Lifestyle Intervention Diet & Exercise

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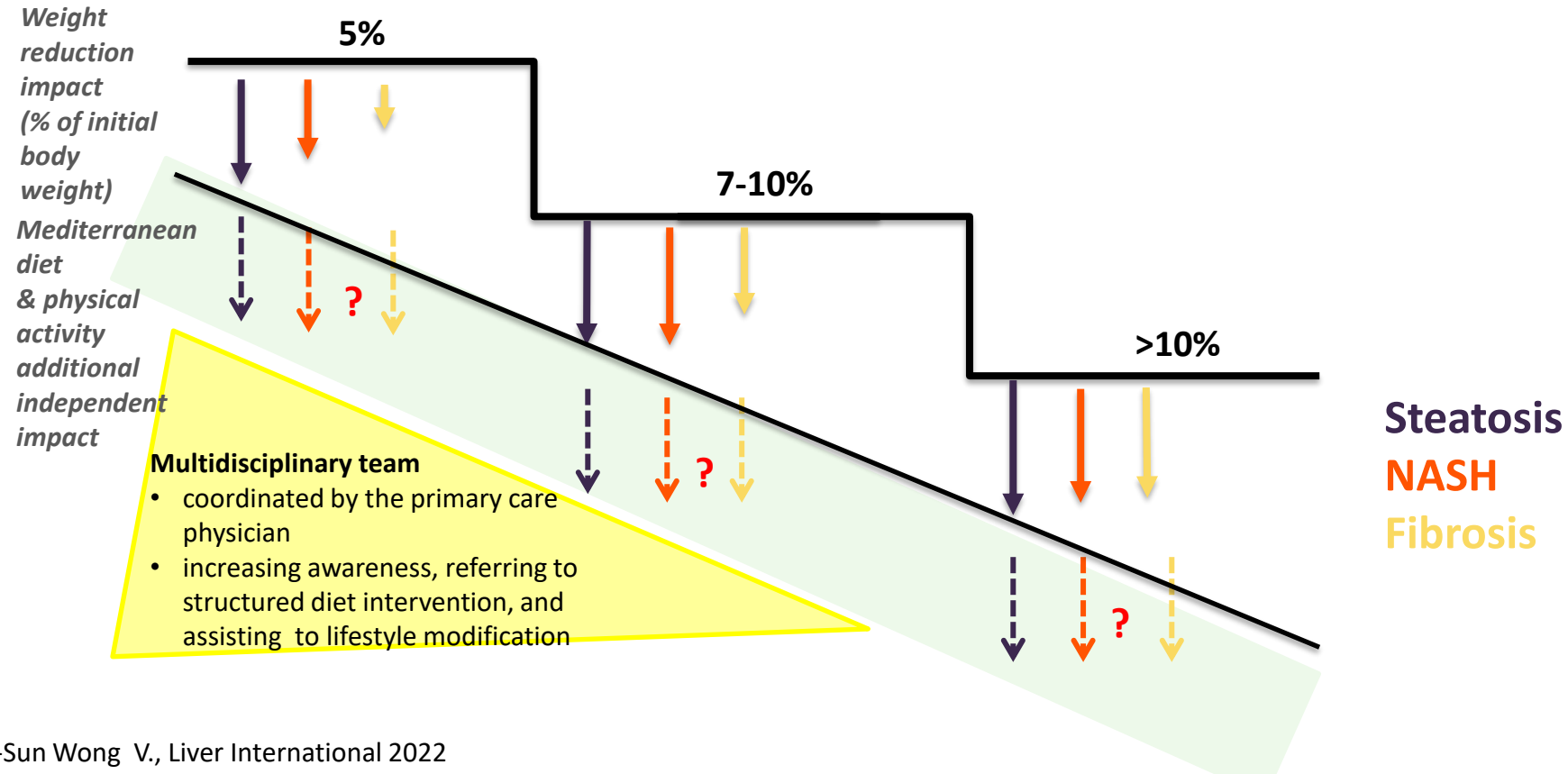
הפקולטה למדעי הרווחה והבריאות

CLDF
Chronic Liver Disease Foundation
3RD ANNUAL
LIVER CONNECT
CONFERENCE

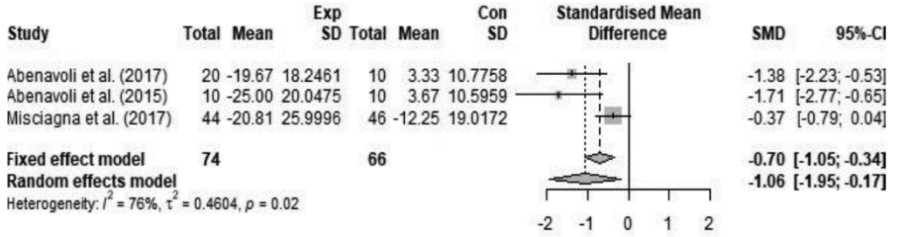
The dose-response effect of weight reduction on features of NAFLD and the added independent impact of the Mediterranean diet and physical activity



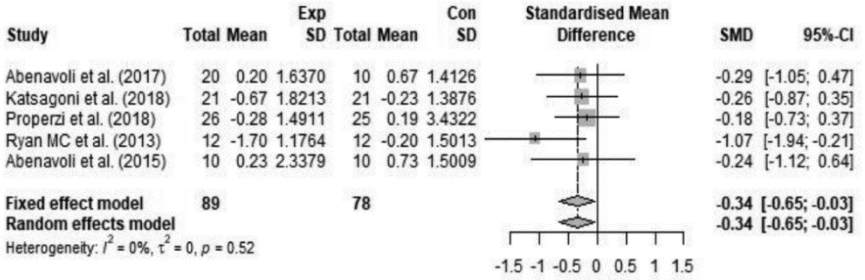
Wai-Sun Wong V., Liver International 2022

Effects of Mediterranean Diet on Patients with NAFLD Meta-Analysis of RCTs

Fatty liver index



HOMA-IR

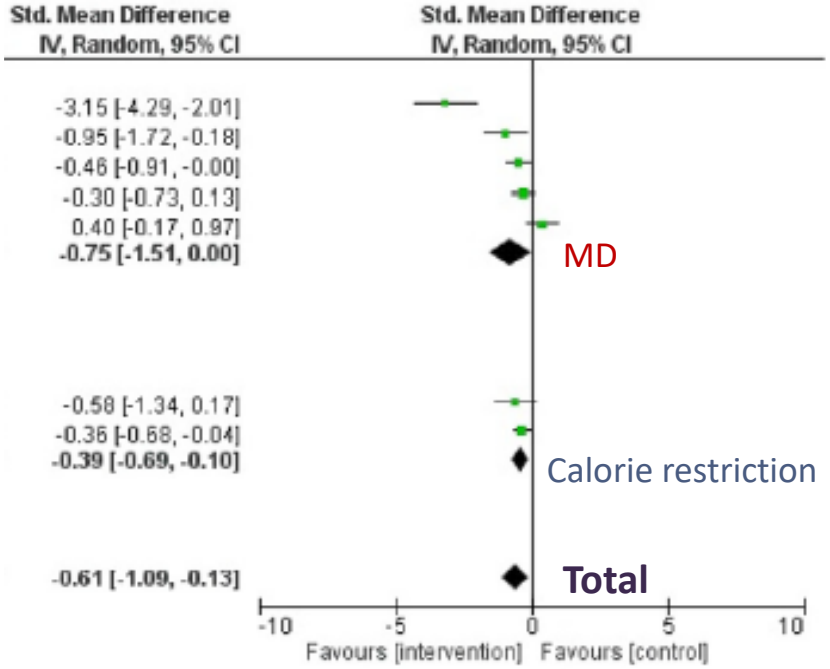


- **Study duration: 6 weeks to 6 months**
- **Intervention arms: Med-Diet vs. no intervention or other diets such as low fat diets**

Kawaguchi T., Seminars in Liver Disease 2021

Mediterranean diet and calorie restriction in NAFLD
Meta-analysis of RCTs and CCTs

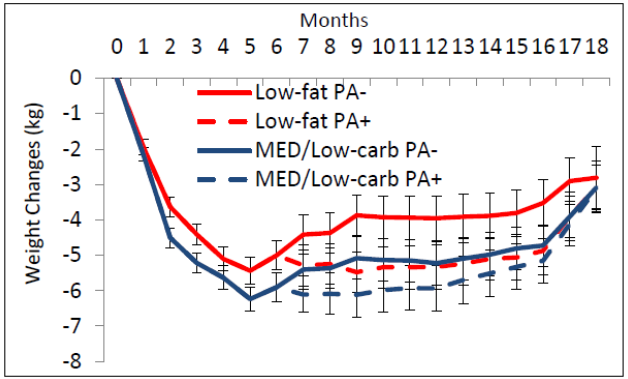
Liver stiffness measurement (LSM)



