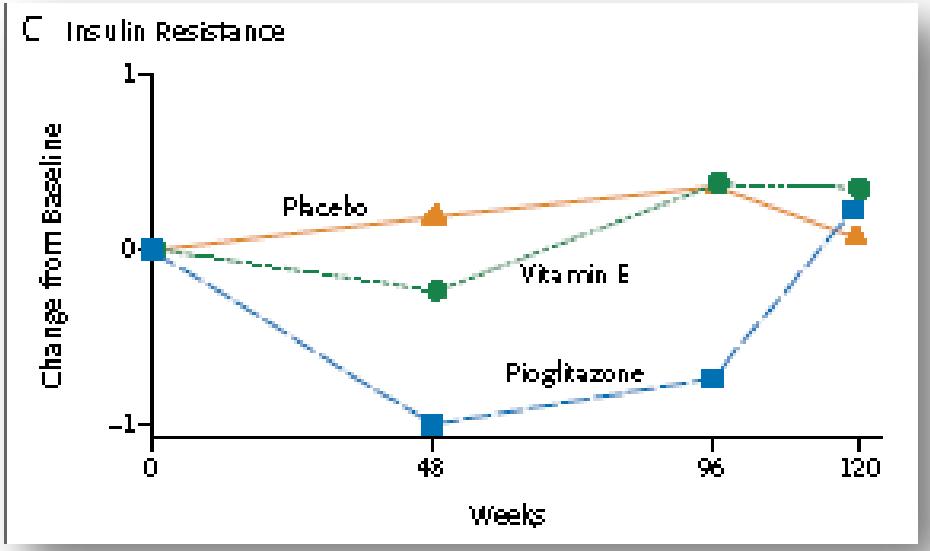
Glitazones

- 7 RCT (n=489)
- 4 placebo controlled (n=355)
- Improvement
  - Fibrosis: RR 1.38
  - Steatosis: RR 2.03
  - Inflammation: RR 1.7
  - Ballooning: 1.62



Mahady *et al. J Hepatology* 20 11

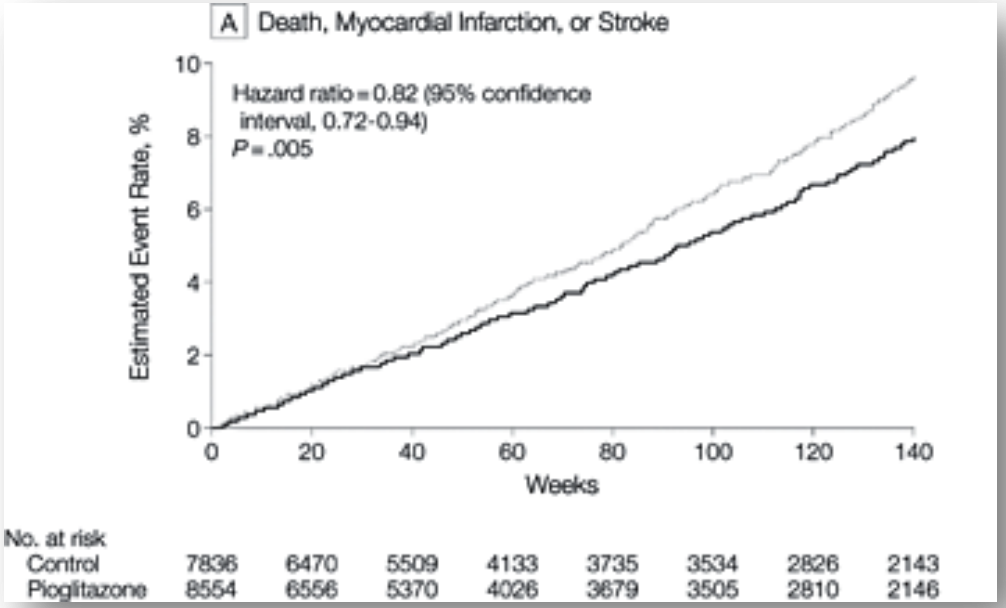
	Placebo	Pioglitazone	P value
Weight (kg)	- 0.55	+ 2.77	0.02
Glucose (mmol/	+ 0.4	- 0.1	0.02
HbA1C (%)	+ 0.16	- 0.18	0.01
C peptide (pmol/l)	+ 42.0	78.2	0.02
Dyslipidemia	+3.4%	-14.8%	0.05



