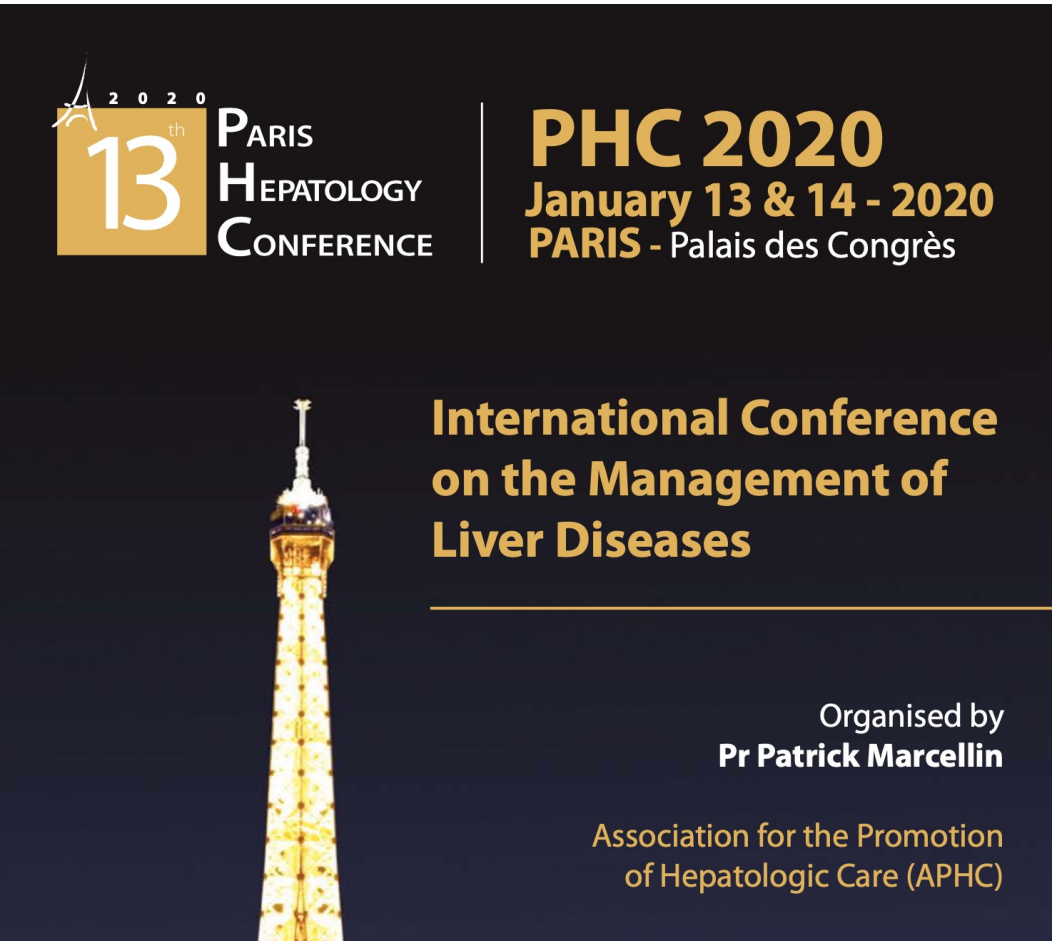


Nutrition and NAFLD

Prof. Manuel Romero-Gómez

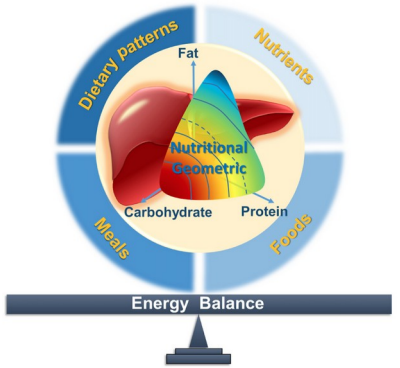
Digestive Diseases Unit. Virgen del Rocio University Hospital.

SeLiverGI. Institute of Biomedicine of Seville

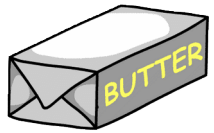
University of Seville, Seville, Spain.

The mission for today

1. Macro- and micronutrients.
2. Aims of dietary modifications.
3. Mediterranean Diet.
4. Nutritional geometry.
5. Artificial Intelligence for personalized nutritional intervention in NAFLD.



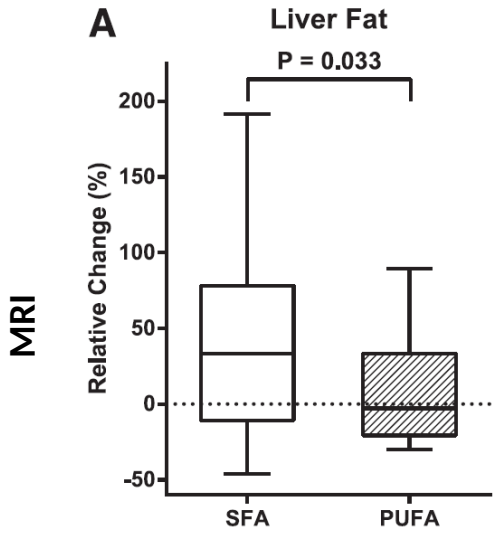
Calories and fats PUFA vs. SFA



Effect of type of fat in hyper-caloric high-fat diet in NAFLD

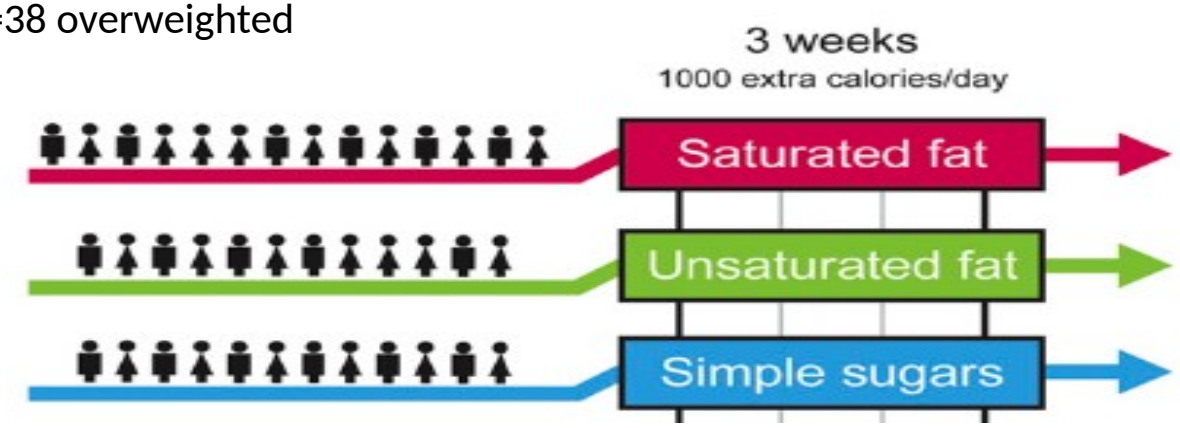
Dietary intake increase: Body weight modestly increased, not different between groups

OW	N=39	7weeks	RCT
P	SFA	PUFA	
0.45	500±550	632±499	Δ Energy, kcal
0.98	5±6	5±6	Δ Fat, E%