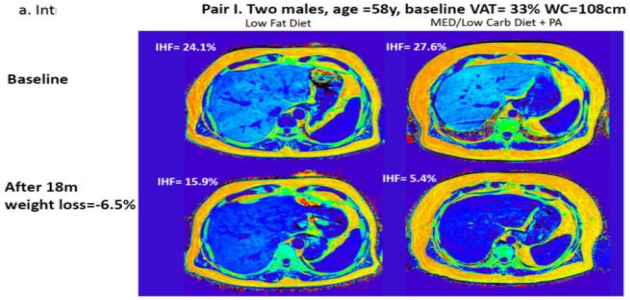
Haigh L., Clinical Nutrition 2022

Effect of different types of Mediterranean diets on liver fat RCTs

- 18-month, 278 obese adults



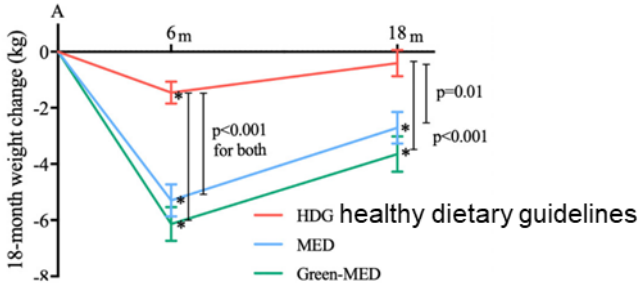
Intrahepatic fat

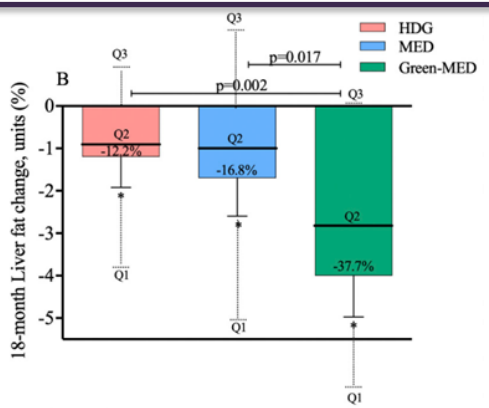


Low-fat diet 34% **MED/Low-carb + PA 80%**

Gepner Y., Circulation 2017

- 18-month, 294 obese adults



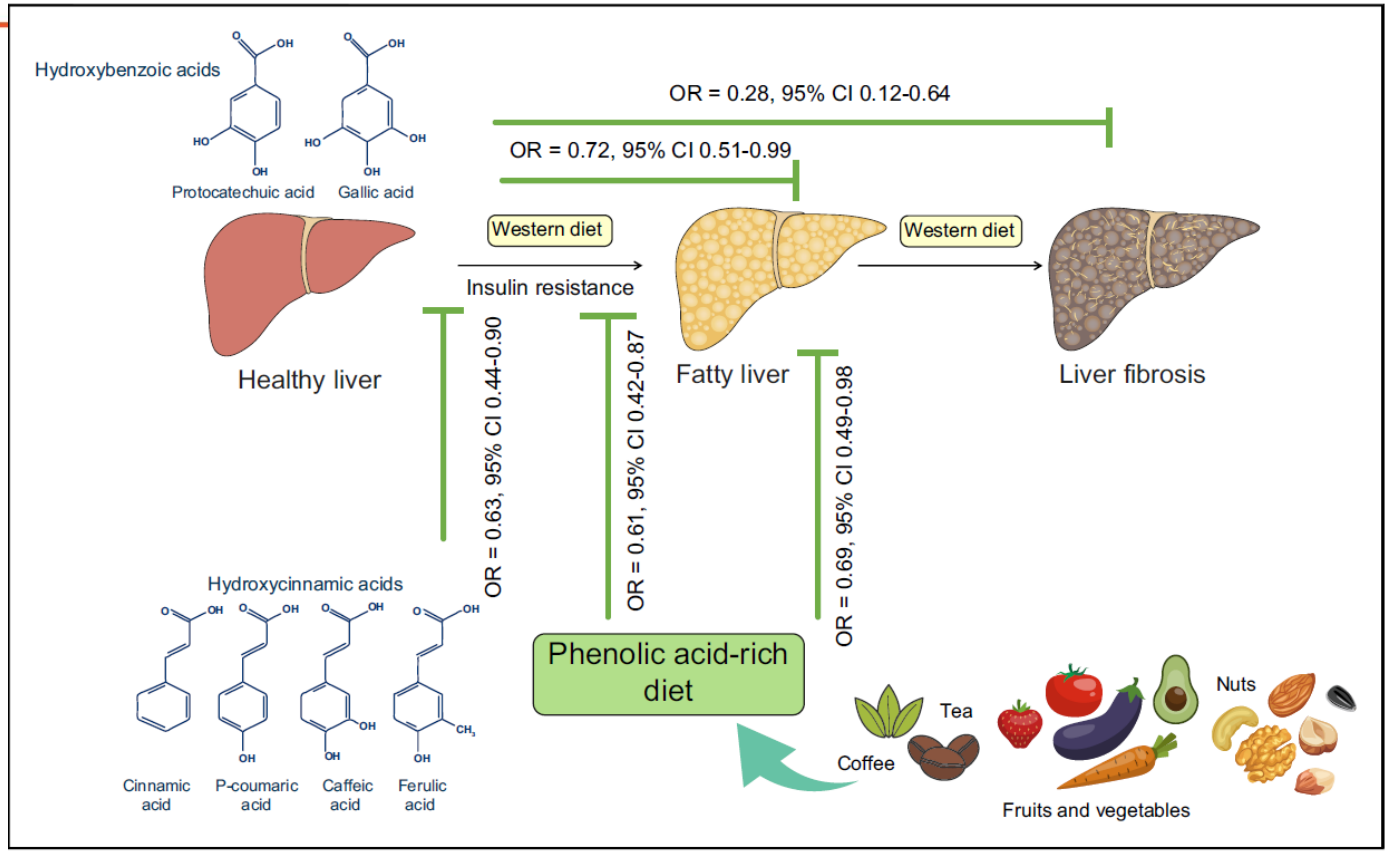


- Green-Mediterranean diet enriched with green plants and polyphenols
  - green tea (3–4 cups/day)
  - Mankai (aquatic plant strain) green shake

Yaskolka Meir A., Gut 2021

Higher phenolic acid intake independently associates with a lower prevalence of insulin resistance and NAFLD

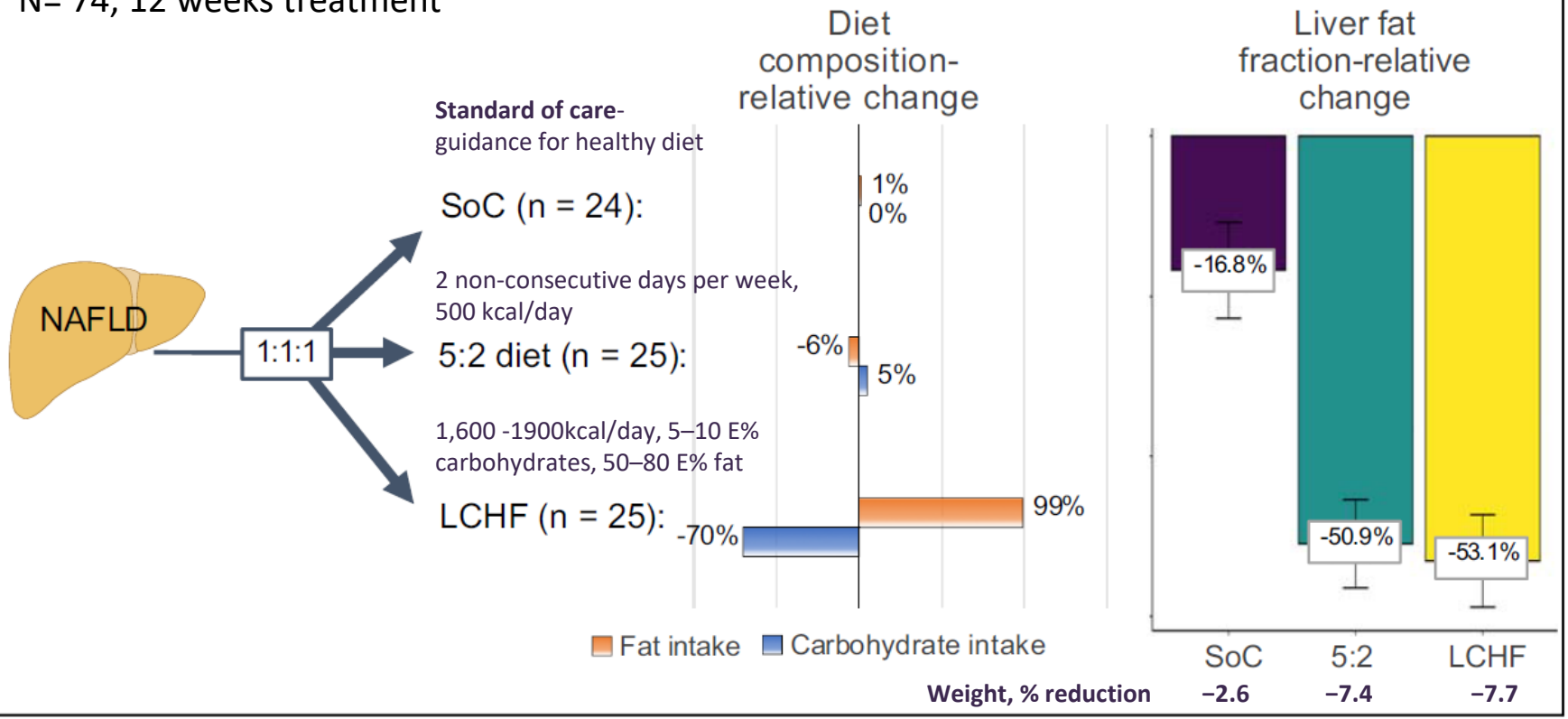
- Cross-sectional study, n= 789
- AUS
- FibroTest
- HOMA
- Phenolic acid content of food calculated by Phenol-Explorer



Salomone F., JHEP Reports 2020

Treatment of NAFLD with intermittent calorie restriction or low-carb high-fat diet RCT

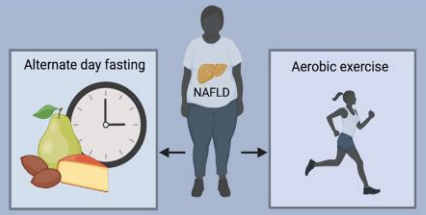
N= 74, 12 weeks treatment



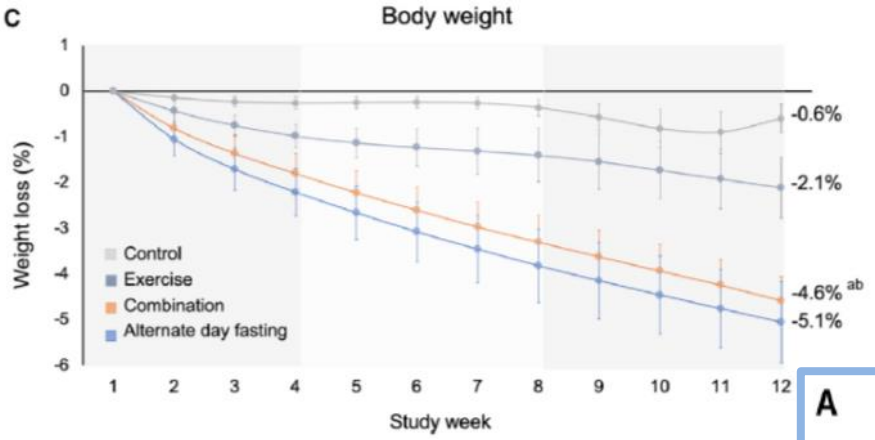
Holmer M., JHEP Reports 2021

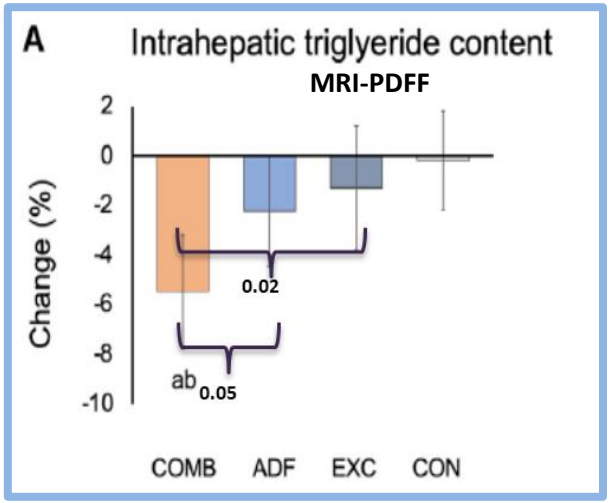
Lindqvist C., Nutrition 2023

Effect of alternate day fasting with aerobic exercise on NAFLD 12-weeks RCT



- Adults with obesity and NAFLD (n = 80)
- ADF- 600 kcal ‘‘fast day’’ / ad libitum intake ‘‘feast day’’
- Moderate-intensity aerobic exercise, 5 session/w/60min

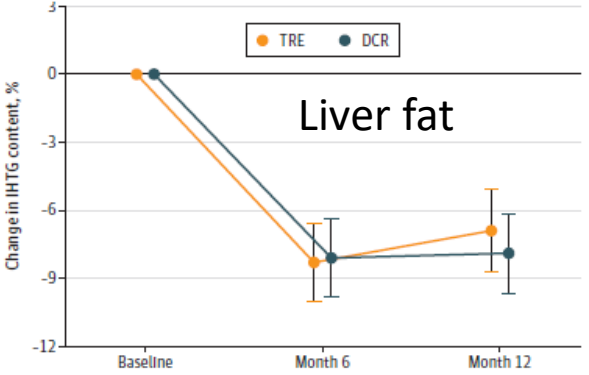




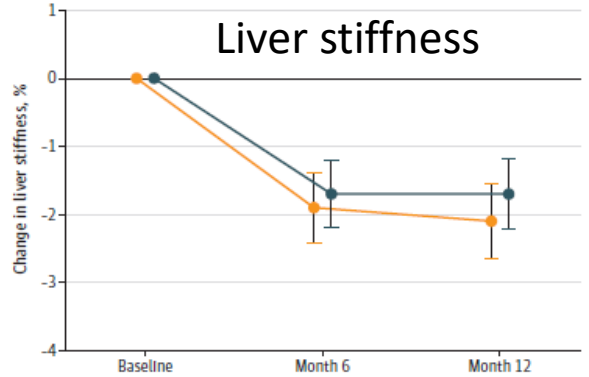
Ezpeleta M., Cell Metabolism 2023

Effects of Time-Restricted Eating on NAFLD RCT

- 12-month, n=88
- TRE (eating only between 8:00 AM and 4:00 PM)
- DCR (habitual meal timing)
- All participants were instructed to maintain a diet of 1500 to 1800 kcal/d for men and 1200 to 1500 kcal/d for women