Secondary outcomes

Sanyal *et al.*, *N Engl J Med* 2010
Aithal *et al.*, *Gastroenterology* 2008

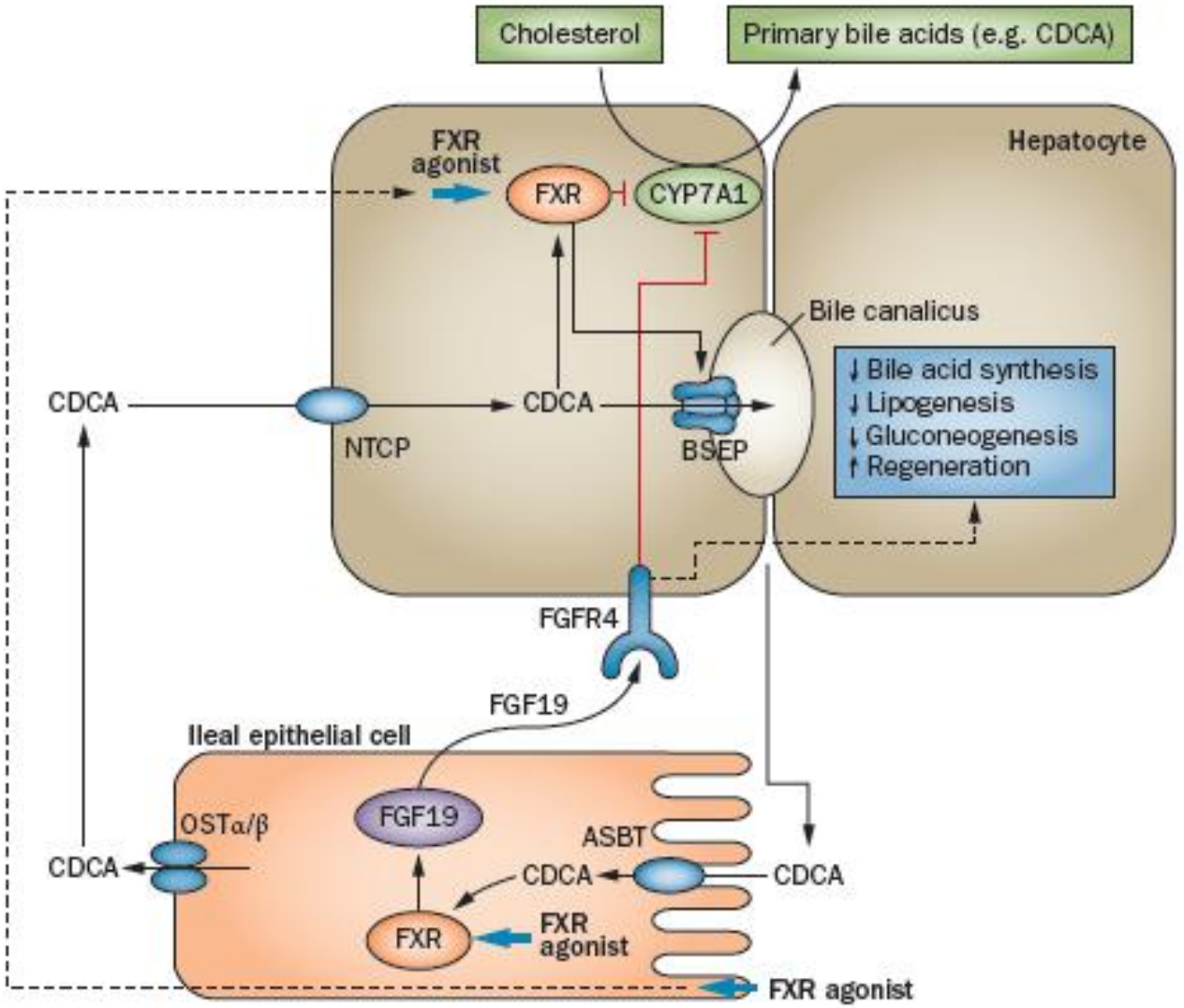
- 19 trials
- 16390 patients
- 4 mo- 3.5 years
- Individual components all reduced
  - HR: 0.8- 0.92
- Heart failure 2.3% vs 1.8%



Pioglitazone: all outcomes

Lincoff *et al. JAMA* 2007

Enterohepatic action of Farconoid Xenosensing Receptor (FXR)



Schaap, FG *et al. Nat. Rev. Gastroenterol. Hepatol. 2014;*11, 55–67.