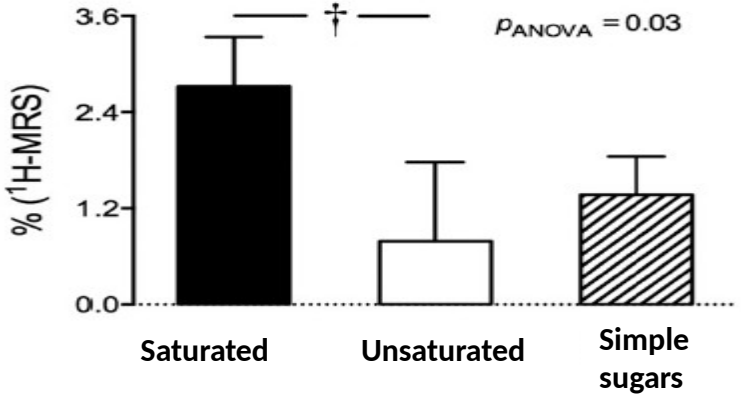
Rosqvist F., Diabetes 2014

N=38 overweighted



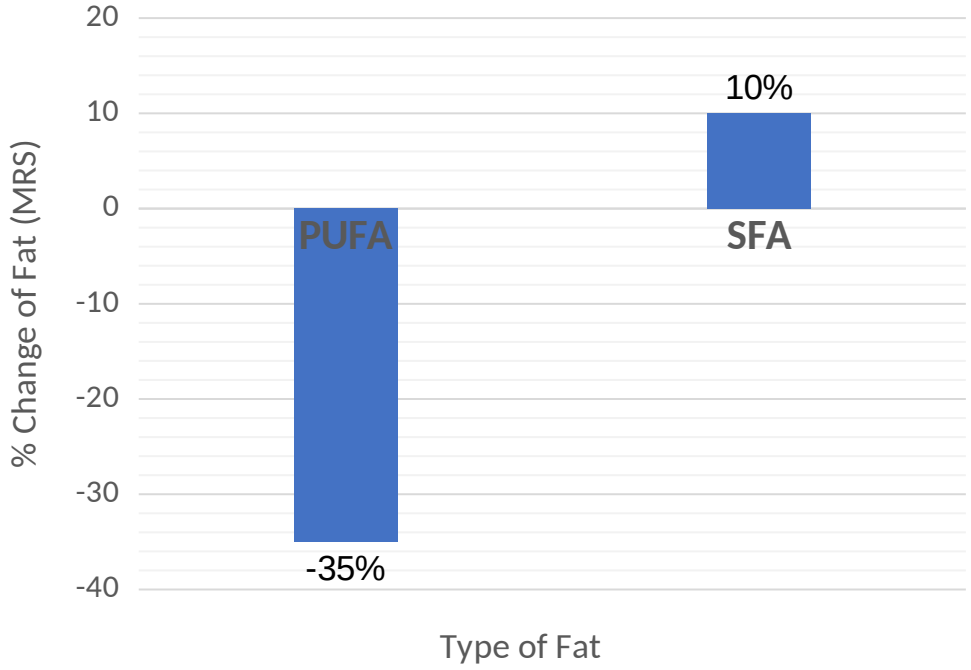
Luukkonen PK., Diabetes Care 2018

Changes in IHTG between the groups



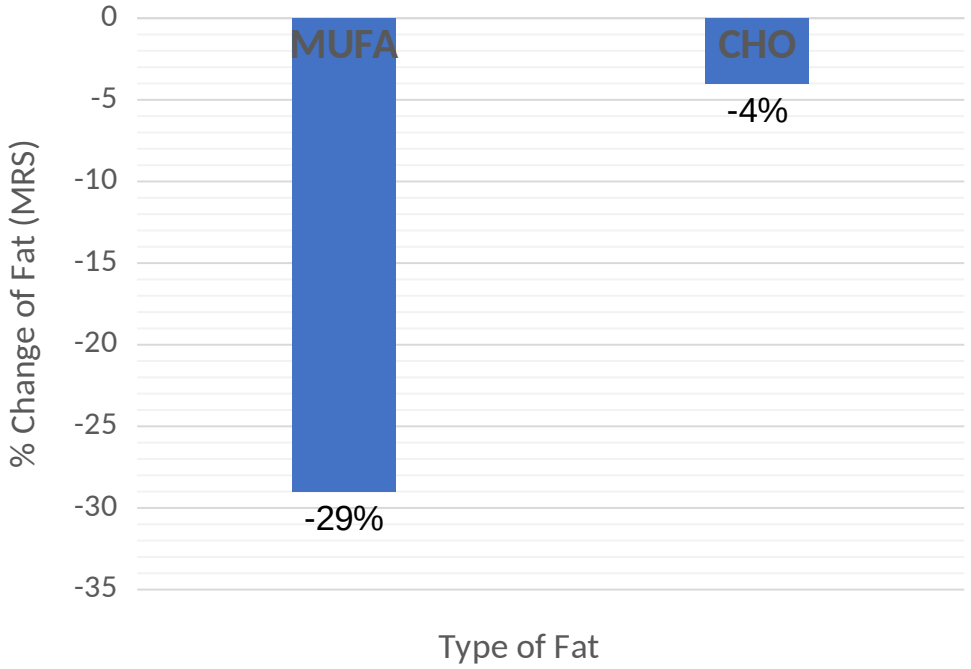
Effect of iso-caloric diets

- RCT, 10 weeks
- 67 obese
- Body weight modestly increased, not different between groups



Bjermo H., Am J Clin Nutr 2012

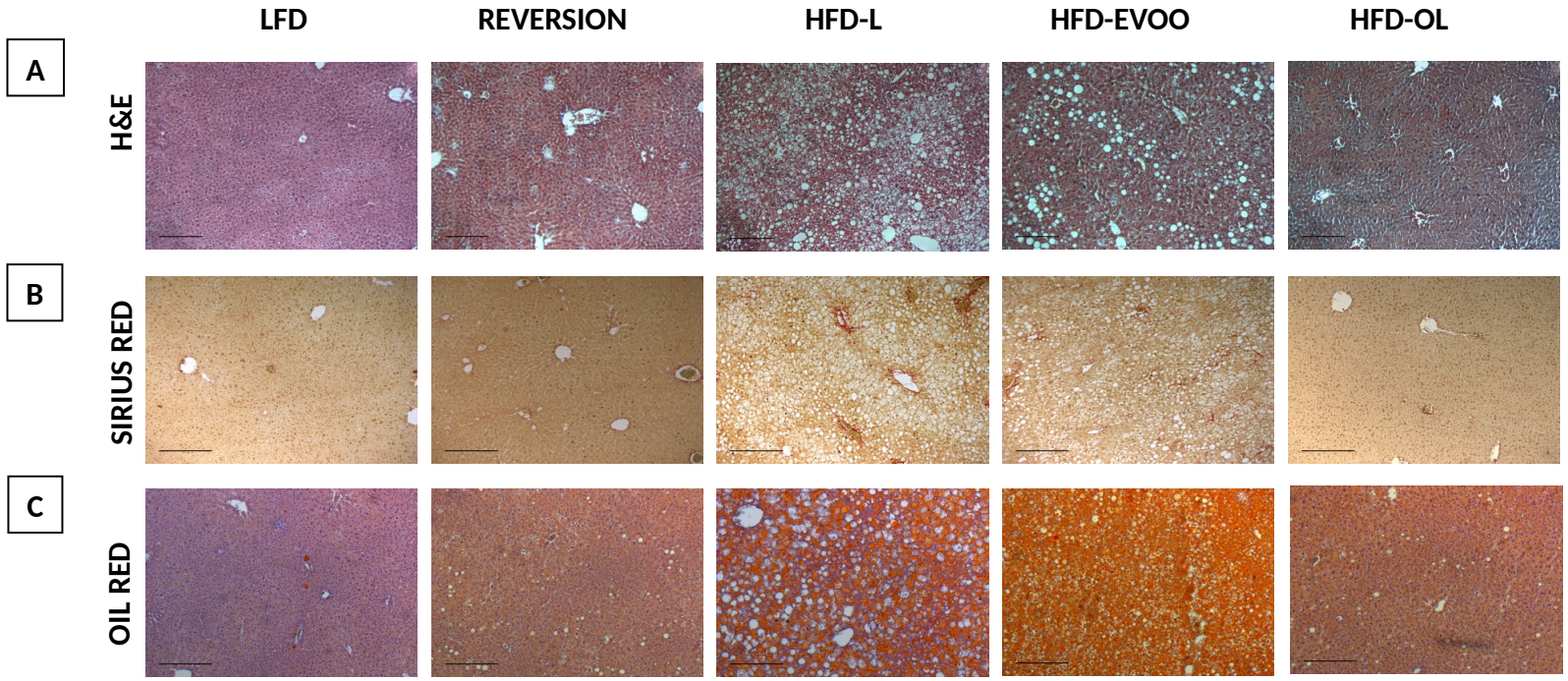
- RCT, 8-weeks
- 45 type-2 diabetes patients
- high-carbohydrate (52% vs. 40%)
- high-MUFA diet (28% vs. 16%/ kcal)
- Body weight remained stable

