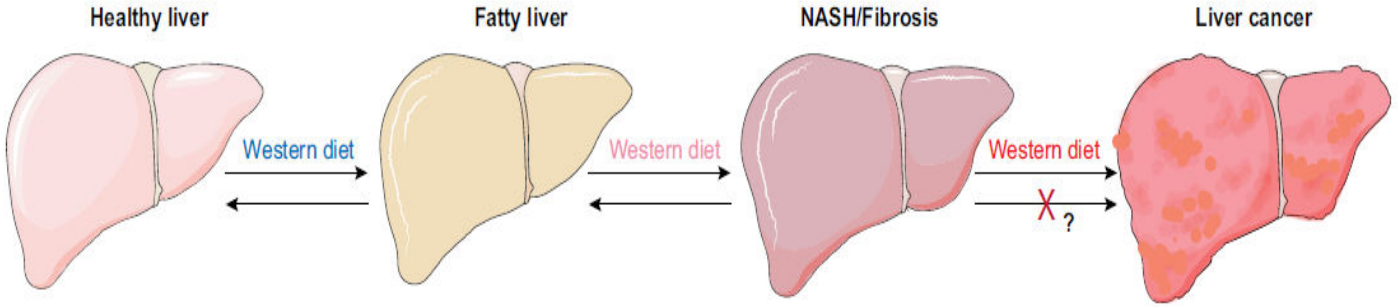
How to implement a Healthy Lifestyle in NAFLD/NASH Patients

Shira Zelber-Sagi R.D. Ph.D
Dept. of Gastroenterology
Tel Aviv Medical Center
School of Public Health,
Haifa University
Israel

Advances in Gastroenterology & Hepatology Conference

Summary of lifestyle treatment options through the course of NAFLD



Hypocaloric or isocaloric - Mediterranean diet

Aerobic or resistance excercise
(Clinical trials)

≥7-10% Weight reduction
by energy deficit of 500-750 kcal/day through either diet:
- low fat
- low carb
- Mediterranean

(Clinical trials)

Dietary composition modification
Reduced fructose
Mediterranean diet
(Observational studies)

Mediterranean diet
- High fibres
- High fish
- High vegetables
- Low cholesterol
- Low sugar

Drinks
- Coffee ≥2-3 cups/day
- No alcohol in cirrhotics

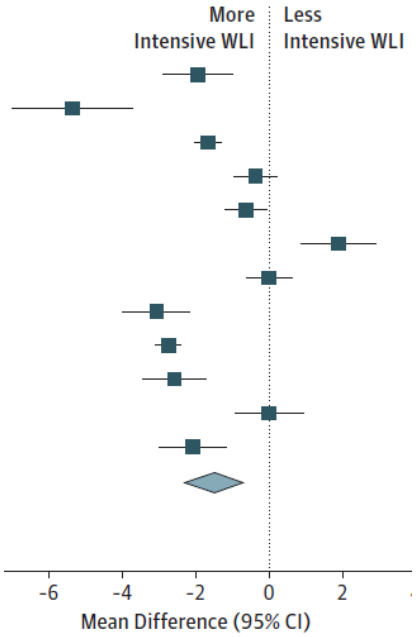
(Observational studies)

Romero-Gómez M., Zelber-Sagi S., Trenell M., Journal of Hepatology 2017

Effect of weight loss on NAFLD
A Systematic Review and Meta-analysis

- 22 RCTs with 2588 participants with NAFLD

Steatosis



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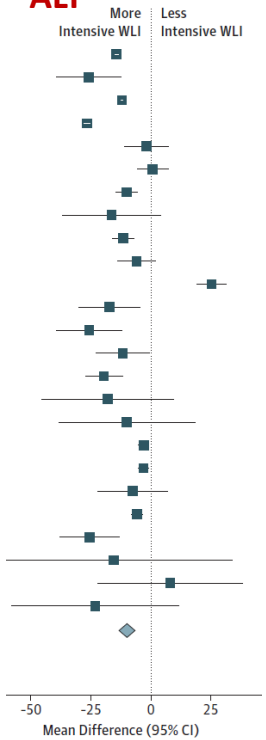
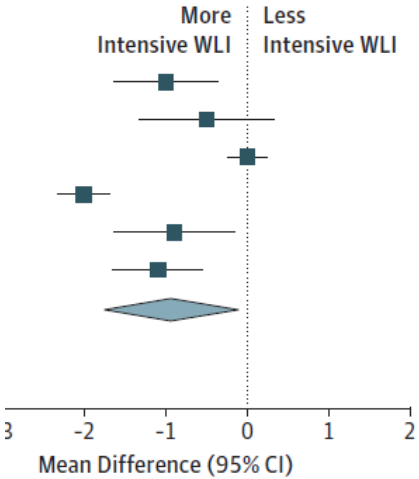
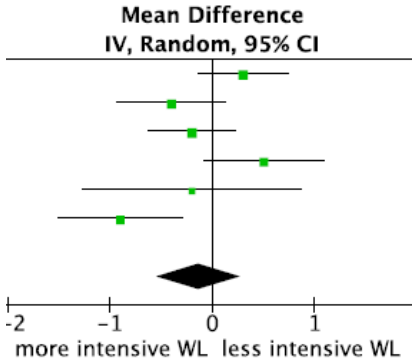


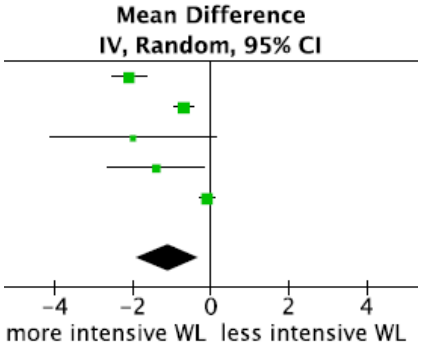
NAS



Fibrosis

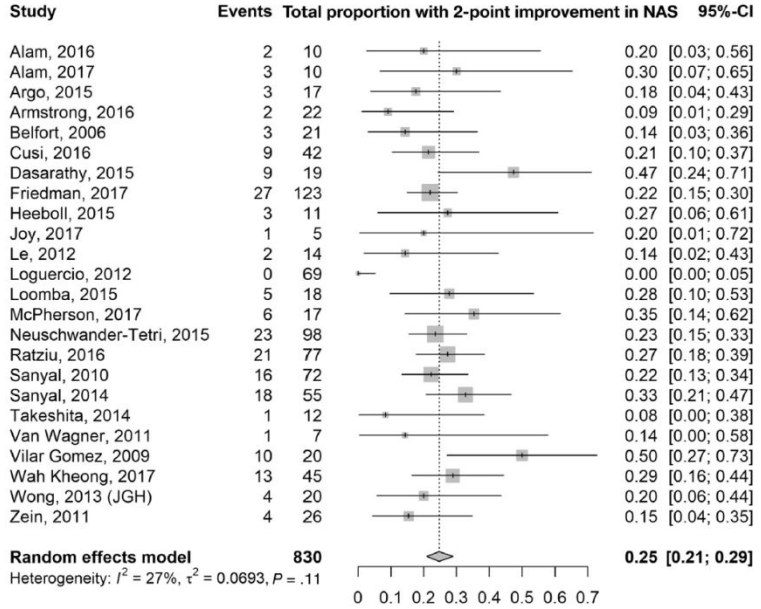


Liver stiffness

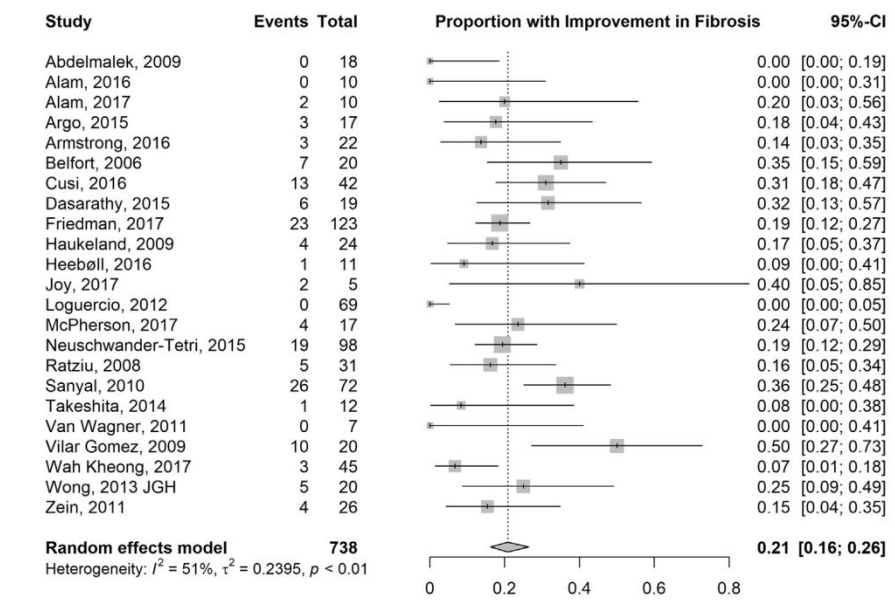


Koutoukidis DA., JAMA Intern Med 2019

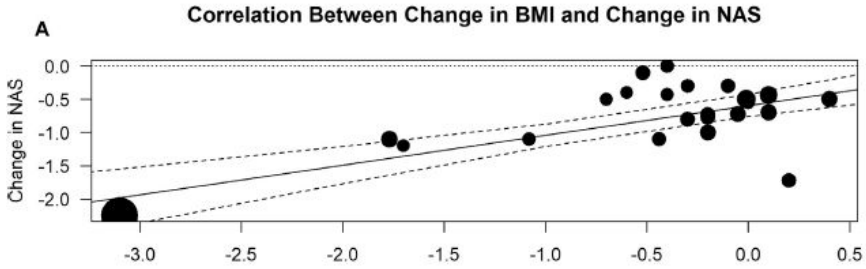
Placebo response in RCTs of pharmacotherapies for NASH