Obeticholic acid

- First in class selective FXR agonist
- 100 fold activity compared to chenodeoxycholic acid
- FGF19 in Ob/Ob mice
  - Reduced weight, adiposity, liver fat
  - Improved insulin sensitivity
  - Favourable lipid profile
- FGF19 in FXR-deficient mice
  - Decreased intrahepatic triglyceride
  - FFA and ALT
- FGF19 in insulin deficient animals
  - Restores glycogen loss from lack of insulin action
- Obeticholic acid is anti-inflammatory and antifibrotic properties

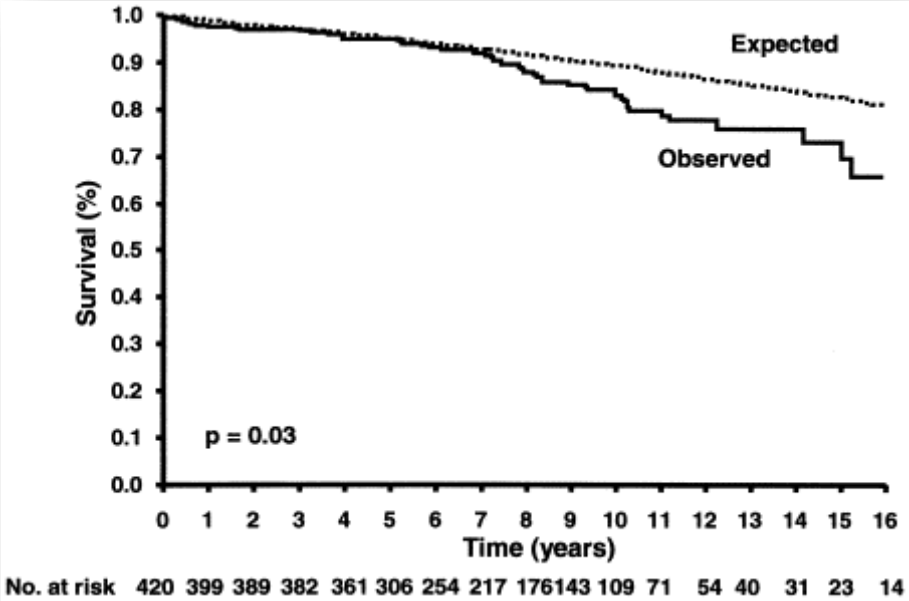
Primary end point

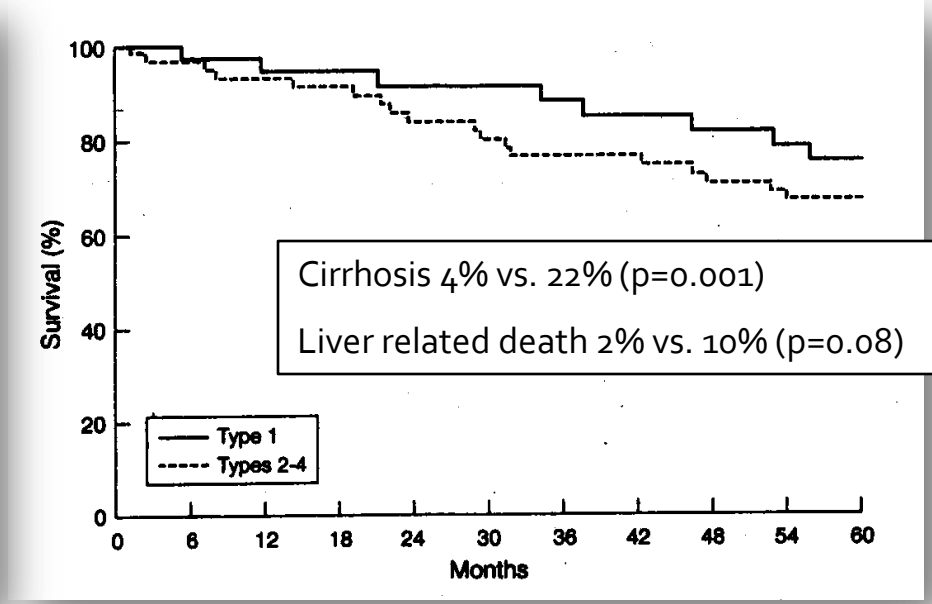
Group	Low dose insulin (mean % change in glucose infusion rate)	P value	High dose insulin (mean % change in glucose infusion rate)	P value
Placebo (n=17)	-5.5%		-5.4%	
OCA 25 mg (n=15)	28.0%	0.019	18.3%	0.036
OCA 50 mg (n=12)	20.1%	0.06	10.8%	0.076
OCA both doses (n=27)	24.5%	0.01	15.0%	0.025