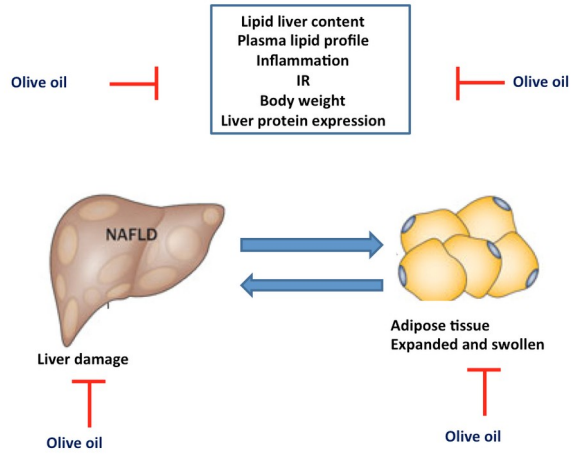


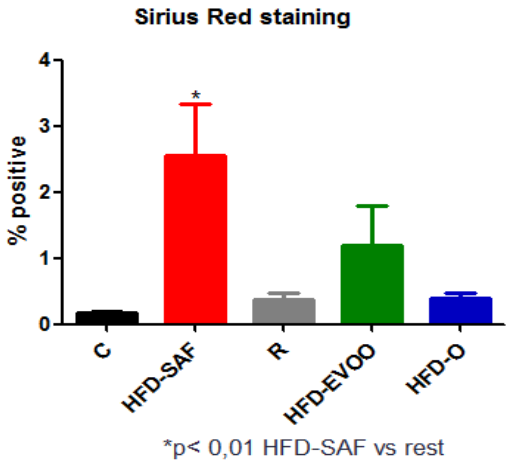
Bozzetto L., Diabetes Care 2012

Olive oil protects against steatohepatitis

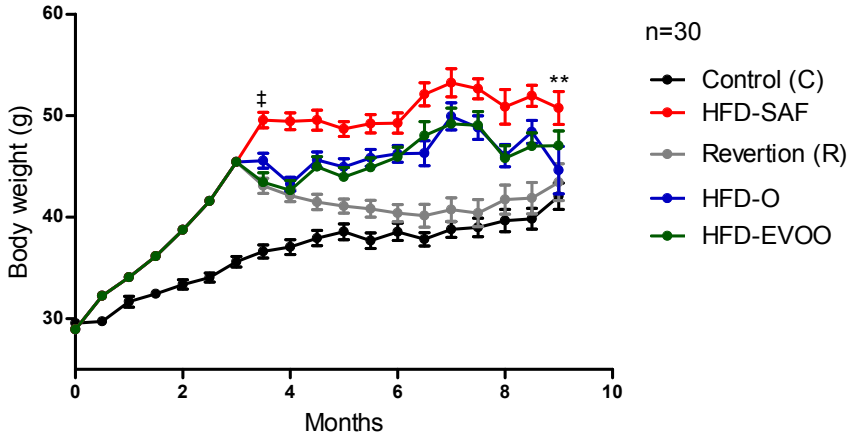
n= 5; Scale bars: 200 µm







*p< 0,01 HFD-SAF vs rest



**p<0,05 HFD-SAF vs HFD-O and HFD-EVOO

‡p<0,001 C vs HFD-SAF

Jurado-Ruiz E et al. Mol Nutr Food Res 2017;61(3)

The dark side of fructose


The toxic truth about sugar

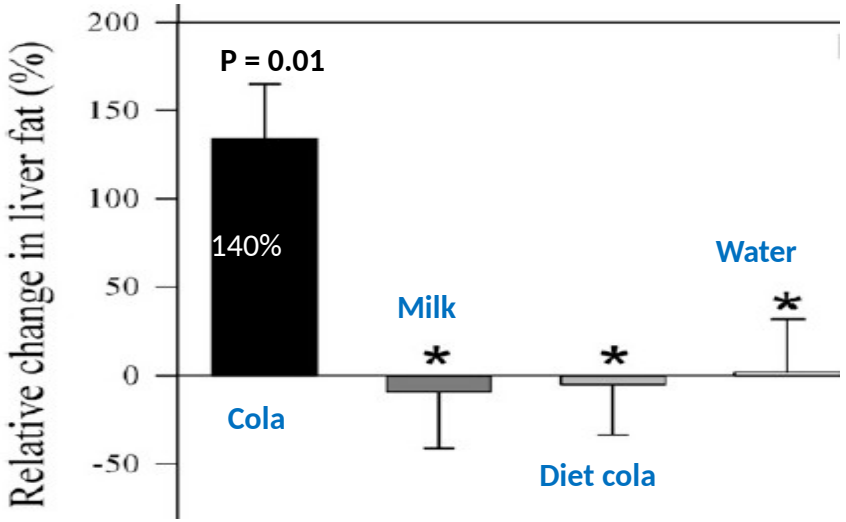
- n=47 overweight subjects
- Randomized to 4 different test drinks
- 1 L/d for 6 mo

Milk	Coke	
47	106	Carbohydrate (g/L)
15	0	Fat (g/L)
454	430	Energy (kcal/d)

DNL (*De Novo Lipogenesis*)
Reduced satiety
Increased VAT
Increase uric acid
NAFLD

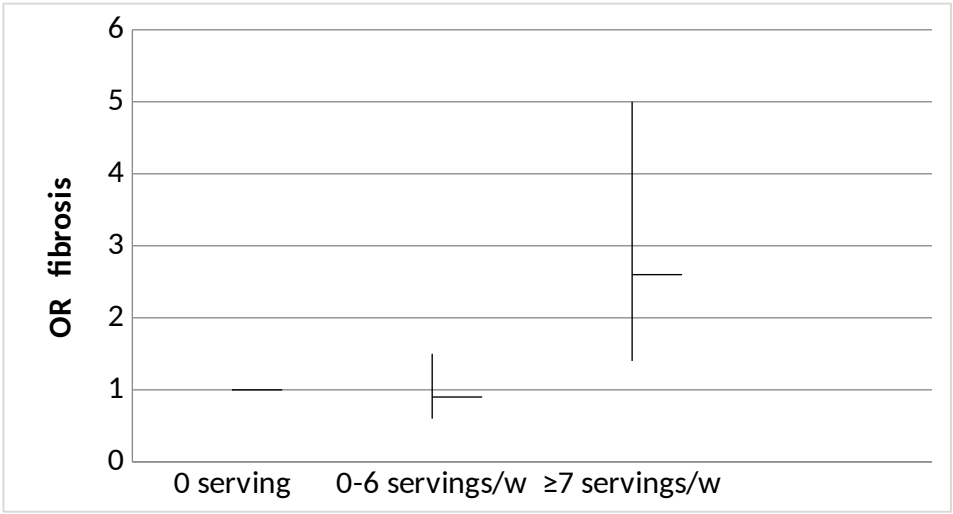
Sucrose-sweetened beverages increase liver fat - RCT

The regular cola group had greater increase in visceral fat not in total fat mass



Maersk M., Am J Clin Nutr 2012

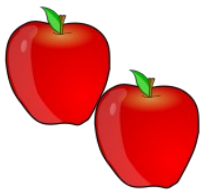
341 NAFLD patients with liver histology data
Reported fructose-containing beverages consumption



Adjusted age, gender, BMI, total calorie intake, serum lipids, uric acid and HOMA

Abdelmalek MF., Hepatology 2010

- Cross-sectional study in Japan > Short dietary intake questionnaire > NAFLD diagnosed by US
- Fructose from fruits did not increase NAFLD risk i.e. in males (93.9g/1000 kcal/d (68-301.6) decreased NAFLD risk 0.68 (0.42-1.11);p=ns.