25% of patients given placebo improved NAS by ≥2 points

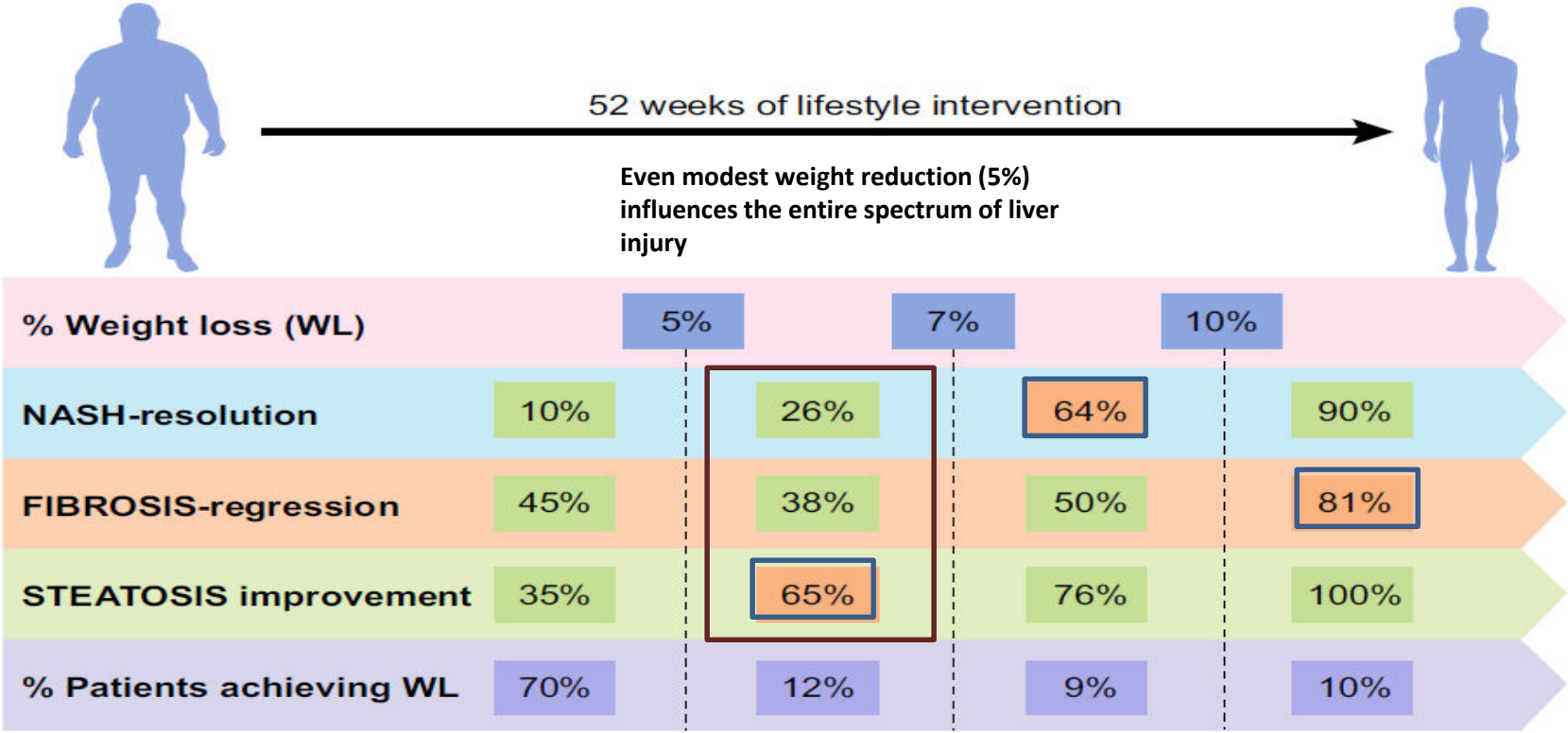


21% of patients given placebo improved fibrosis by ≥1 point



Han MAT., Clin Gastroenterol Hepatol 2019

Probability of reaching NASH resolution, fibrosis regression (at least one stage) and steatosis improvement in patients with NASH under lifestyle intervention

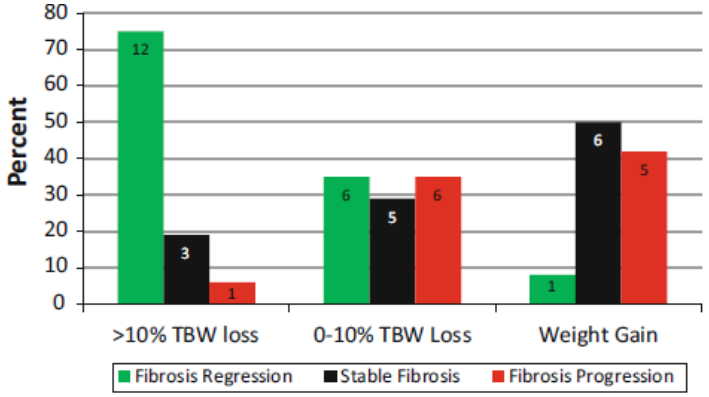


Vilar-Gomez E., Gastroenterology 2015

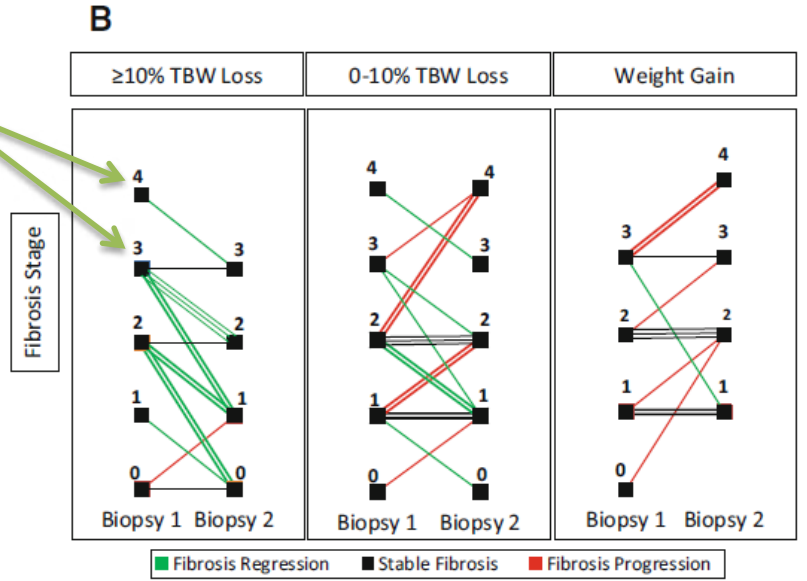
Romero-Gómez M., Zelber-Sagi S., Trenell M., Journal of Hepatology 2017

Weight Loss of 10 % is associated with improved hepatic fibrosis in NASH

- 45 NASH patients with serial liver biopsies for clinical monitoring in tertiary care setting
- Fibrosis regression defined as improvement in fibrosis score ≥1 stage
- Mean follow-up 4.6 years



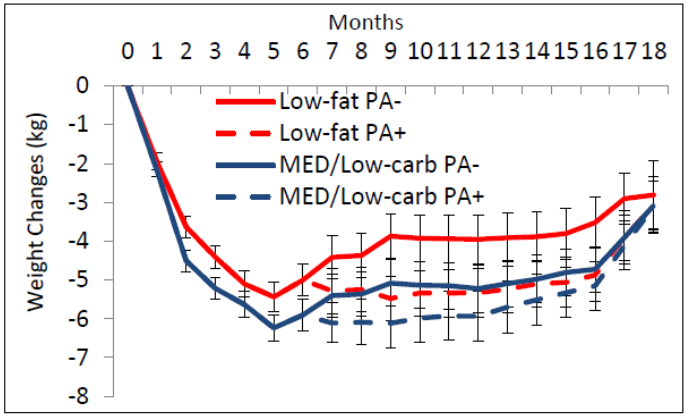
Regression of fibrosis even in advanced stages