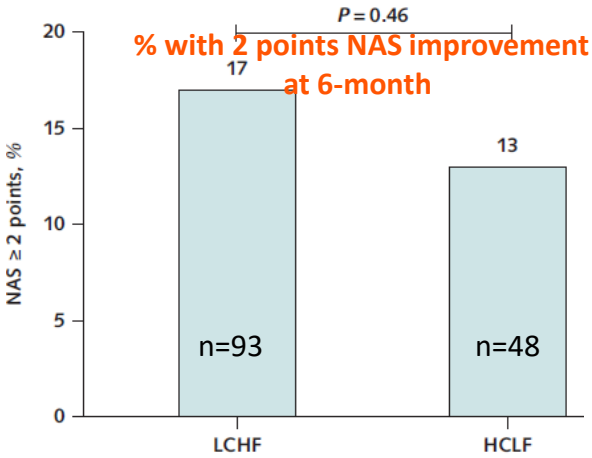
C Change in liver stiffness

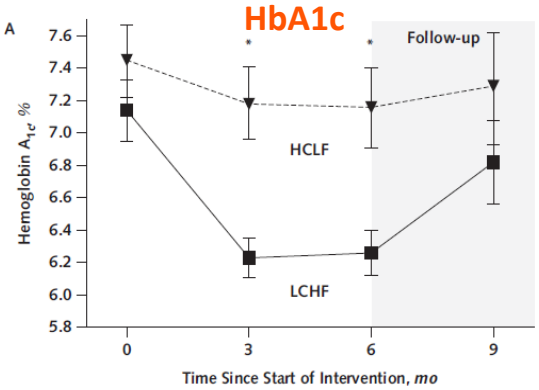


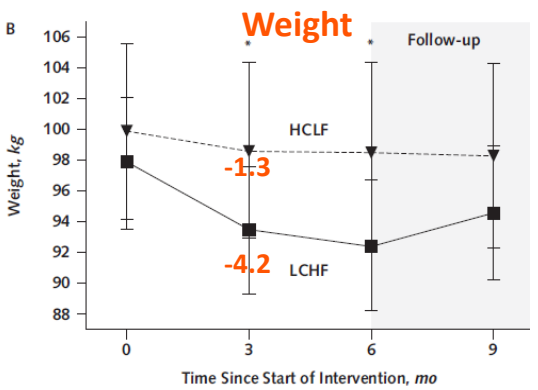
Wei X., JAMA Network Open 2023

Effect of Calorie-Un restricted Diets on Type-2 Diabetes and NAFLD 6-months RCT

- 165 participants with T2DM
- **Two calorie-unrestricted diets**
  - LCHF diet 50-60 E% fat, <20 E% carbs
  - HCLF diet 50-60 E% carbs, 20-30 E% fats
  - *In practice*: reduced 100-200 Kcal/day







- More participants in the LCHF group than in the HCLF group had a 1 or more point improvement in NAS

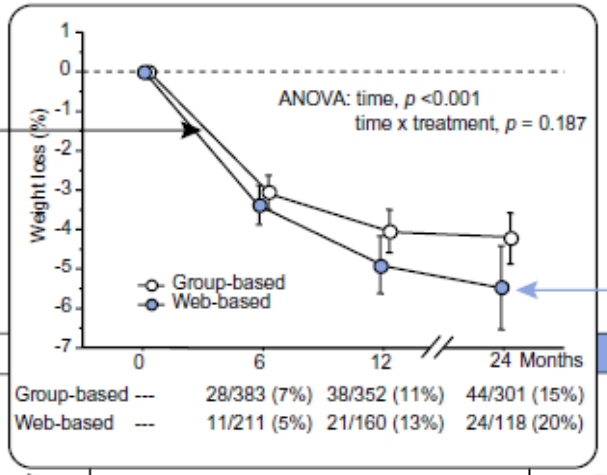
Hansen CD., Annals of Internal Medicine 2022

An internet-based approach for lifestyle changes in NAFLD

716 NAFLD (mean age, 52; type 2 diabetes, 33%)

n= 438

GROUP-BASED PROGRAM



Web-based intervention

- **Individuals who could not attend**
- **Interactive games**
- **Learning tests**
- **Mail contacts**

n= 278

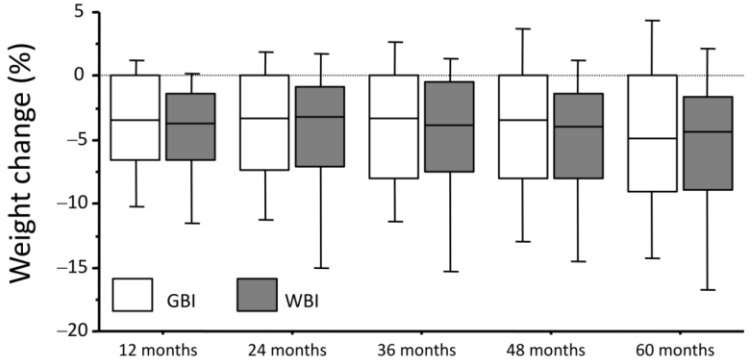
WEB-BASED PROGRAM

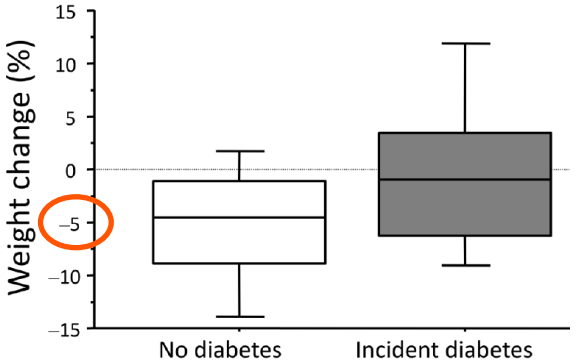
- **Fatty liver index and FIB-4 similarly reduced**
- **Attrition rate higher in the WBI**

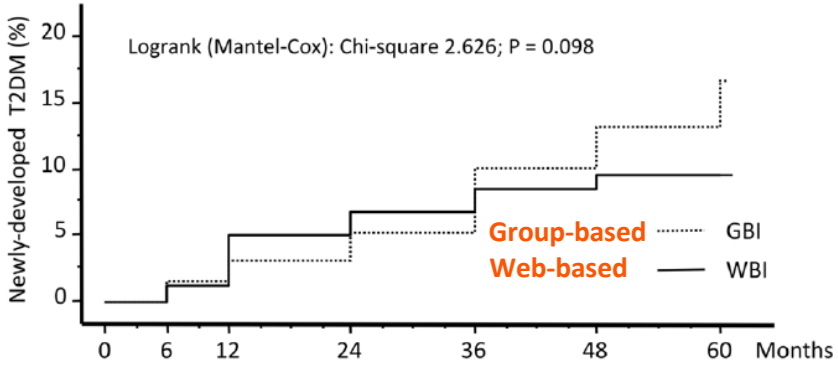
Mazzotti A., J Hepatol 2018

Long-Term Diabetes Incidence in Subjects Treated by Web- and Group-Based Programs

- Cohort study
- 546 NAFLD
- Followed 60 months
- Regular 6- to 12-month hospital visits



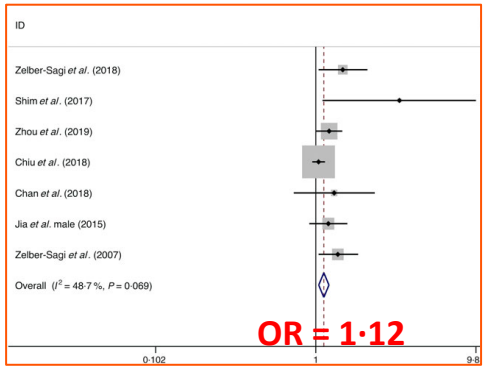




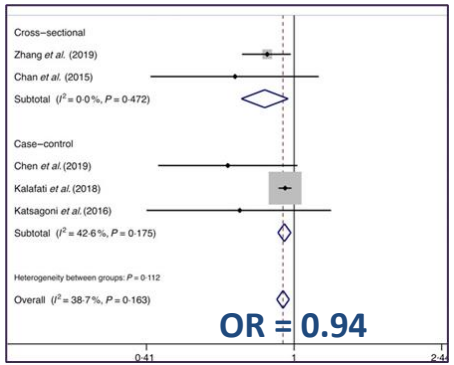
Petroni ML., Nutrients 2023

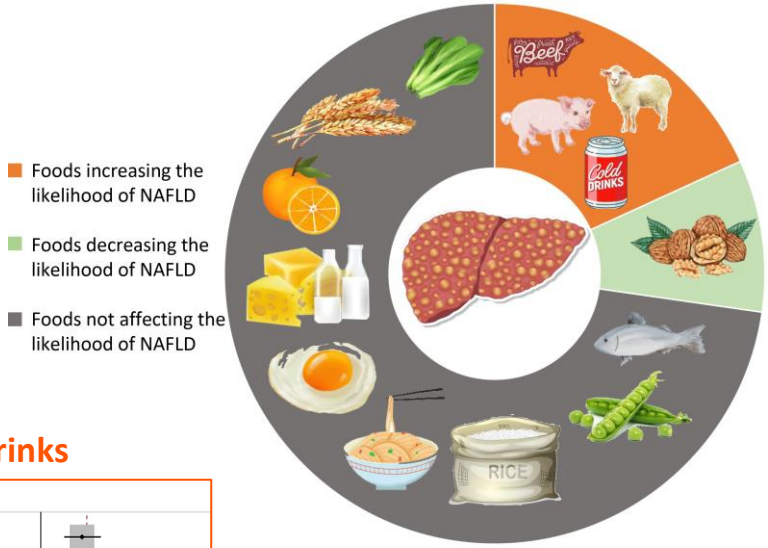
Food groups and the likelihood of NAFLD: meta-analysis of cross-sectional and case-control studies