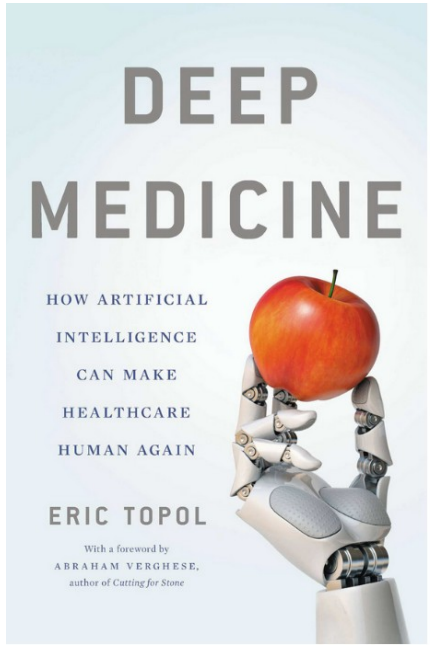


Tajima R., Nutrition 2018; Fernandez-Rodriguez C et al. REED 2019

Twittear

Lisa Pettigrew
@lisapettigrew

Bring on #PrecisionMedicine (the drug we all take multiple times a day that needs to be personalized most is food)



High-sugar diet, but not high-fat diet were associated with raised mortality and cardiovascular disease

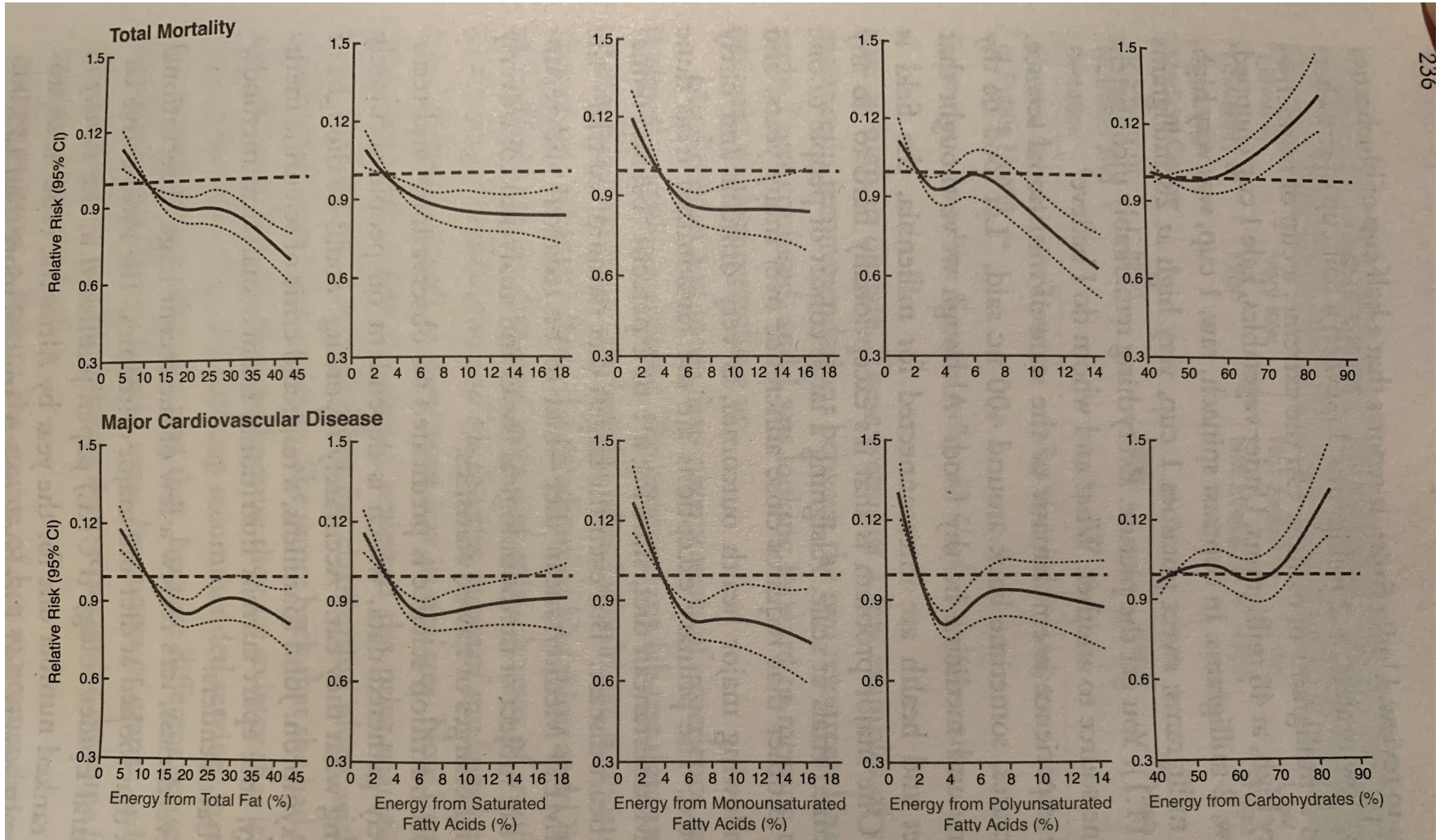


FIGURE 11.1: The PURE study association between estimated percent nutrients and all-cause (total mortality) and major cardiovascular disease. The dotted lines represent the 95 percent confidence intervals. Source: Adapted from M. Dehghan et al., "Associations of Fats and Carbohydrate Intake with Cardiovascular Disease and Mortality in 18 Countries from Five Continents (PURE): A Prospective Cohort Study," *Lancet* (2017): 390(10107), 2050–2062.

Antioxidant, Antifibrotic, Immunomodulatory; Lipoprotective

Zinc
Copper
Iron
Selenium
Magnesium
Vitamin A, C, **D, E**
Choline
Carotenoids
Polyphenols (EVOO)

Micronutrients deficiency (low intake, low levels) linked to NAFLD
Effect in animal models
Supplementation did not improve NAFLD

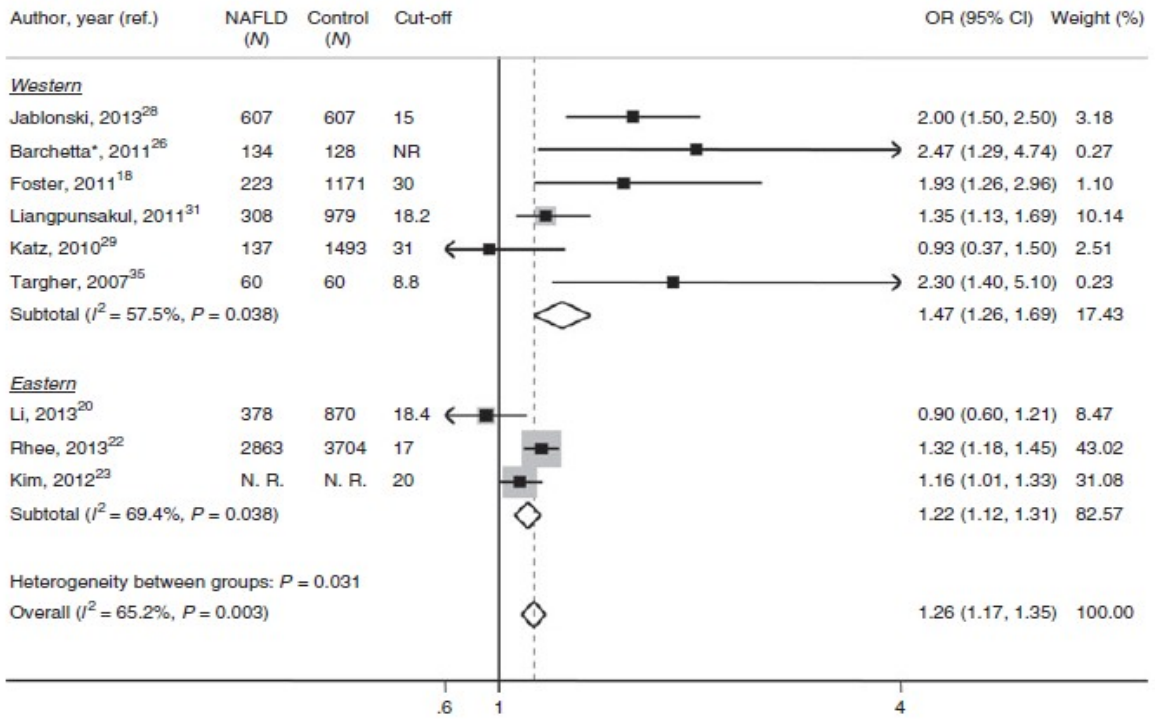
Improving NAFLD at US
Improving ALT/AST
Improving steatosis
NASH resolution
Fibrosis regression
HCC prevention



Salum E., Diabetes Res Clin Pract 2013
Goldin A., Circulation 2006 Vinson JA., J Nutr Biochem 1996 Subratty AH., Nutrition & Food Science 2010 Bengmark S., JPEN 2007

Vitamin D

- 9 studies · n=5202 NAFLD · n=8520 controls



Eliades M., Aliment Pharmacol Ther 2013

Meta-analysis Vit D in NAFLD: Trials (n=9) comprising 467 participants. **No significant effect of vitamin D supplement** intake on ALT (-2.88 U/L; 95% CI, -6.03 to 0.27; I^2 = 85%), AST (-0.10 U/L; 95% CI, -1.18 to 0.97; I^2 = 26%), and γ-GT (0.12 U/L; 95% CI, -5.94 to 6.18; I^2 = 38%).