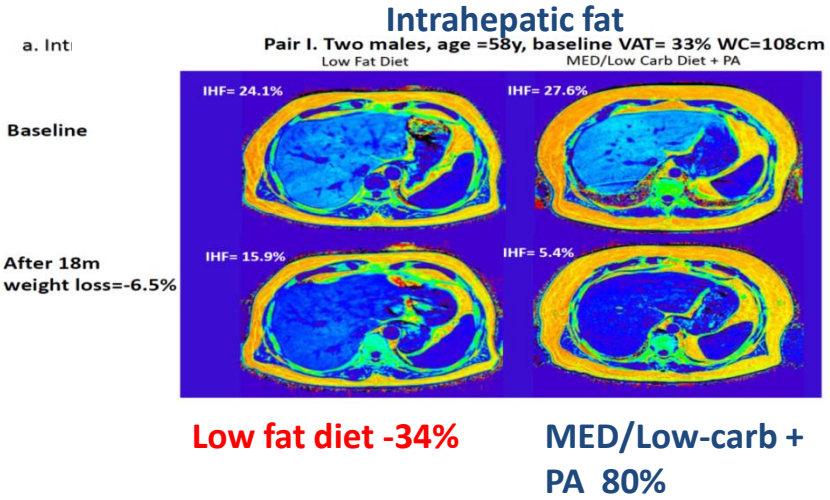


Glass LM., Dig Dis Sci 2014

Effect of diet with or without physical activity on liver and visceral fat

- 18-month RCT, 278 obese adults





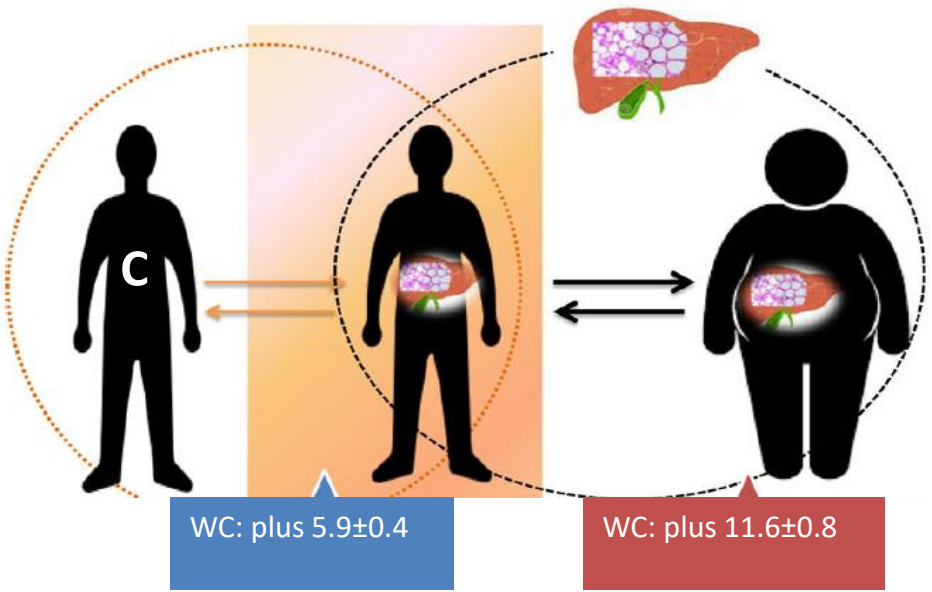
Low fat diet -34%

MED/Low-carb + PA 80%

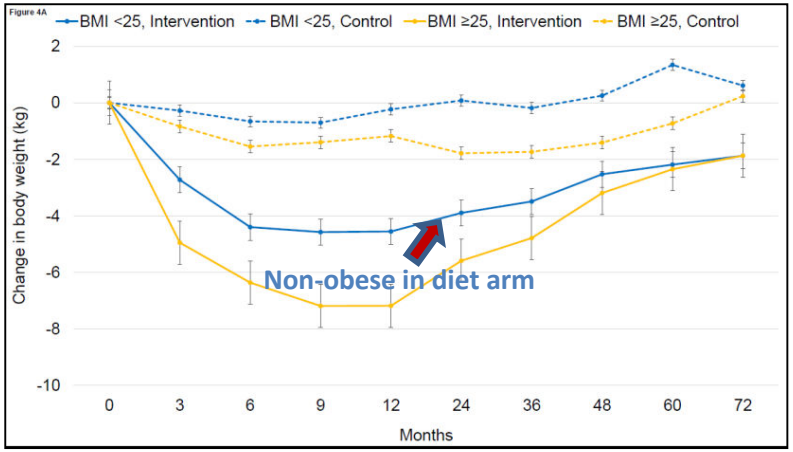
18-Month Changes	Low-Fat Diet		Mediterranean/Low-Carbohydrate Diet	
	PA– (Ref)	PA+	PA–	PA+
Visceral adipose tissue, cm^2	–32.9±33.5	–48.9±43.0†	–31.1±32.7	–47.3±36.6*
Intrahepatic fat, %, absolute units	–3.72±7.12	–3.88±6.32	–3.67±6.51	–4.74±7.63

Gepner Y., Circulation 2017

Beneficial effects of lifestyle intervention in non-obese patients with NAFLD



Change in body weight



+

- Reduction of weight gain even within the normal BMI range
- Reduced intake of fructose/ sugared soft drinks
- Reduced intake of dietary cholesterol (?)
- Physical activity- decrease visceral fat

Wai-Sun Wong V., J Hepatol 2018

Sookoian S., Aliment Pharmacol Ther 2017

Chen F., Hepatology 2019

Younes R., & Bugianesi E., Semin Liver Dis 2019

Ultra processed food and drinks

Major source of added sugar, high energy dense foods & low nutritional value

- Ultra-processed food (UPF) consumption has increased drastically worldwide
  - 50%–60% of total daily energy intake in several high-income countries

Monteiro CA., World Nutrition 2016

Ultra-processed foods are not ‘real food’

- Formulations of food substances modified by chemical processes
- ‘Cosmetic additives’ Flavours, colours, emulsifiers
- Hyper-palatable food and drink products

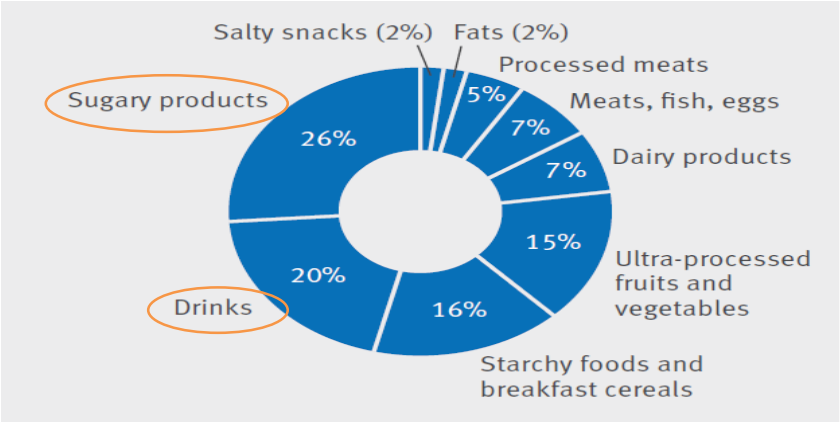
Practical way to identify if a product is ultra-processed

- List of ingredients contains substances rarely used in kitchens
  - Hydrolysed proteins
  - Fructose, high-fructose corn syrup
  - Hydrogenated oil
  - Cosmetic additives

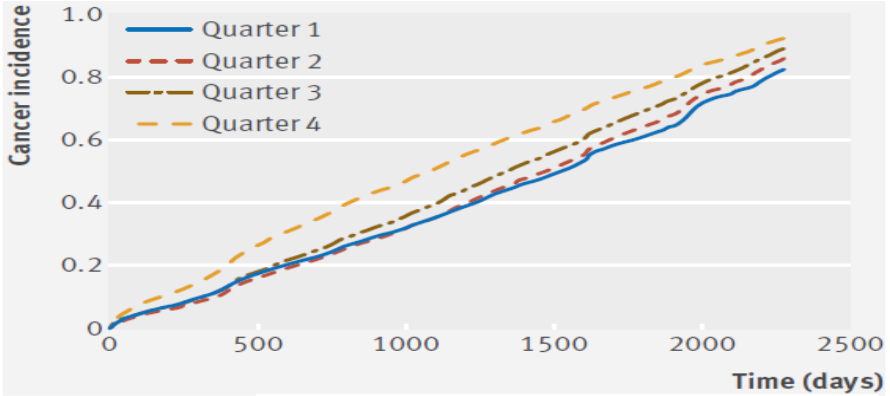
Monteiro CA., Public Health Nutrition 2018

Consumption of ultra-processed foods increases morbidity and mortality

- 104,980 adult participants from the French NutriNet-Santé cohort



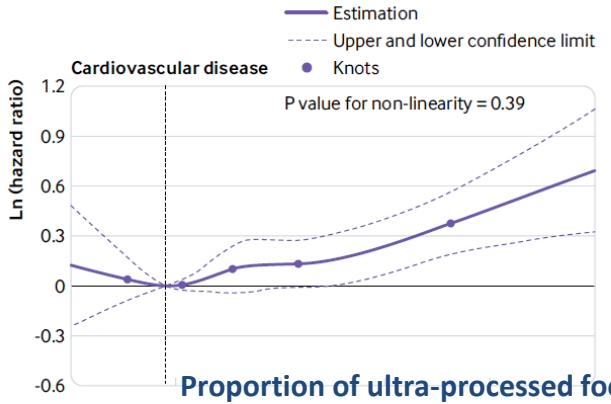
Cancer incidence by quarters of ultra-processed food



10% increase in the proportion of ultraprocessed food consumption

14% higher risk of all-cause mortality

Cardiovascular disease



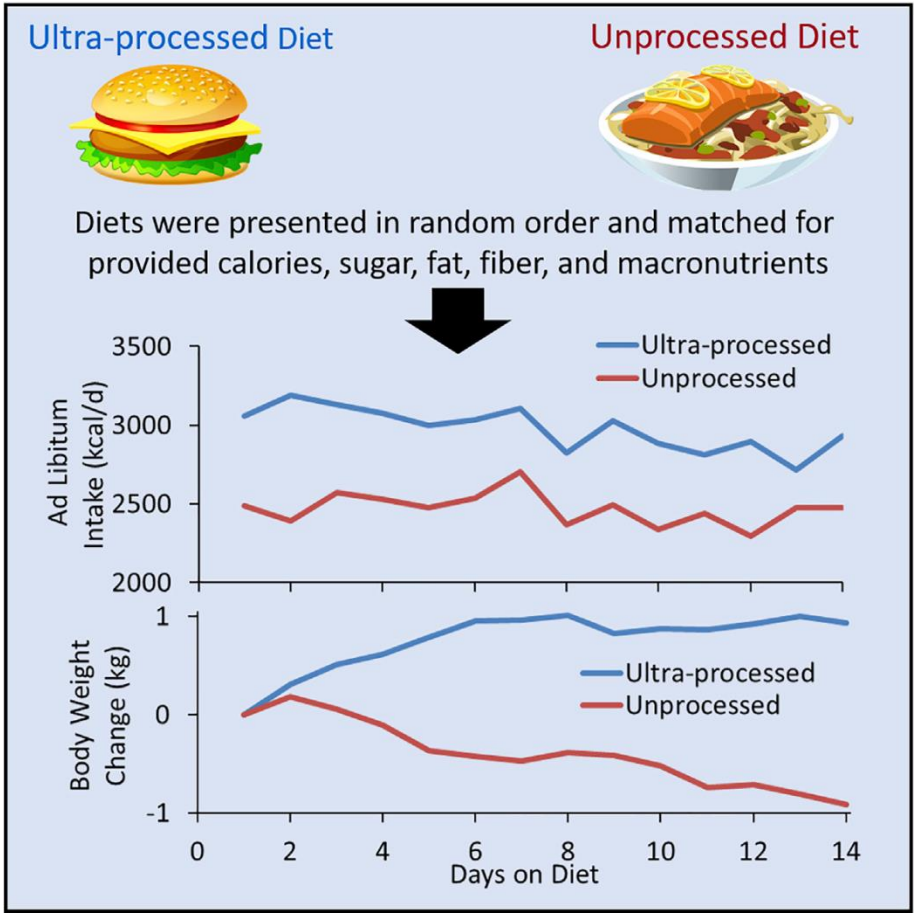
Srour B., BMJ 2019

Fiolet T., BMJ 2018

Schnabel L., JAMA Internal Medicine 2019

Ultra-Processed diets cause excess calorie intake and weight gain
Randomized cross-over trial of Ad Libitum food intake