Secondary endpoints

- Fall in ALT, GGT and ALP (not AST)
- Fall in ELF score
- Fall HA, P3NP and TIMP 1
- Significant changes with 25 mg of OCA; not with 50mg

NAFLD and Outcome

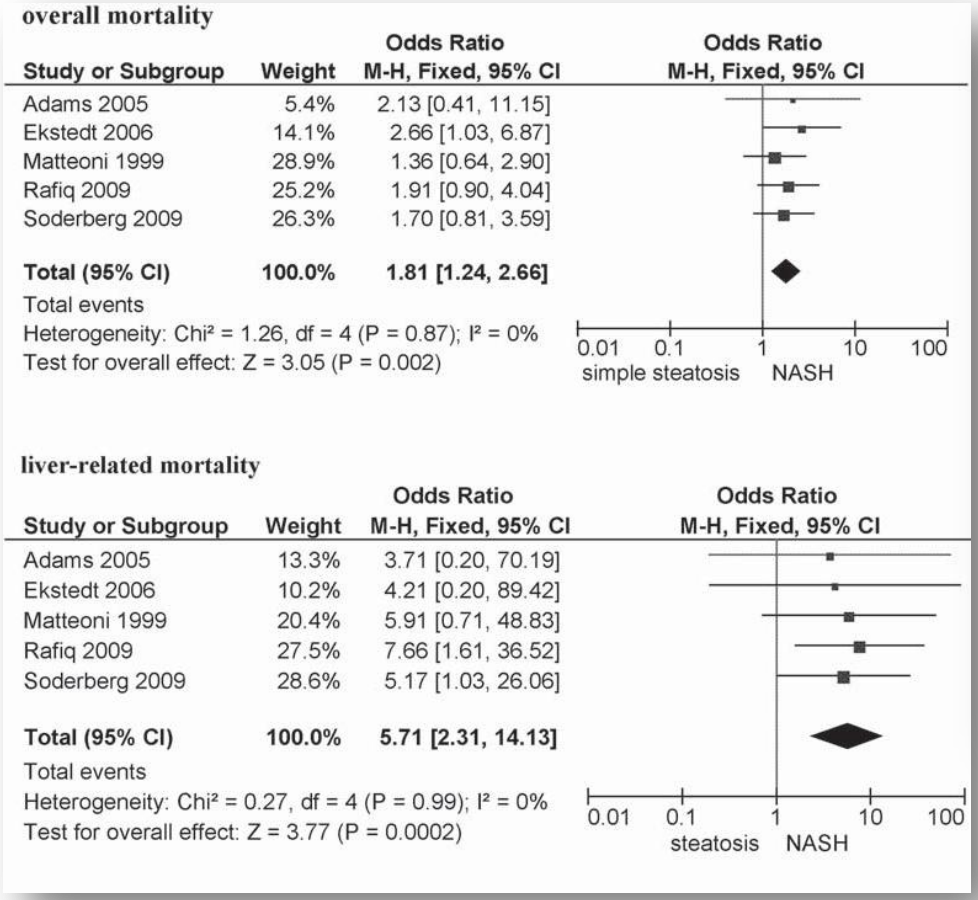


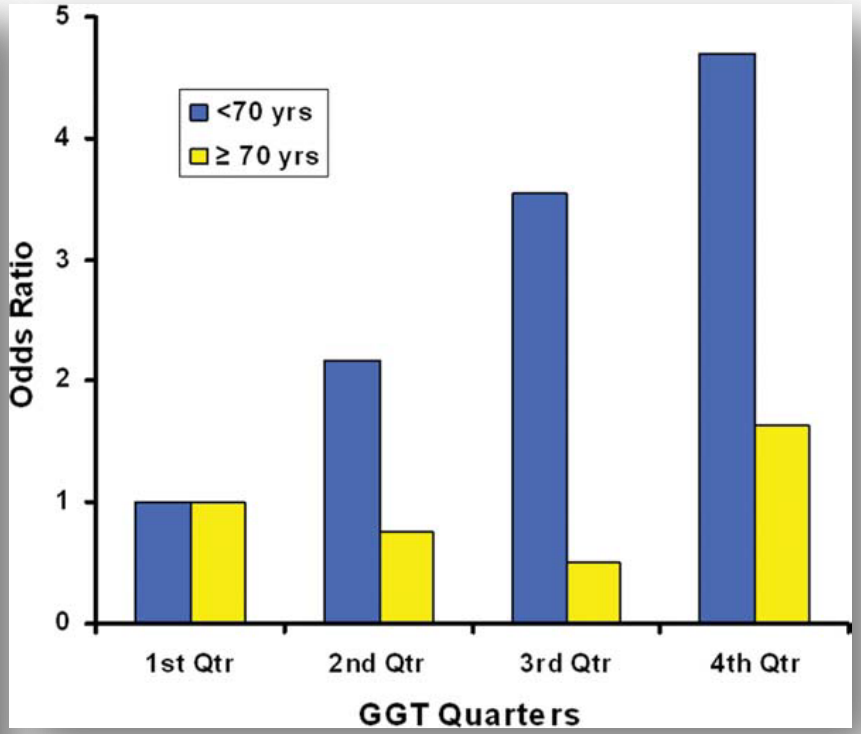


	Fat	Non-specific inflmn.	Ballooning	Fibrosis
Cirrhosis	4%	0	21%	26%
Liver death	2%	0	5%	13%