Mansour-Ghanaei F, et al. J Diet Suppl 2019:1-19.

Vitamin C

Cross-sectional study
NAFLD by US steatosis, NASH and fibrosis by FibroMax (n=714)

Adjusted for: age, gender, energy intake, BMI, physical activity, SFA intake, smoking, alcohol, fibers, cholesterol, red and/or processed meat intake

Vitamin C > 91.4 UI/1000Kcal (Upper tertile)

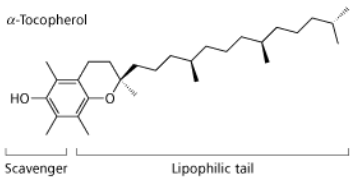
N=305
p=0.045

N=225
p=0.004

N=141
p=0.79

Ivancovsky-Wajcman D. & Zelber-Sagi S., Dig Liv Dis 2019

The effectiveness of Vitamin E in NAFLD/NASH clinical trials



Vitamin E
Lipophilic
antioxidant

Improved steatosis and steatohepatitis but not fibrosis

Varying quality & Conflicting results

Study	Design	Intervention	Duration	Histology	ALT
Lavine et al. (2011)	RCT	Vit E 800IU + (n=58) Vs. placebo (n=58)	24 mo	+	-
Yakaryilmaz et al.(2007)	OL	Vit E 800mg (n=9)	6 mo	+	+
Dufour et al. (2006)	RCT	Vit E 800IU + UDCA (n=15) Vs. UDCA + placebo (n=18) or placebo + placebo (n=15)	24 mo	+	+
Sanyal et al. (2004)	RCT	Vit E 400IU (n=10) Vs. Vit E+ pioglitazone (n=10)	6 mo	+	-
Vajro et al. (2004)	RCT	Vit E 800>100IU + diet (n=14) Vs. diet + placebo (n=14)	5 mo		-
Harrison et al. (2003)	RCT	Vit C+ vit E 1000IU(n=23) Vs. Placebo (n=22)	6 mo	+	-
Kugelmas et al. (2003)	RCT	Diet + aerobic exercise +/- vit E 800IU(n=16)	2 mo		+
Hasegawa et al. (2001)	OL	Vit E 300mg (n=22)	12 mo	+	+
Lavine et al. (2000)	OL	Vit E 400-1200mg (n=11)	4-10 mo		+

Chang CY.. J Clin Gastroenterol 2006

Browning J., J Clin Invest 2004

Deficient choline intake is associated with fibrosis in NAFLD patients

Choline deficiency → **Impaired synthesis of phosphatidylcholine, essential component of lipoproteins** → Reduced secretion of liver triglyceride as VLDL

- Cross-sectional analysis of **664** NASH patients with liver biopsy
- A food-frequency questionnaire
- Deficient intake defined as 50% AI

Fibrosis		Steatosis		
P	values	P	values	
0.07	1.89 (0.94, 3.79)	0.28	0.68 (0.33, 1.38)	Men ≥14 y old
0.05	2.55 (1.00, 6.48)	0.35	1.57 (0.61, 4.06)	Premenopausal women ≥ 19 yo
0.002	3.37 (1.58, 7.19)	0.74	0.88 (0.42, 1.86)	Postmenopausal women

de Wit N.J.W., J Hepatol 2012

In conclusion, **decreased choline intake** is associated with worse fibrosis in a subset of patients with NASH; but:
a) Is low choline intake associated with low plasma choline concentrations?;
b) Is low choline concentrations associated with progression of NAFLD?;
c) Could choline supplementation reverse this entity?.

Guerrerio AL., Am J Clin Nutr 2012

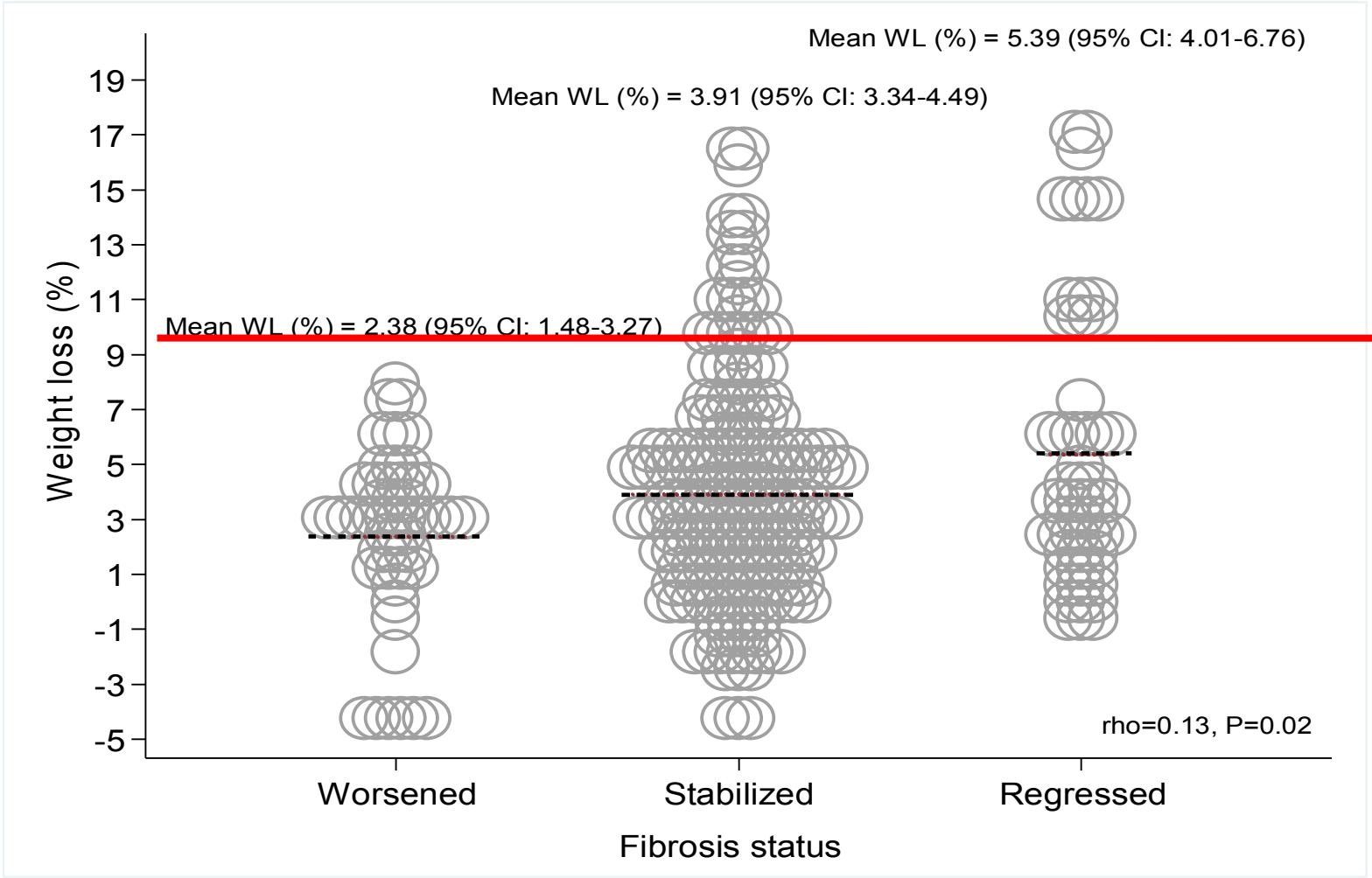
52 weeks of lifestyle intervention

% Weight loss (WL)	5%	7%	10%
NASH-resolution	10%	26%	64%	90%
FIBROSIS-regression	45%	38%	50%	81%
STEATOSIS improvement	35%	65%	76%	100%
% Patients achieving WL	70%	12%	9%	10%

Romero-Gómez M, Zelber-Sagi S, Trenell M. J Hepatol 2017

Vilar-Gomez, Romero-Gomez, Gastroenterology 2015; 149:367-378

E. Correlations between WL and fibrosis status at the end of intervention



Diet associations with NAFLD in an ethnically diverse population the Multiethnic Cohort

- Nested case-control
- 2,974 NAFLD cases
  - 518 with cirrhosis
  - 2,456 without cirrhosis
- 29,474 matched controls
- Cases identified using Medicare claims ICD9/10
- Controls individually matched to cases on birth year, sex, ethnicity
- FFQ