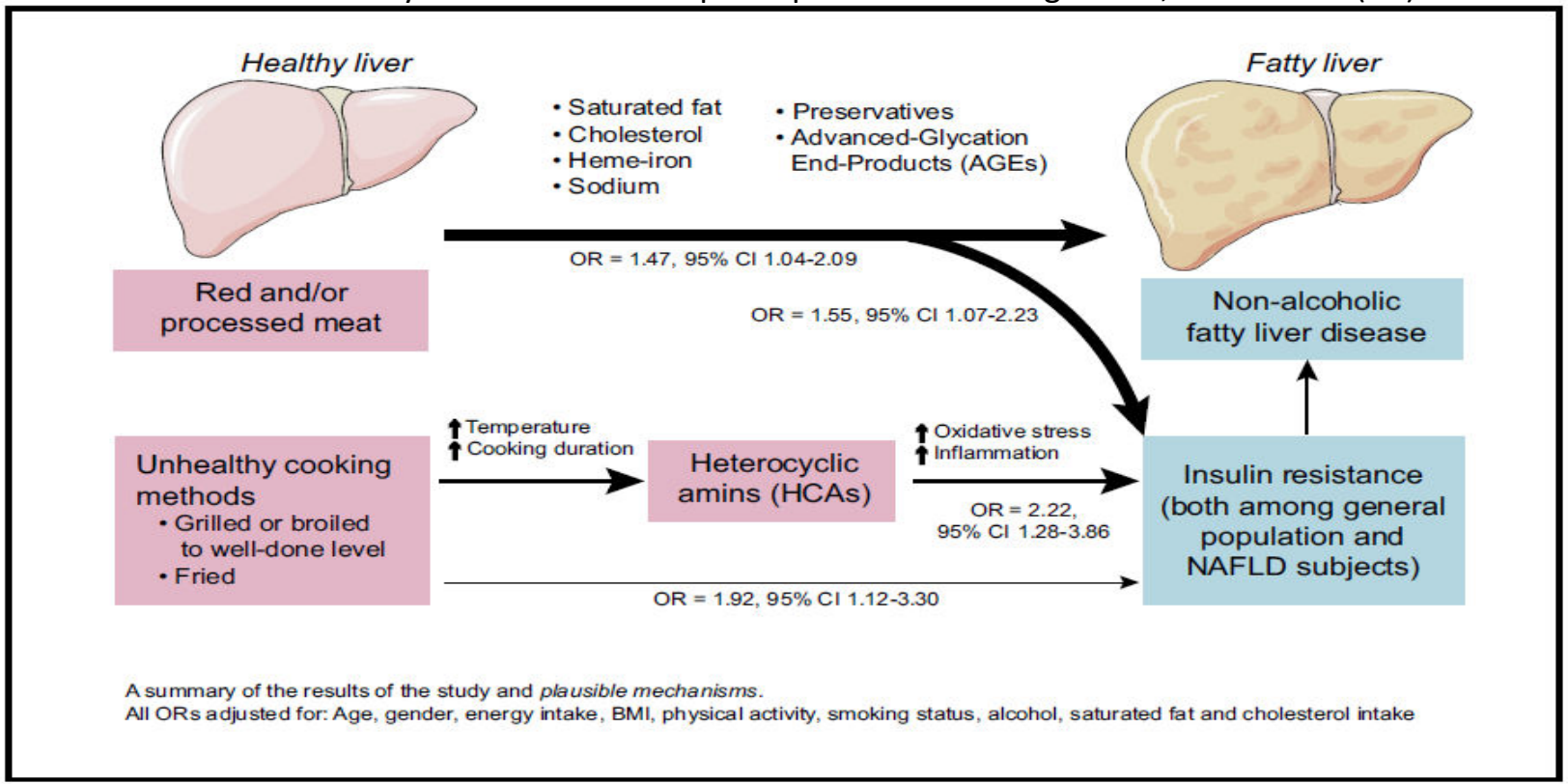
- 20 adults
- NIH Clinical Center
- Weight changes highly correlated with energy intake ($r = 0.8$, $p < 0.0001$)
- **Limiting consumption of ultra-processed foods may be an effective strategy for obesity prevention and treatment**



Hall KD., Cell Metabolism 2019

High red and processed meat consumption is associated with NAFLD and insulin resistance

- A cross sectional study of volunteers who participated in screening n=789, 39% NAFLD (US)



Zelber-Sagi S., Journal of Hepatology 2018

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

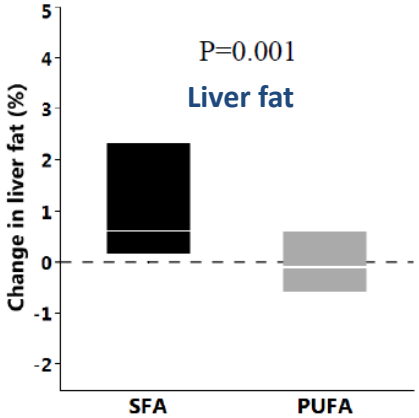
Noureddin M., Hepatology 2019

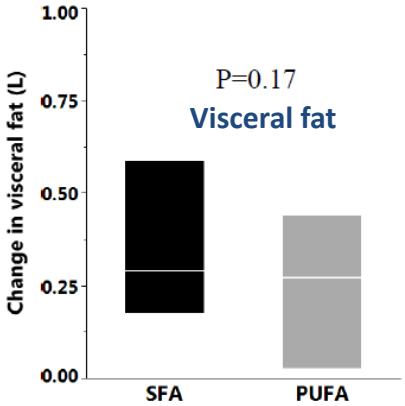
Overeating saturated fat promotes fatty liver compared to polyunsaturated fat RCT

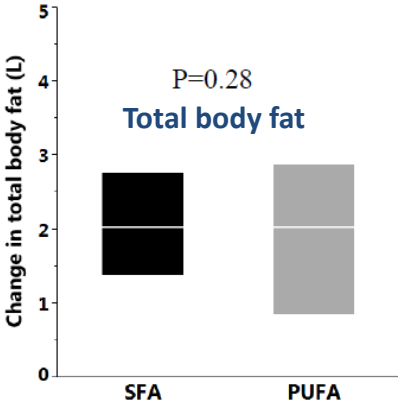
~3 muffins containing either sunflower oil (high in PUFA) or palm oil (high in SFA)
~40 grams of oil/day
Except for fat type, muffins were identical in composition

N= 60 double-blind, parallel-group, RCT

8 weeks







Rosqvist F., The Journal of Clinical Endocrinology & Metabolism 2019

A prospective study of dairy product intake and the risk of hepatocellular carcinoma in U.S. men and women

- 2 large prospective U.S. cohort studies, 51,418 men and 93,427 women
- Diets at baseline and updated every 2-4 years using validated FFQ

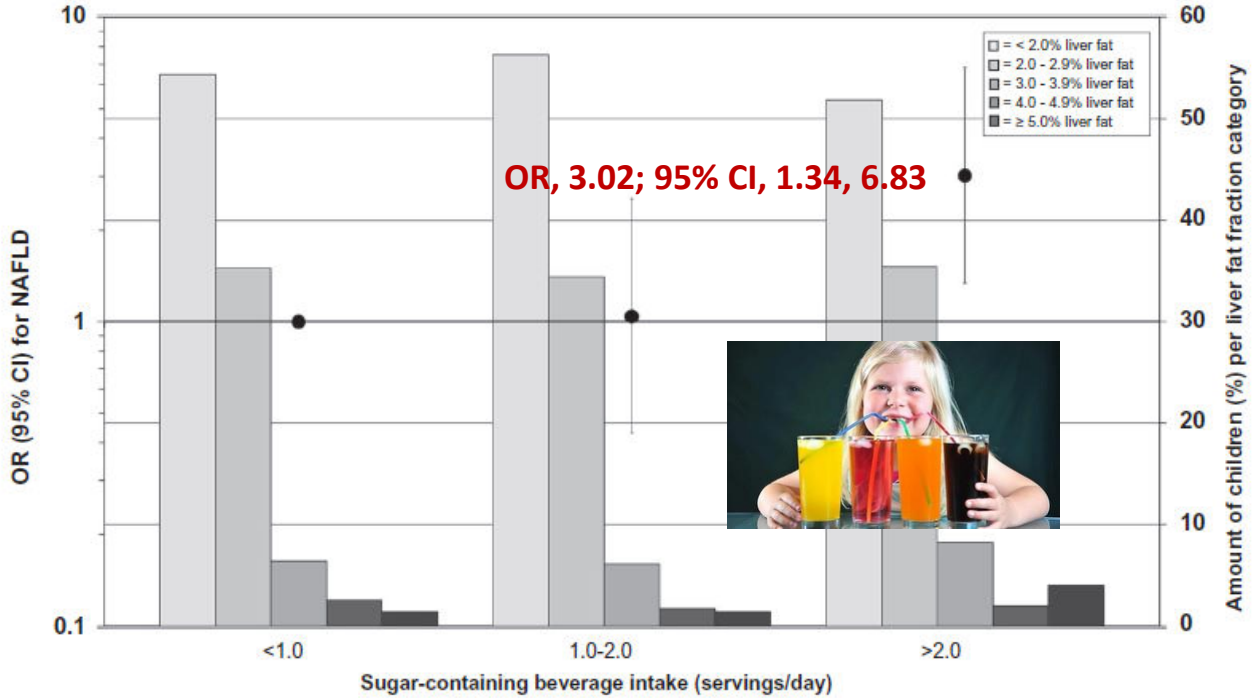
	Dairy products, HR (95% CI)			P trend
	Tertile 1	Tertile 2	Tertile 3	
High-fat dairy products	1 (Reference)	1.5 (0.95-2)	**1.81 (1.2-3)**	0.008
Low-fat dairy products	1 (Reference)	1.2 (0.8-1.8)	1.18 (0.8-1.8)	0.53
Butter	1 (Reference)	1.3 (0.8-2)	**1.58 (1.1-2)**	0.04

Adjusted for age, gender, race, physical activity, BMI, smoking, alcohol, coffee intake, calorie intake, aspirin use and type 2 diabetes

Yang W., Int J Cancer 2019

Sugar-containing beverage intake in infancy increases the risk for NAFLD in school-aged children

- Population-based prospective cohort
- 1,940 infants
- Sugar-containing beverage intake at 1 year: fruit juices, fruit concentrates, soft drinks, and lemonade
- NAFLD assessed with MRI at 10 years of age

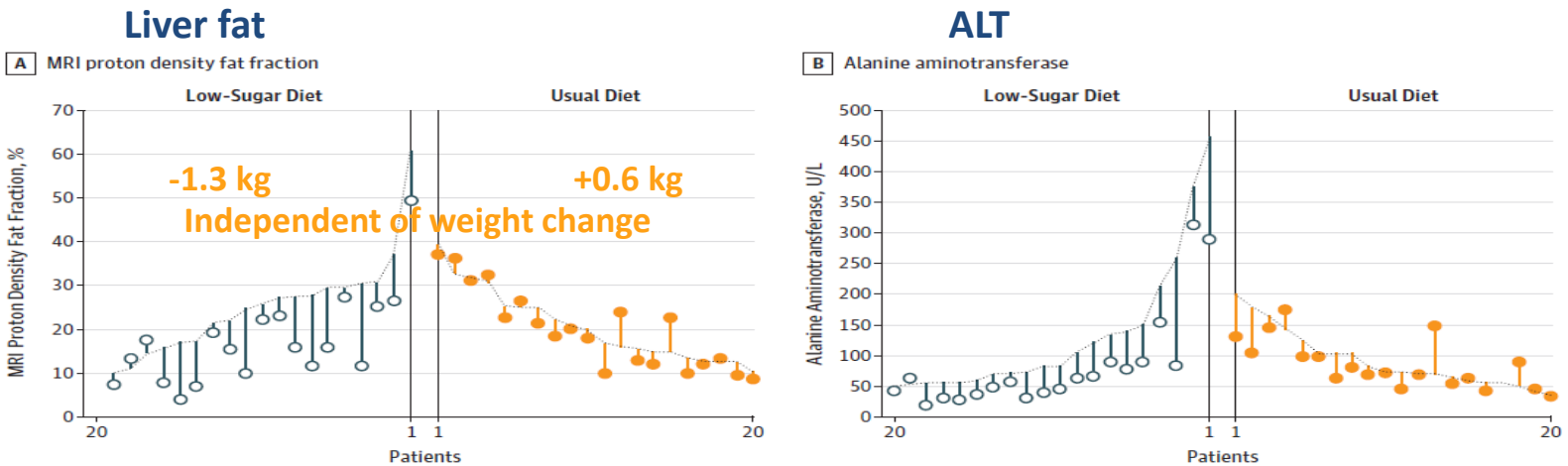


Adjusted for: children at 10 years of age, sex, total energy intake, maternal pre-pregnancy BMI, education, net household income, child ethnicity, physical activity, and screen time