Red meat

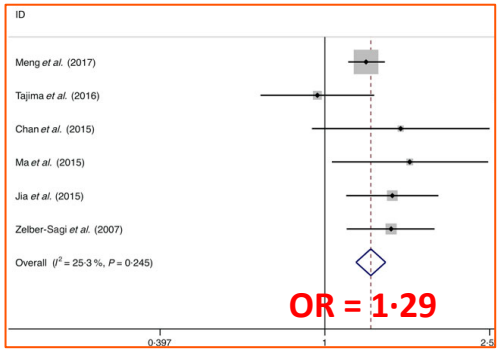


Nuts





Soft drinks



He K., British Journal of Nutrition 2020

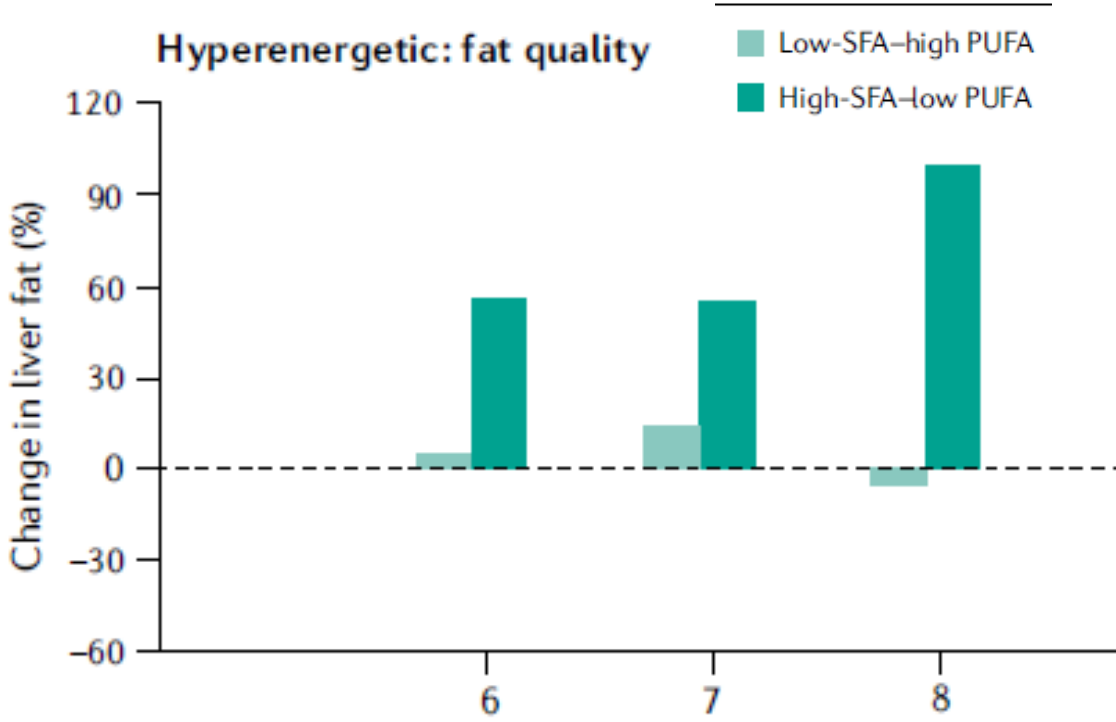
Differential effects of dietary saturated and unsaturated fats on liver fat content

- Short-term (couple of weeks) randomized trials

Saturated fat consistently increase IHTG more than polyunsaturated or monounsaturated fat

The evidence supports the Mediterranean diet

low in saturated fat high in monounsaturated fat



Yki- Järvinen H., Nature Reviews Gastroenterology & Hepatology 2021

Ultra-processed food (UPF)

Industrial processes

Packaging with plastic and other synthetic materials

Highly profitable (low-cost ingredients, long shelf life)

Hyper-palatable

Low nutritional quality, contains **many ingredients** (≥5), and **preservatives**

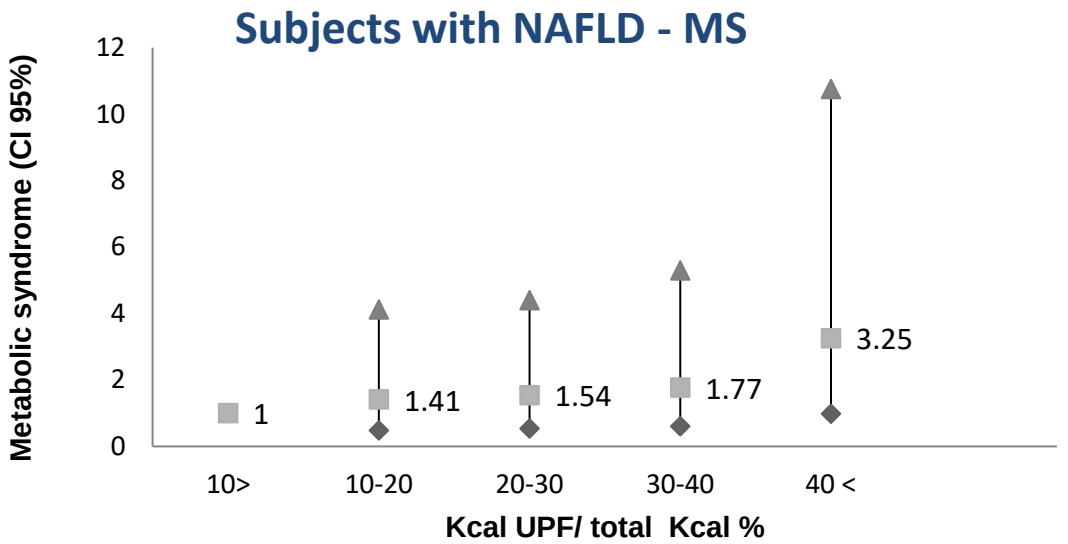
Monteiro CA., FAO 2019

https://harvardpublichealth.org/nutrition/processed-foods-make-us-sick-its-time-for-government-action/

Martinez S., Popul Health Metr 2017

Dose-response association between UPF consumption and metabolic syndrome

- Cross-sectional study, n=789 Liver US
- UPF defined by NOVA classification



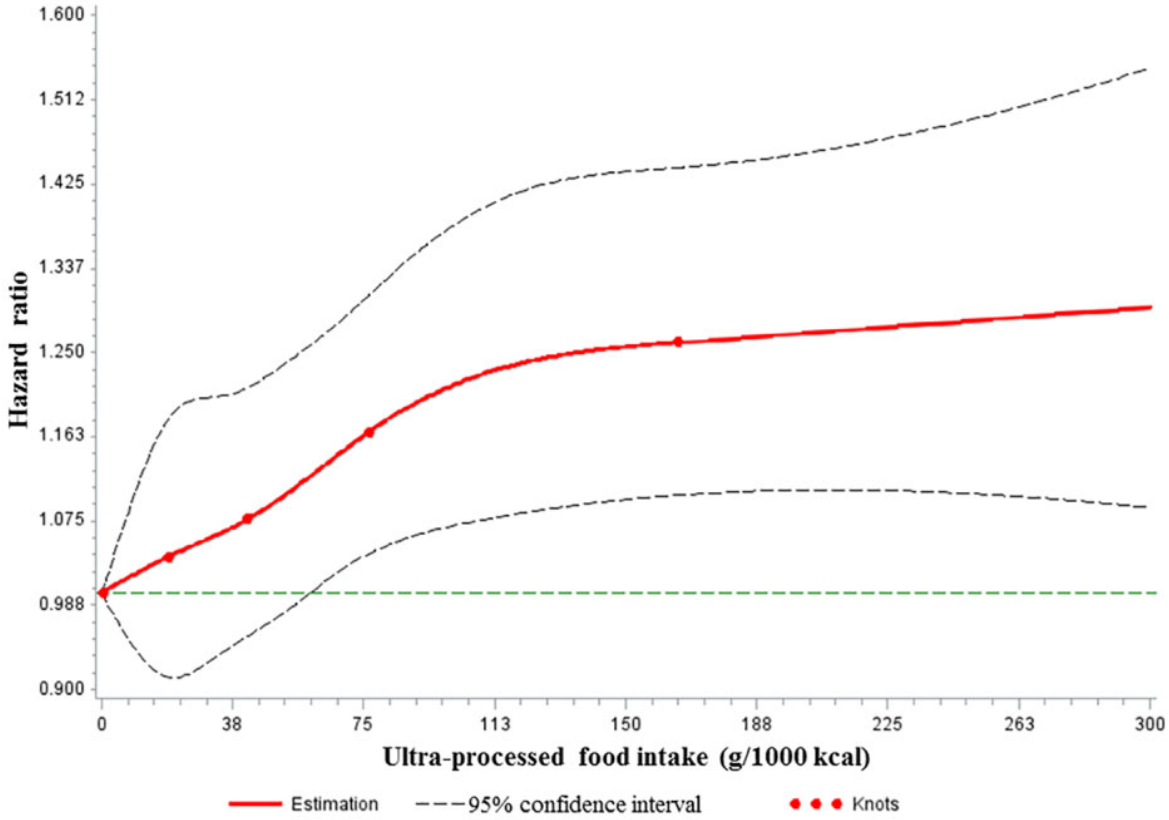
Adjusted for: age, gender, BMI, saturated fatty acids and protein intake, physical activity, coffee and fibers

Ivancovsky-Wajcman D., & Zelber-Sagi S., Liver International 2021

Dose-response association between ultra-processed food consumption (g/1000 kcal) and risk of NAFLD

- Prospective cohort study
- N=16,168
- NAFLD defined by US

Adjusted for age, sex, BMI, smoking, alcohol, education, income, physical activity, total energy intake, healthy diet score, hypertension, hyperlipidaemia and diabetes



Zhang S., International Journal of Epidemiology 2022

Association between ultra-processed foods consumption and risk of NAFLD: A population-based analysis of NHANES 2011–2018

- 6545 participants
- UPF by NOVA food classification
- Liver US

Quartiles (UPF% of total weight)	
Adjustment	**Q4 (>68) *vs.* Q1 (< 42) (ref)**
Demographics, education, smoking, BMI	1.83 (1.33–2.53)
+ Healthy Eating Index (HEI)	1.60 (1.15–2.23)
+ added sugar	1.82 (1.27–2.61)
+ saturated fat	1.80 (1.30–2.48)
+ refined grains	1.78 (1.29–2.45)

Liu Z., Br Journal Nutr 2022

Role of bisphenol A as an environmental factor in the promotion of NAFLD

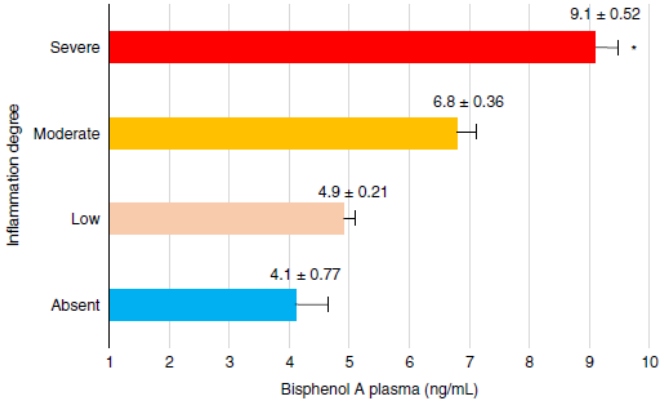
- An endocrine-disrupting chemical associated with T2DM, CVD and liver abnormalities
- A building block of **plastics** and of the lining in **food and beverage containers**
- Disrupts pancreatic b-cells function and whole-body glucose homeostasis

Dallio M., Aliment Pharmacol Ther 2018

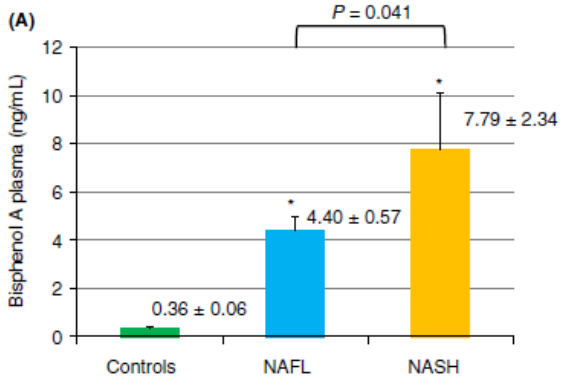
Role of bisphenol A as an environmental factor in the promotion of NAFLD

- N=60, NAFLD with **histological diagnosis** vs. controls

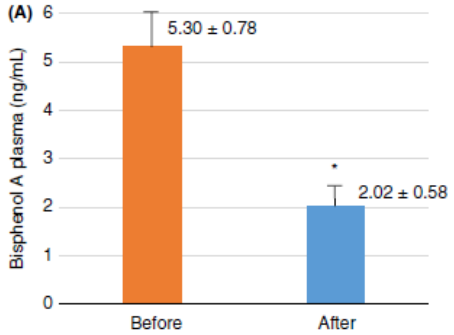
Bisphenol A plasma levels and hepatic inflammation