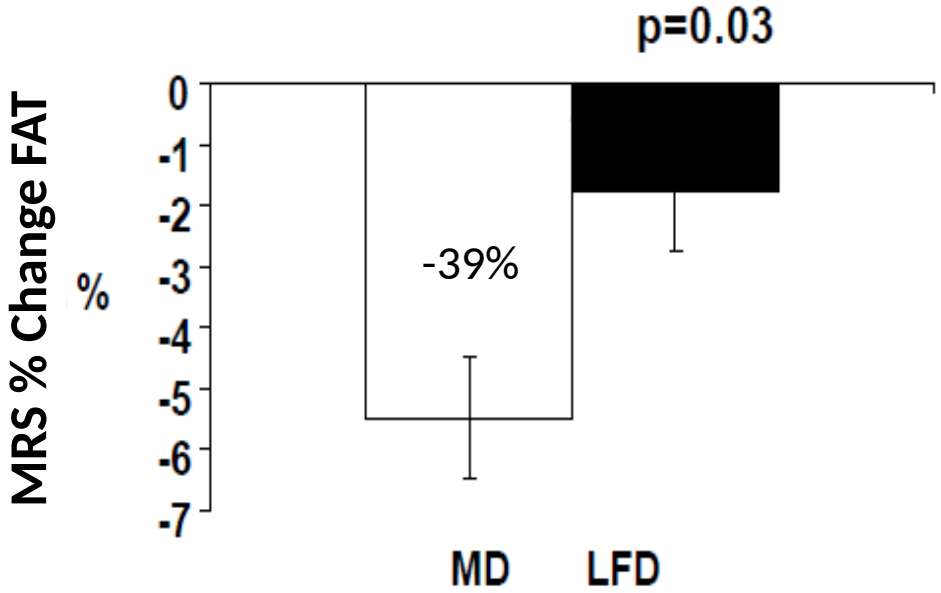
(g/1,000 kcal/day)	NAFLD No Cirrhosis	NAFLD With Cirrhosis
Q 1st vs. 4th	OR (95% CI)	OR (95% CI)
Cholesterol		
≤ 75.4	1.00 (ref.)	1.00 (ref.)
> 121.4	1.09 (0.96-1.23)	1.52 (1.15-2.01)
P-value for trend	0.0889	0.0018
Fiber		
≤ 8.5	1.00 (ref.)	1.00 (ref.)
> 14.0	0.86 (0.75-0.98)	0.75 (0.55-1.02)
P-value for trend	0.0123	0.1018

(g/1,000 kcal/day)	NAFLD No Cirrhosis	NAFLD With Cirrhosis
Q 1ST vs. 4th	OR (95% CI)	OR (95% CI)
Total red meat		
≤ 13.7	1.00 (ref.)	1.00 (ref.)
> 34.0	1.10 (0.97-1.25)	1.43 (1.08-1.90)
P-value for trend	0.1190	0.0121
Red unprocessed meat		
≤ 9.3	1.00 (ref.)	1.00 (ref.)
> 24.1	1.10 (0.97-1.25)	1.52 (1.15-2.01)
P-value for trend	0.1223	0.0033
Processed red meat		
≤ 3.0	1.00 (ref.)	1.00 (ref.)
> 10.0	1.17 (1.03-1.32)	1.31 (0.99-1.71)
P-value for trend	0.0097	0.1123
Total poultry		
≤ 11.4	1.00 (ref.)	1.00 (ref.)
> 27.6	1.19 (1.05-1.35)	1.03 (0.79-1.35)
P-value for trend	0.0028	0.7717

Noureddin M., Hepatology 2019 (ahead of print)

The Mediterranean diet improves hepatic steatosis RCT

Low Fat Diet	Mediterranean Diet	Nutrient
30% /kcal ω6 PUFA	40% /kcal MUFA + ω3 PUFA	fat
50% /kcal	40% /kcal	Carbohydrate
None	Daily	Olive oil & nuts
Fish 2/week, meat daily	Fish 3/w , meat 3/w	Fish & meat



12 NAFLD patients >> 6-week diets >> 1-2 kg weight loss in both

Benefits of Mediterranean Diet		
Lipid metabolism	Inflammation	Insulin Sensitivity
Increases hepatocyte fatty acid oxidation Reduces hepatic lipogenesis Decreases serum triglycerides levels	Anti-inflammatory effect Suppression of pro-inflammatory cytokines	Improves insulin sensitivity

Ryan MC et al. J Hepatol 2013; Paniagua JA., J Am Coll Nutr 2007; Paniagua JA., Diabetes Care, 2007; Fung T., Circulation 2009

nutrients

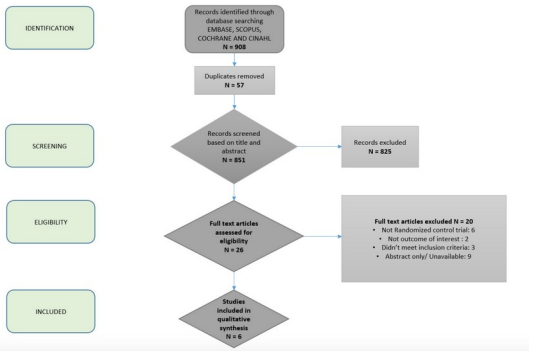
MDPI

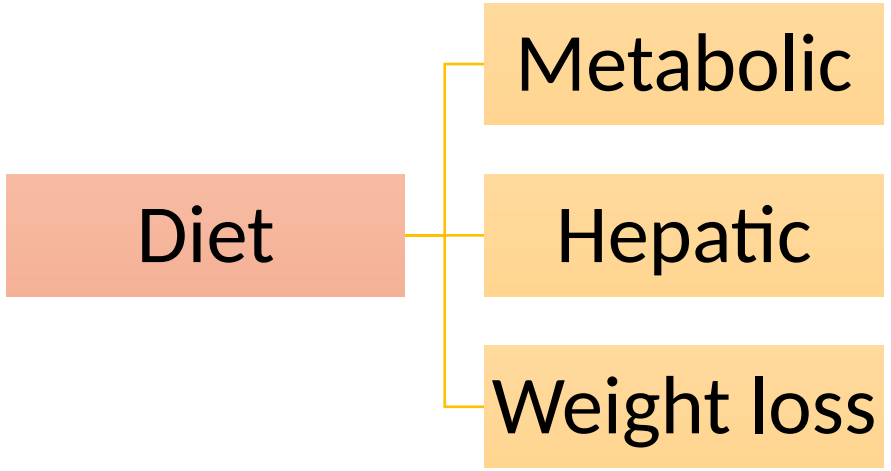
Review

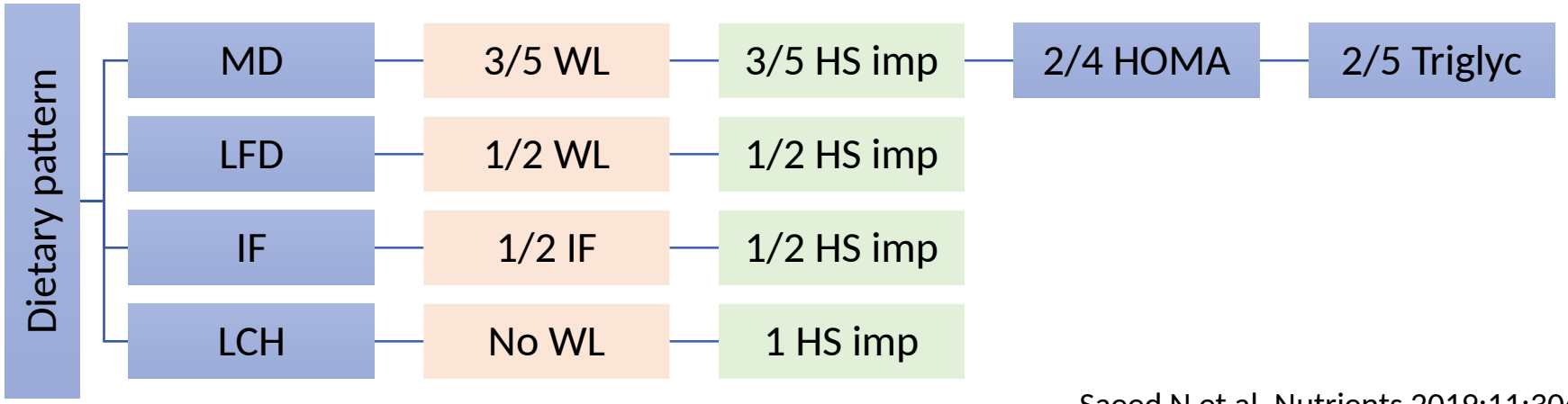
Evaluation of Dietary Approaches for the Treatment of Non-Alcoholic Fatty Liver Disease: A Systematic Review

Naba Saeed [1], Brian Nadeau [1], Carol Shannon [2] and Monica Tincopa [1,*]

N=317 patients; 6 RCT







The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Effects of Intermittent Fasting on Health, Aging, and Disease

Rafael de Cabo, Ph.D., and Mark P. Mattson, Ph.D.