Geurtsen ML., Hepatology, 2021

Effect of a low-free sugar diet in NAFLD

- An open-label, 8-week RCT
- Boys aged 11-16 years (n=40) with NAFLD
- Diet group or usual diet group
  - provision of study meals for the entire household to restrict free sugar intake to less than 3% of daily calories



Schwimmer JB., JAMA. 2019

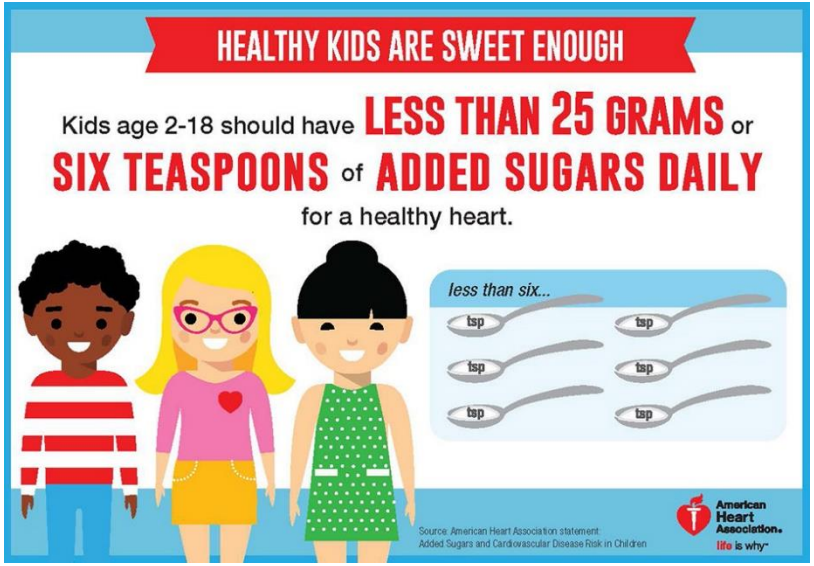
Fructose consumption independently associated with NASH in children & adolescents

- 271 obese children with NAFLD
- Liver biopsy obtained

Adjusted association between fructose consumption & uric acid levels and NASH (NAS≥5)

	Odds ratio (95% CI)	p
Fructose, g/day	**1.612 (1.25,1.86)**	**0.001**
Uric acid, mg/dl	**2.488 (1.87,2.83)**	**0.004**
WC, cm	1.842 (1.11,1.95)	0.03
HOMA-IR	3.21 (1.9, 5.72)	0.024
Triglyceride, mg/dl	1.208 (1.1,1.58)	0.048

Mosca A., Nobili V., Journal of Hepatology 2017



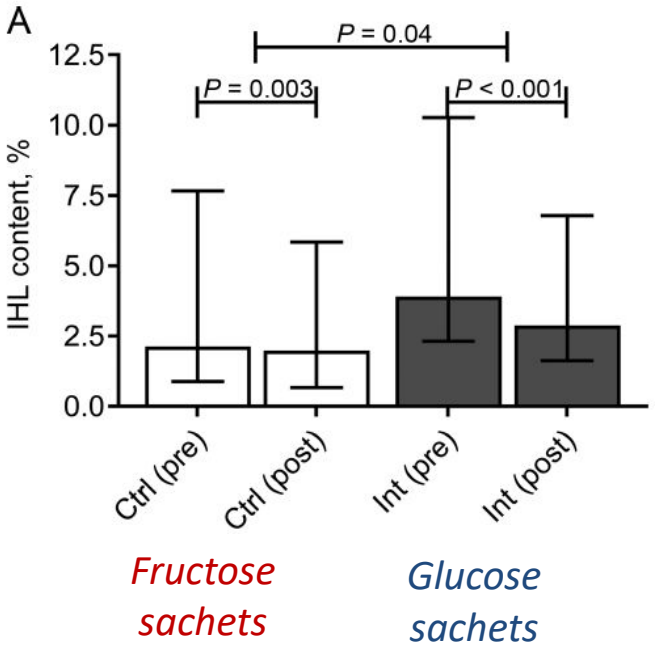
"Excess consumption of added sugars, especially from sugary drinks, poses health threat to children and adolescents, disproportionately affecting children of minority and low-income communities. Public policies, are needed ……"

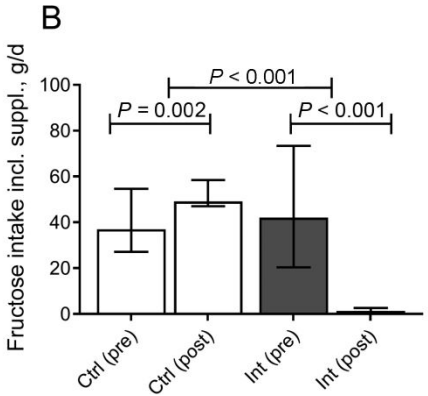
Policy statement 2019

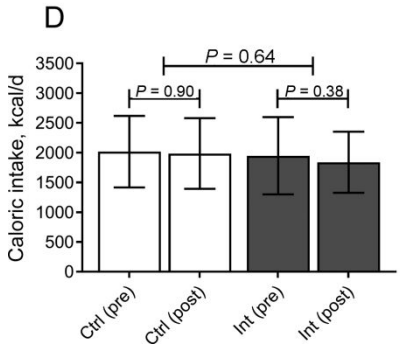
American Academy of Pediatrics

Effects of fructose restriction on liver steatosis a double-blind RCT

- Adult overweight with a fatty liver index ≥ 60
- All underwent 6-wk fructose-restricted diet (<7.5 g/meal and <10 g/d)
- Randomly assigned to supplementation with sachets of glucose or fructose







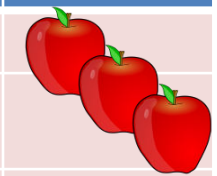
Simons N., Am J Clin Nutr 2021

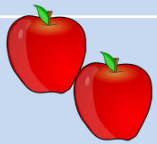
No association of fruits intake with NAFLD

- Cross-sectional study in Japan
- Short dietary intake questionnaire
- NAFLD diagnosed by US

Odds ratios of non-alcoholic fatty liver disease according to quartiles of fruit intake and vegetable intake

	Q1	Q2	Q3	Q4	p-trend
Women (N=1,467)					
Fruit (g/1,000 kcal) median (range)	16.3 (0.0-30.5)	45.4 (30.8-59.9)	74.4 (60.0-93.1)	121.0 (93.2-329.5)	
BMI adjusted OR	1	0.85 (0.49, 1.47)	0.90 (0.49, 1.63)	0.82 (0.44, 1.55)	0.60
Men (N=977)					
Fruit (g/1,000 kcal) median (range)	10.4 (0.0-18.1)	28.2 (18.2-39.3)	52.6 (39.4-67.9)	93.9 (68.3-301.6)	
BMI adjusted OR	1	0.90 (0.58, 1.38)	0.88 (0.56, 1.37)	0.68 (0.42, 1.11)	0.12