Bisphenol A plasma levels



Bisphenol A levels before and after bisphenol A free-diet for 1 month

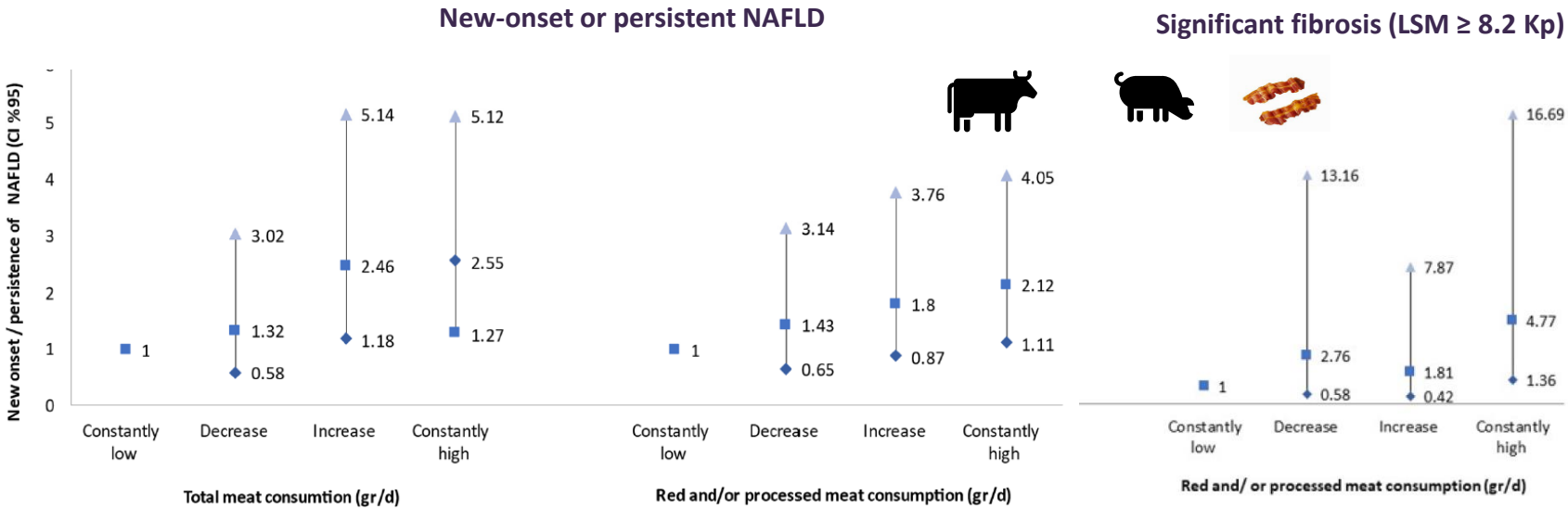


Dallio M., Aliment Pharmacol Ther 2018

High meat consumption is prospectively associated with risk of NAFLD and presumed significant fibrosis

- Prospective cohort, 6.8 y follow-up
- N=316 subjects
- US or CAP, FibroScan

Changes in meat consumption during follow-up



Adjusted for baseline age (years), gender, BMI (Kg/m2), energy, (Kcal), protein (% total Kcal), and cholesterol intake (mg/day)

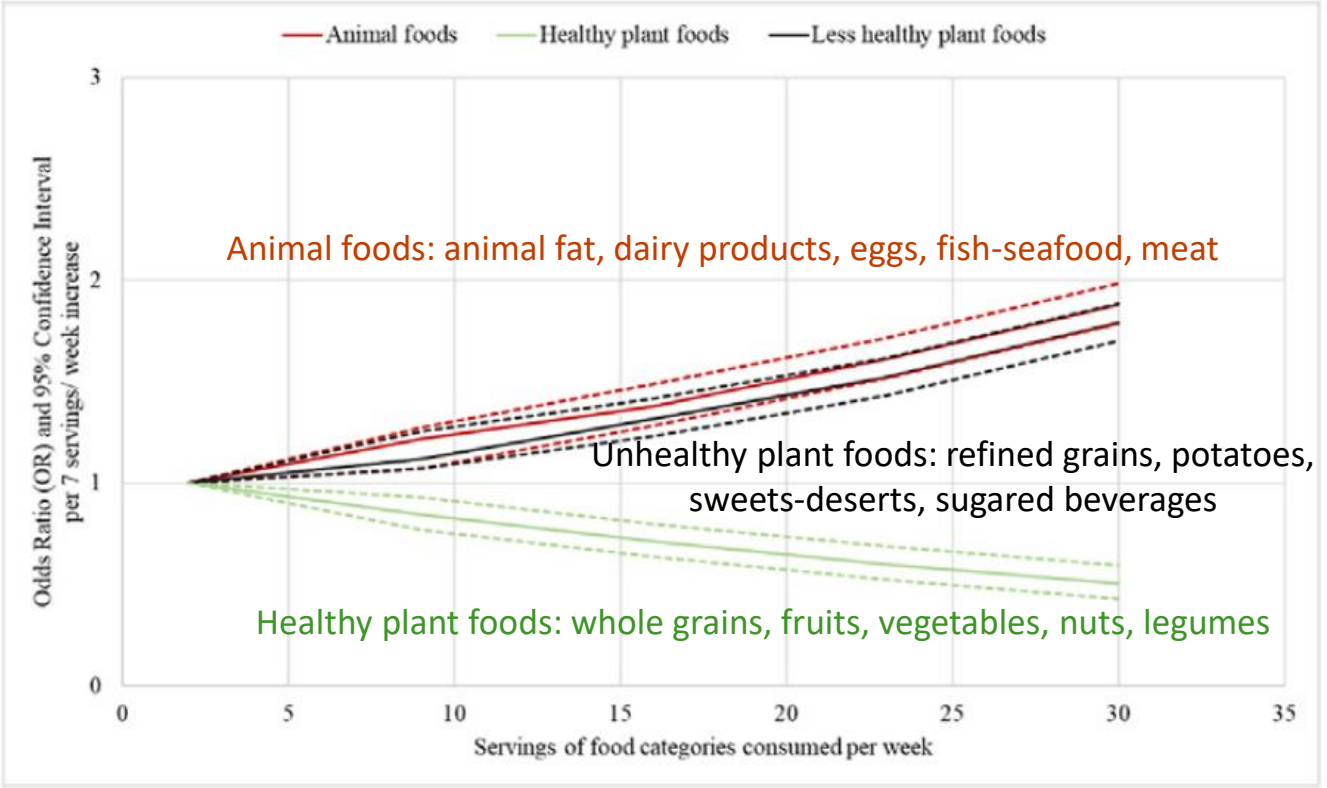
Ivancovsky-Wajcman D., Nutrients 2022

Quality of plant-based diets is associated with liver steatosis

- Greek cohort, n=3042,
- Cross-sectional analysis
- hepatic steatosis index (HSI)

Adjusted for:
education, smoking, physical activity, alcohol, energy intake, waist circumference, DM, HTN, hyper-chol

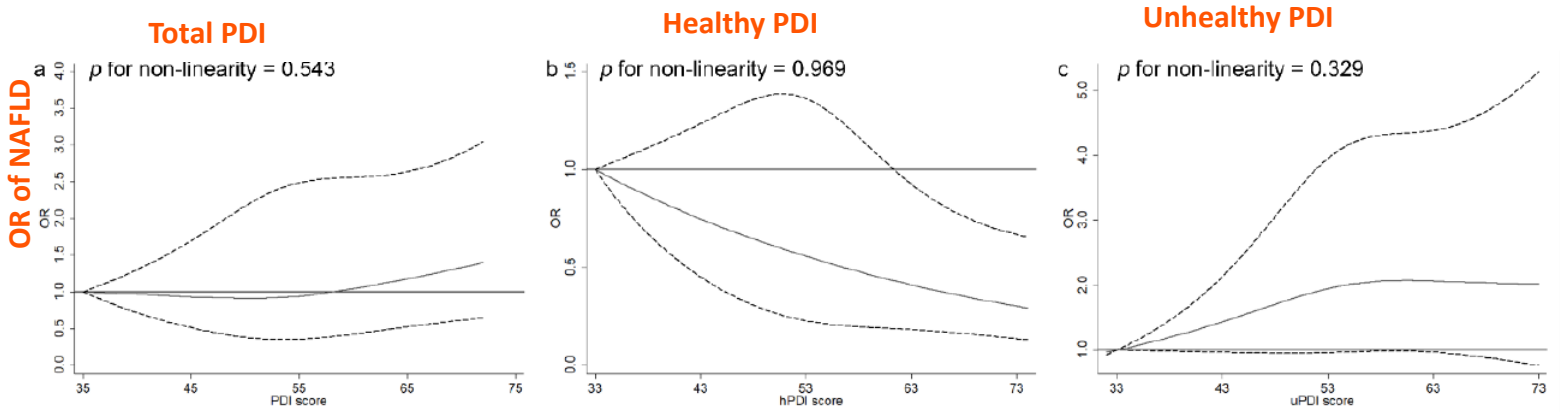
Odds of having NAFL



Kouvari M., Clinical Nutrition 2022

A Healthful Plant-Based Diet Index (PDI) Is Associated with Lower Odds of NAFLD

- Nationwide NHANES US cross-sectional study
- N= 3900
- Diet by 24-h recalls
- CAP



Li X., Nutrients 2022

Adjusted for: poverty, race/ethnicity, energy, marital status, education, smoking, alcohol, diabetes, physical activity, BMI

Lifestyle and NAFLD: an umbrella review of observational studies and RCTs

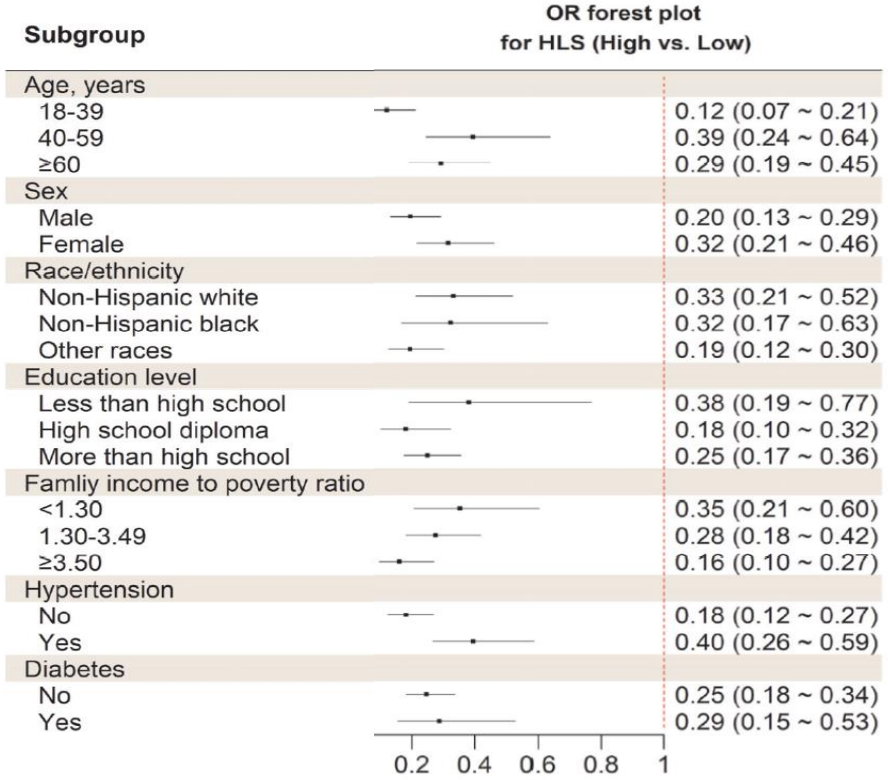
Exposure	Measure	Studies (n)	Subjects (n)	Cases (n)	Random effect model	Effect sizes (95% CI)	I^2 (%)
Smoking	NAFLD	20	92125	20149		OR, 1.43 (1.02, 1.84)	98.50
Passive smoking	NAFLD	2	NA	NA		OR, 1.32 (1.16, 1.50)	59.41
Former smoking	NAFLD	4	2210	784		OR, 1.38 (1.20, 1.59)	0.00
Sugar sweetened beverages	NAFLD	4	5241	1150		OR, 1.40 (1.07, 1.82)	31.00
Sugar-Sweetened Soda	NAFLD	7	4639	NA		RR, 1.53 (1.34, 1.75)	0.00
Soft drinks	NAFLD	7	32788	9947		OR, 1.33 (1.18, 1.49)	23.11
Hypercaloric fructose diet	IHLC	6	NA	NA		OR, 1.13 (1.02, 1.45)	0.00
Red meat	NAFLD	8	NA	8115		OR, 1.26 (1.08, 1.47)	63.73