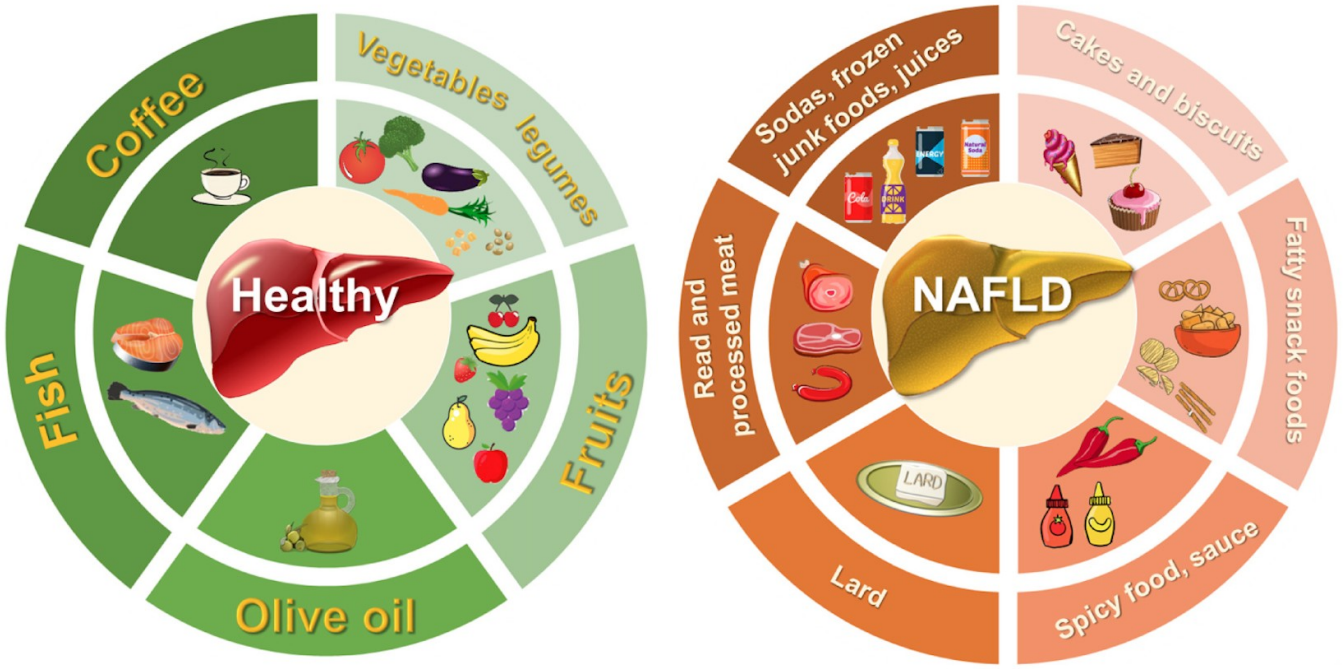
Mediterranean Diet (MD)

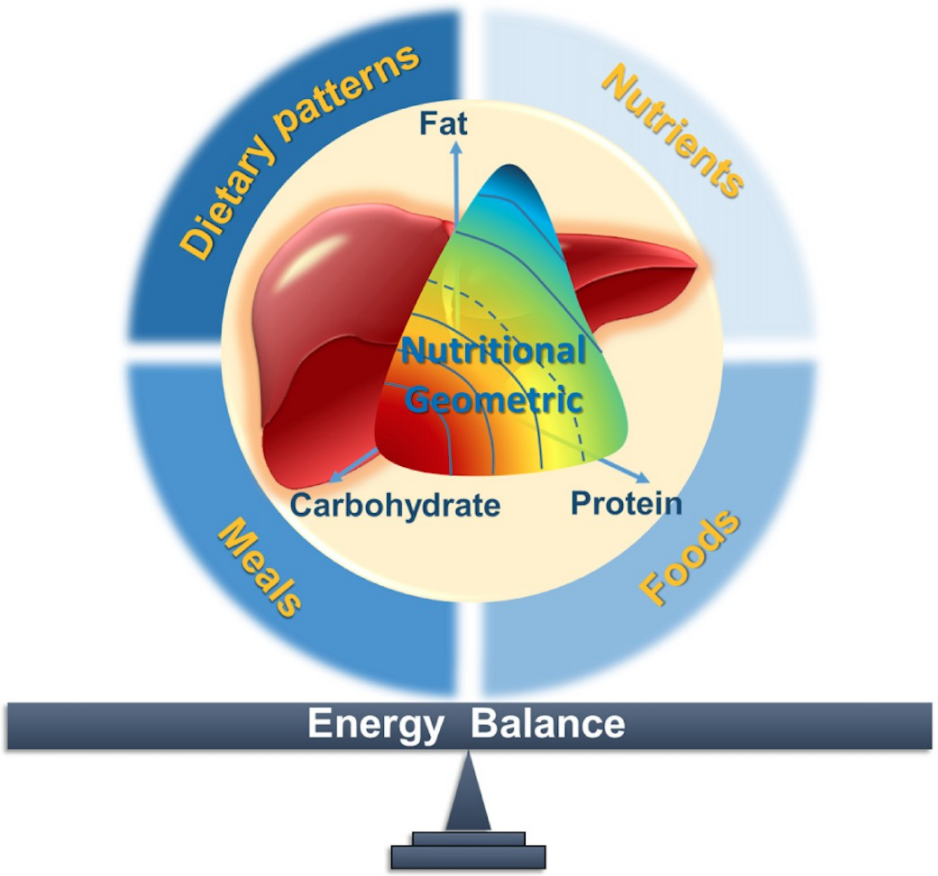
- *Extra virgin olive oil*
- *Vegetables and Fruits*
- *Cereals, legumes, nuts*
- *Moderate intakes of fish and other meat, dairy products and red wine*
- *Low intakes of eggs and sweets.*

↓SFA
↑**MUFA**
↑**PUFA**
↑protein vegetables
↓sugar fructose
↓cholesterol
↑**fiber**
↑**polyphenols,**
↑**carotenoids**