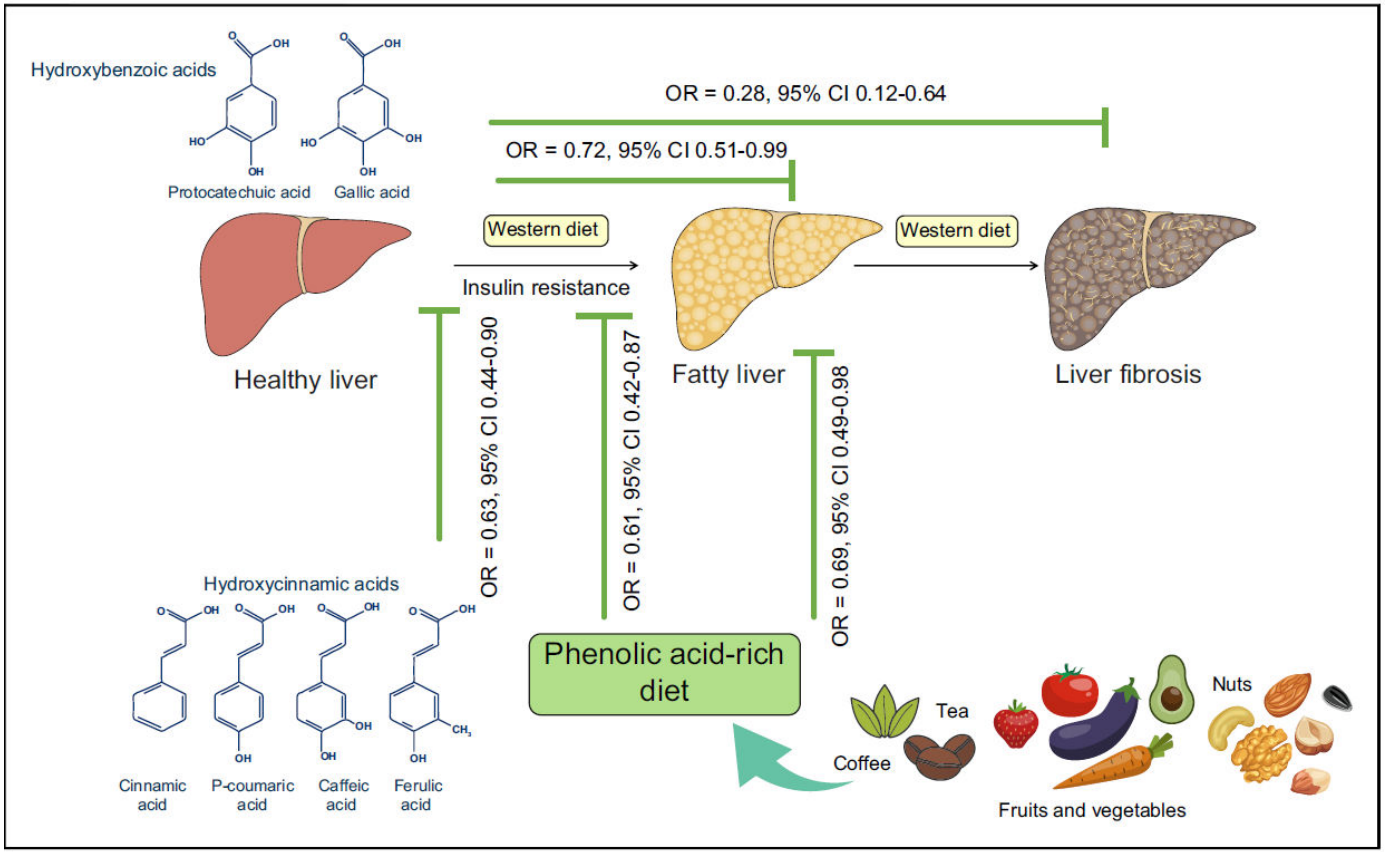




Tajima R., Nutrition 2018

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

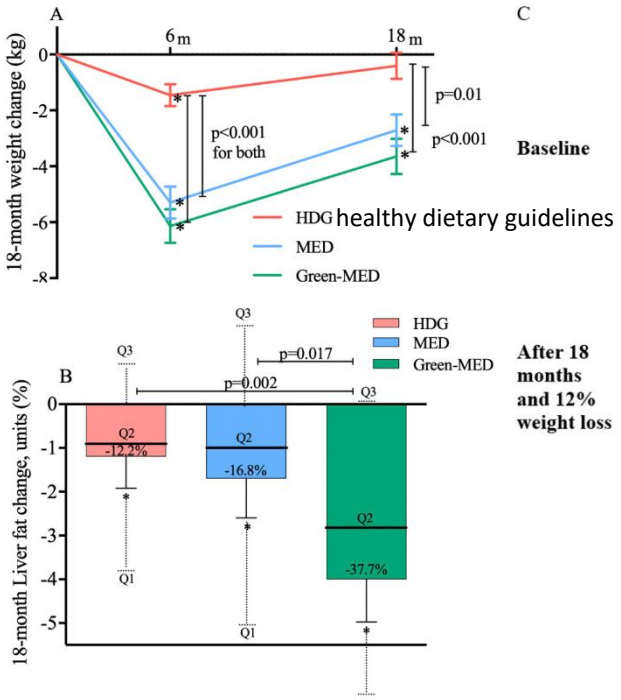
- Cross-sectional study, n= 789
- AUS
- FibroTest
- HOMA
- Phenolic acid content of food calculated by Phenol-Explorer

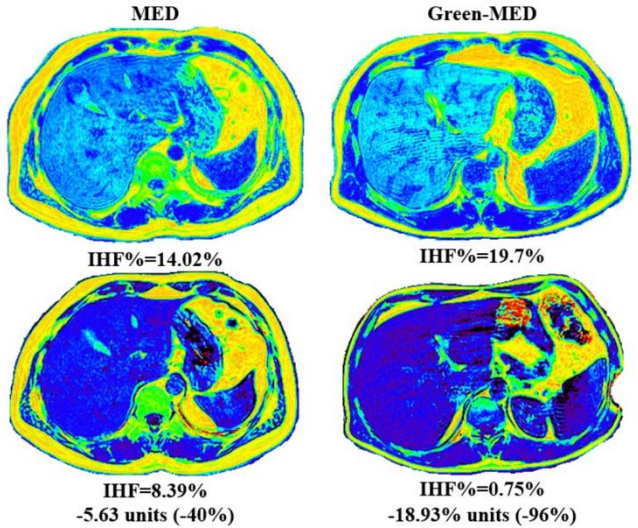


Salomone F., JHEP Reports 2020

Effect of green-Mediterranean diet on intrahepatic fat: RCT

- 18-month RCT
- 294 people with abdominal obesity or dyslipidemia
- Two isocaloric MED groups
- Green-Mediterranean diet, further restricted in red/processed meat, and enriched with green plants and polyphenols
  - green tea (3–4 cups/day)
  - Mankai (a Wolffia globosa aquatic plant strain) green shake



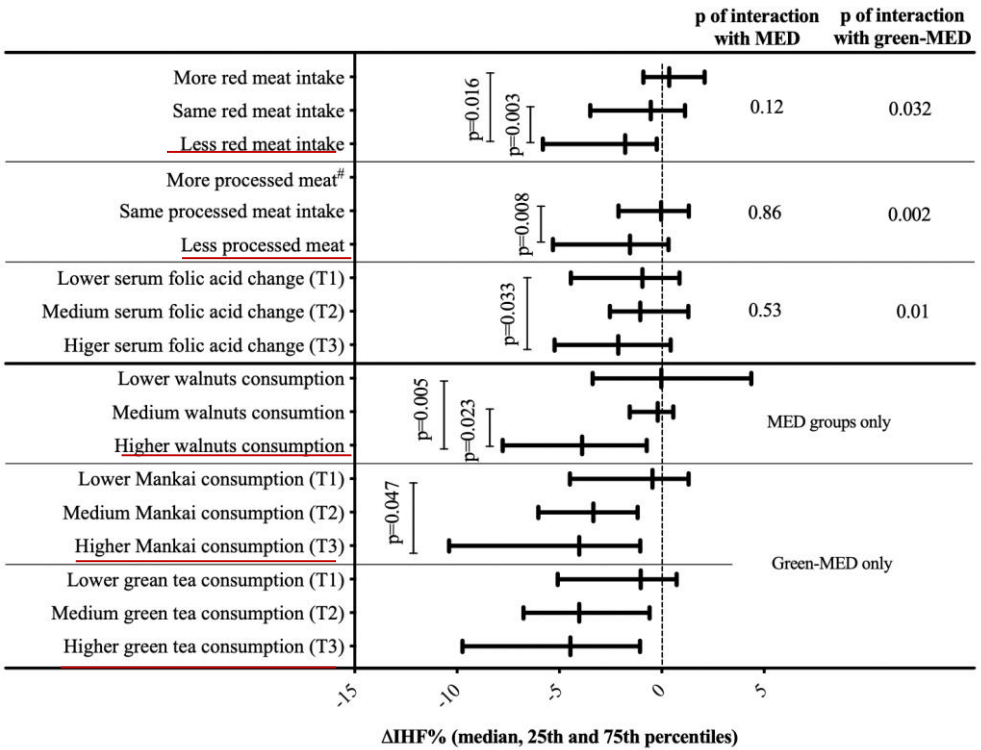


Total plasma polyphenol levels at the end of the intervention were higher in the green-MED participant versus MED participant (0.67 mg/L vs 0.24 mg/L)

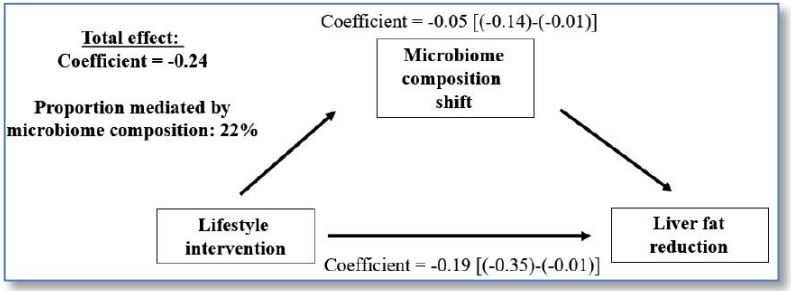
Yaskolka Meir A., Gut 2021

Effect of green-Mediterranean diet on intrahepatic fat

Liver fat loss associated with increased Mankai, green tea and walnuts intake, decreased red/processed meat consumption

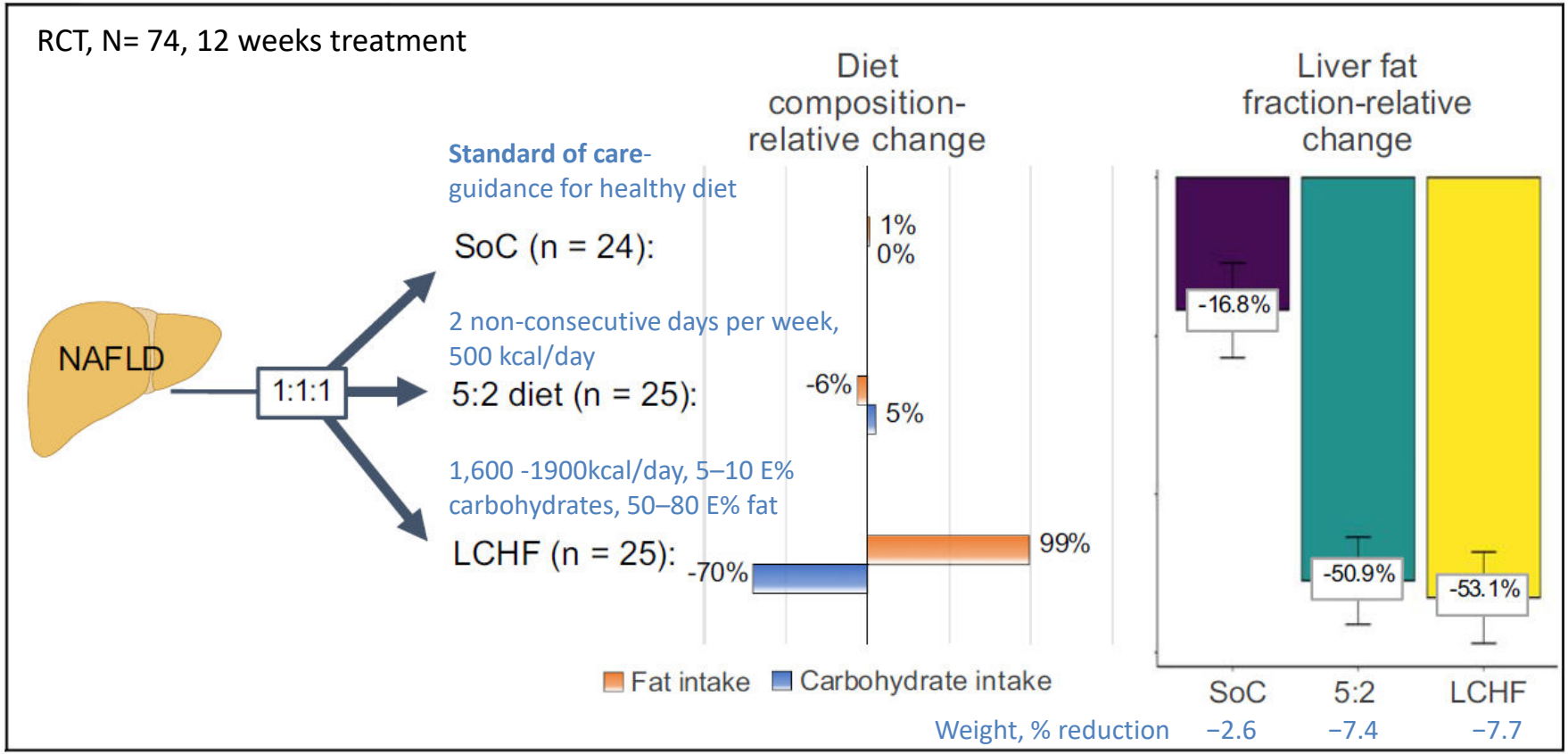


In a mediation analysis, the compositional shift of the microbiome accounted for 22% of IHF change by the lifestyle interventions