Peng X., BMC Endocrine Disorders 2022

Higher Adherence to Healthy Lifestyle Score Is Associated with Lower Odds of NAFLD

- Nationwide U.S. NHANES, cross-sectional study
- **HLS**: dietary pattern, BMI, physical activity, smoking, and sleep duration
- CAP and LSM

Stratified analysis: association between HLS and NAFLD

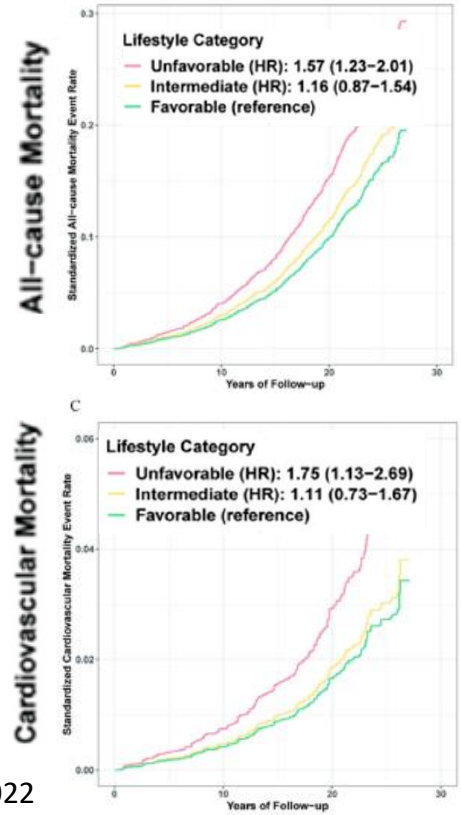


Yu Zhu Y., Nutrients 2022

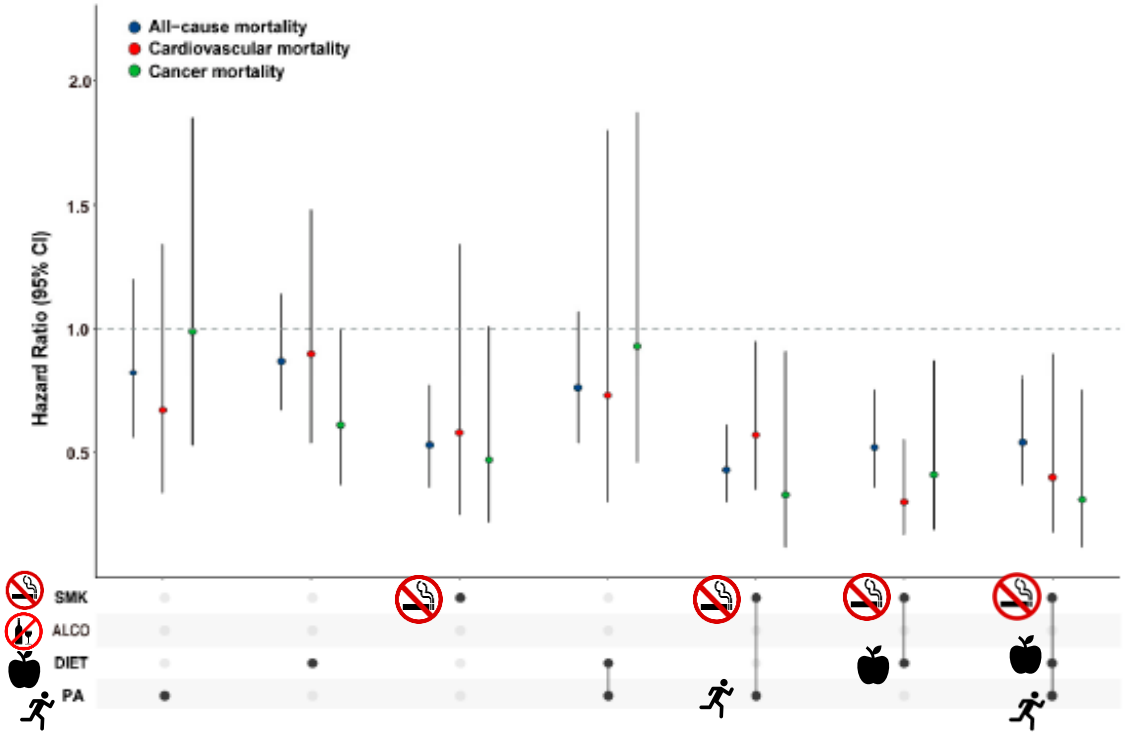
Healthy Lifestyle Is Associated with Reduced Mortality in Patients with NAFLD

- NHANES III 1988-1994
- Mortality through 2015
- N=3578

WHO Healthy Lifestyle Score



Association between combinations of the healthy lifestyle factors and risk of mortality in NAFLD patients



Yu C., Nutrients 2022

Coffee Consumption Is Associated With Lower Liver Stiffness: A Nationally Representative Study

- 4510 subjects from the 2017 to 2018 NHANES cross-sectional study
- TE & CAP

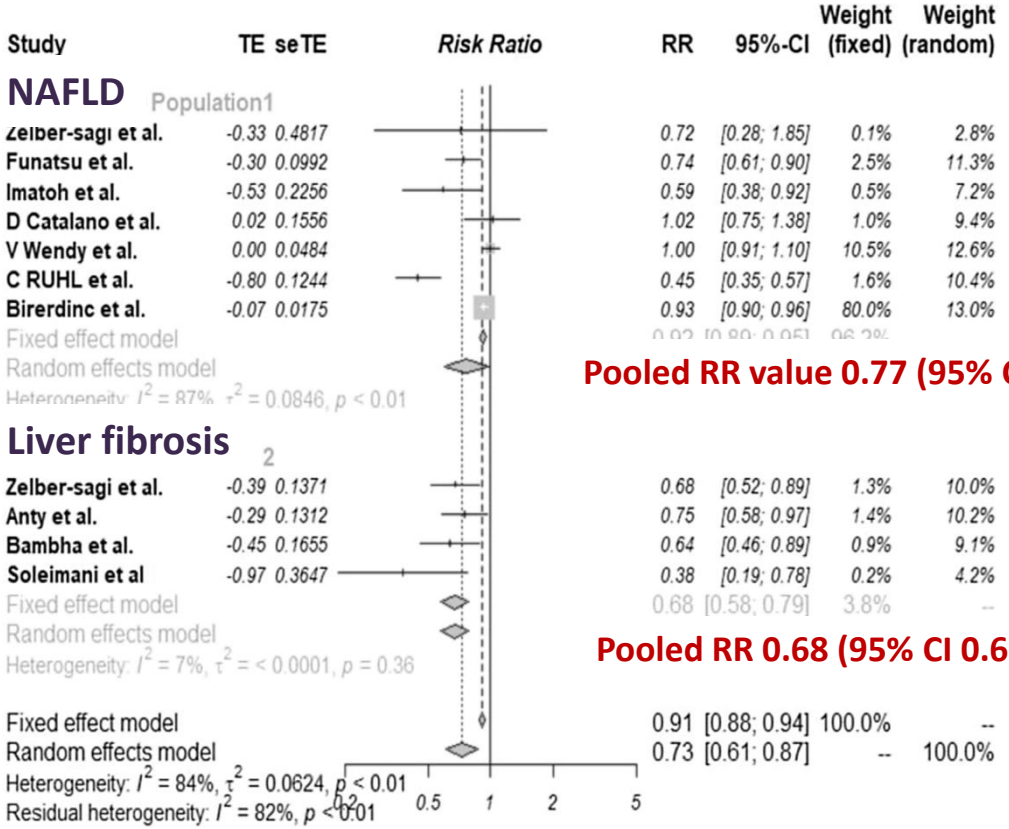
	Advanced fibrosis LSM ≥9.5 kPa, model 1		CAP, *dB/m*, model 2	
Characteristic	OR (95% CI)[a]	*P*	Coef. (95% CI)[b]	*P*
Coffee (ref. = nondrinkers)				
<1 cup	2.5 (0.8–7.5)	.1	0.7 (-9.9 to 11.2)	.8
1–2 cups	1.0 (0.5–1.9)	.9	-0.1 (-5.9 to 5.7)	.9
2–3 cups	1.1 (0.5–2.5)	.7	-3.7 (-10.0 to 2.5)	.2
>3 cups	0.5 (0.2–0.9)	.03	3.3 (-2.1 to 8.6)	.2

Adjusted for: age, sex, race, vigorous activity, alcohol consumption in the past year, smoking history, BMI, and education level

Niezen S., Clinical Gastroenterology and Hepatology 2022

Meta-analyses of coffee consumption impact on NAFLD and liver fibrosis

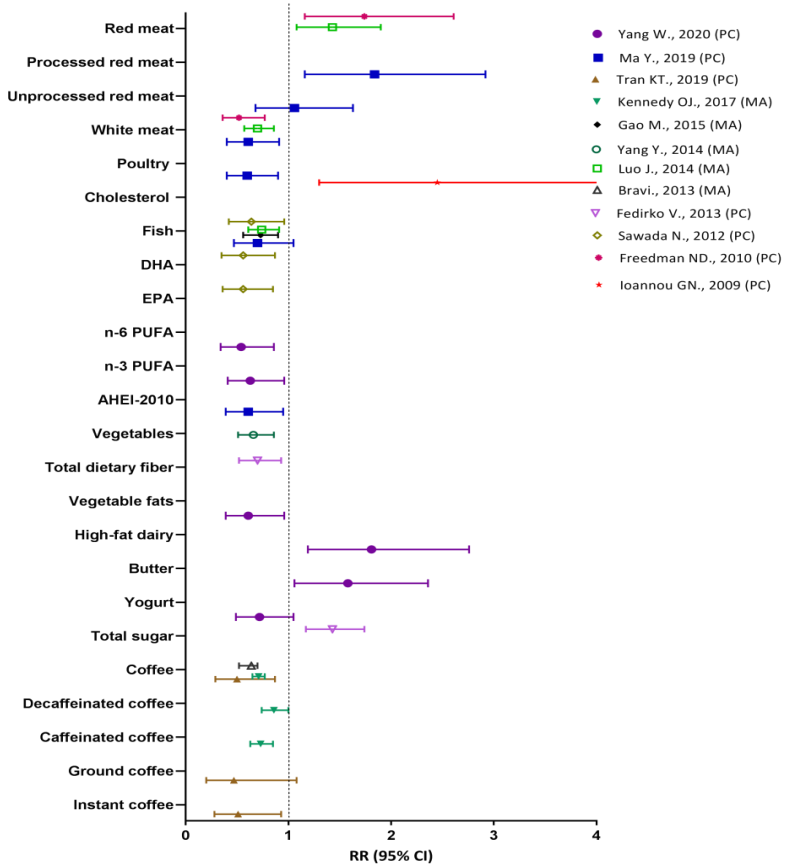
- 11 studies, varying designs



Hayata U., Annals of Hepatology 2021

Lifestyle parameters related with risk for HCC, in large prospective cohort studies and meta-analyses