Saeed N et al. Nutrients 2019;11:3064

Geometry of nutrition

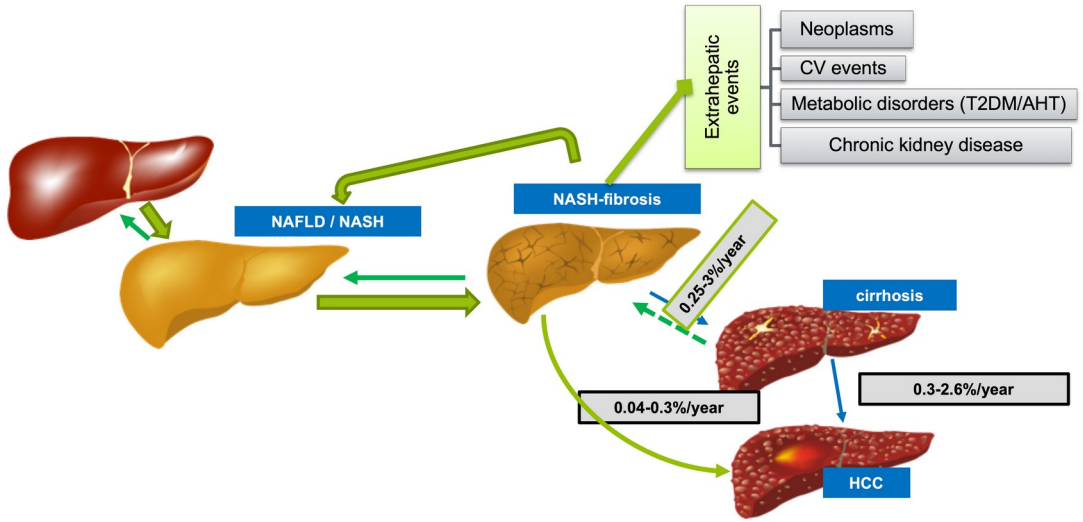


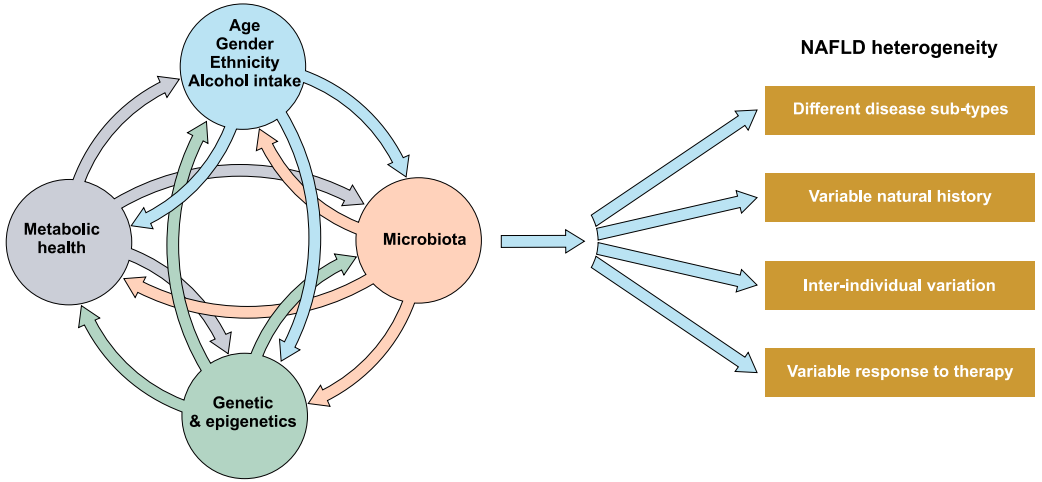


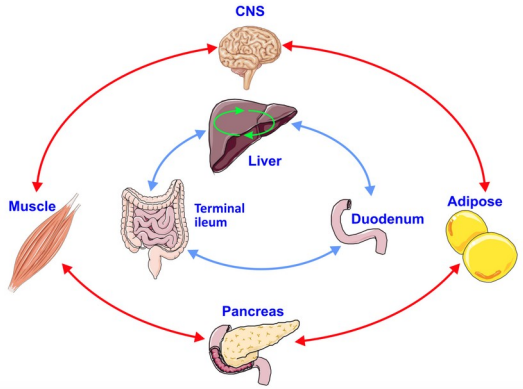
Green arrows represent nutrients that prevent NAFLD. Red arrows represent nutrients that promote NAFLD. SFAs: saturated fatty acids; Trans FAs: trans fatty acids; ω3: omega-3 fatty acids; Zn: zinc; Cu: copper; Fe: Iron.

Barna G, Romero-Gómez M. Liver Intern 2020

NAFLD: A Dynamic, heterogeneous and multiaxis disease

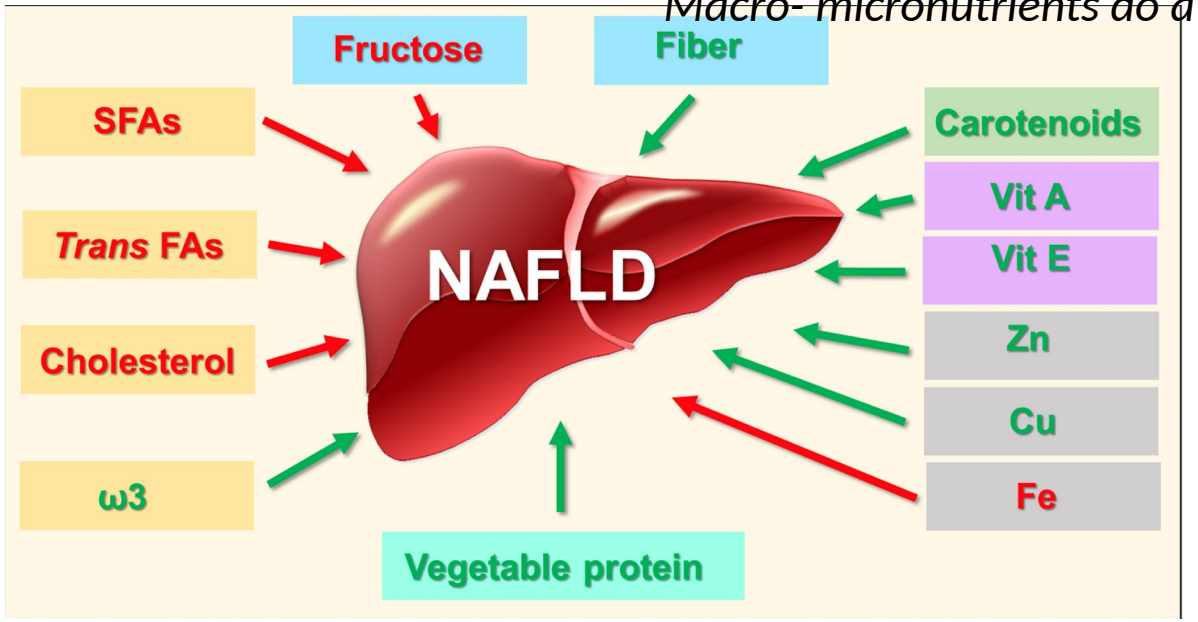


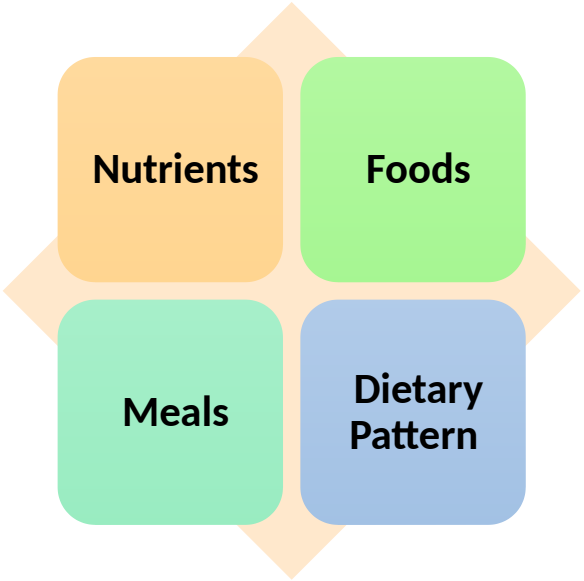




- Gut-Liver axis
  - Microbiome
  - Vascular barrier
  - Ammonia-NASH
- Metabolic-Liver axis
  - Lipid pathways
  - Insulin resistance

Macro- micronutrients do affect NAFLD development: Geometry of Nutrition





Lipogenesis de novo → FFA uptake → Metabolic stress → Inflammation → Oxidative stress → Apoptosis → Fibrosis

FXRa | SGLT2inh | GLP1-RA | PPARa | ACCihb | ASK-1inh | CCR2/CCR5 inh

Life style intervention → T2DM drugs WL drugs → Liver centered drugs → Bariatric endoscopy

Combination therapy

Sequential therapy

Measure personal features

Microbiome

Genetic

Physiological parameters

Nutrients
Foods
Meals
Diets

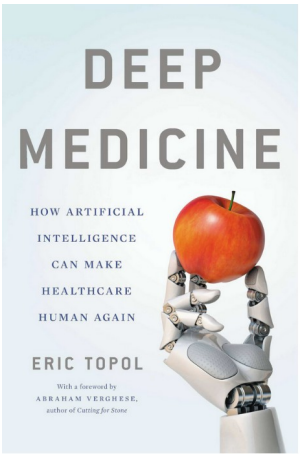
Anthropometrics

Lifestyle

Enviroment

Computational analysis
+
Artificial Intelligence

Design personalized diet to NAFLD patients



Barna G, Romero-Gómez M. Liver Intern 2020

Take home messages

1. Dietary modifications have been shown to be effective in NAFLD.
2. Modifications in the composition of specific macro-or micro-nutrients in the diet are not a central point.
3. The Western diet is associated with a greater risk of disease progression in NAFLD while the Mediterranean diet with an improvement in NAFLD.
4. Nutritional geometry can be an excellent tool to study the relationships between the various aspects of diet and NAFLD pathophysiology.
5. The use of algorithms developed by artificial intelligence for personalized nutritional counselling would be useful to prevent and treat NAFLD.

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Shira Zelber-Sagi
Genoveva Barnà
Franz Martin-Bermudo

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@SeLiver_group