Adams *et al.*, *Gastroenterology* 2006
Matteoni *et al Gastroenterology* 1999

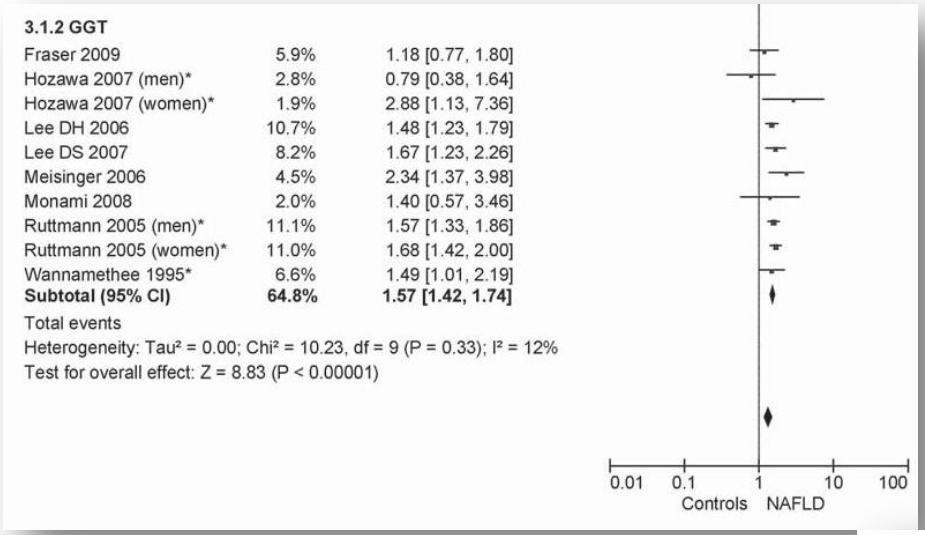
Outcome beyond the liver

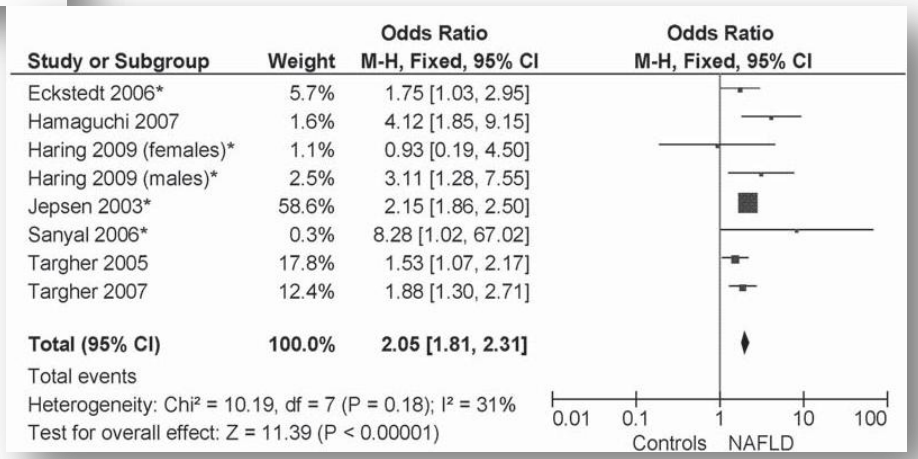




Musso. *Ann. Med.* 2010
Ghouri. *Hepatology* 2010

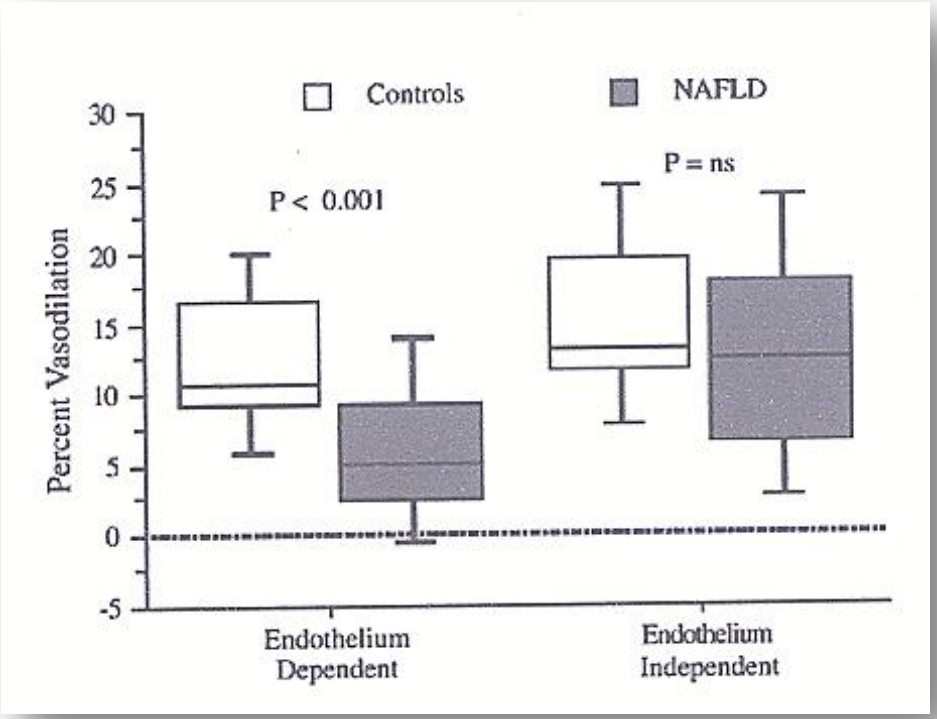
Cardiovascular events





Musso *et al. Ann. Med.* 2010

Inflamed liver and heart



- 52 NAFLD; 28 controls
  - Flow mediated vasodialtion
  - GTN induced
- Adjusted for age, gender, BMI, IR
  - NAFLD < Normal
  - NASH < steatosis
- 10 yr probability of CV events
  - NASH > NAFLD > Normal

Villanova *Hepatology* 2005

Beyond glucose

- **11,140** type 2 DM x 5 yrs
  - No effect on CV events, any death
  - Reduced nephropathy
- **10,251** type 2 DM x 3 yrs
  - No reduction in vascular events
  - Increased mortality- study discontinued
- **1791** type 2 DM x 6 yrs
  - No effect on CV events, death or microvascular complications
- UKPDS: **5,102** patients with type 2DM x 10 years
  - No significant reduction in fatal, non-fatal MI or sudden death

ADVANCE Col. Group. *NEJM* 2008; ACCORD Study Group *NEJM* 2008; Duckworth. *NEJM* 2009; UKPDS. Lancet 1998

Heart of the Matter

- 3246 British women
- 60-79 yr
- None with DM, coronary disease and stroke at base line
- Fasting insulin had a linear relationship with vascular events
- Fasting glucose, HbA1C had no effect

Lawlor. *PLoS Med* 2007

Ode to the liver

…While the heart

plucks mandolin strings,

There, inside

you filter and apportion

you separate and divide

you multiply and lubricate

you raise and gather

the threads and grams of life….

And after cleaning up, you are warmly last

to say good bye…

Pablo Neruda (1904-73)

Nottingham University Hospitals
NHS Trust