The categories compared were the highest dietary intake category vs. the lowest intake

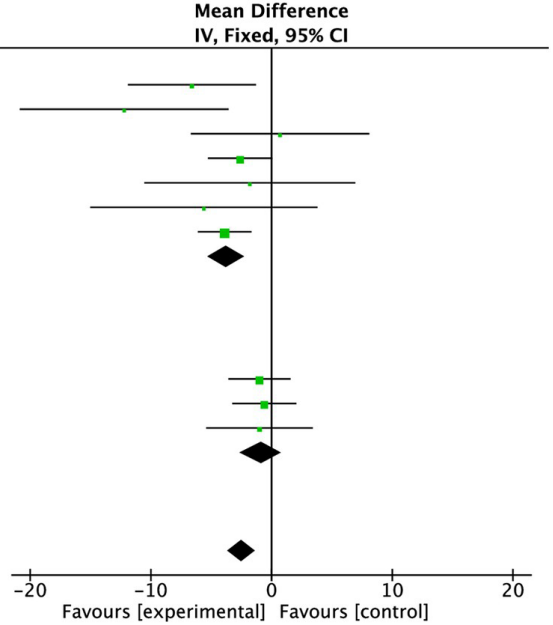


Zelber-Sagi S., Seminars in Liver Disease 2021

Effect of exercise alone on intrahepatic lipids Meta-analysis of RCTs

- Effect of exercise alone compared to the control group of conventional treatment

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
11.5.1 H-MRS								
Cheng, 2017	12.2	9.47	22	18.8	7.64	18	4.6%	-6.60 [-11.90, -1.30]
Cuthbertson, 2016	14.87	16.06	30	27.08	14.76	20	1.7%	-12.21 [-20.86, -3.56]
Hallsworth, 2011	12.2	9	11	11.5	7.4	8	2.4%	0.70 [-6.69, 8.09]
Hallsworth, 2015	7.8	2.4	12	10.4	3.9	11	18.0%	-2.60 [-5.27, 0.07]
Pugh, 2014	18	11.58	13	19.8	8.737	8	1.7%	-1.80 [-10.53, 6.93]
Shojaee-Moradie, 2016	10.68	9.73	15	16.29	14.17	12	1.5%	-5.61 [-15.02, 3.80]
Zhang, 2016	-4.59	9.199	135	-0.7	6.906	73	26.1%	-3.89 [-6.11, -1.67]
Subtotal (95% CI)			**238**			**150**	**55.9%**	**-3.74 [-5.26, -2.22]**
Heterogeneity: $Chi^2 = 7.24$, df = 6 (P = 0.30); $I^2 = 17\%$								
Test for overall effect: Z = 4.83 (P < 0.00001)								
11.5.2 MRI								
Abdelbasset, 2019	10.1	1.3	16	11.1	5.1	16	19.3%	-1.00 [-3.58, 1.58]
Abdelbasset W, 2020	10.5	1.5	15	11.1	5.2	16	18.2%	-0.60 [-3.26, 2.06]
Houghton, 2016	10	6	12	11	5	12	6.6%	-1.00 [-5.42, 3.42]
Subtotal (95% CI)			**43**			**44**	**44.1%**	**-0.84 [-2.54, 0.87]**
Heterogeneity: $Chi^2 = 0.05$, df = 2 (P = 0.97); $I^2 = 0\%$								
Test for overall effect: Z = 0.96 (P = 0.34)								
Total (95% CI)			**281**			**194**	**100.0%**	**-2.46 [-3.59, -1.33]**
Heterogeneity: $Chi^2 = 13.51$, df = 9 (P = 0.14); $I^2 = 33\%$								
Test for overall effect: Z = 4.25 (P < 0.0001)								
Test for subgroup differences: $Chi^2 = 6.22$, df = 1 (P = 0.01), $I^2 = 83.9\%$								



Ferna´ndez T., PLOS ONE 2022

NAFLD and significant fibrosis by meeting leisure-time physical activity guideline

- A cross-sectional, 2017–2018 U.S NHANES, n= 4304
- TE & CAP
- PA questionnaire

>300 min/w was more pronounced for both NAFLD and fibrosis

NAFLD prevention	OR (95%CI)	P
No	1	
Yes >150 min/w	0.64 (0.50–0.81)	0.001
Sitting time Q4 (8 h/d)	1.44 (1.01–2.05)	0.045
Significant Fibrosis prevention		
No	1	
Yes >150 min/w	0.55 (0.35–0.87)	0.013
Cirrhosis prevention		
No	**1**	
Yes >300 min/w	0.42 (0.24–0.73)	0.005

Multivariable model adjusted for age, sex, race/ethnicity, education level, smoking, alcohol hypertension, diabetes, waist circumference

Kim D., Clinical Gastroenterology and Hepatology 2022

Physical activity is inversely associated with hepatic fibro-inflammation: A population-based cohort study- UK Biobank data

Cohort and methods

Men and women in the UK Biobank population cohort (n = 840)

Exposure variables:

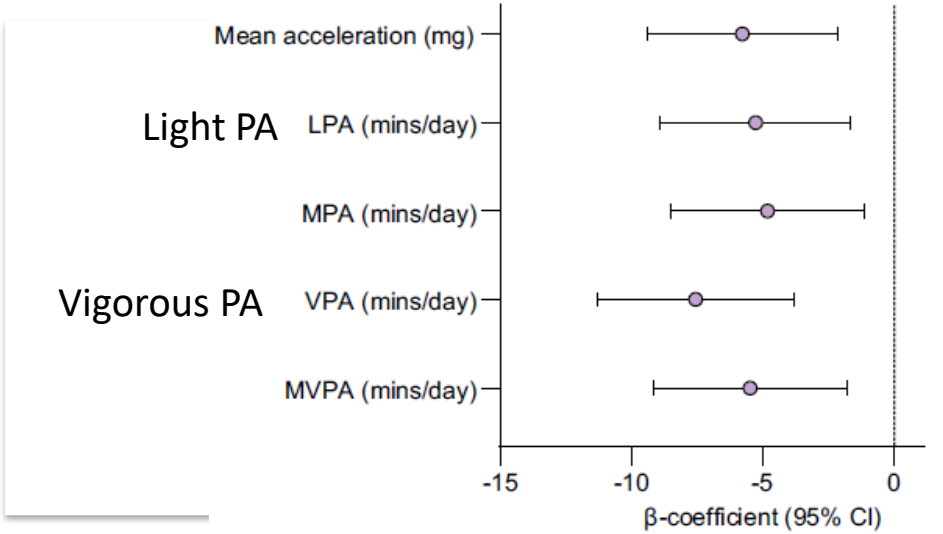
Physical activity measured by accelerometry (LPA, MPA, MVPA, VPA & mean acceleration)

Outcome variable:

- Hepatic fibro-inflammation measured by MRI (cT1)
- Liver and body fat measured by MRI and DEXA

Key outcomes

Per standard deviation of PA



Sherry AP., JHEP Reports 2023

Association of Physical Activity With Risk of Liver Fibrosis & Sarcopenia in NAFLD

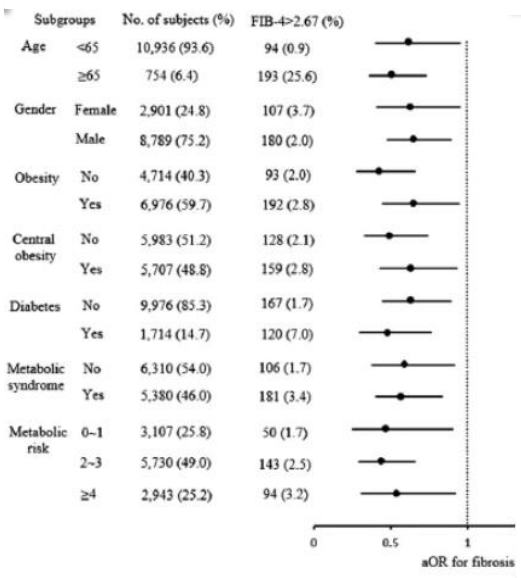
- Retrospective health screening study
- 11,690 NAFLD subjects
- Liver fibrosis- FIB-4>2.67, FibroScan-AST score>0.35
- Sarcopenia- BIA
- Coronary artery calcium (CAC) score

Multivariate analysis for fibrosis by FAST

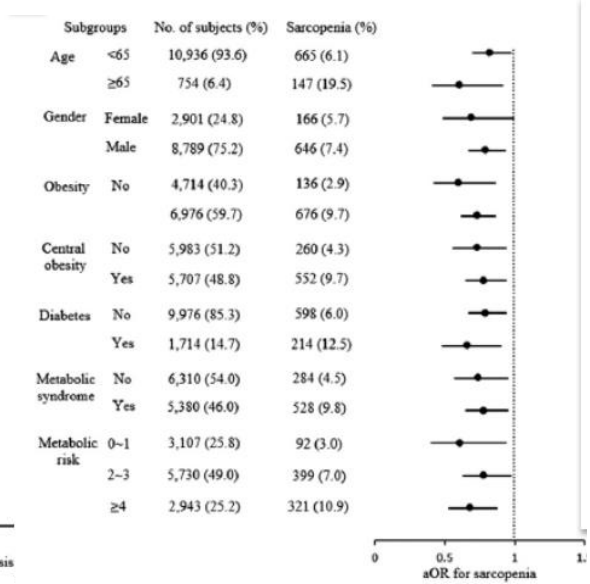
Amounts of physical activity			
Lowest quartile	1.00 (reference)		
Second quartile	0.57	0.31–1.02	.060
Third quartile	0.37	0.19–0.73	.004
Highest quartile	0.32	0.16–0.66	.002