Yaskolka Meir A., Gut 2021

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



Holmer M., JHEP Reports 2021

Modest (~<2 drinks/d) alcohol consumption compared to non-drinking

Author & Year	Design & Population	Steatosis	NASH	Fibrosis	Severe liver event	HCC/ CVD
Chang Y., Hepatology 2019	Cohort study 4-Y FU N=190,048 Korean employees	**Reduced risk**	-	**Increased risk**	-	-
Chang Y., Hepatology 2018	Cohort study 8.3-Y FU N=58,927 Korean employees	-	-	**Increased risk**	-	-
Yamada K., PLOS ONE 2018	Cross-sectional study N=178 NAFLD	-	**Reduced risk**	**Reduced risk**	-	-
Åberg F., Hepatology 2018	Follow-up data from national registers	-	-	-	**Increased risk**	-
Hagström H., Scand J Gastroenterol 2017	Cross-sectional N=120 NAFLD	-	No association	**Reduced risk**	-	-
Moriya A., J of Hepatology 2015	Prospective 2-Y FU N=5297 Japanese	**Reduced risk**	-	-	-	-
Dunn W., J of Hepatology 2012	Cross-sectional N= 582 NASH CRN	-	**Reduced risk**	**Reduced risk**	-	-
Ascha MS., Hepetology 2010	Prospective 3-Y FU N=195 NASH-Cirrhosis	-	-	-	-	**Increased risk**
VanWagner LB., Gastroenterology 2017	Cross-sectional N=570 NAFLD	-	-	-	-	**Not protective from subclinical CVD (e.g. CAC)**

Modest (~<2 drinks/d) alcohol consumption compared to non-drinking in NAFLD patients – only prospective studies

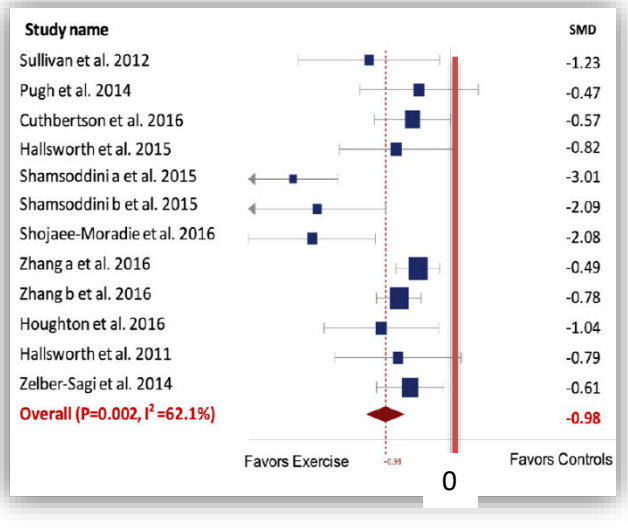
Author & Year	Design & Population	Fibrosis	Severe liver event	HCC
Åberg F., Hepatology 2020	Cohort study 11-y FU N=8,345	-	**Increased risk**	-
Chang Y., Hepatology 2019	Cohort study 4-Y FU N=190,048	**Increased risk**	-	-
Ajmera V., Clin Gastroenterol Hepatol. 2018	Cohort study 4-y FU N= 285	**Lower odds of NASH resolution**	-	-
Chang Y., Hepatology 2018	Cohort study 8.3-Y FU N=58,927	**Increased risk**	-	-
Ascha MS., Hepetology 2010	Prospective 3-Y FU N=195 NASH-Cirrhosis	-	-	**Increased risk**

Alcohol recommendations for NAFLD from international guidelines

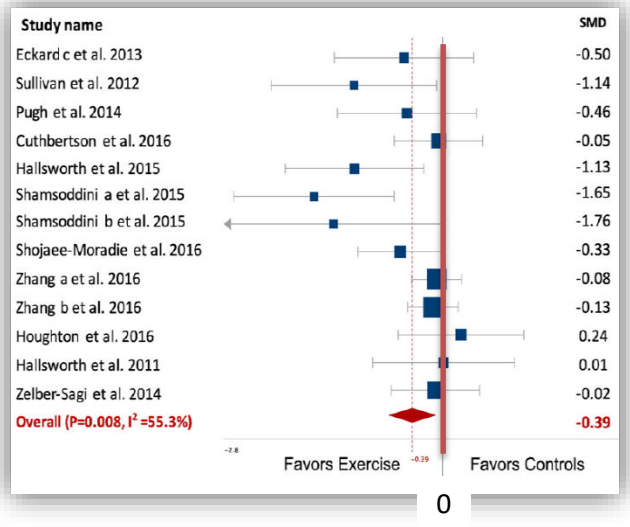
Association	Journal Year of publication	Recommendation
European Association for the Study of the Liver (EASL) European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO)	J of Hepatology 2016	**Total abstinence is mandatory in NASH-cirrhosis**
American Association for the Study of Liver Diseases (AASLD)	Hepatology 2017	**There are insufficient data to make recommendations to non-heavy consumption of alcohol**
The European Society for Clinical Nutrition and Metabolism (ESPEN)	Clinical Nutrition 2019	**NAFL/NASH patients shall be encouraged to abstain from alcohol in order reduce risk for comorbidity and to improve liver biochemistry and histology**

Effect of exercise alone on liver fat and ALT
Meta-analysis of RCTs

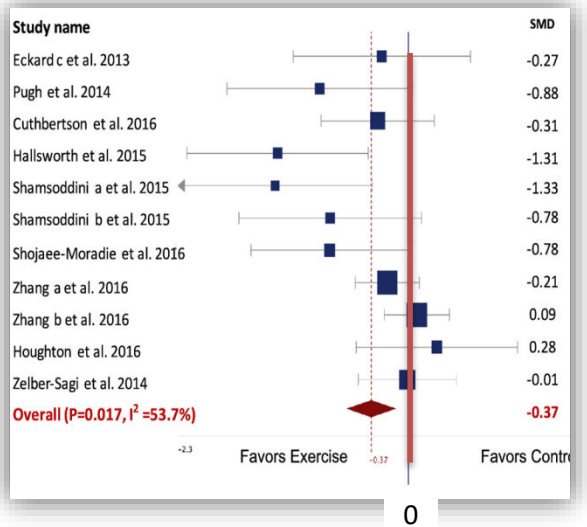
Liver fat



ALT



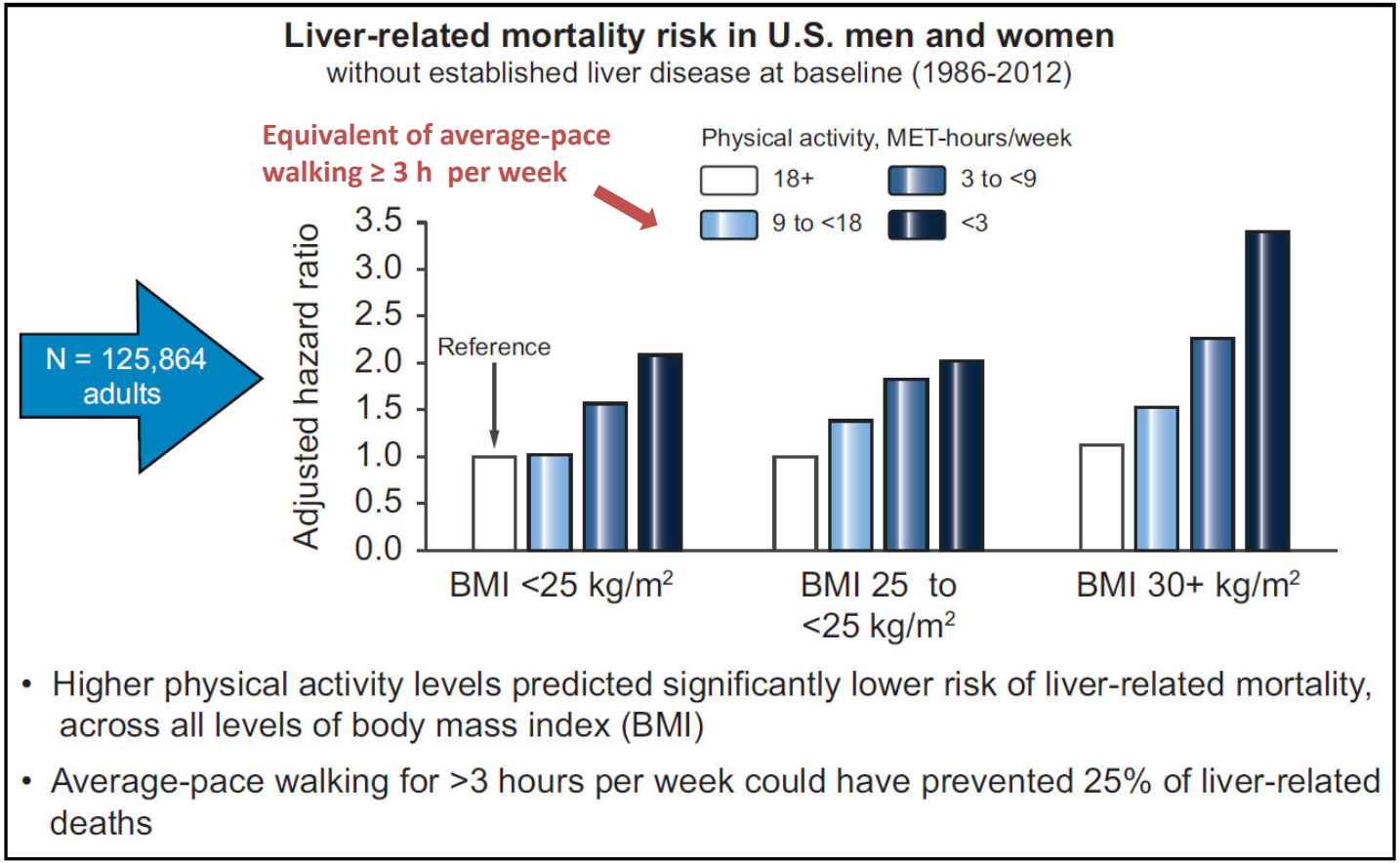
AST



Katsagoni CN., Metabolism 2017

Physical activity is protective from liver related mortality and attenuates the added risk from adiposity