Physical activity above median value

FIB-4



Sarcopenia

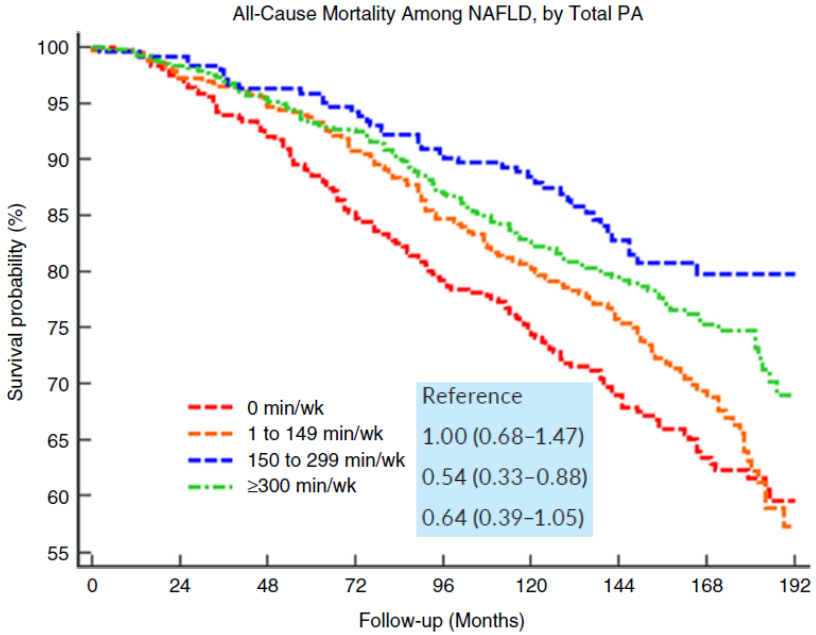


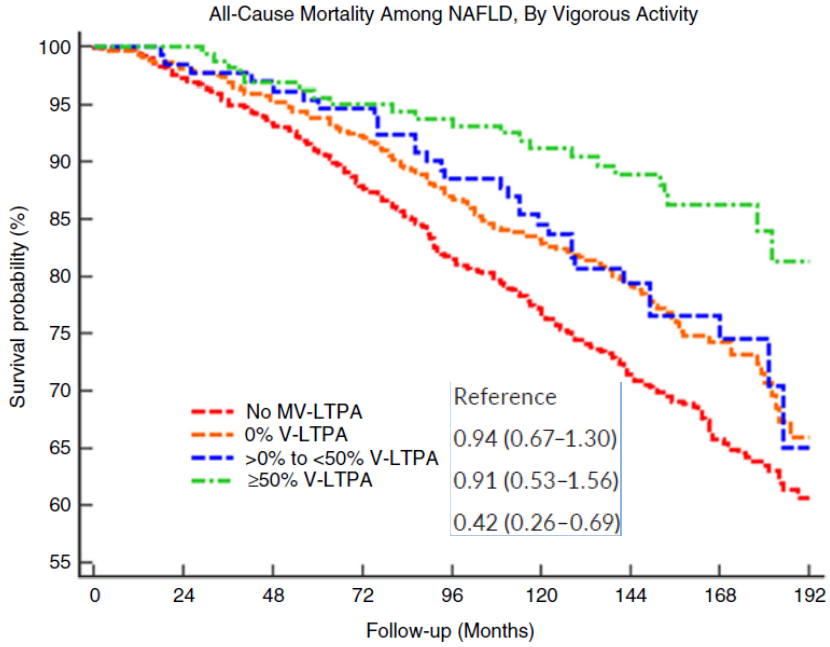
Adjusted for central obesity, hypertension, diabetes, lipids, smoking, alcohol consumption

Chun HS., Clinical Gastroenterology and Hepatology 2023

Vigorous physical activity provides protection against all-cause deaths among adults patients with NAFLD

- NHANES (1999–2006), n = 1706 with NAFLD
- Self-reported PA
- US-Fatty Liver Index





Henry A., Aliment Pharmacol Ther 2022

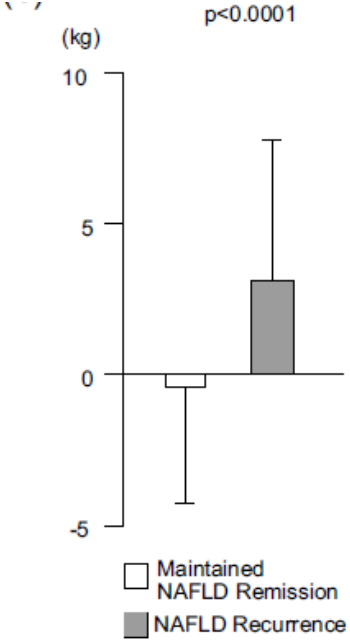
Adjusted for race, education, income, smoking status, household time PA, transportation time PA

Weight regain and lack of exercise are associated with NAFLD recurrence

- Retrospective cohort study
- 10.8 y years
- 1260 men with NAFLD who achieved remission
- 49% NAFLD recurrence at the last visit

Amount of weight change after NAFLD remission

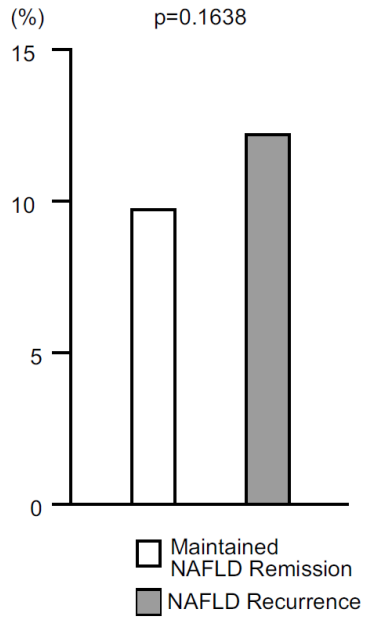
OR of NAFLD recurrence = 1.29 (1.24–1.34) per 1 kg increments



Independent of each other

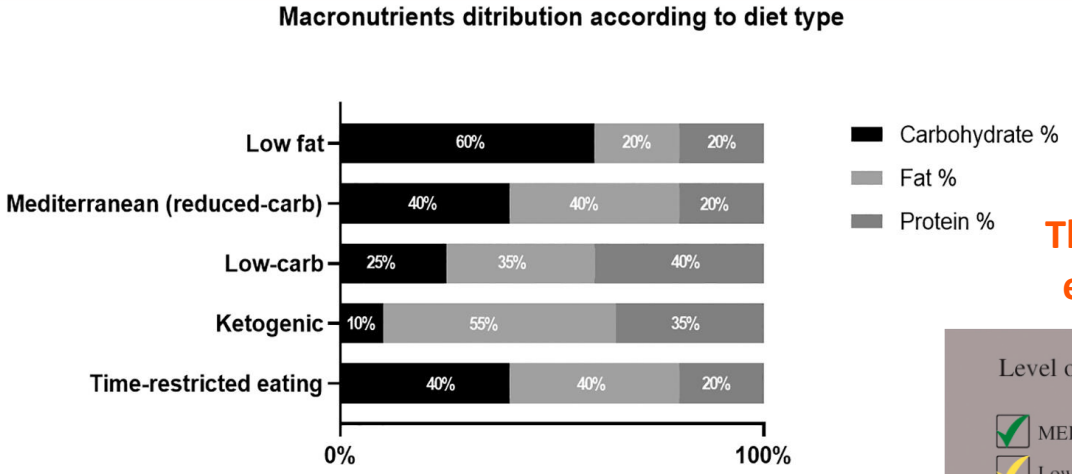
Proportions of participants who stopped regular exercise after NAFLD remission

OR of NAFLD recurrence = 0.67 (0.55–0.89) for regular exercise at the last visit

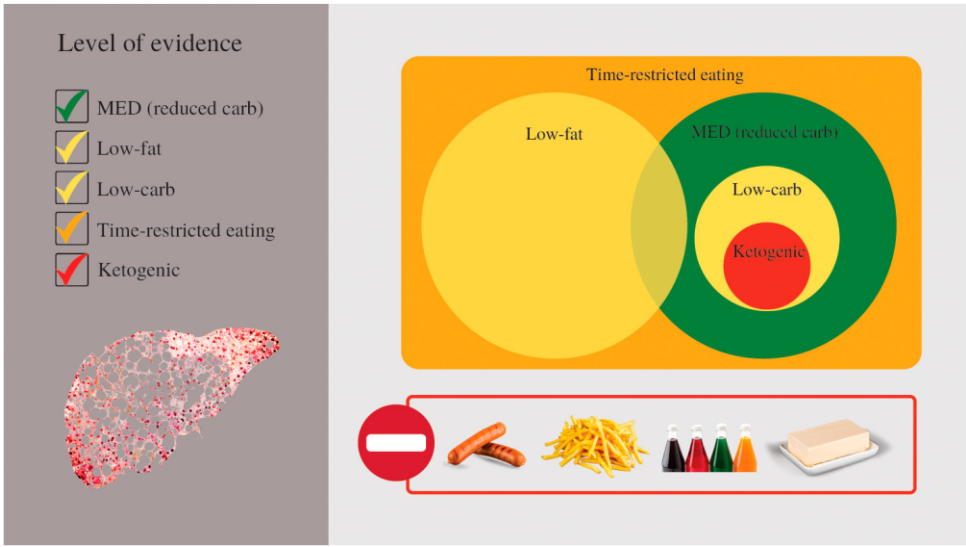


Nakanishi N., Scientific Reports 2021

A conceptual summary of the level of evidence of each type of diet for the treatment of NAFLD and suggested combinations

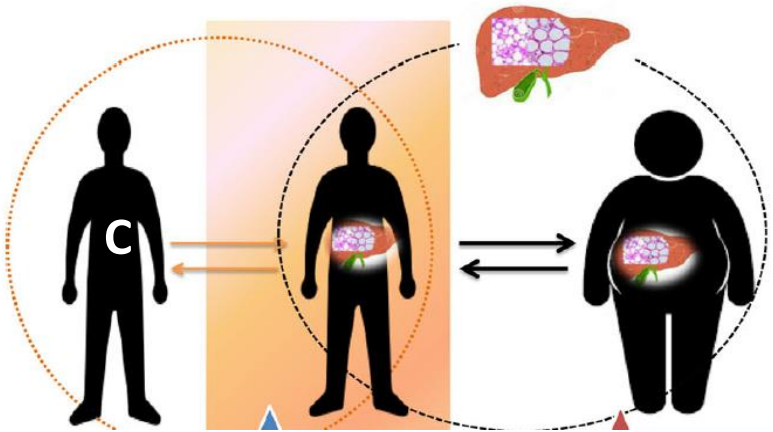


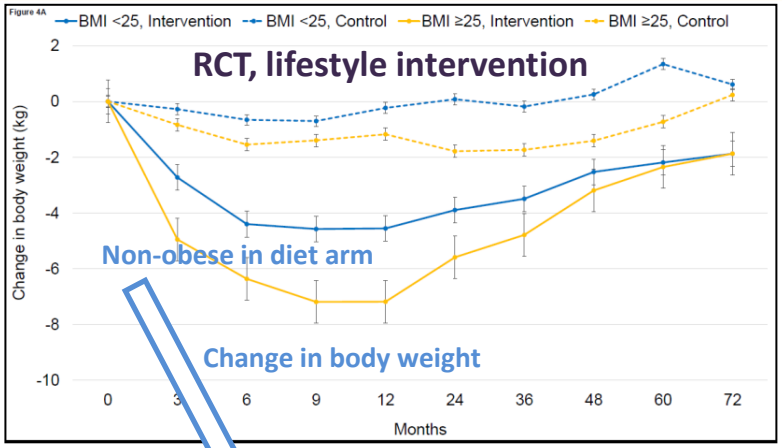
The colours represent the level of evidence of each type of diet in the treatment of NAFLD



Zelber-Sagi S., Liver International 2022

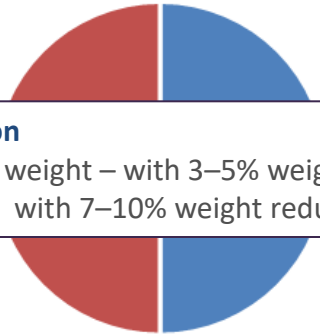
Beneficial effects of lifestyle intervention in non-obese NAFLD





- Reduction of weight even within the normal BMI range
- Reduced intake of fructose/ sugared soft drinks
- Physical activity- decrease visceral fat

- **50% remission**
  - Normal weight – with 3–5% weight reduction
  - Obese - with 7–10% weight reduction



Wai-Sun Wong V., J Hepatol 2018 Chen F., Hepatology 2019 Sinn DH., Eur J Gastroenterol Hepatol 2021
Sookoian S., Aliment Pharmacol Ther 2017

AGA Clinical Practice Update: Management of Lean NAFLD

Best Practice Advice:

In lean patients with NAFLD, lifestyle intervention, including exercise, diet modification, and avoidance of fructose- and sugar-sweetened drinks, to target a modest weight loss of 3%–5%

Long MT., Gastroenterology 2022

Take home messages

- Diet is the cause and the treatment of NAFLD
- Changes in lifestyle are hard to make, but even small ones make a difference
- Normal weight NAFLD is not an excuse to avoid diet
- Dietary composition modification is also important
- Physical activity may improve much more than steatosis and saves lives!