- Liver-related mortality, defined as death from HCC or from a non-HCC complication of cirrhosis



Simon TG., Journal of Hepatology 2020

Physical Activity and Sedentary Behavior Are Independent Predictors of Nonalcoholic Fatty Liver Disease

	OR (95% CI)	P
Sitting time (hour/day)		
Q1 (< 4)	1	For trend<0.001
Q2 (≥ 4 *to* < 6)	0.99(0.89-1.11)	0.891
Q3 (≥ 6 *to* < 8)	1.10(0.98-1.25)	0.106
Q4 (≥ 8)	1.21(1.11-1.31)	<0.001
Total physical activity (minutes/week)		
0	1	For trend<0.001
1-149	0.79(0.71-0.87)	<0.001
150-299	0.73(0.63-0.84)	<0.001
≥300	0.62(0.56-0.68)	<0.001

Regardless of total physical activity

Adjusted for age, sex, race/ethnicity, education level, marital status, economic status, smoking status, hypertension, and total cholesterol , total physical activity

Kim D., Hepatology 2020

Impact of the Interaction Between PNPLA3 Genetic Variation and Dietary Intake on the Risk of Significant Fibrosis in Patients With NAFLD

- Cross-sectional study, NASH Clinical Research Network
- PNPLA3-rs738409 variant genotyped in 452 non-Hispanic whites
- Histologically confirmed NAFLD
- FFQ within 6 months of liver biopsy
- Adjusted for calorie intake, age, gender, BMI and type 2 diabetes

PNPLA3 rs738409 genotypes		
Dietary factors	**CC**	
	OR (95% CI)	**P-value**
Carb (% of energy)	1.02 (0.97-2.53)	0.383
n-3 PUFAs (g/d)[c]	0.24 (0.04-1.51)	0.128
Total isoflavones (mg/d)	1.58 (0.72-3.49)	0.255
Methionine (mg/d)	0.49 (0.13-1.92)	0.311
Total choline (mg/d)	0.48 (0.12-1.87)	0.295
Dietary factors	**CG+GG**	
	OR (95% CI)	**P-value**
Carb (% of energy)	**1.04** (1.01-1.07)	0.019
n-3 PUFAs (g/d)	**0.16** (0.05-0.53)	0.003
Total isoflavones (mg/d)	**0.65** (0.44-0.95)	0.025
Methionine (mg/d)	**0.30** (0.13-0.70)	0.005
Total choline (mg/d)	**0.29** (0.11-0.73)	0.009

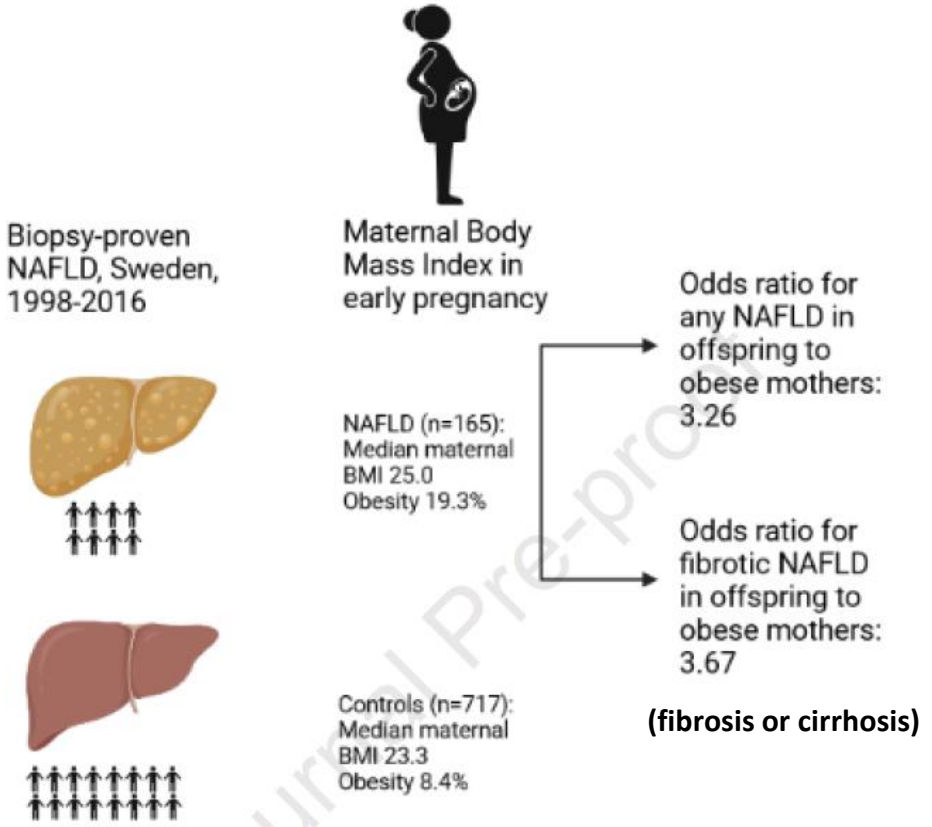
Vilar-Gomez E., Am J Gastroenterol 2021

Maternal obesity increases the risk and severity of NAFLD in offspring

- Nationwide cohort study
- Individuals in Sweden with biopsy-verified NAFLD ≤25 years of age (n=165)

- Matched on age, sex, and calendar year with up to 5 controls

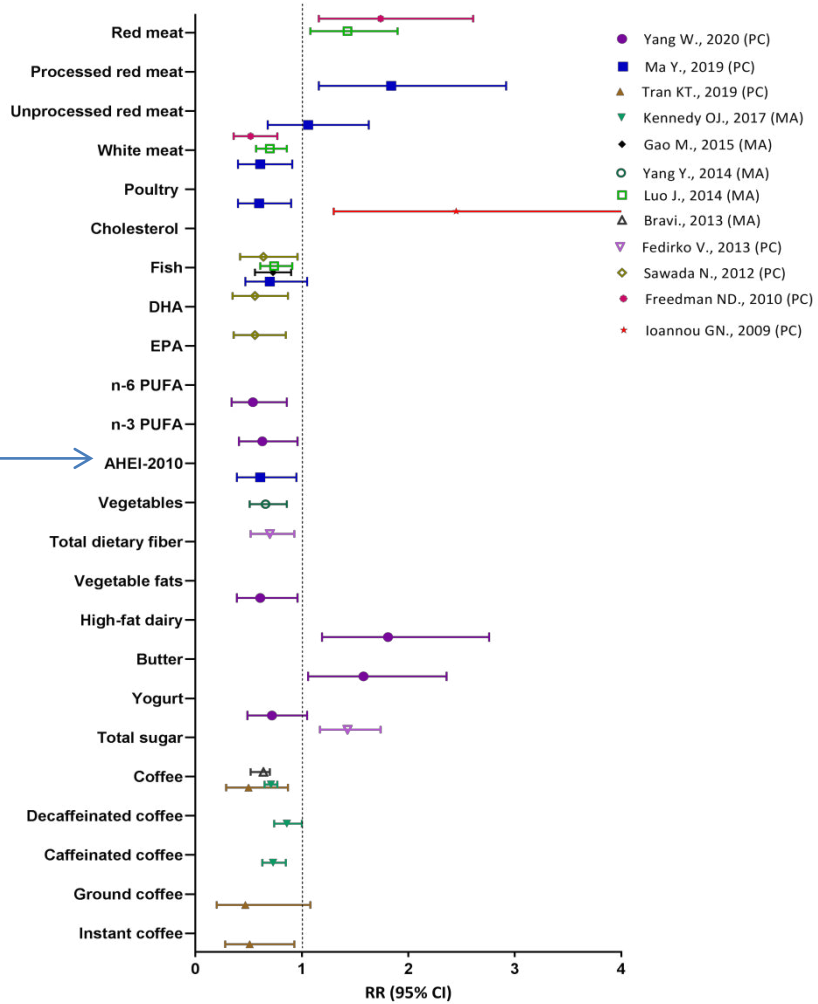
- Adjusted for: maternal age, maternal country of birth, parity, education, and smoking in early pregnancy



Hagström H., Journal of Hepatology 2021

Lifestyle parameters related with increased or reduced risk for HCC, demonstrated in large prospective cohort studies and meta-analyses of cohort studies

- The categories compared were the highest dietary intake category vs. the lowest intake
- **AHEI-2010** consists of high intake of fruit, vegetables, whole grains, nuts and legumes, n-3 fats, and low intake of sugar-sweetened beverages and fruit juice, red and processed meat, trans fat, sodium, and a moderate alcohol consumption



Zelber-Sagi S., Seminars in Liver Disease 2021

Obese NAFLD

Non-obese NAFLD

Nutritional anamnesis

Make sure to ask about surged foods, foods rich in saturated fat, ultra- processed foods sugared drinks, fruit juice, alcoholic drinks and physical activity and sedentary time habits

Weight reduction

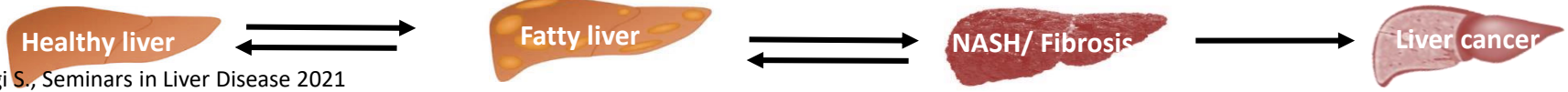
- 5%- 10% reduction of initial body weight, increasing goals with the presence of NASH and fibrosis
- Healthy diet with caloric restriction tailored for the patients' preferences

- 5% reduction of weight even within the normal BMI range (especially if recent weight gain occurred or if abdominal obesity is present)
- Target reduction of visceral fat (waist circumference)

Lifestyle parameters

(advise both obese and non-obese patients)

Positive — Neutral — Negative



Zelber Sagi S., Seminars in Liver Disease 2021

Oren Shibolet

Zamir Halpern

Hanny Yeshua

Sigal Fishman

Revital Kariv

Izabel Zvibel

Muriel Webb

Shiri Sherf-Dagan

Naomi Fliss

Liat Mlynarsky

Dana Ivankovsky